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Case Report

Menkes Kinky Hair Disease: Radiological Relevance in this Entity in Our Case

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Abstract

We present a case report of a 9-month-old male infant with protein-energy malnutrition who was admitted in the hospital with the history of seizures since 5 months of age. The infant had fair complexion and sparse fuzzy woolly hair. Serum copper and ceruloplasmin levels were low, magnetic resonance (MR) imaging showed bilateral extensive SDHs with gliosis, MR angiography revealed tortuosity of cerebral vessels. The patient was diagnosed as Menkes disease and treated symptomatically. For lack of facilities, we were not able to do genetic study. Our case showed the typical neuroradiological and clinical findings of this neurodegenerative condition and we report this case for the rarity of this condition in routine clinics as well as for the role the radiologist played in approaching the differentials as well as for the final diagnosis.

Key words: Menke's, SDH, Copper

INTRODUCTION

We present a case report of a 9-month-old male infant with protein-energy malnutrition who was admitted in the hospital with the history of seizures since 5 months of age. He was also suffering from frequent attacks of cough and cold. The infant had no H/o consanguineous marriage. On proper evaluation of history, mother elicited a history of developmental lag.

On examination, the baby was conscious but irritable, fair complexion chubby cheeks, light-colored steel sparse woolly hair with easy pluckability. On clinical examination, the child had The infant had fair complexion and sparse fuzzy woolly hair. He had also mental retardation.

Central nervous system examination revealed repeated myoclonic seizures of the limbs, limbs were hypertonic, whereas the trunk was hypotonic, generalized muscle wasting present with power grade 3/5 examination of the respiratory system showed signs of wheeze associated respiratory infection. Other systems appeared normal.

Hematological, biochemical, as well as radiological investigations were ordered.

Blood workup revealed mild anemia and leukocytosis, cerebrospinal fluid study was normal.

The skeletal survey of the limb bones showed osteopenia.

The infant was advised for MRI-brain and MR-angiography study, to look for any underlying epileptic neuroparenchymal focus.

Biochemical copper and ceruloplasmin level workup was obtained after the radiological advice, which suggested to rule-out this copper metabolism disorder.

The serum copper level was found to be low (normal value at this age is 46–80 mg/dl), serum ceruloplasmin level was also found low (normal value is approximately 20–40 mg/dl) [Figures 1-3].

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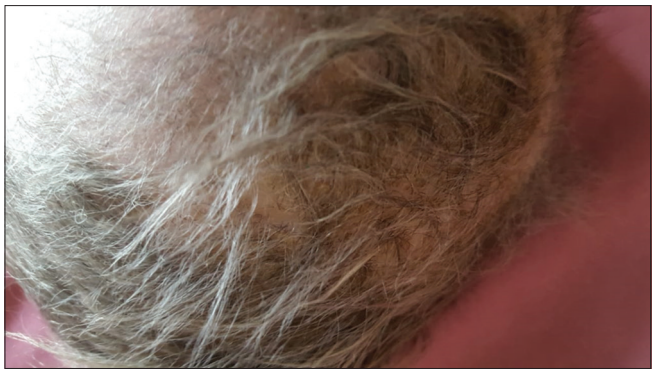

Figure 1: Kinky hair immediately after birth. This picture shows "kinky hair," fuzzy, and woolly hair which means abnormal and brittle hair. However, babies often have a thin head of hair, making kinky hair difficult to identify

DISCUSSION

Menkes disease (MD) is a rare infantile-onset neurodegenerative disorder caused by mutations in the X-linked ATP7A gene.[1] This gene encodes a copper-transporting ATPase, which has the dual role of ATP-driven copper efflux from cells and the intracellular transport of copper to the copper-requiring enzymes.[2] These cuproenzymes catalyze a diverse range of essential biochemical reactions.[3] Affected individuals have unusually low copper levels in serum, brain, hair, and skin.

These include cerebral and cerebellar atrophy, delayed myelination, tortuosity of the intra- and extracranial

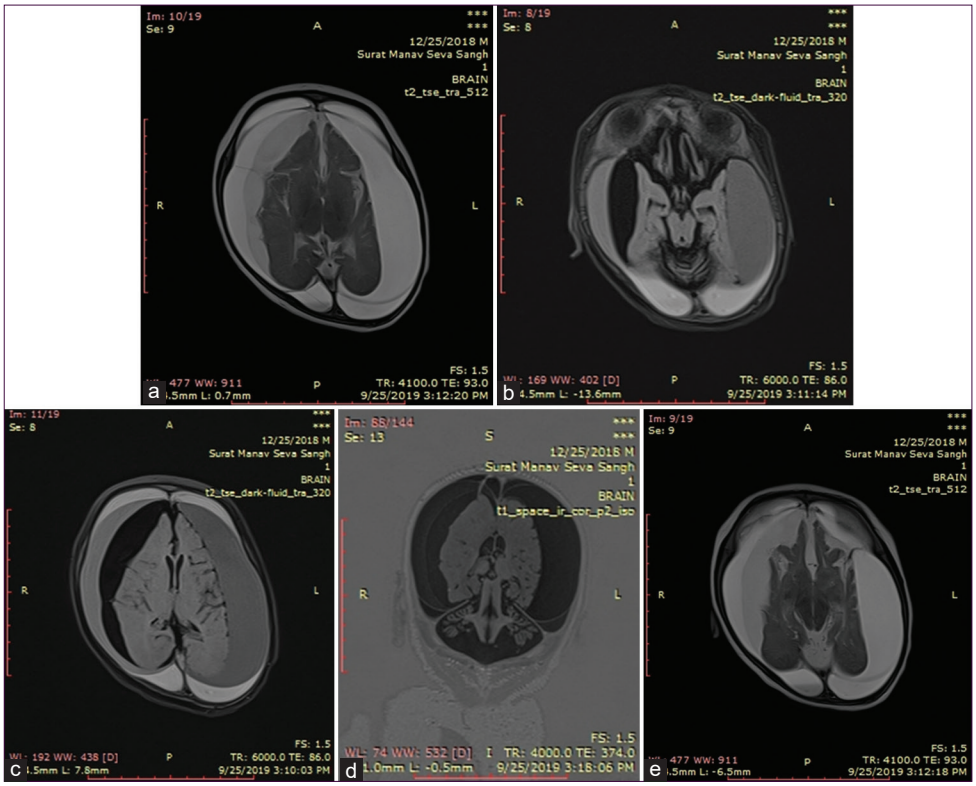

Figure 2: T2 and FLAIR axial (a-c and e) and T1-IR (d) coronal images showing bilateral Subdural hemorrhages in different stages of temporal evolution, along bilateral convexities. Maximum width of the SDH measuring 25 mm. Cerebellar atrophy was seen, as seen on inversion recovery sequences. However, no definitive epileptogenic focus was identified. Myelination was normal for age. No e/o any blooming foci were seen on GRE images (image not shown here)

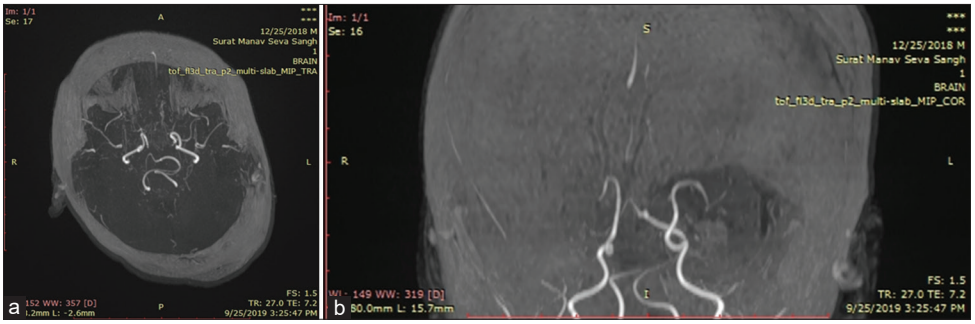

Figure 3: (a and b) TOF-MRA images showed normal intracranial vasculature. Kinking in the vessels was not seen in our case

vessels, involvement of the deep gray nuclei, white matter lesions of the temporal lobe, and subdural fluid collections.[4-6]

CONLCUSION

We found reporting this case as the case was being treated as a case of PEM with WARI and convulsions. The radiological picture and radioclinical correlation enabled the diagnosis of this condition, which was otherwise completely overlooked and the prime role radiology played in this case. The typical clinical picture of this patient was also noteworthy.

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Case Report

Proximal Ureteric Injury: An Unusual Complication of Percutaneous Renal Biopsy

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Abstract

A 30-year-old male developed fever and unrelenting left loin pain following an ultrasound-guided percutaneous left renal biopsy for proteinuria discovered on routine health checkup. On contrast computed tomography imaging, the left proximal ureteric injury along with a small urinoma was identified. The left ureteric double J (DJ) stenting was performed successfully following which the patient was relieved of his symptoms. It is necessary to have a high index of suspicion and a low threshold for imaging for patients who develop even minor symptoms following percutaneous renal biopsy. Partial ureteric injuries can be subjected to endoscopic management in the form of DJ stenting. Complete ureteric tear is rare but possible and needs a definitive surgical repair. Large urinomas and hematomas require placement of percutaneous drain and/or nephrostomy. In case of unrelenting hematuria or an expanding hematoma, angioembolization may be necessary. Finally, if all measures fail and patient continues to deteriorate, nephrectomy may be the last resort.

Key words: Complications, Renal biopsy, Stenting, Ureteric injury

BACKGROUND

Percutaneous renal biopsy is an extremely common procedure performed routinely by nephrologists. Complication rates are low if a strict protocol is followed.[1] However, one should have an eagle's eye view of the patient following biopsy and subject the case to immediate imaging if any suspicion of a complication emerges. Timely intervention in the form of endoscopy, nephrostomy placement, or angioembolization can prevent further renal damage and reduce morbidity.

CASE REPORT

A 30-year-old overtly healthy male underwent routine health check-up and was found to have proteinuria (3+) and microscopic hematuria (four red blood cells/high-power field) on urine examination. After doing an ultrasound of the kidney, ureter, and bladder (KUB) which was normal, the patient was referred to a nephrologist for evaluation and he was advised to undergo renal biopsy after consultation.

The patient underwent ultrasound-guided left renal biopsy under local anesthesia by a nephrologist using an 18-gauge renal biopsy gun. Two biopsy cores were taken from the lower pole and were sent for histopathological examination. Post-procedure, the patient developed mild hematuria which lasted for a period of 10–12 h. An ultrasound of the KUB was done again at this stage which was normal. He was then discharged the next day after hematuria settled, with oral analgesics for his complaints of the left loin pain. Following discharge, the patient experienced continuous non-radiating left loin pain and also developed 100.4° Fahrenheit fever which settled with antipyretics. Unable to tolerate the pain, the patient came to emergency room 1 day later.

INVESTIGATIONS

After confirmation of normal renal function (serum creatinine = 1.1 mg/deciliter), the patient was advised

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computed tomogram abdomen (plain + intravenous contrast) which revealed a left renal lower pole subcapsular collection along with an 18.2 cm^3 urinoma along the left iliopsoas muscle [Figure 1a]. On delayed contrast images, contrast extravasation was noted from the proximal left ureter. Contrast was seen entering left distal ureter and into the bladder suggestive of partial ureteric tear [Figure 1b].

TREATMENT

On admission, a urology consultation was sought for the patient and after reviewing the case, a decision was taken to attempt left ureteric double J (DJ) stenting for him. The patient underwent the procedure under regional anesthesia under antibiotic cover and the findings of partial proximal ureteric tear were confirmed intraoperatively through retrograde pyelography (RGP) [Figure 2a and b]. Procedure was uneventful and the patient was discharged the next day once he was asymptomatic and after X-ray KUB confirmed left DJ stent in position [Figure 2c].

OUTCOME AND FOLLOW-UP

The renal biopsy which was done at the time of first admission revealed IgA nephropathy for which surveillance was advised.

Three weeks following DJ stenting, the patient underwent an ultrasound which was normal and had no residual collection, following which the stent was removed under local anesthesia. The patient was reviewed 1 month and 6 months later and was doing well with no issues (6 months follow-up was obtained over telephonic conversation).

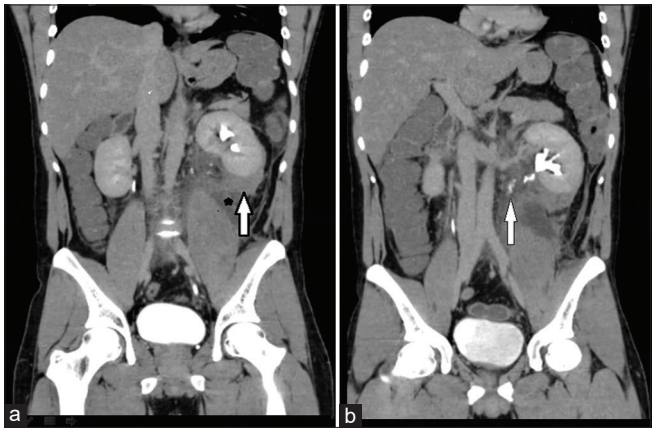

Figure 1: (a) Coronal section of contrast computed tomography abdomen and pelvis showing subcapsular collection in relation to lower pole of the left kidney (arrow) and urinoma over the left iliopsoas muscle (star). (b) Contrast extravasation noted from proximal left ureter (arrow) in delayed phase

DISCUSSION

Renal biopsy is a routinely done procedure. The use of ultrasound guidance for renal biopsy has not only improved the success rates of the procedure but has also increased safety, with <0.1% biopsies resulting in serious complications.[2,3] However, despite the development of automated renal biopsy guns, it remains an invasive procedure with the evident risk of complications such as hematuria, pain, hematoma, and fever.[4] Urinary leak and urinoma are rare complications following renal biopsy as renal parenchyma is the target and not the pelvicalyceal system.[5]

When our patient presented with continuous fever and unrelenting pain, we asked for a contrast computed tomogram with delayed phase imaging, despite the fact that his ultrasound was normal. This led to the provisional diagnosis of the left proximal ureteric injury on the basis of a small urinoma and contrast extravasation from the proximal ureter which was further confirmed on RGP. As the patient was symptomatic and there was a partial tear of the left ureter with maintained ureteric continuity, DJ stent placement proved to be an acceptable option.

LEARNING POINTS/TAKE HOME MESSAGES

- Hematuria, hematoma, fever, and pain are common post-renal biopsy complications; however, urinoma and urine leak which require intervention should also be kept in mind.
- We should maintain low threshold for contrast imaging (computed tomography urogram/RGP) following percutaneous renal biopsy and should be performed even when the patient develops minor symptoms.
- Partial proximal ureteric injuries can be managed endoscopically (such as by DJ stenting).

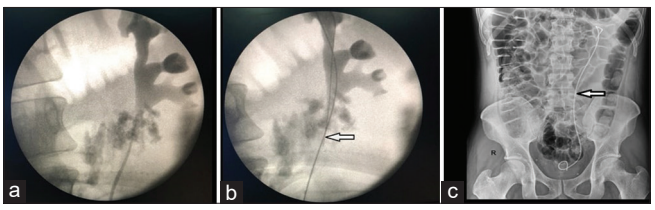

Figure 2: (a) Retrograde pyelography showing partial tear in proximal ureter with contrast extravasation noted and rest of the contrast outlining pelvicalyceal system. (b) Guidewire (arrow) secured in the left ureter and position confirmed under fluoroscopy. (c) Post-operative X-ray kidney, ureter, and bladder region shows double J stent (arrow) in position, which was kept for 3 weeks

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Review Article

Disasters Surpassed Every Previous Years in Cruelty- A Narrative Review

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Abstract

Disasters do not only affect health and well-being of people; frequently, significant numbers of people are displaced, killed, wounded, or at increased risk for epidemics. It is also normal to suffer considerable economic damage. With the second-highest population, increased urbanization, and increased risk of extreme events, India is facing disasters year after year in a vulnerable situation. Combined with poor implementation of planning, relief and rehabilitation measures, and the unplanned and under-standard infrastructure increase the human, physical, and economic losses sustained during and after a catastrophe. It is high time we wake up to reality and enforce strict measures on all fronts to reduce losses. Care should be taken to ensure that even the weakest parts will recover rapidly from disasters. Statistics gathered since 1888 shows a rise in the number of people affected by disasters. Newly discovered coronavirus is a causative agent for coronavirus infectious disease (COVID-19) that arose in December 2019.

Key words: Disasters, Cruelty, Coronavirus, Dentist

INTRODUCTION

Disaster management is stated as "any occurrence that causes damage, ecological disruption, loss of human life, or deterioration of health and health services on a scale sufficient to warrant an extraordinary response from outside the affected community or area." In addition, the world is becoming more and more high tech, with all the attendant risk for human and non-human failures these developments bring.[1,2]

DISASTERS IN 2019-2020 WORLDS

- Australia Bushfire (2019–2020) – Also known as the Black Summer, it started in June 2019 with some significant uncontrolled fires.[3] The fires burned an estimated 18.6 million hectares as of March 9, 2020, destroyed more than 5900 buildings (including 2779 homes), and killed at least 34 people.[4]
- Taal Volcano eruption (2020) – On January 12, 2020, the eruption of the Taal Volcano in Batangas, the Philippines, was a phreatomagmatic eruption from its main crater that ignited ashes across Calabarzon surrounding area of the city.[5]
- Turkey Earthquake (January 26, 2020) – At least 36 people died, and more than 1607 were hospitalized in eastern Turkey following a 6.7 magnitude earthquake that rattled the area.[6]
- Huge fuel spill inside Arctic Circle (Moscow, June 4, 2020) – Vladimir Putin has ordered a state of emergency after 20,000 tonnes of diesel fuel spilled into a river inside the Arctic Circle. The plant is operated in the area have made the city one of the most heavily polluted places on Earth.[7]
- New Zealand earthquake (June 27, 2020) – Magnitude 4.9 earthquake 24 km from Taupo, New Zealand, June 27, 2:11 am.[8]

DISASTER IN INDIA

- Moradabad Hail (1888) – The 1888 Moradabad Hail was a severe hailstorm that occurred on April 30,

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1888, in Moradabad. Hailstones as big as "goose eggs, oranges and cricket balls," 246 people, 1600 cattle and sheep were killed by this hailstorm.[9]

- Gangaram building collapse (September 12, 1983) – In Bengaluru, India, a seven-story building belonging to N Gangaram collapsed resulting in 123 deaths and over 120 casualties. This building collapse is regarded as one of Bangalore's worst tragedies.[10]
- Bhopal disaster (December 2–3, 1984) – Bhopal Gas Tragedy in India on December 3, 1984, in which tons of methyl isocyanate were released into the air by a leakage in Union Carbide Pesticide Plant storage tank. Approximately 2 million people have been exposed to gas leaving some 3000 dead. People continue to suffer from the adverse effects of the gas.[11,12]
- New Kenda disaster (1994) – The tragedy of the New Kenda coal mine at Bihar on January 25, 1994, killed 55 people. Owned by Eastern Coalfields Ltd., the miners long waited for help but ended up with painful death as the coal mine turned into a carbon monoxide filled gas chamber. Meanwhile, the large chunks of coal also evolved and blocked the escape.[13]
- Kota Atomic Power Station leak (February 2, 1995) – The Rajasthan Nuclear Power Station spills radioactive helium and heavy water into the Rana Pratap Sagar River, causing a 2-year closure of 280 dollars in 2006 for repairs.[14,15]
- Amarnath Yatra tragedy (1996) – Amarnath Yatra tragedy refers to the deaths of more than 250 pilgrims due to bad weather in the Indian state of Jammu and Kashmir. Nearly to 242 yatris died of exhaustion, exposure, freezing, etc. More than 263 dead bodies were found in and around the temple surroundings.[16,17]
- Uphaar Cinema fire (June 13, 1997, Delhi) – 59 people were trapped inside and died of asphyxiation, while in the resulting stampede, 103 were seriously injured.[18,19]
- Gujarat earthquake (2001) – In January 26, 2001, it was also known as the Bhuj earthquake. On the moment magnitude scale, the intraplate earthquake reached 7.7. The earthquake killed some 13,805 people and injured another 167,000.[20,21]
- Kadalundi train derailment (June 22, 2001) – 57 were eventually reported as killed or missing and 300 were injured.[22]
- Jammu and Kashmir legislative assembly car bombing (October 1, 2001) – The attack killed 38 people and three Fidayeen.[23-25]
- Indian Parliament attack (December 13, 2001) – The attack resulted in the deaths of six Delhi Police officers, two Parliament Security Service officers and a gardener, in total nine.[26,27]
- Indian Ocean earthquake and tsunami (December 26, 2004) – Also known as the Boxing Day Tsunami and the Sumatra-Andaman earthquake.[28,29] It was an earthquake on an undersea megathrust. A series of massive tsunami waves grew up to 30 m (100 ft.) high. An estimated 2.27.898 people were killed in 14 countries by the tsunamis, making it one of the deadliest natural disasters in history.
- Mumbai attacks (November 26–29, 2008) – At least 174 people died and more than 300 were injured, including 9 attackers.[30,31]
- Jaipur fire (October 29, 2009) – The fire at the Jaipur oil depot erupted killing 12 people and injuring more than 300. The blaze continued to rage out of control for more than a week after it began and half a million people were evacuated from the region during the period.[32-34]
- Eastern Indian storm (April 13, 2010) – A severe storm hit parts of Bangladesh and eastern India[35] around 11 pm local time. More than 140 deaths have been reported as of April 16. At least 91 people were killed in Bihar,[36] 44 in West Bengal, and 4 in Assam, Indian state.
- Lalita Park building collapse (November 15, 2010, New Delhi) – The building has an estimated 200 people, mostly poor migrant families.[37]
- Pune bombings (2012) – The 2012 Pune bombings were a series of four coordinated low-intensity bombing attacks across India's ninth-largest metropolis, Pune, on August 1. The only one who got hurt was a local tailor. A total of 8 suspected Indian Mujahideen (IM) terrorist operatives were arrested on December 27, 2012.[38]
- Indian cold wave (2012) – In the 2012 winter months, Indian cold wave killed at least 92 people all over North and East India.[39,40] The majority of the dead were homeless and elderly, living in the Uttar Pradesh state. This cold snap has also affected other northern and eastern states including Rajasthan, Punjab, Haryana, New Delhi, Jammu and Kashmir, Himachal Pradesh, Madhya Pradesh, Bihar, and Tripura. New Delhi was also captured in cold weather, with the temperature dropping to 7°C on Christmas Day and 1°C after New Year.[41]
- Kumbh Mela stampede (February 10, 2013, Allahabad) – 42 people killed and at least 45 were injured.[42]
- Mumbai building collapse (September 27, 2013) – At least 61 people died in the tragedy, and 32 others were wounded.[43]
- North Indian floods (June 2013) – Heavy rain on the North Indian states, primarily Uttarakhand and nearby states, caused severe floods and landslides because of cloudburst. Over 5700 people have been presumed dead.[44]
- Gas Authority of India Limited (GAIL) pipeline explosion (June 27, 2014) – Approximately 18 people were reportedly killed in the accident and more than 40 injured.[45]

- Gujarat flood (June 2015) – In June 2015, heavy rain resulted in massive flooding in Gujarat area of Saurashtra resulting in more than 72 deaths. Gir Forest National Park and surrounding area have also been impacted by the wildlife.[46]
- South Indian floods (2015) – Heavy rain in November–December 2015 led to flooding of Adyar, Cooum Rivers in Chennai, Tamil Nadu, leading to financial loss and human lives. More than 500 people were killed and over 1.8 million (18 lakh) people were displaced. With estimates of damages and losses ranging from nearly □ 200 billion (US$3 billion) to over □ 1 trillion (US$14 billion).[47]
- Siachen Glacier avalanche (2016) – An avalanche struck an Indian military base in the North Siachen Glacier area on February 3, 2016, trapping 10 soldiers under deep snow.[48]
- Puttingal temple fire (April 10, 2016) – During the firework festivities an explosion and fire went awry. As a result, 111 people were killed and more than 350 injured some of them along with severe burns.[49]
- Uttarakhand forest fires (2016) – Such fires raged unchecked, settled mainly in pine forests on the slopes of the sub-Himalayan region, and spread to oak and board leaf forests producing heavy clouds of smoke that turned the normally blue skies into grey; the smog also affected the tourism of the state.[48]
- Puttingal Devi temple Kollam Kerala (2016) – A stampedes in Puttingal Devi temple Kollam Kerala on April 10, 2016, an at least 111 were killed and 383 were injured.[50]
- Assam floods (2016) – Heavy rains in July–August resulted in flooding affecting 1.8 million people and flooding of about 200 wild animals in the Kaziranga National Park.[51]
- Uri attack (September 18, 2016) – At around 5:30 a.m. on September 18, 2016, they were lobbed 17 grenades in 3 minutes. In the course of the attack, 17 army personnel were killed with tents caught fire as a rear administrative base camp. Further, 19–30 soldiers were reportedly wounded.[52,53]
- Ennore oil spill (January 28, 2017, near Chennai, Tamil Nadu) – When an empty outbound tanker BW Maple collided with a Dawn Kanchipuram oil tanker charged inbound.[54]
- Gujarat flood (2017) – Following heavy rain in July 2017, the Indian state of Gujarat experienced extreme flooding causing more than 224 deaths.[55]
- Nepal and India power plant explosion (November 1, 2017) – The plant is run by National Thermal Power Corporation (NTPC) Limited, in Unchahar, Uttar Pradesh, India, which is owned by government. There was an explosion in the boiler that killed 32 people who may have washed ash from the interior of the boiler.[56]
- Kerala Flood (2018) – Following high rainfall in late July 2018 and heavy Monsoon rainfall since August 8, 2018, the Indian state of Kerala experienced extreme flooding resulting in more than 483 deaths and 140 are missing. [57]
- Kolkata Bridge collapse (September 4, 2018) – The consequence was 3 people died and at least 25 others are injured.[58,59]
- Indian dust storms (2018) – From May 2–3, 2018, storms of high-velocity dust swept through parts of North India, killing more than 125 people and injuring more than 200. Forty-three died in Uttar Pradesh, in the town of Agra and about 30 died elsewhere in the state. About 35 people died in neighboring Rajasthan.[60]
- Cyclone Fani (May 2, 2019) – Fani has been named an extremely strong cyclonic storm that this month struck the Indian state of Odisha. It left behind a trail of destruction killing more than 40 people, eradicating trees and communication system, crippling the economy, and normal life of the country. Fani quickly developed into an extremely severe cyclonic storm and as a high end, extremely severe cyclonic storm, reached its peak strength on May 2.[61]
- Kullu bus accident (June 20, 2019) – At least 44 people died in the crash, and 34 others were wounded.[62,63]
- South Asia floods (2019) – Monsoonal downpours triggered severe flooding and landslides in South Asia by mid-July 2019. At least 89 people died in Bangladesh, China, India, and Nepal as of July 14; Nepal is the hardest hit, with at least 55 deaths.[64]
- Vadodara flood (2019) – Extreme flooding affected the town of Vadodara and its administrative district in the Indian state of Gujarat due to heavy rain in July–August 2019. Almost 50 cm of rain fell on Vadodara in 12 hours on July31, 2019, with 424 mm reported in one 6 hour period.[65-67]
- Maharashtra (September 2019) – In Maharashtra, the highest 382 people died, followed by 227 deaths in West Bengal in rains, floods, and landslides that hit as many as 357 districts in the country.[68]
- Uttar Pradesh and Bihar (October 2019) – In the 4 days leading up to October 1, 2019, large-scale flooding has killed 111 people in Uttar Pradesh and 28 in Bihar.[69]
- Vattapara accident zone Kerala, India (2019) – Over a 4-year period, there were 265 accidents, 151 injuries, and 21 deaths.[70]
- Coronavirus 2019 (COVID-19)[71] – Coronavirus disease is an infectious disease caused by coronavirus 2 (SARS-CoV-2), a severe acute respiratory syndrome. It was first detected in Wuhan, China, in December 2019 and has since spread around the globe leading to

a continuing pandemic. Common symptoms include fever, cough, tiredness, shortness of breath, and taste and odor loss. While most patients have mild symptoms, some progress has been made with acute respiratory distress syndrome (ARDS), multiorgan failure, septic shock, and blood clotting. Usually, the time from exposure to onset of symptoms is around 5 days but may vary between 2 and 14 days.

Diagnostic test: rRT-PCR testing, CT scan

- Pakistan-administered Kashmir avalanches (January 14, 2020) – 76 people died in weather-related incidents in Pakistan-administered Kashmir.[72]
- Vizag Gas Leak (May 7, 2020) – The Visakhapatnam gas leak, also known as the Vizag gas leak, was an industrial accident at the LG Polymers chemical plant in the village of R R Venkatapuram, Andhra Pradesh, India. The resulting vapor cloud distributed over approximately 3 km radius, impacting the surrounding areas and villages. At 5 pm; May 8, the death toll was 13, and after being exposed to the gas, more than 1000 people became sick.[73]
- Aurangabad railway accident (May 8, 2020) – On the morning, an empty goods train ran over and killed 16 migrant workers sleeping on or by the tracks near Aurangabad, Maharashtra, India. One additional worker sleeping nearby was injured.[74]
- Cyclone Amphan (May 21, 2020) – Coastal areas in Odisha as well as Kolkata, Hooghly, Howrah, West Bengal, were affected by the cyclone minimum of 72 people has been died. This has also caused tremendous damage in Bangladesh.[75]
- Uttarakhand Forest Fire (May 22, 2020) – The state has been burning up with wildfires breaking out in various Uttarakhand regions. More than 50 Hectare Land Gutted and 46 caused wildfires. There are more than half species of birds and wildlife at risk. For the past 4 days, our Uttarakhand was burning, 2020 is getting worst.[76]
- Jammu and Kashmir Kulgam encounter (May 27, 2020) – An encounter broke out between militants and security forces in Jammu and Kashmir's Kulgam district on Monday. Three terrorists have been killed. Security forces have launched a search operation in Hiranagar, Kathua district along the Jammu-Pathankot highway.[77]
- Assam gas and oil leak (May 27, 2020) – The 2020 Assam gas and oil leak, also referred as Tinsukia gas leak or Baghjan gas leak, is a petroleum gas and oil leak that happened in Oil India Limited Baghjan Oil field operated by John Energy Pvt. Ltd. in Tinsukia district, Assam, India, on May 27, 2020. There have been reported deaths of several aquatic animals in nearby region.[78]
- Earthquake in Delhi NCR (May 29, 2020) – Tremors were felt in Haryana, Punjab, and NCR on May 29. The National Centre for Seismology said the quake occurred at around 9:08 pm and the epicenter is at Haryana's Rohtak. Two quakes hit Rohtak (7 km from Samalkha, Haryana) within 60 minutes; tremors felt in Delhi-NCR.[79]
- Thunderstorm Taj Mahal Complex Damaged (Agra, 2020) – A deadly thunderstorm that rolled across northern parts of the country damaged sections of the Taj Mahal complex, including the main gate and a railing running below its five lofty domes on May 31, 2020.[80]
- Cyclonic Storm in Maharashtra and Gujarat (June 3, 2020) – A low-pressure area developing over the Arabian sea will intensify into a cyclonic storm in the next 48 hours and will reach parts of Maharashtra and Gujarat coasts on June 3, weather agency India Meteorological Department said on May 31.[81]
- Pulwama terrorists encounter (June 3, 2020) – Security forces on June 3 killed terror outfit. Security forces killed three Jaish terrorists, two local terrorists during an encounter in Pulwama district of South Kashmir.[82]
- Gujarat chemical plant explosion (June 3, 2020) – The Gujarat chemical plant explosion was an industrial accident that occurred at the Yashashvi Rasayan Pvt. Ltd. chemical factory at Dahej in Gujarat, India, around 12:00 h.[1,2] Five people were killed and 57 were injured in the explosion.[83,84]
- Rajkot earthquake (June 14, 2020) – An earthquake of magnitude 5.5 struck near Rajkot in Gujarat on Sunday evening at 8:13 pm, according to the National Center for Seismology (NCS). The epicenter of the quake was 118 km north-northwest of Rajkot.[85]
- Jawans killed in Chinese troops violent face-off (June 16, 2020) – An Indian Army Colonel and two other soldiers were killed in a violent clash with Chinese troops.[78]
- Bihar lightning thunderstorms (June 25, 2020) – 83 killed in Bihar due to lightning and thunderstorms in single day. At least 83 people died due to thunderstorms in Bihar in the past 24 hours, according to Chief Minister's Office. Bihar Chief Minister Nitish Kumar announced Rs. 4 lakhs each for the families of deceased.[86]

PRECAUTION THAT SHOULD BE TAKEN DURING TREATMENT OF COVID PATIENT

Dentists should be aware of the following recommendations in certain emergency cases, such as dentoalveolar trauma, fascial space infection, and so on:

- The use of disposable dental equipment for cross-contamination prevention is compulsory.

- Radiographs: Intraoral radiographs should be avoided, as gag reflex or cough may occur. Extraoral radiographs should be done. To avoid cross-contamination, double barriers are made on sensors when intraoral imaging is mandated.[79]
- Rubber dam should of course be used for non-surgical endodontic treatment to reduce splatter production.[87]
- Dental procedures that produce higher aerosol content, for example, should be avoided for ultrasonic devices, high-speed handpieces. and three-way syringes.
- Suspected or confirmed cases of COVID-19 should only be treated in negative pressure rooms or isolation rooms for airborne infection isolation rooms and not in daily dental practice.
- Coronavirus survival time is up to 9 days at room temperature on inanimate surfaces or objects, with greater preference for humid conditions. Hence, to avoid SARS-CoV-2 spread, dry conditions should be maintained. Chemicals recently approved for COVID-19 should be used to disinfect.[88]

CONCLUSION

In any large-scale disaster, there will always be too few medical professional and allied personnel to care for the large number of injured requiring prompt medical care. Any mass fatality response plan of India must incorporate international systems for mass victim identification. If planned properly, the problem of dead body identification would be solved in a much better way and will help the community in the most befitting manner.

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Review Article

Pathogenesis of Gustatory and Olfactory Dysfunction in Coronavirus Disease 2019 Patients: A Neurophysiological Hypothesis

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Abstract

Coronavirus disease 2019 (COVID-19), the global pandemic, has taken a toll on health and socioeconomic status of the entire world. Clinical spectrum and outcome of this disease still remain a mystery. Centers for Disease Control and Prevention has recently included olfactory and gustatory dysfunction in the key symptoms suggestive of COVID-19 infection. In spite of various studies since the outbreak of this disease, the exact pathological mechanism of this ailment is yet unclear. Cyclic adenosine monophosphate (cAMP), the ubiquitous protein essential for many biological processes, has been proved as a key factor in signal transduction of taste and smell as well as in viral replication. This article hypothesizes that virus utilizes cAMP for its replication in oral and olfactory mucosa resulting in depleted level of cAMP available for transmission of chemosensory impulse and thereby resulting in dysregulated taste and smell in COVID-19 patients.

Key words: ACE2 receptor, Coronavirus disease 2019, Cyclic adenosine monophosphate, Gustatory dysfunction, Insular cortex, Olfactory dysfunction

INTRODUCTION

Coronavirus disease 2019 (COVID-19), a zoonotic infection caused by SARS-CoV-2, started as an outbreak in Wuhan, China, in December 2019 and quickly became an epidemic. Within no time, it attained pandemic status to shudder the entire world and has caused an unprecedented and unimaginable psychosocial impact on millions of people. Clinical spectrum of COVID-19 is exceedingly varied and can range from asymptomatic form to severe multiorgan dysfunction and failure. In extremes of life and in people who are immunologically compromised, the disease can run a fatal course. In symptomatic cases, the disease manifests as fever, dry cough, tiredness, and shortness of breath which appears 2–14 days after exposure. Mild-to-moderate symptomatic cases, if not treated adequately, may progress to more severe condition within a couple of days leading to dire consequences. Unfortunately, there are no specific clinical symptoms to secernate COVID-19 from other viral respiratory infections.

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Chemosensory dysfunction was not a commonly reported symptom from the initial epicenter of COVID-19. Subsequently, both olfactory and gustatory dysfunctions were found to be prevailing in patients with mild-to-moderate infection. The American Academy of Otolaryngology-Head and Neck Surgery and The British Association of Otorhinolaryngology are now recommending these symptoms to be added to the list of primary screening symptoms for COVID-19.[1,2] Centers for disease control and prevention has recently included olfactory and gustatory dysfunction in the key symptoms for COVID-19 infection.

Olfactory and gustatory dysfunction may appear before, during, or after the general symptoms. The altered taste

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sensation in COVID-19 varies from decreased sensitivity to taste (hypogeusia), taste confusion (dysgeusia), or complete loss of taste (ageusia). Altered smell sensation can be in the form of reduced ability to detect odors (hyposmia), complete inability to detect odors (anosmia), change in the normal perception of odors (parosmia), or sensation of an odor that is not present (phantosmia). Gustatory and olfactory dysfunction can occur as a separate entity or in combination in COVID-19 patients with a patent nasal airway with or without other clinical presentations.[3]

The altered chemosensory perception in COVID-19 patients is sudden in onset and majority of cases shows fast recovery, but few cases of delayed recovery have also been reported. Olfactory and gustatory dysfunction unassociated with rhinorrhea and nasal obstruction suggests a distinguishable mechanism from that of other viral infections. The pathophysiological mechanisms leading to the olfactory and gustatory dysfunctions in COVID-19 infections are still obscure. This paper tries to elucidate the probable mechanism for altered olfactory and gustatory dysfunction in COVID-19 patients.

HYPOTHESIS FOR ALTERED TASTE AND SMELL PERCEPTION

In both the oral and olfactory epithelium, the SARS-CoV-2 virus utilizes the cyclic adenosine monophosphate (cAMP) for replication. This utilization of cAMP hampers with the generation of action potential in response to taste and smell. The level of utilization of cAMP depends on viral load and the immune status of the patient, and depending on these parameters, there can be different grades of altered sensation. The alteration will be transient as action potential is prevented from reaching the brain and not due to direct injury to the receptor cells [Figure 1]. Virus reaches the brain through the olfactory nerves, eventually affecting the thalamus and the brain stem.

SARS-CoV-2 virus can enter the nerve cell either by direct fusion or penetration of plasma membrane or by endocytosis. Virus initially attacks the peripheral nerve terminals and then gradually ascends through the afferent nerves of gustatory and olfactory sense to reach the brain. This explains the lack of recovery of both taste and smell sensation even after weeks or months.

EVALUATION OF HYPOTHESIS

cAMP is a universal second messenger found in many life forms including microorganisms, plants, animals, and humans. This biological regulator controls multiple cytokinetic processes such as cell differentiation and

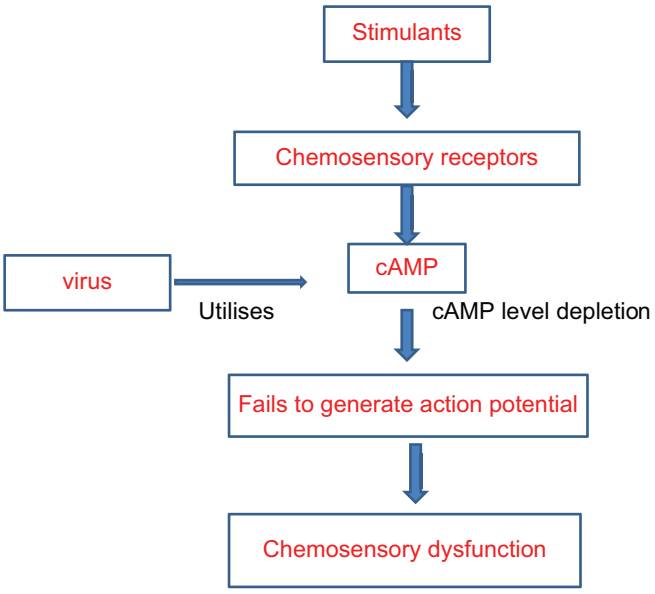

Figure 1: Schematic representation of Viral-induced chemosensory dysfunction

proliferation, ionic influx, excitability, gene expression, and cell-specific processes such as glycogenolysis and lipolysis.[4,5] The role of recently identified exchange protein directly activated by cAMP (EPAC) in viral infection was first reported in Middle East respiratory syndrome coronavirus (MERS-CoV). EPAC protein has been reported to regulate the replication of MERS-CoV.[6] Blocking of exchange proteins directly activated by cAMP in MERS-CoV has shown to stop viral replication.[5]

ACE 2, the specific binding site for SARS-CoV-2, is abundantly expressed in olfactory epithelium and epithelial lining of tongue.[7,8] Spike protein of the virus binds with ACE 2 receptors to set off chemical changes, which results in the fusion of host and viral cell membranes and facilitates viral entry into host cells.[9] The previous studies have shown viral infiltration into the brain through olfactory nerves, affecting the thalamus and brain stem. Once higher centers of CNS are affected it results in prolonged loss of taste and smell.[10]

Physiology of Gustatory Sensation

Gustatory sensation is perceived by taste buds which are a group of modified epithelial cells called taste cells. At resting stage, taste cell membrane is negatively charged inside and positively charged outside. Taste cells are stimulated by binding of chemicals to their receptor proteins to cause depolarization of taste cell which generates action potential to be transmitted to central nervous system. Taste impulse from anterior two-third of tongue passes through lingual nerve, chordae tympani, and facial nerve to reach nuclei of tractus solitarius. Impulse from posterior one-third of tongue and posterior region of mouth and throat is

transmitted through glossopharyngeal nerve to the tractus solitarius. Taste from base of tongue and pharyngeal region is conveyed through the vagus nerve. All these fibers synapse at tractus solitarius, and from there reaches the ventral posterior medial (VPM) nucleus of thalamus and then to postcentral gyrus of parietal cerebral cortex and finally into Sylvian fissure and opercular insular area in cerebral somatic area of frontal lobe.[11]

When gustatory stimulants bind with their respective receptors, adenylyl cyclase will be activated and induce the release of intracellular second messenger cAMP. This activates protein kinase A which further leads to activation of cation channels. This results in cellular depolarization and generation of action potential which leads to an increase Ca^{2+} or Na^{+} influx through voltage-gated membrane channels resulting in release of cations from intracellular stores. In response to this cation release, neurotransmitters are secreted, which generates action potentials in afferent nerve fibers to the brain [Figure 2].[12,13]

Physiology of Olfactory Sensation

Olfactory cells (bipolar nerve cells) derived from central nervous system are receptors of smell sensation. The odorant substance which comes in contact with the olfactory membrane binds with receptor protein and activates adenylyl cyclase which converts ATP into cAMP. cAMP activates sodium ion channel and thereby increases electrical potential inside the cell membrane and excites olfactory nerve and this impulse relays into central nervous system. Olfactory nerves penetrate the small foramina in the cribriform plate of the ethmoid bone to enter the cranial cavity. In the cranial cavity, the olfactory nerve fibers enter the olfactory bulb, where it synapses with the mitral cells, to form collections known as synaptic glomeruli. Axons of mitral cells leave the olfactory bulb to form olfactory tract which runs backward to end in olfactory cortex, located on the base of frontal lobe and medial aspect of temporal lobe. From the olfactory cortex, olfactory sensation is relayed via the mediodorsal nucleus of the thalamus to the insular and orbitofrontal cortex. The insular cortex also receives taste input from the medial part of VPM nucleus and is considered to be the site of integration of olfactory and taste information to produce the sensation called flavor.[11,14]

Binding of olfactory stimulants to its receptors releases cAMP, which activates cationic channels leading of cation influx and results in membrane depolarization. This excites the olfactory nerve which is transduced to the CNS. Action potential frequency in both gustatory and olfactory nerves is proportional to the concentration of specific sensory molecules. Action potential frequency will be attenuated by

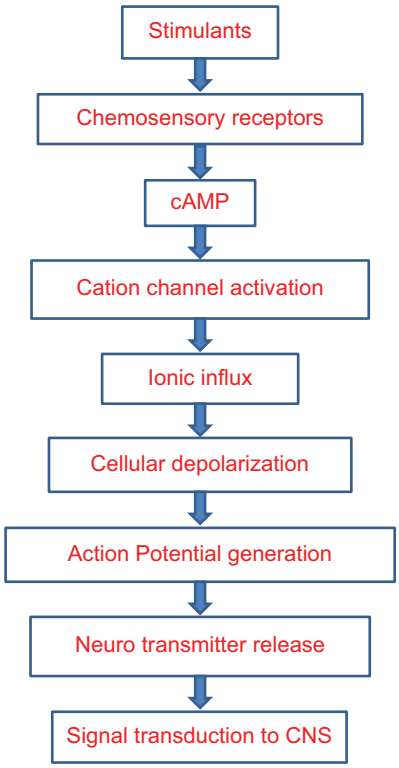

Figure 2: Schematic representation of normal chemosensory perception

adaptation or desensitization of the receptor and reduced production of cAMP leads to taste and smell dysfunction [Figure 2].[15]

CONCLUSION

The clinical spectrum as well as the long-term clinical consequences and the molecular mechanism of this ailment are still to be discerned. Studies have shown exhortatory results in preventing the viral replication by blocking exchange proteins directly activated by cAMP in MERS-CoV. The same stratagems may be applied against SARS-CoV-2 and cAMP can be utilized as a therapeutic target in COVID-19 patients which could reduce viral replication and thereby improving taste and smell dysfunctions. Elaborate follow-up studies of COVID-19 patients should be undertaken to comprehend more about chemosensory dysfunction, as these could be initial or the only reported symptoms.

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Original Article

Utilization of Dental Services by Patients Visiting Dental College and Private Dental Clinics of Twin Cities of Chhattisgarh

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Abstract

Objectives: The present study was undertaken with the aim to assess the utilization of dental services by patients visiting dental college and private dental clinics of Durg-Bhilai.

Methodology: The present study is focused on patients visiting dental college and private dental clinics of Durg-Bhilai to provide information on utilization of services. Data on the assessment of dental care services were recorded on a pre-tested specially designed close-ended questionnaire by face-to-face interview of the patients.

Results: The study was carried out on a total of 544 patients visiting dental college and private dental clinics of Durg-Bhilai. The most common reason for choosing any dental care facilities is the better service which was reported by 102 (47.2%) patients of private dental clinics and 139 (42.4%) of dental college followed by the second common reason, that is, reasonable cost reported by 50 (23.1%) and 107 (32.6%) patients.

Conclusion: Utilization of dental services differs across the sample and the pattern of use can serve as indicators of oral health-related behavior and believes. Thus, it is important to make them aware by educating them about the good oral health and motivating them to use the services available for them so that they can lead an overall healthy life.

Key words: Utilization, Barriers, Need, Demand, Dental health care

INTRODUCTION

The duty of dentists is to adequately and efficiently provide oral health-care services to a population growing at large and to specially cater to the need of the underserved populations. The ultimate goal is, therefore, to deliver dental care facilities to all people regardless of their financial status, geographic location, or health status.[1,2]

General health cannot be attained or maintained without good oral health that is why the mouth is regarded as a mirror and the gateway to health. The two leading dental diseases, that is, caries and periodontal disease, are common health problems, affecting nearly everyone during his or her lifespan. However, it can be prevented through simple and effective measures at all stages of the life course, both at the individual and population levels. Hence, to prevent the disease at an early stage, it is important to design the health-care system which will maintain and improve the health outcomes.[3-6]

Andersen defined three main concepts explaining the use of health services; namely, predisposing factors, enabling factors and the need for the use of services.[7] Good access to health services means the provision of "appropriate services in the right place and at the right time." Access to health services is considered as one of the social justice determinants and a scarce resource which is dependent on the fair distribution of services through suitable planning.

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Furthermore, access to health resources has been taken into consideration as an indicator of public health.[8,9]

It is said that a healthy body and healthy mouth go hand in hand; the same is for the health services and dental health services. If good dental health is to be attained, integration is required between the dentist and the patient.[10] It has been reported that despite requiring treatment <50% of patients refer to the dentists because of the barriers to access dental care.[8,11-13]

Utilization studies can serve as an important tool to know the factors that initiate and hinder dental service utilization.[14] In developed countries, dental care services are properly designed with highly sophisticated techniques, but in developing countries like India with 70% of the rural populations, there is an acute shortage of oral health personnel and lack facilities and equipment, materials, supplies, and maintenance. Thus, dental visits are infrequent and the capacity of the systems is generally limited to pain relief, emergency care, and tooth extraction.[15,16]

At present, in India, there are more than 267 dental schools, producing approximately 19,000 dental graduates per year. Despite this, even the most basic oral health education and simple interventions are unavailable to the vast majority of the population, especially the rural and urban poor.[17] Thus an efficient health-care system is needed which can identify possible risk factors whose modification could reduce the incidence of disease and illness in the future.[18,19]

Hence there is a definite lack of valid and reliable information about the factors affecting utilization of dental care services in Chhattisgarh state. The present study was undertaken with the aim to assess the utilization of dental services by patients visiting dental college and private dental clinics of Durg, Bhilai.

MATERIALS AND METHODS

Study Design

This is a time bound, descriptive cross-sectional study carried out in 2016 over a period of 2 months, that is, from February to April. For this proposed study, Durg, Bhilai city was included in the study.

Sample Size Estimation

For such studies, the universe of the study populations comprises people who are potential users of dental services within the study area. Since this variable cannot be ascertained to allow the estimation of sample size, so we will interview all the patients visiting Dental College and Private Dental Clinics of the study area over the period of 2 months.

Sampling Procedure

In Durg-Bhilai area, there are two Dental Colleges and 40 Indian Dental Association (IDA) registered private dental clinics. Data will be collected from the selected study areas of Durg and Bhilai.

Selection of dental college

Among the two dental colleges one dental college, that is, Rungta College of Dental Sciences and Research, Bhilai was randomly selected using a flip of coin method.

Selection of private dental clinics

Among 40 Indian Dental Association registered dental clinics, 20 clinics were randomly selected through lottery dip method to ensure randomness. This formed the entire skeleton of the study through which data were collected regarding the study.

Questionnaire

The questionnaire was designed after reviewing the literature about factors affecting utilization of dental services along with barriers to the same. Questionnaire included general and sociodemographic characteristics of the study. The questionnaire comprises close-ended questions regarding self-perception of oral health, visits to dentists, and self-perceived oral health problems. The questionnaire also focused on the emphasis given by the study subjects toward dental treatment and their level of satisfaction with the previous and existing dental care services in the set-up.

This questionnaire was given to experts in the department to check for face validity and necessary corrections were made as per their suggestions. The questionnaire was then translated into local language easily understood by the study population. For the purpose of translating the questionnaire into Hindi, the help of experts was sought and to check the reliability of translation; the Hindi questionnaire was re-translated to English and assessed for any change in the meaning of the questions. The questionnaire was pilot tested on 10 individuals to check for internal consistency (kappa coefficient = 0.91) and also to see if the individuals are able to understand the questions and whether they are having any specific problem answering to the questionnaire.

Ethical Clearance

The ethical clearance for the present study was obtained from the Ethical Committee of Rungta College of Dental Sciences and Research, Bhilai, Chhattisgarh (2016-28).

Permission

The required official permission for the study was obtained from the Dean, Rungta College of Dental Sciences and Research, Bhilai, Chhattisgarh and the

respective Dental Surgeons of the Private Dental Clinics of Durg, Bhilai.

Informed consent

A prior written, voluntary informed consent was taken from each study subject after explaining the nature of the study. Confidentiality and anonymity of the respondents were assured.

Training and calibration of examiner

The single trained examiner carried out the entire interview in the study. The examiner was trained and calibrated in the department of public health dentistry under the direct supervision of the guide before the study. The examiner was trained and calibrated by carrying out interviews on the pre-selected subjects twice at an interval of 1 h. The variability in the two assessments was very low. To validate the findings, some of the subjects were re-interviewed by experienced staff members.

Data Collection

For the purpose of data collection regarding utilization of dental services by patients visiting dental college and private dental clinics of Durg-Bhilai, all the patients aged 18–74 years attending on the particular days of the study (as decided earlier with permissions from the authorities) were invited to participate and those providing consents were included in the study. Patients who did not give consent and patients below 18 years and above 75 years of age were excluded from the study. A detailed schedule of the study was prepared well in advance (weekends and holidays were avoided) and the concerned authorities were informed regarding the study beforehand. On an average, around 10 subjects were interviewed each day. Data on the assessment of dental care services were recorded on a pre-tested specially designed close-ended questionnaire by face-to-face interview of the patients. The investigator gave required information and clarified doubts wherever necessary.

Statistical Analysis

The data collected were entered into MS Office Excel Sheet 2007 and subjected to statistical analysis using the Statistical Software SPSS version 18.0. Descriptive statistics were used to summarize the results.

RESULTS

The study was carried out on a total of 544 patients visiting dental college and private dental clinics of Durg, Bhilai. The percentage-wise response of patients to some of the questions in the questionnaire is tabulated in Table 1.

The most commonly experienced problem in both the groups was toothache (25.5%) and (32.3%) followed by discoloration of teeth which was experienced by (22.2%) patients of private dental clinics and (16.8%) patients of dental college [Graph 1]. Most of the patients, 155 (71.8%) of private dental clinics and 184 (56.1%) patients of dental college were satisfied with the treatment provided to them. Expensive treatment and time required were the most commonly reported reason for dissatisfaction regarding to dental treatment [Graph 2].

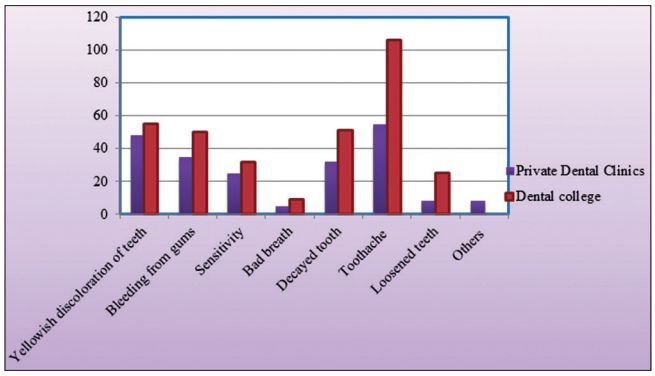
The most common reason for choosing any dental care facilities is the better service which was reported by 102 (47.2%) patients of private dental clinics and 139 (42.4%) of dental college followed by the second common reason, that is, reasonable cost reported by 50 (23.1%) and 107 (32.6%) patients. The most common reason for choosing any dental care facilities is the better service which was reported by 102 (47.2%) patients of private dental clinics and 139 (42.4%) of dental college followed by the second common reason, that is, reasonable cost reported by 50 (23.1%) and 107 (32.6%) patients [Graph 3].

DISCUSSION

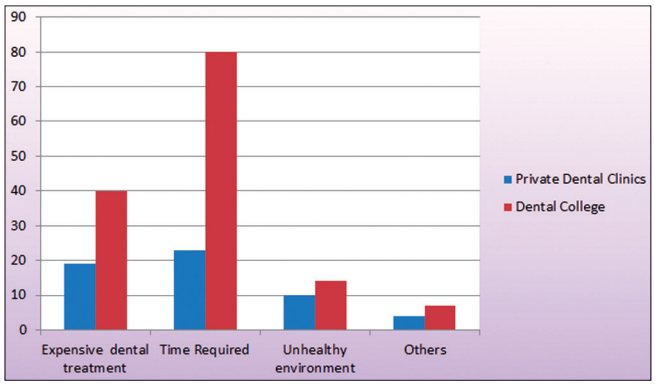
The present study is focused on patients visiting dental college and private dental clinics of Durg, Bhilai to provide information on utilization of services. This study is undertaken by considering the target groups, the time scale for the study and factors that increase compliance of

Table 1: Percentage response of patients to the questionnaire

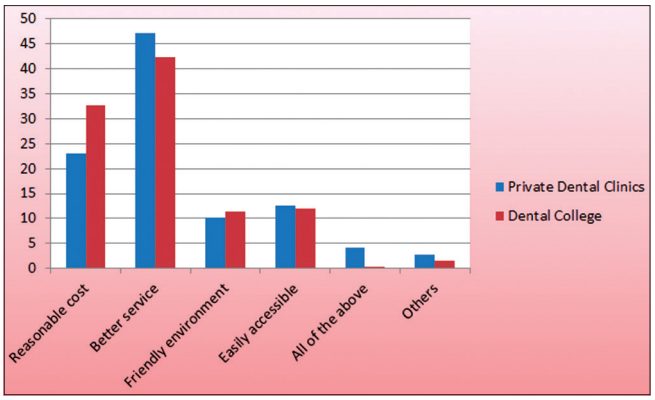
Question	Private dental clinic (%)				Dental college (%)			
How would you rate your oral health?	Poor	Fair	Good	Excellent	Poor	Fair	Good	Excellent
	9.3	50	33.3	7.4	11.3	60.1	25.9	2.7
How often you go to the dentist?	Never	Only at time of pain	Once in 6 months	Once in a year	Never	Only at time of pain	Once in 6 months	Once in a year
	19	55.1	10.6	15.3	22	55.8	10.7	11.6
How important is receiving dental care to you?	Not at all	Some-what	Very important	Only at time of pain	Not at all	Some-what	Very important	Only at time of pain
	6.5	25.5	56.9	11.1	9.8	24.4	49.1	16.8
Where you visited for previous dental-related problems?	Government Hospital	Private Hospital	Dental Clinic	Dental College	Government Hospital	Private Hospital	Dental Clinic	Dental College
	17.1	6.9	44.9	31.1	32.9	8.5	33.2	25.4



Graph 1: Distribution of response regarding previous dental-related problems



Graph 2: Reason for dissatisfaction regarding dental treatment



Graph 3: Response for choosing the dental care facilities

the respondents. Hence, we used an instrument that is less time consuming, that is, a self-administered questionnaire that included the most important components of the dental service utilization.

Majority of the patients in both the study groups considered that receiving dental care is very important, but still a fraction of population considered that receiving dental care is not at all important. This may be due to their belief that dental conditions are not serious or life threatening or may reflect their unawareness or lack of knowledge about the importance of visiting the dentist to maintain good oral health and to avoid the dental diseases.

This study illustrates that the majority of the participants prefer visiting a private dental clinic rather than public dental care facilities for their previous dental-related problems. And also a higher rate of satisfaction was seen among the patient visiting private dental clinics; this may be because of the usual/high quality of dental treatment and comparatively short waiting time. The present study showed that 55.1% patients visiting private dental clinics and 55.8% patients visiting dental college utilized dental care services only for a symptomatic reason, that is, when they feel pain, while only small numbers visited the dentist for regular checkups. This is not a new finding for our environment as oral health surveys in other regions also showed that visits to dental-care facilities are mostly undertaken for symptomatic reasons rather than for preventive care.[20,21] This further corroborates previous studies by Al Shammari *et al.*[22] and Braimoh and Ofili[23] and Ogunrinde *et al.*[24]

Long waiting time has been reported as an item of dissatisfaction in literature.[25,26] In the present study also the time required for the previous dental treatment was the component causing most dissatisfaction among both the study groups. The similar findings were reported by the other studies[5,22,25] and this finding was in contrast with the study conducted by Jain *et al.*[27] Hence, by reducing the time spent in the dental center, that is, at the registration desk, waiting time, consultation time, and time with the radiographer would go a long way toward increasing the satisfaction rate of the consumers.

Knowing patients concerns and views about dental care services and ensuring their satisfaction with dental care will ultimately increase the utilization of dental care services, which in turn will promote the desired oral health among the population.

Our study has some inherent limitations: It presents the data from the users of dental services in a system where these services are paid out-of-pocket, thus making the results not generalizable to the systems where dental care is provided in the public system. To address this limitation, comparative studies need to be conducted in different health care systems. The study though carried out on a small sample size still it may provide initial steps in understanding which variables are important in utilization or non-utilization of dental services.

CONCLUSION

Utilization of dental services differs across the sample and the pattern of use can serve as indicators of oral health-

related behavior and believes. In India, people encounter various obstacles in utilization of dental services. These barriers can be removed by motivating people and making them aware of the oral health problem which will develop a positive attitude toward dental treatment.

This study gives an insight into utilization of dental services among the patients visiting private dental clinics and dental college of Durg, Bhilai. Thus, it is important to make them aware by educating them about the good oral health and motivating them to use the services available for them so that they can lead an overall healthy life.

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Original Article

A Study of Various Surgical Procedures in Intestinal Obstruction and their Outcome in Relation to Etiological Factors

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Abstract

Introduction: For a surgeon difficulty in diagnosing and managing, a case of intestinal obstruction is to be emphasized. With a better understanding of management, the mortality still ranges from 3% to 30% depending on the severity.

Materials and Methods: A retrospective study of surgical management of 50 cases of intestinal obstruction with age groups ranging from 11 years to 70 years admitted to various surgical wards in IMS and SUM Hospital, Bhubaneswar. After admission, a detailed history and informed consent were taken. Relevant blood and radiological investigations were done and operative procedures were performed. Data were recorded and systematically analyzed.

Results: A total of 27 male and 23 female patients belonging to the age group 11–70 years were enrolled in the study. Intestinal obstruction was commoner in the elderly age group, 40% belonged to the age group 41–60 years. The present study showed that pain abdomen (100%), distension of abdomen (100%), and vomiting (88%) were the salient clinical symptoms with which the patients presented to us. Most common etiological factor was post-operative adhesions 46% and next is hernia 22%. The most common surgical intervention was found to be resection and end-to-end ileoileal anastomosis 40%, followed by the release of adhesions and bands 30%. Most important post-operative complications were wound infection (12%) and sepsis (10%).

Conclusion: Due to the increase in the number of abdominal and pelvic surgeries, there is an associated increase in the incidence of post-operative adhesions, leading to intestinal obstruction.

Key words: Adhesions, Bands, Colonoscopy, CT scan, Gangrenous bowel, Hernia, Intussusception, Large intestine, Malignancy, Mesenteric vascular occlusion, Resection and anastomosis, Serum electrolyte, Small intestine, Strangulated internal hernia, Stricture, Tuberculosis of intestine, Ultrasonography, Volvulus

INTRODUCTION

"Intestinal obstruction" is obstruction in forward propulsion of the contents of the intestine. Diagnostic improvement, pre-operative preparation, skillful operation, and proper technique during surgery and post-operative treatment carry good outcome. The outcome of patients is becoming appreciable due to improved techniques and better management protocol, but still mortality and morbidity range from 3% to 30% depending on the severity.[1]

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Aims and Objectives

The aims of this study were to study the various clinical features, causes, treatment modalities, and various surgical procedures in patients with intestinal obstruction.

MATERIALS AND METHODS

This is a retrospective study during the period of June 2017–October 2019. All cases of intestinal obstruction admitted in IMS and SUM Hospital, Bhubaneswar, were

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included in our study. A total number of 50 patients were included in the study.

Exclusion criteria	Inclusion criteria
< 11 years old	Patients with features of acute intestinal obstruction
SAIO who were managed conservatively	>11 years of age group

All cases who were included in our study were evaluated thoroughly with regard to clinical features, history.

All the cases were operated and findings were duly noted.

The cases were investigated thoroughly. Blood investigations, X-ray, USG, CT were needed, which were done.

RESULTS

A study of 50 cases of intestinal obstruction during the period from June 2017 to October 2019 at IMS and SUM Hospital, Bhubaneswar, were as follows:

1. Age and sex distribution

The study included patients of age group 11 years to 70 years. Majority of patients were in the age group of 31–60 years (57%). The highest incidence was seen in 4th and 5th decades (20% of each). We had a slight predominance of males over females (54% and 46%).

Age group	Male	Female	Total	Percentage
11–20	2	4	6	13
21–30	5	2	7	14
31–40	5	4	9	17
41–50	6	4	10	20
51–60	4	6	10	20
61–70	5	3	8	16
	27	23	50	100

2. Incidence

Out of 1666 patients admitted to our hospital, we had 50 cases of acute intestinal obstruction requiring surgery. Incidence of acute intestinal obstruction was 3%.

3. Previous history of surgery

All the patients were evaluated for past surgery. There were 18% of the patients reporting gynecological surgical procedures. There were 14% of post-appendectomy patients and 14% with surgery for hernias.

4. Symptoms/signs presentation

All the patients (100%) had pain abdomen and distension. This was followed by vomiting (88%) and constipation (62%). The most common signs were increased bowel sounds (88%) followed by tenderness over the abdomen (82%). Dehydration was seen in 60% and guarding in 40% of the patients. Palpable mass was seen in 24% of the patients.

Clinical features	Number of Cases	Percentage
Pain abdomen	50	100
Vomiting	44	88
Distension of abdomen	50	100
Constipation	31	62
Dehydration	30	60
Fever	7	14
Tenderness over the abdomen	41	82
Guarding	20	40
Palpable mass	12	24
Increased bowel sounds	44	88
Absent bowel sounds	6	12

5. Incidence based on etiology

The study showed that adhesion (46%) was the most common cause of intestinal obstruction followed by hernia (22%). Malignancy constituted 16% of the cases, especially in the elderly age group, followed by TB abdomen (14%) and volvulus constituted 2% of the cases.

Etiology of intestinal obstruction	Number of patients (*n*=50)	Percentage
1. Adhesion and band	23	46
2. Hernia	11	22
3. Malignancy	08	16
4. T.B stricture	07	14
5. Volvulus	01	02

6. Surgical procedures adopted

Resection with end-to-end ileoileal anastomosis was done in 40% of the patients. Adhesiolysis and release of bands were done in 30% followed by herniorrhaphy/hernioplasty in 20%, hemicolectomy was needed in 8% of the patients with malignancy, untwisting of volvulus 2%.

Types of operation	Number of patients (*n*=50)	Percentage
(a) Resection and end-to-end ileoileal a. anastomosis	20	40
(b) Release of adhesions and bands	15	3
(c) Herniorrhaphy	10	20
(d) Hemicolectomy	4	8
(e) Untwisting of volvulus	1	2

7. Post-operative complications

Post-operative complications were seen in 30% of the patients. The study demonstrated a wound infection rate of 12%, followed by respiratory infection in 2%, enterocutaneous fistula was seen in 2%, and prolonged ileus 4% of the cases. Mortality was 10%, especially of the cases with delayed presentation. Five patients succumbed and causes of mortality included Septicemia due to peritonitis, ARDS due to respiratory infection, and multiorgan failure due to Septicemia.

Postoperative complications	Number of patients (*n*=50)	Percentage
(a) Wound infection	6	12
(b) Respiratory infection	1	2
(c) Enterocutaneous fistula	1	2
(d) Prolonged ileus	2	4
(e) Deaths (Septicemia)	5	10

DISCUSSION

Intestinal obstruction is one of the frequently encountered surgical emergencies. They constitute a major cause of laparotomy. In 1976, Brewer *et al.*[2] analyzed 1000 consecutive cases of abdominal surgeries where acute intestinal obstruction constituted 2.5%. In 1973, Jain *et al.*[3] reported an incidence of 3.2%. In our study, we found an incidence of 3% out of the total number of abdominal surgeries conducted during our study period. In our study, the majority of intestinal obstruction was encountered in the age group of 40–60 years (40%). About 17% were seen in the age group of 31–40 years. The age group of 11–20 years had the lowest incidence of 13%. Harban Singh *et al.*[4] got maximum number of acute intestinal obstruction in the age group of >60 years, followed by 18% in the age group of 31–40 years. The study by Ramachandran[5] shows maximum cases in the age bracket of 21–40 years.

In our study, we had almost equal number of males and females (27 and 23, respectively). However, studies by Budharaja *et al.*[6] and Singh *et al.*[4] reported a predominance of males (4:1).

In our study, we got adhesion in 46% of the cases, followed by hernia in 22%.

Biarj *et al.*[7] 1999 had 53% of cases having adhesions as their etiology. However, studies by western researchers showed a predominance of hernia. Gill and Egglestion, in 1965,[8] had an incidence of 27% of hernia, Brooks and Butler 1996 – 25%.[9]

In the present series, tuberculosis found to be a causative factor in seven cases (14%) in the form of ileocecal tuberculosis with stricture and adhesions which are lower than what was reported by Harbans *et al.* 17.2%.[4]

In the present study, eight cases (16%) presented with acute intestinal obstruction. Five cases out of the eight, were due to large bowel malignancy and rest three were due to small bowel malignancy. Harbans *et al.*[4] reported an incidence of 15% of bowel obstruction which is similar to our study.

Iwuagwu *et al.*,[10] in 1999, reported an incidence of 3.5% to 6.2%. Our study had 2% of small bowel volvulus.

All the cases of our study were subjected to surgery. The most common operation performed was resection of ileal segment and end to end ileoileal primary anastomasis 40%, release of adhesions and bands 30%, hernia repair in 20%, hemicolectomy in 8% cases, and reduction and untwisting of volvulus in 2%.

Post-operatively, IV fluids and nasogastric decompression and antibiotics were given till the good bowel movements appeared.

Mortality – five cases died following surgery for acute intestinal obstruction (10%).

Wangensteen[11] reported mortality of 11%, Cheadle *et al.*[12] 9%.

CONCLUSION

Adhesions secondary to previous surgery is now becoming a leading cause of intestinal obstruction.

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Original Article

A Cross-sectional Study on Self-assessment of Dental Health and Oral Hygiene Awareness among Delhi NCR Region

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Abstract

Background: Oral health is an essential and vital component of overall health and general well-being of an individual determining its general health as mouth reflects the diseases in the body. Hence, the dental health and hygiene should be taken care off.

Purpose: The purpose of the study was to assess the dental health and oral hygiene awareness among Delhi NCR region.

Materials and Methods: A cross-sectional study was conducted in Delhi NCR region. The study population consisted of 250 individuals in whom 53.6 % were female and rests were male. The World Health Organization questionnaire was sent to the participants online through social media.

Results: Total participants in the age group of 18 years to 63 years has responded to aids of cleaning teeth, 98.8%, 4.4%, 6%, and 23.2% individuals were using toothbrush, charcoal, neem stick, and dental floss, respectively. About 32.8% respondents reported that they do not know about the fluoride in the toothpaste and 23.2% said that they do not use fluoridated toothpaste. About 23.6% individuals go to the dentist when they have pain. About 17.2% has interrupted sleep and 24% participants feel tense because of the teeth problems.

Conclusion: The results from the study show that the participants are not interested in maintaining oral health and dental hygiene. The reason lies in the fact that they do not know the importance of it. Therefore, the study suggests that advocacy program should be conducted to spread awareness on oral health and dental hygiene among people of Delhi NCR region.

Key words: Assessment, Awareness, Dental health, India, Oral hygiene

INTRODUCTION

According to the World Health Organization, "Health is a state of physical, mental, and social well-being and not merely the absence of disease or infirmity."[1] Oral health is an essential and vital component of overall health and general well-being of an individual determining its general health.[2] Mouth is considered a mirror of the body and gateway to good health.[3] For example, dental caries, periodontal diseases, and infections in oral mucosa show imbalance nutrition in the diet.[4] Most of the oral diseases and conditions share modifiable risk factors with the leading NCDs (cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes) associated with the tobacco use, alcohol consumption, and unhealthy diets high in free sugars, which are increasing at the global level. There has been a proven relationship between oral and general health. It is reported, for example, that diabetes mellitus is linked with the development and progression

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of periodontitis and oral cancer was within the top three of all the cancers in some Asian-Pacific countries in 2018, stated by the International Agency for Research on Cancer.[5]

FDI World Dental Federation has defined oral health as "Oral health is multi-faceted and includes the ability to speak, smile, smell, taste, touch, chew, swallow, and convey a range of emotions through facial expressions with confidence and without pain, discomfort, and disease of the craniofacial complex."[6] The Global Burden of Disease Study 2017 had estimated that oral diseases affect 3.5 billion people worldwide, with untreated dental caries being among the most prevalent non-communicable diseases.[7] Therefore, it proves that oral diseases are still a burden on the country.[8]

Dental caries is one of the ubiquitous, non-communicable disease prevailing all around the world.[9] According to the Global Oral Health Data Bank, the prevalence of dental caries varies from 49% to 83% across different countries.[10] Increased refinement of foods, lifestyle, and the greater availability of sugar has been found to be responsible for the modern pattern of dental caries.[11]

The national health survey conducted by Dental Council of India (DCI) stated that caries prevalence was 85%in Nagpur.[12] Goel *et al.* reported a 100% caries prevalence in rural Delhi.[13] The reason of such prevalence is lack of awareness among the people in India. People are more focused on their systemic health than on dental health unknowing the fact that it is related to general health. Therefore, the aim of the study is to report self-assessment of dental health and oral hygiene and their concern toward the dental health among people of Delhi-NCR region.

MATERIALS AND METHODS

A cross-sectional study was conducted in the month of August 2019. The study population consisted of 250 individuals from Delhi – NCR region. Participants were requested to take part in the study. The questionnaire was sent to the participants online using social media apps like WhatsApp and Gmail. This questionnaire consisted of monthly family income in Indian Rupees and self-assessment questionnaire on dental health and oral hygiene available on the WHO website.[14]

Frequencies along with the percentages were reported for categorical data. Graphical representations was done for important characteristics of data. Data analysis has been done using the IBM SPSS Statistics for Windows, Version 21.0 Armonk, NY: IBM Corp.

RESULTS

Out of 250 study participants, 46.4% were male and 53.6% were female. The age group of 18–63 years was selected for the study. Majority (84.8%) of them were residing in urban areas. Regarding the education majority (66.8%) of them were graduates. With reference, to the family income majority, 40.4% had a family income of >2 lakhs [Table 1].

Figure 1 indicates the number of times participants clean their teeth. The bar graph represents that only 36.8% of the participants clean their teeth twice daily, whereas more than half (59.2%) individual brush their teeth once in a day. Further, the percentage of participants those who brush less than once a day was 2.8%. We also found that 1.2% participants never brushed their teeth.

Table 2 shows the cleaning aids for cleaning the teeth. About 98.8% participants use a toothbrush to clean their

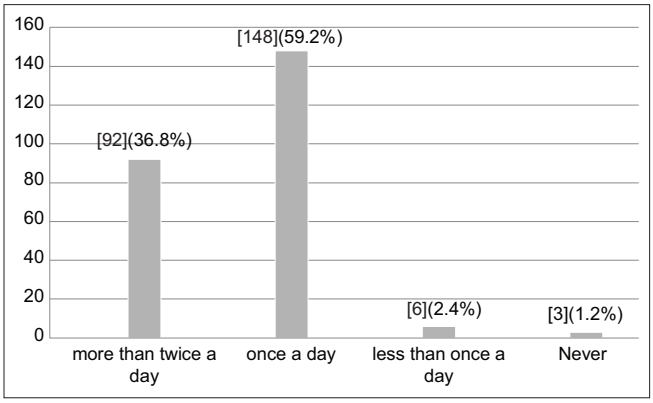

Figure 1: Self-reported frequency of cleaning teeth by study participants

Table 1: Sociodemographic characteristics of study participants

Variables	Frequency (*n*)	Percentage
Gender		
Male	116	46.4
Female	134	53.6
Location		
Urban	212	84.8
Peri-urban	11	4.4
Rural	27	10.8
Education		
No formal schooling	3	1.2
Primary school completed	2	0.8
Secondary school completed	3	1.2
High school completed	16	6.4
College/University completed	167	66.8
Postgraduate degree	59	23.6
Family income		
<50,000	47	18.8
50,000–1 L	63	25.2
1 L–2 L	39	15.6
>2 L	101	40.4

teeth followed by the use of wooden toothpick (27.2%), plastic toothpick (7.2%), thread (23.2%), charcoal (4.4%), chew stick (6%), and other cleaning aids are used 13.2% by the participants.

Figure 2 shows that 44% individuals use fluoridated toothpaste and 32.8% individuals do not know about the fluoridated toothpaste. About 23.2% of the participants responded that they do not use fluoridated toothpaste. This figure shows the lack of awareness among the participants about fluoride-based toothpaste.

Table 3 shows the frequency and percentage of the last visit to the dentist by the study participants. Majority (26.8%) of study participants have their last visit to the dentist in < 6 months. About 12.4% of them had their last visit between 6 and 12 months, 15.2% had their last visit between 1 and 2 years, 12.4% had their last visit between 2 and 5 years, and 11.2% had their last visit in >5 years. However, 22% of the study participants had never received dental care. This table also shows the frequency and percentage for the reason of the last visit to the dentist by the study participants. Majority (30%) of study participants had their last visit to the dentist for routine check-up/treatment. About 23.6% of them had their last visit to the dentist for pain or trouble with teeth, gums, or mouth and 11.6% of them had their last visit to the dentist for consultation/advice and for treatment/follow-up treatment. However, 23.2% of the study participants do not know/do not remember the reason for the last visit to the dentist.

Table 4 shows the frequency and percentage of problems experienced by the study participants because of the state of their teeth/mouth during the past 12 months. The most frequent problems faced by the study participants were: Difficulty in biting foods (26.8%), difficulty in chewing foods (26.4%), and dry mouth (25.2%). About 26% of them felt embarrassed due to the appearance of teeth and 24% of them felt tensed because of the problem of teeth or mouth. The less frequent problems faced by them were: Avoided smiling because of teeth (19.6%), had a sleep that is often interrupted (17.2%), difficulty with speech/trouble pronouncing words (16.8%), reduced participation in social activities (14.4%), have taken days off work (14%), and difficulty doing usual activities (13.6 %).

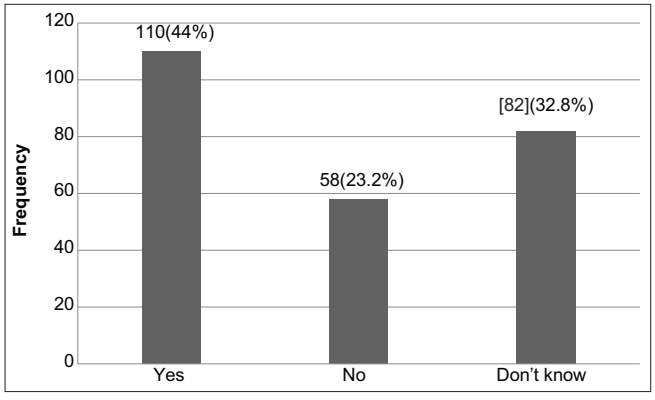

Figure 2: The use of toothpaste that contains fluoride for brushing

Table 2: Cleansing aids used to clean the teeth

Cleaning aids	Yes	No
Toothbrush	24 (98.8)	3 (1.2)
Wooden toothpicks	68 (27.2)	182 (72.8)
Plastic toothpicks	18 (7.2)	232 (92.8)
Thread	59 (23.2)	192 (76.8)
Charcoal	11 (4.4)	239 (95.6)
Chewstick	15 (6.0)	235 (94)
Other	33 (13.2)	217 (86.8)

Table 3: Frequency of last visit along with the reasons to visit the dentist by the study participants (*n*=250)

Characteristics	Frequency (*n*)	Percentage
<6 months	67	26.8
Between 6 and 12 months	31	12.4
Between 1 and 2 years	38	15.2
Between 2 and 5 years	31	12.4
>5 years	28	11.2
Never received dental care	55	22.0
Consultation/advice	29	11.6
Pain or trouble with teeth, gums, or mouth	59	23.6
Treatment/follow-up treatment	29	11.6
Routine check-up/treatment	75	30
Do not know/do not remember	58	23.2

Table 4: Frequency and percentage of problems experienced by the study participants because of the state of their teeth/mouth during past 12 months

Characteristics	Frequency (*n*)	Percentage
Difficulty in chewing foods	66	26.4
Difficulty with speech/trouble pronouncing words	42	16.8
Dry mouth	63	25.2
Felt embarrassed due to the appearance of teeth	65	26
Felt tense because of problems of teeth or mouth	60	24
Have avoided smiling because of teeth	49	19.6
Had sleep that is often interrupted	43	17.2
Have taken days off work	35	14
Difficulty doing usual activities	34	13,6
Reduced participation in social activities	36	14.4

DISCUSSION

The present study was aimed for the self-assessment of dental health and oral hygiene and their concern toward the oral health and dental hygiene in Delhi NCR region. The results which we governed from the study are as follows: Considering the Figure 1, most (59.2%) brush their teeth once daily and (36.8%) individuals brush the teeth twice in a day. These results are contrasted with the study of Naseem *et al.* (2017), most of the participants (55.9%) brushed 2 times a day while (36.7%) brushed only 1 time.[15] The American Dental Association recommends that an individual should brush twice in a day with fluoride toothpaste for 2 min to maintain oral hygiene.[16] Another important finding of our study was that 32.8% respondents reported that they do not know about the fluoride in the toothpaste and 23.2% said that they do not use fluoridated toothpaste [Figure 2]. Fluoride is recommended in the toothpaste by the FDI in the appropriate dose for the prevention of caries.[17,18]

This finding of our study is similar to the study conducted by Harikiran *et al.* (2019) which shows that more than half (60%) did not know whether their toothpaste contained fluoride.[19] Another study conducted by Jain *et al.* In the year 2018 found 82% of respondents were unaware of the same fact.[20] These numbers represent a lag of awareness about oral health among study respondents.

In response to aids of cleaning teeth [Table 2], 4.4%, 6%, and 23.2% individuals were using charcoal, neem stick, and dental floss, respectively, whereas the study conducted by Jain *et al.* represents the use of above items as 23%, 18%, and 0.0%, respectively.[21] These differences in percentages of aids used could be due to cultural differences of both study populations. In addition, our study portrays that toothbrush and toothpaste were used by 98.8% of the respondents followed by the use of wooden toothpick (27.2%). These findings of our study were similar to many studies.[22,23] Kapoor *et al.* as in their study, 90.3% patients cleaned their teeth with toothbrush and toothpaste.[22] On similar lines, Freire *et al.* reported most common oral hygiene aids were toothbrush (97.6%) and toothpaste (90.5%).[23]

Table 3, shows the frequency of visit to the dentist and the most common reasons for the visit. About 26.8% participants visit to the dentist in <6 months, 12.4% participants in between 6 and 12 months, and 15.2% individual visit to the dentist in between 1 and 2 years of time. About 23.6% individuals go to the dentist when they have pain. These results are comparable with the results of Devraj *et al.* study, 2012 in which 31.4% visit the dentist in <6 months followed by the 14.6% participants in 6 months–1 year and 15.5% in 1 year–2 years. About 35.2% individuals have responded that pain is the main reason to visit the reason.[24] Such similar results are observed in the other studies as well in which pain in the tooth is the main reason to visit the dentist.[25-29]

Another finding of our study discusses the problems faced by the people due to dental problems [Table 4]. These results were comparable with the study of Jayasvasti *et al.* in the year 2019, our study has shown 17.2% has interrupted sleep and 24% participants feel tense because of the teeth problems and similar results were seen in the Jayasvasti *et al.* study, 3.9% depressive symptoms and 11.2% sleep problems because of the dental problems.[30]

These percentages show their lack of interest for dental health in spite of its appearance. Other studies have shown similar results that due to lack of awareness, interest, and knowledge people have poor oral hygiene.[31-33]

Strength and Limitations

This study was conducted in the resourceful region, that is, Delhi NCR, whereas most of the studies are being conducted in the rural/ backward area for the self-assessment of oral health. Since there is dearth of studies on this topic in urban areas, the strength of our study lies in the fact that it aims to explore the self-reported pattern of dental health and oral hygiene in urban settings. Findings of this study can be utilized to frame the hypothesis for larger prospective analytical studies. In addition, our study utilizes a WHO standard questionnaire, which makes it easier to compare our findings with future studies on the same topic.

This study has several limitations. First, the cross-sectional nature of our study design could not establish a cause and effect relationship. Second, due to lack of time and resources, our study was based on limited sample size.

CONCLUSION

The preliminary data obtained from our study indicate that participants show disinterest in maintaining their oral health and dental hygiene, unknowing the fact that oral health is related to general health. Therefore, based on our findings, we suggest promoting advocacy program to spread awareness on oral health and dental hygiene among people of Delhi NCR region.

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Original Article

Evaluation of Different Doses of Pregabalin for Post-operative Analgesia in Ankle and Foot Surgeries

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Abstract

Background: Administration of pre-emptive analgesia with pregabalin is more potent than gabapentin. The aim of this study is to evaluate the effect of different doses of pregabalin on post-operative analgesia after ankle and foot surgeries when used before the onset of pain.

Materials and Methods: Total 90 patients of the American Society of Anesthesiology Grade I or II, posted for ankle and foot surgeries under spinal anesthesia, were randomized to three groups using computer generated random number list. Patient of Group A received oral pregabalin 150 mg, Group B received oral pregabalin 75 mg, and Group C received oral diazepam 10 mg. Tablet paracetamol 1 g given to all three groups after 2 h of surgery. Injection tramadol was used for rescue analgesia as requested by patients when VAS was more than 3. Outcomes measured include the total consumption of tramadol, VAS score, sedation, and other side effects recorded at 2, 4, 6, 12, and 24 h.

Results: The total consumption of tramadol was 133.56 ± 49.27 mg in Group A, 206.33 ± 77.19 mg in Group B, and (210.73 ± 63.35 mg) in Group C. VAS score was lowest up to 24 h in Group A, then Group B, and Group C. There was no significant difference in other variables between the groups. Sedation score was more in Group A, then Group B, and Group C.

Conclusion: Oral pregabalin in a dose of 150 mg offer prolonged analgesia and reduced the consumption of rescue analgesics when used preoperatively, as compared to oral pregabalin 75 mg with fewer side effects also.

Key words: Pregabalin, Diazepam, Post-operative analgesia

INTRODUCTION

Pain control in the post-operative period can have a notable effect on the overall outcome of the patient and surgical procedure. Orthopedic surgeries are among the most painful surgical procedure and the patient is at high risk of inadequate post-operative pain control.[1,2] Many types of medicines are available to help control pain, including opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and local anesthetics, etc., but are not free from their side effects, that is, respiratory depression, gastrointestinal bleeding and hemorrhage, toxicity etc.[3]

Gabapentin and pregabalin have antiallodynic and antihyperalgesic properties.[4] Mechanism of pregabalin is same as to gabapentin, it binds to the α2-δ subunit of presynaptic, voltage-dependent calcium channels that are widely distributed throughout the central and peripheral nervous system.[5,6] Thereby reduces the release of several neurotransmitters such as glutamate, norepinephrine, serotonin, dopamine, and substance P. Pregabalin is structurally and functionally related to inhibitory neurotransmitter GABA also.

Thus, the objectives of our study, to evaluate the efficacy 150 mg and 75 mg of pre-operative pregabalin on post-operative analgesia, requirement of additional analgesic in

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the post-operative period, and the incidence of side effect, that is, dizziness, headache, nausea, vomiting, etc.

MATERIALS AND METHODS

This prospective, randomized, and double-blind study was conducted in the Department of Anesthesiology, N.S.C.B. Medical College, Jabalpur (M.P). After local institutional ethics committee approval, and informed consent of the patient, 90 patients (30 each) between 20 and 40 years of age, ASA Class I and II, undergoing foot or ankle surgeries under spinal anesthesia were included in the study. The patient refuses for study or any contraindication to spinal anesthesia were excluded from the study.
Group A (n = 30): Oral pregabalin 150 mg.
Group B (n = 30): Oral pregabalin 75 mg.
Group C (n = 30): Oral diazepam 10 mg.

The study drugs were packed in identical capsules and were further packed and sealed in an opaque plastic container labeled with the randomization number. The randomization code was not opened until the last study patient was interviewed.

After securing an I.V. access and attaching of non-invasive monitors such as ECG, NIBP, and pulse oximeter, all patients were preloaded with 10 ml/kg of ringer lactate within 15 min before the spinal anesthesia. Spinal anesthesia was given in sitting position under all aseptic precautions with 25 G Quincke's needle at L3–L4 interspace using 3 ml of 0.5% heavy bupivacaine. Surgery was proceed after confirmation of adequate block. After 2 h of surgery, 1 g paracetamol orally, 8 h given to all patients. Assessment of pain was done using VAS score.

Postoperatively vital parameters such as pulse rate, blood pressure, and respiratory rate were recorded at 2 h, 4 h, 6 h, 12 h, and 24 h. VAS score at 2 h, 4 h, 6 h, 12 h, and 24 h was noted for pain. VAS zero was represented as no pain and ten represented as "worst possible pain." VAS was assessed at the time of giving rescue analgesia. Rescue analgesia was provided with intravenous tramadol 0.5 mg/kg when VAS >3. Total dose of tramadol consumption in 1st 24 h was noted and level of sedation was defined in accordance with the modified Ramsay sedation scale.

Modified Ramsey Sedation Scale

1. Anxious, agitated, restless
2. Cooperative, oriented, tranquil.
3. Drowsy, but responds to commands only.
4. Brisk response to light glabellar tap or loud noise.
5. Sluggish response to light glabellar tap or loud noise.
6. No response, unarousable.

Quantitative data were represented as mean ± standard deviation; number and percentage were used for qualitative data. Statistical analysis was done for comparing observed data using Student's t-test and analysis of variance. $P < 0.05$ was considered statistically significant.

RESULTS

There was no statistically significant ($P > 0.5$) difference among the three groups in terms of demographic data, duration of surgery, and changes in the hemodynamic parameters [Table 1].

The VAS score was lowest in Group A up to 12 h, then Group B, and Group C. On comparison statistically, VAS score was significant between Group A, Group B, and Group C at 4, 6, 12, and 24 h. VAS score was also significant between Group B and Group C up to 6 h [Table 2].

Meantime to rescue analgesia was significantly prolonged in Group A (12.33 ± 3.47 h) as compared with Group B (5.87 ± 1.40 h) and Group C (3.47 ± 8.19 h) ($P < 0.0001$). The total number of intravenous tramadol requirements in 24 h was less in Group A (133.56 ± 49.27 mg) than Group B (206.33 ± 77.19 mg) and Group C (210.73 ± 63.35 mg) (P < 0.0001) [Table 3].

Median of sedation score in the studied groups, at 2 h, 10 cases in Group A, 7 in Group B, and 3 in Group C were > median MRSS scores. At 4 h, 7 cases in Group A, 2 in Group B, and 0 case in Group C showed > median MRSS scores. While at 6, 12, and 24 h, all the three group cases were higher than the median MRSS score. Hence, the level of sedation at 2 and 4 h in Group A was significantly higher ($P < 0.05$) as compared to Group B/C. Level of sedation at 6, 12, and 24 h was comparable in all three groups ($P > 0.05$) statistically not significant [Table 4].

Post-operative nausea, vomiting, headache, and dizziness were not statistically significant in the different groups. Only 4 patients complain nausea and dizziness in Group A but were not very significant [Table 5].

Table 1: Distribution of demographic profile and duration of surgery

Parameter	Group A	Group B	Group C
Age (in years)	30.67±6.88	30.9±6.81	30.3±6.22
Weight (in kg)	60.27±8.63	57.57±9.93	60.17±9.55
Height (in m)	1.673±0.041	1.747±0.050	1.669±0.049
Duration of surgery (in min)	106.33±12.99	105.33±11.36	107.87±10.95

Values are expressed as mean ± SD (P>0.05)

Table 2: VAS sore at different time interval

Vas score time	Group A	Group B	Group C	*P* value b/w Group A/B	*P* value b/w Group A/C	*P* value b/w Group B/C
2 h	0.0±0.0	0.0±0.0	0.0±0.0	≥0.05	≥0.05	≥0.05
4 h	0.01±0.0	1.51±0.50	1.75±0.82	< 0.0001	< 0.0001	< 0.0001
6 h	0.01±0.1	2.02±0.75	3.33±0.83	< 0.0001	< 0.0001	< 0.0001
12 h	1.13±0.34	2.60±0.69	2.80±1.10	< 0.0001	< 0.0001	0.402
24 h	2.02±0.75	3.27±1.01	3.44±0.72	< 0.0001	< 0.0001	0.455

A Values are expressed as mean±SD. B one way ANOVA test

Table 3: Total rescue analgesia (tramadol in mg) requirement

Group	Time of first rescue analgesia in h	Rescue analgesia in 24 h (tramadol in mg)
A	12.33±3.47	133.56±49.27
B	5.87±1.40	206.33±77.19
C	3.47±8.19	210.73±63.35

Values are expressed as mean ± SD (*P*>0.05)

Table 4: Median test showing sedation score

Modified Ramsey sedation scale		Group		
		A	B	C
MRSS2	>Median	10	7	3
	≤Median	20	30	29
MRSS4	>Median	7	2	0
	≥Median	23	30	30
MRSS6	>Median	0	0	0
	≤Median	30	30	30
MRSS12	>Median	0	0	0
	≥Median	30	30	30
MRSS24	≤Median	0	0	0
	≥Median	30	30	30

Table 5: Incidences of side effects

Side effects	Group I	Group II	Group III
Nausea	4 (13.33%)	0	0
Vomiting	0	0	0
Headache	1 (3.34%)	1 (3.34%)	2 (6.67%)
Dizziness	4 (13.33%)	3(10%)	2 (6.67%)
Respiratory depression	0	0	0
Total	30	30	30

DISCUSSION

Perioperative pain is thought to involve primary hyperalgesia (peripheral nociceptor sensitization) and secondary hyperalgesia (central sensitization).[7,8]

Gabapentin and pregabalin appear to have no effect on primary hyperalgesia, but suppress the tissue damage induced hyperexcitability of dorsal horn neurons and hence decrease secondary hyperalgesia. Analgesic action of gabapentin and pregabalin is mediated through their binding to the α (2)-δ subunit of voltage-gated calcium channel. The affinity of this unit is six times more in pregabalin then gabapentin and less side effect.[9] Pregabalin is a gamma-amino butyric acid analog shown to be effective in several models of neuropathic pain, incisional injury, and inflammatory injury. Pre-operative administration of pregabalin reduces opioids consumption and opioids related adverse effects in 1st 24 h following surgery.[4,10] Adverse effect such as visual disturbance, sedation, dizziness, and headache is associated with the higher dose.

The present study was conducted to find out whether the pre-emptively administered pregabalin along with paracetamol reduces the post-operative analgesic requirement and to evaluate the efficacy of 150 mg and 75 mg for post-operative analgesia.

Patient's VAS pain scores were assessed using 10 cm visual analog scale (VAS), rescue analgesia was given as IV tramadol 100 mg when VAS > 3, side effects such as nausea, vomiting, dizziness, and vital parameters were noted at 2, 4, 6, 12, and 24 h after operation. Sedation was defined in accordance with the modified Ramsay sedation scale.

We performed the study as a prospective case series and the mean age of the patient in Group A, B, and C were 30.67 ± 6.88, 30.9 ± 6.81, and 30.3 ± 6.22, respectively, and there was no any significant difference ($P > 0.05$).

In our study of the total of 90 patients, 62 were males (68.8%) and 28 were females (31.11%). The male to female ratio in all the three groups did not differ significantly ($P > 0.05$).

The changes in mean pulse rate and mean systolic blood pressure for Group A, B, and C at an interval of 2 h, 4 h, 6 h, 12 h, and 24 h after surgery were not significant ($P > 0.05$). This observation also correlates with the study of Sahu *et al*.[11]

The mean total amount of analgesic dose required over a 24 h period in Group A was 133.56 ± 49.27 mg, in Group B was 206.33 ± 77.19 mg, and Group C was 210.73 ± 63.35 mg ($P < 0.0001$). Group A showed a highly significant reduction in the total amount of analgesic requirement in comparison to Group B and Group C. This is similar to the findings reported by Cabrera Schulmever *et al*.[12] (2010).

Pain VAS scores were analyzed with the ANOVA test. The results showed that the VAS score was considerably lower in Group A than those of Group B and Group C at all the observational periods. These findings were statistically highly significant ($P < 0.0001$) showing the better VAS results in Group A (P150 mg) patients compared to Group B (P75 mg) and Group C (D10 mg). Group B (P75 mg) also showed considerably better VAS finding than those of Group C (D10 mg) compared to the studies of Jokela *et al*.[13]

Paech *et al*.[14] reported that a single pre-operative dose of 100 mg pregabalin was ineffective in reducing acute post-operative pain or improving recovery after surgery, so we had administered pregabalin 150 mg and compared it with smaller dose 75 mg for a better outcome.

SUMMARY AND CONCLUSION

This was concluded from our study that "Preemptive use of Pregabalin 150 mg in patients undergoing ankle and foot surgeries under spinal anesthesia resulted in better analgesia, decreased need for rescue analgesia without cardiovascular and respiratory adverse effects."

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Original Article

Evaluation of C-reactive Protein Level in Aggressive and Chronic Periodontitis Patients Before and After Phase 1 Therapy: A Case Control Study

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Abstract

Background: Many studies have been carried out till date that talks about the chronic periodontitis and aggressive periodontitis but none correlates with C-reactive protein (CRP) level in blood. Since CRP is an important biomarker for systemic inflammation, it must be interesting to check whether periodontal health status has anything to do with the CRP level in blood. Hence, the present study was carried out to determine CRP level in blood before and after instituting Phase I periodontal therapy and to find out whether it has any effect on systemic health as shown by the correlating CRP level.

Aim: The aim of the study was to determine and compare the levels of serum C-reactive protein before and after Phase I therapy in patients with chronic periodontitis and patients with aggressive periodontitis.

Materials and Methods: A total of 30 subjects were selected, 10 each of generalized chronic periodontitis, generalized aggressive periodontitis and non-periodontitis (control group). Blood sample was collected from all the subjects at baseline and 3 months after Phase I therapy. Clinical parameters such as plaque index, gingival bleeding index, probing pocket depth, and clinical attachment level were recorded at baseline and at 3 months after Phase I therapy.

Results: Significant reduction was observed in the serum CRP level in both chronic periodontitis and aggressive periodontitis patients 3 months after Phase I therapy as compared to baseline level while in non-periodontitis patients, no significant reduction was noted in serum CRP level 3 months after Phase I therapy as compared to baseline.

Conclusion: Within the limits of the present study, it can be concluded that both forms of periodontitis may play a role in systemic inflammation as indicated by elevated serum CRP level and more importantly, treating periodontal disease alone could bring down the inflammation as indicated by reduced serum CRP levels which help in minimizing the risk of systemic inflammation.

Key words: Periodontal therapy, Periodontitis, Phase I therapy, Serum C-reactive protein

INTRODUCTION

Periodontitis is one the most common inflammatory disease of the tooth-supporting structures which if left untreated will progress to alveolar bone destruction and tooth loss.[1] Advances in science and technology over the last three decades have greatly expanded our knowledge about the pathogenesis of periodontal diseases.[2] Periodontitis is an infectious disease associated with microorganisms, predominantly gram negative that exists in subgingival biofilm and individuals are not uniformly susceptible to periodontal diseases.[3]

The host responds to the periodontal infections with an array of events involving both innate and adaptive

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immunity. Although periodontitis is chronic in nature, acute phase elements are also part of the innate immunity in periodontitis and their presence confirms that in periodontitis, the systemic inflammation is present.[4,5] The acute phase reactant receiving the most attention is C-reactive protein (CRP) that serves as a systemic marker of inflammation[6] produced by the liver and concentration exceeding 10 mg/l is generally regarded as the threshold indicative significant inflammatory disease[7] which is generally low in 98% of the general population.

CRP possesses the ability to reveal inflammation at an early stage as it rises in serum within 48 hours. Its long plasma half-life of 12–18 h is constant under most of the conditions and hence that the sole determinant of circulating CRP is the synthesis rate,[8] which directly reflects the intensity of the pathological process stimulating CRP production. This property is useful for early detection of patients who are at risk for inflammatory disease.

The reason for interest in serum CRP level in periodontitis lies in the fact that periodontitis is associated with CVD.[9] The emergence of periodontal infections as a possible risk factor for cardiovascular disease is leading to convergence in oral and medical care. A number of studies have demonstrated an association between periodontal disease and the risk of myocardial infection and stroke as well as the underlying condition atherosclerosis.[10-12]

It is conceivable that elevated levels of CRP in both forms of periodontitis and decrease in their level after phase 1 therapy can explain partly an association between periodontitis and CVD and if a relationship exists between periodontal diseases and systemic CRP, it has a substantial clinical relevance in helping to explain circumstances in which an intraoral source of infection can create a systemic inflammatory response, therefore placing apparently healthy patients at increased risk of cardiovascular diseases.[13]

Chronic and aggressive forms of periodontitis show disparity in the rate of progression. Their effect on CRP levels seems to be an appealing area of research. Thus, the present study was undertaken to determine the relative levels of serum CRP and compare them in aggressive and chronic periodontitis patients and correlating the serum CRP levels with severity of the disease.

Aim and Objectives

The aim of the study was to determine and compare the levels of CRP in serum before and after Phase I therapy in

- Patients with chronic periodontitis
- Patients with aggressive periodontitis
- Non-periodontitis patients (control group).

MATERIALS AND METHODS

Study Design

Institution Ethical Committee issued the ethical clearance for the following protocol. The study was carried out in 30 subjects divided into three groups, with 10 subjects in each group:

Selected samples are from the outpatient section of the Department of Periodontics, Tamil Nadu Government Dental College and Hospital, Chennai.

Sample size: 30 (10 in each group)

Test Groups

Group I-CGP patients

Probing pocket depth (PPD) of ≥5 mm and/or clinical attachment loss (CAL) >30% sites with varying degree of disease severity.

Group II-GAP patients

≤30 years of age having probing depth (PD) of ≥5 mm and/or CAL on 8 or more teeth, at least three of which were not first molars and incisors with varying degree of disease severity.

Control Group

Group III – Non-periodontitis patients – PD ≤2 mm along with no evidence of attachment loss.

Inclusion Criteria

The following criteria were included in the study:

1. Patients with untreated chronic periodontitis
2. Patients with untreated aggressive periodontitis
3. Non-periodontitis patients with PD ≤2 mm along with no evidence of attachment loss.

Exclusion Criteria

The following criteria were excluded from the study:

1. Smokers and tobacco users
2. Patients with hematological disorders
3. Patients who are pregnant and lactating
4. Patients who are medically compromised (diabetes and other immunodeficiency syndromes, cardiovascular diseases, kidney, liver, and lung diseases)
5. Patients who were under systemic antibiotic therapy during the last 3 months
6. Patients who have undergone any sort of dental treatment under local anesthesia in the past 3 months
7. Patients with history or presence of any other chronic infections.

A thorough medical and dental history of the subjects was taken. All the subjects underwent full-mouth periodontal probing and charting and clinical and laboratory evaluation.

Method of Collecting Data

Clinical parameters assessment

The following clinical parameters were evaluated for all the subjects:

1. Plaque index (PI) – Silness and Loe, 1964[14]
2. Gingival bleeding index (GBI) – Ainamo and Bay, 1975[15]
3. PD in mm – Carranza 10th ed[16]
4. Clinical attachment level (CAL) in mm – Carranza 10th ed.[16]

Estimation of CRP

The subjects were informed and consent was taken. Three milliliters of venous blood were drawn from the antecubital vein of the participants. Samples were centrifuged in the centrifuge machine at 3000 rpm for 10 min to separate the serum from blood. Separated serum was collected in Eppendorf and stored in the deep freeze at –20°C. Quantitative determination of CRP in patient's serum was done by enzyme-linked immunosorbent assay (ELISA) method.

Principle of the Assay

Qualitative determination of CRP in patient blood was done by a double antibody sandwich ELISA method. In this assay, the CRP present in the sample reacts with anti-CRP antibodies which had been adsorbed to the surface of polystyrene microtiter wells. After the removal of unbound sample proteins by washing, anti-CRP antibodies conjugated with horseradish peroxidase proteins were added. These enzyme-labeled antibodies formed complexes with the previously bound CRP. Following another washing step, the enzyme bound to the immunosorbent is assayed by the addition of a chromogenic substrate 0,3'-8'5-tetramethylbenzidine (TMB). The quantity of bound enzyme varies directly with the concentration of CRP in the test sample.

The quantity of CRP in the test sample can be interpolated from the standard curve constructed from standard and corrected for serum dilution.

Reagents Used

1. Diluent concentration (running buffer) one bottle containing 50 ml of a ×5 conc. diluents running buffer
2. Wash solution concentrate: One bottle containing 50 ml of a ×20 concentrated wash solution
3. Enzyme antibody conjugate ×100: One vial containing 150 ul of affinity-purified anti-human CRP antibody conjugated with horseradish peroxidase in a stabilizing buffer
4. Chromogen substrate solution one vial containing 12 ml of 0,3'–8'5- TMB and hydrogen peroxide in citric buffer at pH 3.3
5. Stop solution one vial containing 12 ml of 0.3 M sulfuric acid
6. Anti-human CRP ELISA microplate 12 removable eight well Microwell Strips in well holder frame. Each well is coated with affinity-purified anti-human CRP
7. Human CRP calibrator. One vial containing a lyophilized human CRP calibrator.

Procedure

1. All reagents were brought to room temperature before use
2. Pipette 100 ul of
   - Standard 0 (0.0 ng/ml) in duplicate
   - Standard 1 (1.56 ng/ml) in duplicate
   - Standard 2 (3.125 ng/ml) in duplicate
   - Standard 3 (6.25 ng/ml) in duplicate
   - Standard 4 (12.5 ng/ml) in duplicate
   - Standard 5 (25 ng/ml) in duplicate
   - Standard 6 (50 ng/ml) in duplicate
   - Standard 7 (100 ng/ml) in duplicate.
3. Pipette 100 µl of serum sample in duplicate into predesignated wells
4. Incubate the microtiter plate at room temperature for 15 min (15 ± 2) min. Keep plate covered during incubation and following incubation, aspirate the contents of the well
5. Fill each well with appropriately diluted wash solution and aspirate. Repeat three times, for a total of four washes. Finally, invert the plate on absorbent paper (paper towel) and blot the excess fluid from the wells
6. Pipette 100 ul of the appropriately diluted enzyme-antibody conjugate to each well. Incubate at 22°C (room temperature) for 15 (15 ± 2) min
7. Wash and blot the wells as described in steps 5/6. Pipette 100 µl of TMB substrate solution into each well and incubate at room temperature for precisely 10 min
8. After 10 min, add 100 µl of stop solution to each well and determine the absorbance (450 nm) of the contents of each well. Calibrate the plate reader to air.

Optical density (OD) of standard, control, and samples was read at 450 nm. Difference of OD was calculated, thereby plotting a standard curve and concentration of control, standard, and sampled were read and corrected for sera dilution.

RESULTS

In the present interventional study, among in Group I, II, and Group III. Five males and 5 females in each group, with a mean age of 39.40 ± 6.89 years in Group I, 23.90 ± 3.41 in Group II, and 35.00 ± 11.27

years in Group III. The parameters were assessed and recorded at baseline and 3 months postoperatively as follows,

PI

Intragroup comparison

Group I: The mean PI score at baseline was 2.48 ± 0.26 and at 3 months was 1.05 ± 0.23. The mean difference in plaque score from baseline to 3 months was statistically significant ($P = 0.032$) [Tables 1,2 and Figure 1].

Group II: The mean PI score at baseline was 2.20 ± 0.15 and at 3 months was 0.68 ± 0.16. The mean reduction in plaque score from baseline to 3 months was statistically significant ($P = 0.0001$).

Group III: The mean PI score at baseline was 0.61 ± 0.14 and at 3 months was 0.53 ± 0.09. The mean reduction in

Table 1: Comparison of plaque scores

Groups	Time duration (mean ±SD)		*P*-value
	Baseline	3 months post-operative	
Chronic periodontitis group	2.48±0.26	1.05±0.23	0.032*
Aggressive periodontitis group	2.19±0.15	0.68±0.16	0.0001*
Control group	0.61±0.14	0.53±0.09	0.122*
P-value	0.0001**	0.0001**	-

*Paired sample *t*-test, **One-way ANOVA

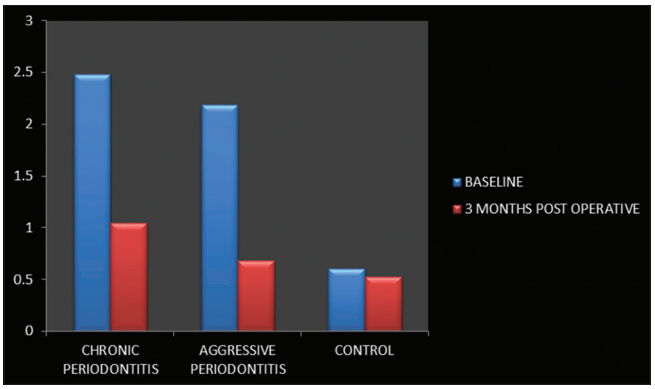

Figure 1: Comparison of plaque index between Group I, Group II, and Group III

Table 2: Individual comparison with Tukey post hoc- plaque score

			Tukey HSD				
Dependent Variable	(I) Groups	(J) Groups	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Baseline plaque score	Chronic periodontitis group	Aggressive periodontitis group	0.28300*	0.08646	0.008	0.0686	0.4974
		Control group	1.87300*	0.08646	0.000	1.6586	2.0874
	Aggressive periodontitis group	Chronic periodontitis group	−0.28300*	0.08646	0.008	−0.4974	−0.0686
		Control group	1.59000*	0.08646	0.000	1.3756	1.8044
	Control group	Chronic periodontitis group	−1.87300*	0.08646	0.000	−2.0874	−1.6586
		Aggressive periodontitis group	−1.59000*	0.08646	0.000	−1.8044	−1.3756
Plaque score 3 months	Chronic periodontitis group	Aggressive periodontitis group	0.37200*	0.07493	0.000	0.1862	0.5578
		Control group	0.51800*	0.07493	0.000	0.3322	0.7038
	Aggressive periodontitis group	Chronic periodontitis group	−0.37200*	0.07493	0.000	−0.5578	−0.1862
		Control group	0.14600	0.07493	0.145	−0.0398	0.3318
	Control group	Chronic periodontitis group	−0.51800*	0.07493	0.000	−0.7038	−0.3322
		Aggressive periodontitis group	−0.14600	0.07493	0.145	−0.3318	0.0398

**P*-Value <0.05

Table 3: Individual comparison with Tukey *post hoc*- probing pocket depth

Dependent variable	(I) Groups	(J) Groups	Mean difference (I-J)	Std. Error	Sig.	95% Confidence interval	
						Lower Bound	Upper Bound
Baseline PPD	Chronic periodontitis group	Aggressive periodontitis group	0.39800	0.37577	0.547	–0.5337	1.3297
		Control group	2.11500*	0.37577	0.000	1.1833	3.0467
	Aggressive periodontitis group	Chronic periodontitis group	–0.39800	0.37577	0.547	–1.3297	0.5337
		Control group	1.71700*	0.37577	0.000	0.7853	2.6487
	Control group	Chronic periodontitis group	–2.11500*	0.37577	0.000	–3.0467	–1.1833
		Aggressive periodontitis group	–1.71700*	0.37577	0.000	–2.6487	–0.7853
PPD 3 months	Chronic periodontitis group	Aggressive periodontitis group	–0.10100	0.26222	0.922	–0.7512	0.5492
		Control group	0.58800	0.26222	0.082	–0.0622	1.2382
	Aggressive periodontitis group	Chronic periodontitis group	0.10100	0.26222	0.922	–.5492	0.7512
		Control group	0.68900*	0.26222	0.036	0.0388	1.3392
	Control group	Chronic periodontitis group	–0.58800	0.26222	0.082	–1.2382	0.0622
		Aggressive periodontitis group	–0.68900*	0.26222	0.036	–1.3392	–0.0388

**P*-Value <0.05

PI from baseline to 3 months was statistically insignificant ($P = 0.122$) [Table 3 and Figure 1].

Intergroup comparison

Mean difference between Group I and Group II at baseline was 0.283 which was statistically significant ($P = 0.008$) and at 3 months post-operative was 0.372 which was statistically significant ($P = 0.000$).

Mean difference between Group I and Group III at baseline was 0.518 which was statistically significant ($P = 0.000$) and at 3 months post-operative was 0.588 which was statistically significant ($P = 0.000$).

Mean difference between Group II and Group III at baseline was 1.590 which was statistically significant ($P = 0.000$) and at 3 months post-operative was 0.146 which was statistically non-significant ($P = 0.145$).

Table 4: Comparison of gingival bleeding index

Group	Time duration (frequency)				*P*-value
	Baseline		3 months		
	Absence	Presence	Absence	Presence	
Chronic periodontitis	0	10	10	0	0.0001**
Aggressive periodontitis	0	10	7	3	0.023**
Control	10	0	10	0	1.00**
P-value	0.0001*		0.036*		-

*Chi-square test, **McNemar test

Table 5: Comparison of probing pocket depth

Groups	Time duration (mean±SD)		*P*-value
	Baseline	3 months post-operative	
Chronic periodontitis group	4.27±1.31	2.71±0.83	0.0001*
Aggressive periodontitis group	3.87±0.62	2.82±0.567	0.0001*
Control group	2.15±0.16	2.13±0.16	0.606*
P-value	0.0001**	0.029**	-

*Paired sample *t*-test. **One-way ANOVA

GBI

Gingival bleeding score was 1 at all cases of Group I and II at baseline, negative (score 0) in all Group I and 7 cases of Group II, only 3 cases of Group II remains with score 1 after 3 months postoperatively. Group III cases present only with score 0 at baseline and after 3 months [Table 4 and Figure 2].

PPD

Intragroup comparison

Group I: The mean PPD at baseline was 4.27 ± 1.30 and at 3 months was 2.71 ± 0.82. The mean reduction in PPD from baseline to 3 months was statistically significant ($P = 0.0001$).

Group II: The mean PPD at baseline was 3.87 ± 0.62 and at 3 months was 2.82 ± 0.57. The mean reduction in PPD from baseline to 3 months was statistically significant ($P = 0.0001$) [Tables 3,5 and Figure 3].

Group III: The mean PPD at baseline was 2.16 ± 0.16 and at 3 months was 2.713 ± 0.16 the mean reduction in PPD

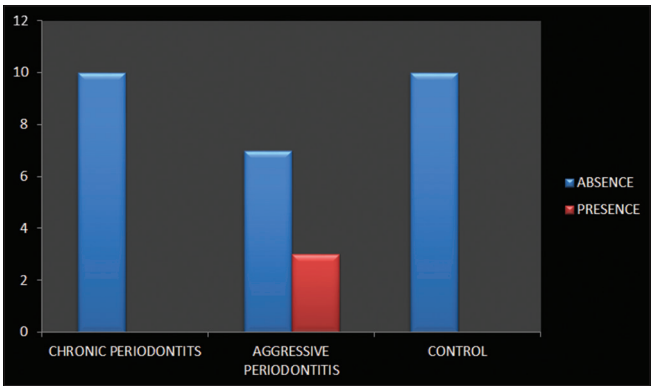

Figure 2: Comparison of a gingival bleeding index between Group I, Group II, and Group III

Table 6: Individual comparison with Tukey post hoc test-serum CRP level

Dependent variable	(I) Groups	(J) Groups	Mean difference (I-J)	Std. Error	Sig.	95% Confidence interval	
						Lower bound	Upper bound
Baseline CRP	Chronic periodontitis group	Aggressive periodontitis group	1.61427*	0.57214	.023	.1957	3.0328
		Control group	4.09860*	0.57214	0.000	2.6800	5.5172
	Aggressive periodontitis group	Chronic periodontitis group	–1.61427*	0.57214	0.023	–3.0328	–0.1957
		Control group	2.48433*	0.57214	0.001	1.0658	3.9029
	Control group	Chronic periodontitis group	–4.09860*	0.57214	0.000	–5.5172	–2.6800
		Aggressive periodontitis group	–2.48433*	0.57214	0.001	–3.9029	–1.0658
CRP 3 months	Chronic periodontitis group	Aggressive periodontitis group	.65460	0.47539	0.367	–0.5241	1.8333
		Control group	1.77650*	0.47539	0.002	0.5978	2.9552
	Aggressive periodontitis group	Chronic periodontitis group	–.65460	0.47539	0.367	–1.8333	0.5241
		Control group	1.12190	0.47539	0.064	–0.0568	2.3006
	Control group	Chronic periodontitis group	–1.77650*	0.47539	0.002	–2.9552	–0.5978
		Aggressive periodontitis group	–1.12190	0.47539	0.064	–2.3006	0.0568

**P*-Value <0.05

from baseline to 3 months was statistically non-significant ($P = 0.606$) [Table 6 and Figure 3].

Intergroup comparison

Mean difference between Group I and Group II at baseline was 0.398 which was statistically non-significant ($P = 0.547$) and at 3 months post-operative was −0.101 which was statistically non-significant ($P = 0.922$).

Mean difference between Group I and Group III at baseline was 2.115 which was statistically significant ($P = 0.000$) and at 3 months post-operative was 0.588 which was statistically non-significant ($P = 0.082$).

Mean difference between Group II and Group III at baseline was 1.717 which was statistically significant ($P = 0.000$) and at 3 months post-operative was 0.689 which was statistically significant ($P = 0.036$).

CAL

Intragroup comparison

Group I: The mean CAL at baseline was 4.00 ± 1.33 and at 3 months was 3.06 ± 1.00. The mean reduction in CAL from baseline to 3 months was statistically significant ($P = 0.032$) [Tables 7,8 and Figure 4].

Group II: The mean CAL at baseline was 3.98 ± 0.67 and at 3 months was 2.97 ± 0.54. The mean reduction in CAL from baseline to 3 months was statistically significant ($P = 0.0001$).

Group III: There was no CAL either at baseline or 3 months post-operative.

Intergroup comparison

Mean difference between Group I and Group II at baseline was 0.024 which was statistically non-significant ($P = 0.998$) and at 3 months post-operative

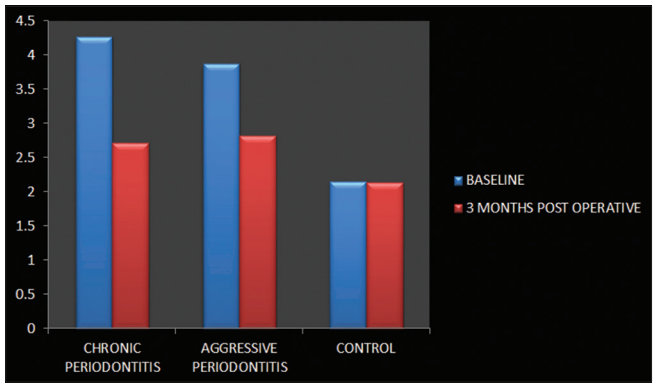

Figure 3: Comparison of probing pocket depth between Group I, Group II, and Group III

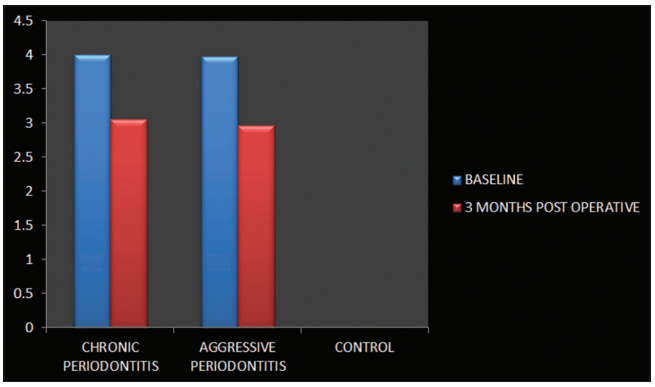

Figure 4: Comparison of clinical attachment level between Group I, Group II, and Group III

Table 7: Comparison of clinical attachment loss

Groups	Time duration (mean±SD)		*P*-value
	Baseline	3 months post-operative	
Chronic periodontitis group	4.00±1.33	3.06±1.01	0.032*
Aggressive periodontitis group	3.98±0.67	2.97±0.55	0.0001*
Control group	0.00±0.00	0.00±0.00	***
P-value	0.0001**	0.0001**	-

*Paired sample *t*-test, **One-way ANOVA

Table 8: Individual comparison with Tukey post hoc test-clinical attachment loss

Dependent variable	(I) Groups	(J) Groups	Mean difference (I-J)	Std. Error	Sig.	95% Confidence interval	
						Lower bound	Upper bound
Baseline CAL	Chronic periodontitis group	Aggressive periodontitis group	0.02400	0.38529	0.998	–0.9313	0.9793
		Control group	4.00400*	0.38529	0.000	3.0487	4.9593
	Aggressive periodontitis group	Chronic periodontitis group	–0.02400	0.38529	0.998	–0.9793	0.9313
		Control group	3.98000*	0.38529	0.000	3.0247	4.9353
	Control group	Chronic periodontitis group	–4.00400*	0.38529	0.000	–4.9593	–3.0487
		Aggressive periodontitis group	–3.98000*	0.38529	0.000	–4.9353	–3.0247
CAL 3 months	Chronic periodontitis group	Aggressive periodontitis group	0.09700	0.29647	0.943	–0.6381	0.8321
		Control group	3.06800*	0.29647	0.000	2.3329	3.8031
	Aggressive periodontitis group	Chronic periodontitis group	–0.09700	0.29647	0.943	–0.8321	0.6381
		Control group	2.97100*	0.29647	0.000	2.2359	3.7061
	Control group	Chronic periodontitis group	–3.06800*	0.29647	0.000	–3.8031	–2.3329
		Aggressive periodontitis group	–2.97100*	0.29647	0.000	–3.7061	–2.2359

**P*-Value <0.05

Table 9: Comparison of serum CRP level

Groups	Time duration (mean±SD)		*P*-value
	Baseline	3 months post-operative	
Chronic periodontitis group	4.93±1.69	2.57±1.33	0.0001*
Aggressive periodontitis group	3.32±1.38	1.91±1.20	0.0001*
Control group	0.83±0.39	0.79±0.40	0.286*
P-value	0.0001**	0.003**	-

*Paired sample *t*-test, **One-way ANOVA

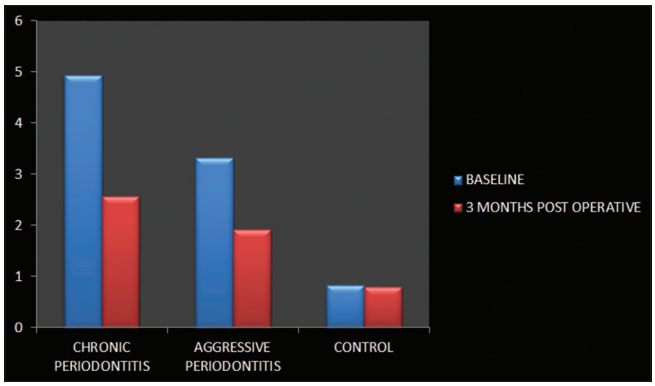

Figure 5: Comparison of serum CRP between Group I, Group II, and Group III

was 0.097 which was statistically non-significant (*P* = 0.943).

Mean difference between Group I and Group III was 4.00 which was statistically significant (*P* = 0.00) and at 3 months post-operative was 3.068 which was statistically significant (*P* = 0.000).

Mean difference between Group II and Group III was 3.98 which was statistically significant (*P* = 0.00) and at 3 months post-operative was 2.971 which was statistically non-significant (*P* = 0.000).

Serum CRP

Intragroup comparison

Group I: The mean serum CRP at baseline was 4.93 ± 1.67 and at 3 months was 2.57 ± 1.39. The mean reduction in serum CRP from baseline to 3 months was statistically significant (*P* = 0.0001) [Tables 6,9 and Figure 5].

Group II: The mean serum CRP at baseline was 3.32 ± 1.38 and at 3 months was 1.91 ± 1.20. The mean reduction in serum CRP from baseline to 3 months was statistically significant (*P* = 0.0001).

Group III: The mean serum CRP at baseline was 0.83 ± 0.40 and at 3 months was 0.79 ± 0.4. The mean reduction in serum CRP from baseline to 3 months was statistically non-significant (*P* = 0.286).

Intergroup comparison

Mean difference between Group I and Group II at baseline was 1.61 which was statistically significant (*P* = 0.023) and at 3 months post-operative was 0.654 which was statistically non-significant (*P* = 0.367).

Mean difference between Group I and Group III at baseline was 4.098 which was statistically significant (*P* = 0.000) and at 3 months post-operative was 1.776 which was statistically non-significant (*P* = 0.002).

Mean difference between Group II and Group III at baseline was 2.484 which was statistically significant (*P* = 0.001) and at 3 months post-operative was 1.121 which was statistically non-significant (*P* = 0.064).

DISCUSSION

Periodontitis is a progressive inflammatory disease of the supporting tissues surrounding the teeth caused by specific microorganisms.[1] Periodontitis is broadly classified into two groups; chronic periodontitis and aggressive periodontitis. Both forms represent the same disease with varying nature of disease severity and rate of progression. Earlier considered simply as a localized infection confined to the oral cavity, a growing body of evidence suggests that the pathology of periodontitis may affect the outcome of several systemic diseases, such as myocardial infarction, stroke, or preterm low birth weight babies.[17] The host responds to periodontal infections with an array of events involving both innate and adaptive immunity. This response in the periodontium can influence the systemic levels of many inflammatory mediators and acute-phase proteins. The acute phase reactant receiving the most attention is CRP. CRP has been the focus of attention as a key marker of acute-phase response to inflammation and its elevated levels constitute a risk predictor for cardiovascular disease.[5] As a consequence of its kinetics, it best describes the inflammatory status of an individual.[18]

Studies have indicated that serum CRP is elevated in patients with periodontal diseases (aggressive and chronic)[19] and treatment of periodontal infection significantly lowers the serum CRP levels whereas local factors such as pulp vitality,[20] excessive occlusal forces[21,22] also can influence the healing of periodontium after therapy. Hence, the local factors should be identified and eliminate at the initial stage itself.

The present study was carried out to compare the serum levels of CRP in patients of chronic and aggressive patients at the baseline level and 3 months after phase 1 therapy.

Several studies[13,23-26] have been carried out that have evaluated CRP level in saliva, serum, or GCF in patients of chronic periodontitis and aggressive periodontitis individually but very few have compared the serum CRP level before and after Phase 1 therapy in both forms of periodontitis.

In the present study, subjects with any acute or chronic systemic conditions such as diabetes or inflammatory conditions such as rheumatoid arthritis and cardiovascular disease have been excluded because these conditions can cause increased CRP level on their own, which may lead to confounding effect in the study.[26] Smoking is also a potential confounding factor because it is responsible for increases in CRP levels and is the principal environmental risk factor for periodontitis[27] and hence smokers were also excluded from the study.

Patients under medications such as antibiotics, corticosteroids, and anti-inflammatory drugs for past 3 months and those underwent periodontal therapy within past 6 months have been excluded because these therapies can suppress the inflammatory process and may lead to confounding effect in the study.

Quantitative determination of CRP in the present study in all the groups was done by double antibody sandwich ELISA method which is a very sensitive method for detecting CRP as compared to other methods.

In the present study, clinical parameters such as PI, PPD, CAL, and GBI were also assessed and compared among the three groups to correlate with the levels of serum CRP to establish a relationship between altered CRP levels and periodontal disease status.

In present study, PI, PPD, and CAL values at baseline in Group I (2.48 ± 0.26, 4.27 ± 1.30, and 4.00 ± 1.33, respectively) and in Group II (2.20 ± 0.15, 3.87 ± 0.62, and 3.98 ± 0.67, respectively) and in Group III were (0.61 ± 0.14, 2.16 ± 0.16, and 0.00). Were compared and the difference was highly significant.

The present study showed a significantly higher level of serum CRP in Group I (4.93 ± 1.67) and Group II (2.57 ± 1.39) as compared to Group III (0.83 ± 0.40) at the baseline level. The results of the present study indicate a significant correlation between PI, PPD, CAL, and CRP which is consistent with the findings of Noack *et al.*[25] who observed a statistically significant increase in CRP levels in 174 subjects with periodontal disease (4.06 ± 5.55 vs. 1.70 ± 1.91 mg/l) and a positive correlation between elevated levels of CRP and PI, PPD, and CAL. They found increased CRP levels in deeper pockets which could be due to the presence of periodontal Gram-negative pathogens like *Porphyromonas gingivalis* in the subgingival region.

In this study, it was found that the baseline CRP level in GCP and GAP was 4.93 and 3.32 mg/l, respectively and in the non-periodontitis control group at 0.83 mg/L which is in accordance with the study conducted by Ebersole and Cappelli (1997)[23] who detected that CRP levels were significantly increased in serum of adult periodontitis patients with CRP Levels at 9.12 mg/L versus 2.17 mg/L in healthy controls.

There are very few studies that have evaluated CRP levels in aggressive periodontitis subjects. One study by Salzberg *et al.*[28] reported an increase in CRP levels in generalized aggressive periodontitis patients (3.72 mg/L). The present study found similar CRP values (3.32 mg/l) in GAP patients at baseline.

After performing phase 1 therapy in all the patients, a significant reduction was found in serum CRP levels in chronic periodontitis and aggressive periodontitis patients (2.57 ± 1.39 and 1.91 ± 1.20, respectively) when compared to their baseline levels. This was in accordance with work done by D'Aiuto *et al.* (2004)[29] who found that systemically healthy subjects suffering from severe generalized periodontitis had higher CRP associated CVD risk and after receiving non-surgical periodontal therapy, the inflammatory level and risk of systemic diseases had reduced considerably. Whereas in non-periodontitis patients, serum CRP levels (0.79 ± 0.4) were found to be similar to their baseline levels.

Kumar *et al.*[30] also mentions that CRP levels strongly and independently predict the risk of myocardial infarction, stroke, peripheral artery disease, and sudden cardiac death, even among apparently healthy individuals. PI (1.05 ± 0.23 and 0.68 ± 0.16), PPD (2.71 ± 0.82 and 2.82 ± 0.57), and CAL (3.07 ± 1.00 and 2.97 ± 0.54) also showed a significant reduction in chronic and aggressive periodontitis patients at 3 months after phase 1 therapy when compared to their baseline values. Reduction in the values of the above mentioned clinical parameters exhibits a positive correlation with serum CRP level.

This is in accordance with work done by Santosh *et al.* (2013)[31] who found a 37% reduction in PPD and 45% gain in CAL and a reduction of about 90% reduction of CRP levels in the gingival crevicular fluid after 45 days.

Nakajima *et al.* (2010)[32] also confirmed that chronic periodontitis had high CRP level and subsequent periodontal treatment decreased the serum levels of CRP.

The present study was aimed at determining whether CRP is raised in periodontitis patients who are systemically healthy and if phase 1 therapy in these patients reduces inflammation which can reduce the risk of systemic inflammatory diseases like CVD. This is reflected in the reduction of CRP values at 3 months after phase 1 therapy as compared to baseline values. There are studies which show that patients with periodontitis had increased risk of CVD such as one done by De Stefano (1993)[33] which reported that patients with periodontitis had a 25% increased risk of coronary heart disease relative to those with minimal periodontal disease. Rosenberger *et al.*, 1996[34] stated that subjects with severe periodontitis had 4.3 times higher risk for cerebral ischemia than subjects with mild or without periodontal disease.

CONCLUSION

The following conclusions were drawn from the study:

- The serum CRP level is raised above normal values in both chronic and aggressive periodontitis
- In non-periodontitis patients, serum CRP level is only slightly raised above normal levels and is very less when compared to chronic and aggressive periodontitis
- After carrying out phase 1 therapy in all the groups, serum CRP levels show an appreciable reduction in chronic and aggressive periodontitis while in the non-periodontitis group, serum CRP levels do not show much change from baseline values.

Within the limits of our study, it can be concluded that both forms of periodontitis may play a role in systemic inflammation as indicated by elevated serum CRP level and more importantly, treating periodontal disease alone could bring down the inflammation as indicated by reduced serum CRP levels which help in minimizing the risk of systemic inflammation.

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Original Article

Transcutaneous Electrical Nerve Stimulation and Ultrasound Massage Therapy as an Adjuvant in Controlling Pain Modality in Temporomandibular Joint Disorders: A Comparative Study

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Abstract

Introduction: The temporomandibular joint disorders (TMJDs) consist of varieties of pathologies affecting the temporomandibular joint, the masticatory muscles, and associated structures. The majority of these patient's who have TMJ pain and dysfunction visits to the dental practice. Electrophysical modalities such as transcutaneous electrical nerve stimulation (TENS), ultrasound massage therapy, microwave, laser, and manual therapy techniques are used to relieve pain and restore normal mouth opening.

Aims and Objectives: This study aims to evaluate and compare the efficacy of TENS and ultrasound massage therapies in TMJDs and concerning the effectiveness of physical therapy interventions.

Study Design: The study comprised 40 patients received with temporomandibular disorders (TMDs) will be included in the study with the mean age of 18–50 years.

Materials and Methods: A total of 40 patients with TMDs, according to research diagnostic criteria (RDC) for TMD/RDC, participated in the study with the age group of 18–50 years, all the patients were randomly divided and treated with ultrasound massage therapy and TENS therapy, and pain intensity, mouth opening, and reduction in the tenderness of muscles of mastication individually were evaluated using visual analog scale, at every follow-up visits.

Results: In TENS therapy, a significant improvement in reduction of pain as well as in tenderness of masseter, temporalis, medial pterygoid, lateral pterygoid, and accessory muscles on both right and left sides of TMJ when compared to ultrasound massage therapy was found. Improvement in the mouth opening by TENS therapy than US massage therapy in management of TMDs was also found.

Conclusion: The results of our study showed a significant decrease in pain and tenderness of muscles by TENS therapy rather than ultrasound massage therapy in the management of TMDs. These therapies bring favorable safety characteristics to clinics being non-invasive modalities.

Key words: Pain, Physiotherapy, Temporomandibular disorders, Transcutaneous electrical nerve stimulation therapy, Ultrasound massage therapy

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INTRODUCTION

Temporomandibular disorders (TMDs) represent a heterogeneous group of pathologies affecting the temporomandibular joints, the jaw muscles, or both. They are the most common orofacial pain conditions of non-dental origin and are frequently encountered in

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clinical practice.[1] TMDs include conditions affecting the masticatory musculature, temporomandibular joint (TMJ), and associated structures.[2] Clinical presentation of TMDs is characterized by several symptoms such as orofacial pain, limitations of jaw movement, joint noises, headache or earache, dizziness, and ear symptoms such as tinnitus, vertigo, and deviation of mandible on opening and closing to affected side. In addition, patients often report with depression, poor sleep quality, and low morale.[3]

Treatment for TMDs can be non-surgical and surgical, although most TMDs patients respond on non-surgical treatment that can be coordinated by a dentist.[4] Many conservative forms of therapies have been the first line of management of TMDs. The non-surgical treatment includes education, self-care, physical therapy, physiotherapy, intraoral removable appliances, relaxation techniques, and pharmacological applicators.[5] Various forms of physical therapy intervention such as transcutaneous electrical nerve stimulation (TENS) and therapeutic ultrasound massage therapy can be potentially effective in the management of TMDs.[6]

According to the available literature, a very few studies have been done in comparing both treatment modalities. Hence, this study is intended to conduct and to correlate the efficacy of TENS therapy and ultrasound massage therapy in TMJDs. Therefore, a need was felt to conduct a study to assess the efficacy between TENS therapy and ultrasound massage therapy in evaluating TMJDs.

MATERIALS AND METHODS

This study was carried out in the Department of Oral Medicine and Radiology, Teerthanker Mahaveer Dental College and Research Center, Moradabad, Uttar Pradesh, India. This study was carried out to evaluate the efficacy of TENS Therapy and Ultrasound massage therapy in management of temporomandibular joint disorders, in the Department of Oral Medicine and Radiology, Teerthanker Mahaveer Dental College and Research Center, Moradabad, Uttar Pradesh, India.

A total of 40 patients were included for the study with the age group of 18–50 years of either gender. Patients were clinically designated for TMJDs using research diagnostic criteria and were included in the study, traumatic conditions of TMJ region, TMJ ankylosis patients, patients with cardiac pacemakers and cardiac arrhythmias, pregnant ladies, any history of patients suffering from seizures, vascular disorders and neurological pain, any history of patient suffering from benign and malignant neoplastic conditions of TMJDs, mentally disabled patients, and patients with undiagnosed dental pain or who has skin lesions or facial abrasion at the site of acoustic gel placement were excluded from the study.

These subjects were informed in detail about the treatment modality being provided to them and a required to sign a written informed consent. These patients were subjected for radiographic examination to rule out any bony changes in the condylar region as well as odontogenic infection. The subjects were divided into two groups, of which Group I (TENS) and Group II (Th. ultrasound massage). The data were recorded in the given case pro forma. Pain was evaluated using visual analog scale and the evaluation was done later, for pain intensity, mouth opening and masticatory muscle tenderness such as masseter, medial pterygoid, lateral pterygoid and temporalis and other accessory muscles, on both right and left side of TMJs. Machine that has been used was a combined ultrasound and TENS unit manufactured by relief medical system [Figures 1 and 2]. Power supply with two channels and four adhesive percutaneous electrodes for TENS and for ultrasound massage therapy a transducer head is provided and coupling gel that is to be applied on the area before the application of transducer head of ultrasound massage which serves as a medium for the transmission of energy and the therapy was done in the figure of "8" motion. TENS therapy was provided with frequency of 2–50 Hz and pulse width 10–100 ms, intensity according to the tolerance of the patient and

Figure 1: Ultrasound massage therapy machine

Figure 2: transcutaneous electrical nerve stimulation therapy machine

time duration for 40 min in each session [Figure 3], in a week for 4 weeks and on each visit, subjects were evaluated for pain intensity, mouth opening, and masticatory muscle tenderness and for accessory muscles. The ultrasound massage therapy was provided with a frequency of 1 MHz, pulse continuous, setting at 1:1, 1:3, 1:5, and 1:10 for 10 min in each session, in a week for 4 comparative weeks [Figure 4], Later, the data were tabulated and subjected to statistical analysis using, Microsoft Excel 2007 and analyzed using the SPSS statistical software 19.0 version. The intragroup comparison for the different time intervals was done using repeated measures ANOVA to find the difference between the individual time intervals. The intergroup comparison for the difference of mean scores between two independent groups was done using the unpaired/independent *t*-test.

RESULTS

A total of 40 patients with TMDs are taken, out of which 20 patients treated with TENS therapy and 20 patients with ultrasound massage therapy, reduction of pain, as well as in tenderness of masseter, temporalis, medial pterygoid, lateral pterygoid, and accessory muscles on both right and left sides of TMJ at different time intervals between TENS and ultrasound massage therapy in the 2nd, 3rd, 4th, and 5th follow-up visits were observed.

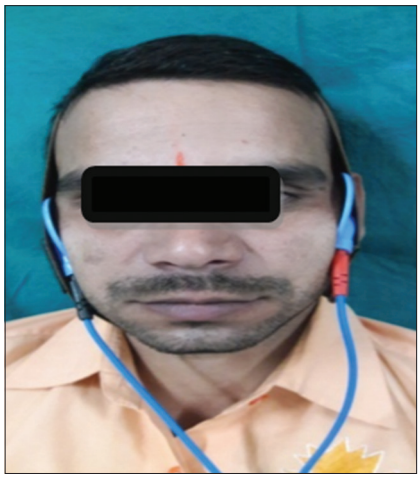

Figure 3: Patient receiving transcutaneous electrical nerve stimulation therapy

Figure 4: Patient receiving US massage therapy

In TENS therapy, a significant improvement in reduction of pain as well as in tenderness of masseter, temporalis, medial pterygoid, lateral pterygoid, and accessory muscles on both right and left sides of TMJ when compared to ultrasound massage therapy was found. Improvement in the mouth opening by TENS therapy than US massage therapy in the management of TMDs was also found.

DISCUSSION

TMJ disorder includes any condition occurring from muscular and/or mechanical stress or trauma to the jaw and it is a major cause of non-dental pain in orofacial region. Among the most traditional treatment for TMD, physical therapy modalities and manual techniques are widely used, these modalities and techniques are applied to the TMJ and surrounding musculature such as temporalis, masseter, and on other accessory muscles such as sternocledomastoid and trapezius is often also treated.

In the present study, it was observed that the distribution of age group is 18–50 years. In which the age of occurrence was second to the fourth decades of life, which is accordance with the studies done by Singh *et al.*, 2014,[7] Mukkannavar, 2008,[8] Kamtane and Sable, 2017,[9] Moger *et al.*, 2011,[10] and Shanavas *et al.*, 2014.[1] All these authors stated that occurrence of disorder is at the age group between 2nd to 5th decade of life.

The predominance of females (65%) is greater than male patients (35%), noted in this study. This predilection of females is similar to the work done by Geissler and McPhee, 1986[11] and Kamtane and Sable, 2017.[9]

In comparison with the reduction of pain between the TENS and US therapy in all 2nd, 3rd,4th and 5th, follow up visits, a significant reduction in pain between two therapies is seen [Table 1] which is statistically significant. Which is in accordance to the studies conducted by Rai. S. *et al.*, in 2016[12] and Trakoo A. *et al.*, 2014.[13]

In our study, it was found that TENS therapy showed comparatively reduction in pain from 1st visit to 5th follow-up visits than the US massage therapy, they found that the US massage therapy is better than TENS therapy, but in this study, it was found that TENS therapy is better than US massage which is in harmony with studies done by Rai *et al.* in 2016[12] and Aarti *et al.*, 2014,[13] they found in their

studies that the US massage therapy is better than TENS therapy. However, in our study, it was found that TENS therapy is better than US massage therapy.

In the present study the TENS therapy showed reduction in the tenderness of masseter muscle on the left side between TENS and US massage therapy which is non significant in 2nd and 3rd visit, where as a significant improvement is seen in the reduction of tenderness in 4th and 5th follow up visits. Similarly, on the right side of masseter muscle, it was found that there is no reduction in pain between the two therapies in the 2nd and 3rd visits but in follow-up 4th and 5th visits. It showed a significant improvement in reduction of pain. It was observed that TENS therapy showed reduction in tenderness of both right and left masseter muscles [Table 2], which is in accordance with the study done by Aarti *et al.*, 2014.[13] A similar study done by Arora *et al.*, 2014,[14] stated and compared the US massage therapy and ozone therapy in TMDs. They reported where the ozone therapy showed significant reduction of pain and tenderness of masticatory muscles.

In our study, a significant reduction in the tenderness of the left and right temporalis muscles with both TENS and US massage therapies was found. In the 2nd, 3rd, and 4th visits, it showed as no improvement between two therapies. However, in the 5th follow-up visit, a significant improvement is seen in the left temporalis muscles in both the therapies. Similarly, the reduction in tenderness of the right temporalis muscle showed no improvement in the 2nd visit, but in follow-up 3rd, 4th, and 5th visits, a significant reduction in tenderness of muscle by both therapies was found. The right and left temporalis muscle when compared, a reduction in tenderness was found by TENS therapy and it was observed to be more beneficial than US massage therapy [Table 3], which is in accordance with the study done by Aarti *et al.*, 2014[13] and Arora *et al.*, 2014.[14]

Table 1: Intergroup comparison of percentage reduction in pain at different time intervals between transcutaneous electrical nerve stimulation and ultrasound

Groups	Mean	Std. deviation	*P* value	Significance
Reduction at IInd visit				
Ultrasound	13.28	13.51	0.001	Significant
Transcutaneous electrical nerve stimulation	23.12	11.45		
Reduction at IIIrd visit				
Ultrasound	26.53	12.97	0.001	Significant
Transcutaneous electrical nerve stimulation	44.43	15.06		
Reduction at IVth visit				
Ultrasound	46.99	20.36	0.001	Significant
Transcutaneous electrical nerve stimulation	62.96	21.93		
Reduction at Vth visit				
Ultrasound	48.65	22.58	0.001	Significant
Transcutaneous electrical nerve stimulation	66.40	25.44		

Table 2: Intergroup comparison of percentage reduction in tenderness of the left and right masseter muscle at different time intervals between transcutaneous electrical nerve stimulation and ultrasound

Groups	Left masseter Mean	Std. deviation	*P* value	Significance	Right masseter Mean	Std. deviation	*P* value	Significance
Reduction at IInd visit								
Ultrasound	3.03	10.05	0.519	Non-significant	00.00	00.00	1.000	Non-significant
transcutaneous electrical nerve stimulation	00.00	00.00			00.00	00.00		
Reduction at IIIrd visit								
Ultrasound	48.48	45.61	0.750	Non-significant	33.33	18.25	0.458	Non-significant
Transcutaneous electrical nerve stimulation	40.00	54.77			50.00	50.00		
Reduction at IVth visit								
Ultrasound	78.78	26.96	0.001	Significant	61.11	31.03	0.041	Significant
Transcutaneous electrical nerve stimulation	100.00	00.00			92.85	18.89		
Reduction at Vth visit								
Ultrasound	78.78	26.96	0.001	Significant	61.11	31.03	0.001	Significant
Transcutaneous electrical nerve stimulation	100.00	00.00			100.00	00.00		

When both therapies were compared with right and left medial pterygoid muscle tenderness, TENS therapy showed significant reduction, so it is more beneficial in reducing tenderness. It is in harmony with the research done by Aarti *et al.*, 2014[13] and Arora *et al.*, 2014.[14] There is no significant improvement found in the 2nd, 3rd, and 4th follow-up visits of tenderness of the left medial pterygoid muscle but in the 5th visit, it showed a significant reduction in tenderness of the left medial pterygoid muscle with both the therapies. However, the right side of medial pterygoid muscle also found no significant improvement of tenderness in both 2nd and 3rd visits. However, in the follow-up, 4th and 5th visits found to be a significant improvement with both TENS and US massage therapy.

Similarly in intragroup comparison of both left and right medial pterygoid muscles, by TENS and US massage therapy, both showed a significant reduction in tenderness with P value of 0.001 [Table 4].

Similarly, no improvement observed in reduction in tenderness of the left lateral pterygoid muscle between both therapies in the 2nd visit, whereas the regular follow-up 3rd, 4th, and 5th visits showed a significant reduction in tenderness of the left pterygoid muscle. Similarly, on the right side of the lateral pterygoid muscle, no improvement was found in both 2nd and 3rd visits between two therapies. However, a significant improvement found in the right lateral pterygoid muscle. However, TENS therapy showed a significant reduction in tenderness of the left and

Table 3: Intergroup comparison of percentage reduction in tenderness of the left and right temporalis at different time intervals between transcutaneous electrical nerve stimulation and ultrasound

Groups	Left temporalis Mean	Std. deviation	*P* value	Significance	Right temporalis Mean	Std. deviation	*P* value	Significance
Reduction at IInd visit								
Ultrasound	00.00	00.00	1.000	Non-significant	00.00	00.00	1.000	Not significant
Transcutaneous electrical nerve stimulation	00.00	00.00			00.00	00.00		
Reduction at IIIrd visit								
Ultrasound	53.33	38.005	0.458	Non-significant	30.00	18.257	0.001	Significant
Transcutaneous electrical nerve stimulation	62.50	47.87			72.91	17.67		
Reduction at IVth visit								
Ultrasound	93.33	14.90	0.765	Non- Significant	63.33	34.15	0.010	Significant
Transcutaneous electrical nerve stimulation	87.50	15.95			85.41	20.77		
Reduction at Vth visit								
Ultrasound	100.00	00.00	1.00	Significant	63.33	34.15	0.001	Significant
Transcutaneous electrical nerve stimulation	100.00	00.00			100.00	00.00		

Table 4: Intergroup comparison of percentage reduction in tenderness of the left and right medial pterygoid at different time intervals between transcutaneous electrical nerve stimulation and ultrasound

Groups	Left medial pterygoid Mean	Std. Deviation	*P* value	Significance	Right medial pterygoid Mean	Std. deviation	*P* value	Significance
Reduction at IInd visit								
Ultrasound	5.55	13.60	0.513	Non-	00.00	00.00	0.479	Non-significant
Transcutaneous electrical nerve stimulation	00.00	00.00		significant	12.50	25.00		
Reduction at IIIrd visit								
Ultrasound	55.55	40.36	0.516	Non-	27.77	25.45	0.192	Non- significant
Transcutaneous electrical nerve stimulation	38.88	34.69		significant	54.16	41.66		
Reduction at IVth visit								
Ultrasound	75.00	29.34	0.668	Non-	27.77	25.45	0.001	Significant
Transcutaneous electrical nerve stimulation	83.33	16.66		significant	87.50	15.95		
Reduction at Vth visit								
Ultrasound	75.00	29.34	0.001	significant	27.77	25.45	0.001	Significant
Transcutaneous electrical nerve stimulation	100.00	00.00			100.00	00.00		

right lateral pterygoid muscles than US massage therapy [Table 5], which is in harmony to studies done by Aarti *et al.*, 2014[13] and Arora *et al.*, 2014.[14]

However, it was found that there was no improvement in the reduction in the tenderness of left accessory muscles in between both the therapies. Similarly, on the right side, it showed no improvement in the tenderness of muscles in both 2nd and 5th follow-up visits, whereas a definite reduction in the tenderness was noted on the 3rd and 4th follow-up visits. We observed that the TENS therapy showed a significant reduction in the tenderness of both the left and right accessory muscles compared to US massage therapy [Table 6], which is in accordance with studies done by Aarti *et al.*, 2014 and Saloni *et al.*, 2014.

In the present study, there was a reduced mouth opening in the 2nd visit, whereas in follow-up 3rd, 4th, and 5th visits, a significant improvement in mouth opening between the TENS therapy and US massage therapy was seen. However, in intragroup comparison of mouth opening between the TENS and US massage therapy, increased mouth opening was found with TENS therapy, with $P \leq 0.001$, which is statistically significant [Table 7]. Which is in accordance to studies done by Rai S. et al 2016[12], Kamtane S. *et al.*, 2017,[9], Ucar M. *et al.*, 2014,[2],

Table 5: Intergroup comparison of percentage reduction in tenderness of the left and right lateral pterygoid at different time intervals between transcutaneous electrical nerve stimulation and ultrasound

Groups	Left Lateral pterygoid	Std. deviation	*P* value	Significance	Right lateral pterygoid	Std. deviation	*P* value	Significance
	Mean				Mean			
Reduction at IInd Visit								
Ultrasound	00.00	00.00	1.000	Non-significant	00.00	00.00	0.479	Non-significant
Transcutaneous electrical nerve stimulation	00.00	00.00			7.14	18.89		
Reduction at IIIrd visit								
Ultrasound	56.25	23.46	0.038	Significant	29.16	34.35	0.192	Non- significant
Transcutaneous electrical nerve stimulation	83.33	18.25			57.14	30.21		
Reduction at IVth visit								
Ultrasound	79.16	30.53	0.010	Significant	37.50	28.46	0.001	Significant
Transcutaneous electrical nerve stimulation	100.00	00.00			90.47	13.11		
Reduction at Vth visit								
Ultrasound	79.16	30.53	0.023	Significant	37.50	28.46	0.001	Significant
Transcutaneous electrical nerve stimulation	100.00	00.00			100.00	00.00		

Table 6: Intergroup comparison of percentage reduction in tenderness of the left and right accessory at different time intervals between transcutaneous electrical nerve stimulation and ultrasound

Groups	Left accessory	Std. deviation	*P* value	Significance	Right accessory	Std. deviation	*P* value	Significance
	Mean				Mean			
Reduction at IInd visit								
Ultrasound	00.00	00.00	1.000	Non-significant	00.00	00.00.	0.685	Non-significant
Transcutaneous electrical nerve stimulation	00.00	00.00			16.67	33.33		
Reduction at IIIrd visit								
Ultrasound	66.67	00.00	0.192	Non-significant	00.00	00.00	0.001	Significant
Transcutaneous electrical nerve stimulation	50.00	13.60			63.89	44.790		
Reduction at IVth visit								
Ultrasound	100.00	00.00	0.897	Non-significant	66.67	0.00	0.020	Significant
Transcutaneous electrical nerve stimulation	87.50	15.95			91.67	16.66		
Reduction at Vth visit								
Ultrasound	100.00	00.00	1.000	Non-significant	100.00	0.00	1.000	Non-significant
Transcutaneous electrical nerve stimulation	100.00	00.00[a]			100.00	00.00		

Table 7: Intergroup comparison of percentage gain in mouth opening at different time intervals between transcutaneous electrical nerve stimulation and ultrasound

Groups	Mean	Std. deviation	*P* value	Significance
Improvement at IInd visit				
Ultrasound	0.49	1.20	0.234	Non-significant
Transcutaneous electrical nerve stimulation	1.46	2.83		
Improvement at IIIrd visit				
Ultrasound	1.32	1.88	0.016	Significant
Transcutaneous electrical nerve stimulation	4.08	4.04		
Improvement at IVth visit				
Ultrasound	2.65	3.62	0.012	Significant
Transcutaneous electrical nerve stimulation	5.02	5.11		
Improvement at Vth visit				
Ultrasound	3.14	4.70	0.013	Significant
Transcutaneous electrical nerve stimulation	5.02	5.11		

Knezevic M. *et al*., 2008[15], Bijjarangi *et al*., 2015[16] and Moger G. *et al*., 2011.[10]

CONCLUSION

TMDs are known as the most commonly occurring chronic orofacial pain conditions challenging dentists and other oral health providers. The main goal of treatment for TMDs is to relieve pain. Various treatment modalities are proposed in available literature. Another mode of management in TMDs is TENS and ultrasound massage therapies. The results of our study showed a significant decrease in pain and tenderness of muscles by TENS therapy rather than ultrasound massage therapy in the management of TMDs. These therapies bring favorable safety characteristics to clinics being non-invasive modalities.

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Original Article

Role of Transbronchial Lung Biopsy in Diffuse Parenchymal Lung Diseases

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Abstract

Introduction: Diffuse parenchyma lung disease (DPLD) encompasses a heterogeneous group of disorders, characterized by a spectrum of inflammatory and fibrotic changes affecting alveolar walls and air spaces. Lung biopsy is generally required to make an etiological diagnosis of DPLD's. Transbronchial lung biopsy (TBLB) is a minimally invasive method to achieve a lung sample which has been found to be a useful diagnostic tool in patients with DPLD. Despite the small size, TBLB provides information regarding pathology that is located beyond the cartilaginous airways that may include elements of the small airways of the distal bronchial tree, the alveolar space, the vasculature, and lymphatic structures immediately surrounding the alveoli.

Aim: This study aims to obtain a specific diagnosis by subjecting the TBLB specimen for histopathological examination.

Materials and Methods: It is a prospective observational study. Twenty adult patients with radiologically diffuse parenchymal lung disease admitted between January 2010 and March 2012 in Mahavir Hospital and Research Centre, Hyderabad, were subjected for TBLB through flexible fiber-optic bronchoscopy, without fluoroscopic guidance.

Results: It was observed that the lung tissue yield of the procedure is 75% (15/20) and the diagnostic yield of the procedure is 93.3% with overall diagnostic yield being 70%. No significant bleeding was observed in any patient. Moreover, no mortality was observed after the procedure.

Conclusion: Transbronchial lung biopsy through flexible bronchoscopy is a very simple procedure. It is a relatively safe and effective procedure and helps in early diagnosis of diffuse parenchymal lung diseases. In the present study, adequate lung tissue was obtained successfully in 75% patients. Of these cases, the procedure was diagnostic in 93.3%. Complications (pneumothorax) were observed in only two patients out of twenty, which were successfully managed with ICD. Advent of HRCT chest and C-arm/Fluoroscopy help the bronchoscopist to accurately localize the lobe/segment of maximum disease for transbronchial lung biopsy and to increase the yield of the procedure.

Key words: Diffuse parenchymal lung diseases, High-resolution computed tomography, Transbronchial lung biopsy

INTRODUCTION

Diffuse parenchyma lung disease (DPLD) encompasses a heterogeneous group of disorders, characterized by a spectrum of inflammatory and fibrotic changes affecting alveolar walls and air spaces.[1-3] They comprise over 200 entities and include a wide spectrum of diseases, many uncommon and many of unknown etiology and account for 15% of diseases seen in pulmonary medicine practice.[4] The onset, rate of progression, and duration of symptoms are extremely variable. The presentations range from and asymptomatic patient with long-standing radiological changes to an acute onset of breathlessness over days leading rapidly to respiratory failure and death. The incidence and prevalence rates of DPLD have not been precisely estimated due to difficulties in ascertaining a specific diagnosis on a specific disease. Moreover, interstitial lung diseases (ILD) usually remains a diagnosis of exclusion requiring extensive investigations to differentiate ILD from other diseases.[5]

Open lung biopsy though is considered as the "gold standard" for DPLD, it is often associated with significant morbidity and mortality, and hence a safer method, the transbronchial lung biopsy (TBLB), is gradually gaining wide acceptance among the medical society.[3] Laboratory

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blood testing alone is rarely diagnostic, but may be strongly supportive in the appropriate clinical setting.

PFTs cannot diagnose a specific ILD and cannot distinguish between active lung inflammations versus fibrosis, but are important in the objective assessment of respiratory symptoms as well as in paring the differential diagnosis, grading the severity of disease, and monitoring response to therapy or progression. Chest radiograph is an essential test, diagnostic in at least 50% of cases. It has limited sensitivity and specificity in diagnosis of DPLD. Up to 10% of patients of biopsy proven DPLD have normal chest X-ray.[6] High-resolution computed tomography (HRCT) is more sensitive than plain chest radiograph in identifying ILD (sensitivity greater than 90%) and the image pattern of parenchymal abnormalities on HRCT often suggest a particular set of diagnostic abnormalities. Fiber-optic bronchoscopy with bronchoalveolar lavage (BAL) may substantiate specific diagnosis in some patients (e.g., sarcoidosis, LCG, LAM, CEP, and COP) and BAL may be adequate in to diagnose specific infections. TBLB achieves a high diagnostic yield in DPLDs with centrilobular attenuation, such as granulomatous and metastatic diseases, infection, alveolar proteinosis, and eosinophilic pneumonias.[7-9]

MATERIALS AND METHODS

Twenty adult patients with radiologically diffuse parenchymal lung disease admitted between January 2010 and March 2012 in Mahavir Hospital and Research Centre, Hyderabad, were subjected for TBLB through flexible fiber-optic bronchoscopy, without fluoroscopic guidance.

Study Design

This was a prospective observational study.

Setting

A total of 300 bedded tertiary care hospital, Hyderabad.

The patients were enrolled into the study according to the inclusion criteria.

The study was commenced after obtaining approval from the Institution's Ethical Committee.

Inclusion Criteria

All adult patients having radiologically (chest X-ray posteroanterior view and HRCT – chest) diffuse parenchymal lung disease, who were not diagnosed by clinical, radiological, and routine laboratory investigations were included in the study.

Exclusion Criteria

Patients having

1. Obvious lung mass
2. Sputum for acid-fast bacillus (D/S) positive
3. Not willing to give informed consent
4. Unfit for bronchoscopy.

Technique

After obtaining informed consent from the patients, the procedure was performed using flexible fiber-optic bronchoscope (Olympus BfTE2 and Fujinon). Pre-medication was done with atropine 0.6 mg IM and 2% lignocaine spray was done through atomizer in patients mouth in the direction of fauces and transnasal topical 2% lignocaine gel was given into each nostril.

The lung lobe having the maximum radiological abnormality was chosen and fiber-optic bronchoscopy wedged into the bronchus of that segment. When the pulmonary disease was equally distributed in both lungs, the basal segments of lower lobes were selected for TBLB.

Biopsy forceps was advanced beyond the tip of the scope until resistance was met. The forceps was then withdrawn by 1–2 cm and cup of the forceps was opened. The patient was then asked to inhale deeply and the forceps was readvanced during inhalation for 2–3 cm or till resistance was met. The patient was asked to exhale and forceps was closed at the end of expiration and the biopsy forceps were withdrawn and the sample was collected.

An average of four lung biopsy samples was taken (ranging between 3 and 6) and kept in 10% formalin and was subjected for histopathological examination.

RESULTS

Sex Ratio

This study has a female-to-male ratio of 3:2.

One study reported that 80.9 per 100,000 men and 67.2 per 100,000 women suffer from interstitial disease in the United States, with 31.5 new cases diagnosed per 100,000 men per year and 26.1 new cases diagnosed per 100,000 women per year.[10]

In the references to the study by Song *et al.*,[11] the sex ratio was equal in males and females in idiopathic pulmonary fibrosis (IPF), collagen vascular disease (CVD)–PF, and hypersensitivity pneumonitis. However, the female incidence was greater in sarcoidosis and male incidence in pneumoconiosis.

Characteristic Radiographic Appearances

Glazer study[12] of patients on radiographic appearances in ILD described the characteristic radiographic appearances of ILD – the ground glass effect, consolidation, and cysts – honey combing pulmonary nodules and interstitial thickening. They also included the advantage of HRCT in ILD.

In the current study, the characteristic radiographic appearances observed are honey combing (10%), reticulation (20%), and reticulonodular (35%).

Study	Characteristic appearance
Glazer C study	Ground glass Consolidation Honeycombing Nodules Interstitial thickening
Present Study	Honeycombing (10%) Reticular (20%) Reticulonodular (35%)

HRCT chest was done in all cases. HRCT is more sensitive than chest X-ray in ILD. HRCT showed changes such as reticulonodular pattern, traction bronchiectasis, and honey combing.

Diagnostic Yield

This study was undertaken to evaluate the diagnostic yield of TBLB in diffuse parenchymal lung disease in this institution.

The present study has a diagnostic yield of 70%, which is comparable with many other studies.

Reference	No. of patients	Diagnostic yield
Kalra et al	26	76%
R.K.Ailani	30	77%
Andersen	939	79.4%
Milman et al	126	66.7%
Mitchell et al	183	61%
Szlubowski et al	123	65%
Ibrahim AS et al	71	81.7%
Hanson et al	164	57%
Ahluwalia et al	25	80%
Present study	**20**	**70%**

Complications

In the present study, two patients developed pneumothorax, which was treated with closed tube thoracostomy. In the study done by Ensminger and Prakash.[13] TBLB was done with the aid of fluoroscopy with a diagnostic yield of 75.9% and complications (pneumothorax) were observed in 1.26% of patients.

TBLB can be performed safely and effectively on outpatient basis in selected cases as done by Suri *et al*.[14] and Blasco *et al*.[15].

DISCUSSION

ILDs are heterogeneous group of diseases involving lung interstitium. They have features in common such as similarities of symptoms, comparable radiographic appearances, consistent alterations in the pulmonary physiology, and typical histological features.

In the present study, patients of ILD were selected and studied during the period from 2010 to 2012 in the Department of Pulmonary Medicine, Mahavir Hospital and Research Centre, Hyderabad.

The diagnosis of diffuse parenchymal lung disease is often challenging due to wide variety of causes included in the group and their varied presentations. Fiber-optic bronchoscopy with TBLB is a widely accepted technique for the diagnosis of diffuse parenchymal lung disease. The study group included various etiological forms of ILD such as IPF, ILD due to CVD, military metastasis, PCP, and pneumoconiosis. TBLB through flexible bronchoscopy is a simple, safe, and effective procedure for the diagnosis of diffuse parenchymal lung diseases.

However, the study was not without limitations. The various limitations include the lack of efficacy in results due to the relatively small size. The relatively small size of patients and the lack of a control group imposed limited value to statistical analysis of group difference between groups exposed to smoking or dust. The study also had many female patients. In our study, biopsy samples taken are only 4. The study would have been more effective had the sample size been 6. Even though there are many trials in DPLD, histological support for a specific diagnosis can be obtained using TBLB in 29–79% of cases. This wide range reflects the multiplicity of factors influencing the yield of the procedure, including the distribution of the lesion (focal or diffuse), status of the immune system of the patient, small size of the obtained samples, confounding due to crush artifacts, and failure to penetrate beyond the peribronchial sheath.

CONCLUSION

Transbronchial lung biopsy through flexible bronchoscopy is a very simple procedure. It is a relatively safe and effective procedure and helps in early diagnosis of diffuse parenchymal lung diseases. In the present study, adequate

lung tissue was obtained successfully in 75% patients. Of these cases, the procedure was diagnostic in 93.3%. Complications (pneumothorax) were observed in only two patients out of twenty, which were successfully managed with ICD. Advent of HRCT chest and C-arm/Fluoroscopy help the bronchoscopist to accurately localize the lobe/segment of maximum disease for transbronchial lung biopsy and to increase the yield of the procedure.

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Original Article

Impact of Coronavirus Disease 19 Pandemic Lockdown on Ophthalmic Practice

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Abstract

Introduction: On January 30, 2020, the outbreak of coronavirus disease (COVID-19) was declared as public health emergency of international concern by the WHO. Subsequently, it was declared a pandemic on March 11, 2020. India reported the first case of this COVID-19 on January 30, 2020, in the state of Kerala in South India. In view of COVID-19 pandemic, only essential services were made available.

Purpose: The purpose of the study was to assess the impact of lockdown on ophthalmic practice in tertiary care center.

Methodology: Cases attending the ophthalmology outpatient department from March 23, 2020, to May 23, 2020, were examined as per AIOS guidelines of COVID practice patterns 2020.

Results: A total of 160 patients were examined, out of which 77 were male and 83 were female. Viral conjunctivitis constituted 32.5% (52/160). Bacterial conjunctivitis constituted 12.5% (20/160). Allergic causes of red eyes constituted 13.75% (22/160). Trauma to the eye constituted 22.5% (36/160). Follow-up cases including post-operative were 6.87% (11/160).

Conclusion: Lockdown resulted in a decrease in the number of follow-up cases including post-operative cases to ophthalmology outpatient department.

Key words: Coronavirus disease 19, Lockdown, Ophthalmology, Severe acute respiratory syndrome

INTRODUCTION

In the present time line, pandemic of cases with low respiratory tract infection was first detected in Wuhan city in China's Hubei Province and reported to the WHO on December 31, 2019.[1] After this, these cases were initially classified as pneumonia of unknown etiology. Chinese center for disease control and prevention identified this virus as novel virus belonging to the corona family and named it as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).[2]

On January 30, 2020, the outbreak was declared as public health emergency of international concern by the WHO. It had spread to 18 countries by then with 4 countries having human-to-human transmission.[3]

The WHO named it as coronavirus disease on February 11, 2020.[3]

By March 11, total number of cases worldwide exceeded 118,000 with 114 countries affected and more than 4000 deaths and subsequently it was declared a pandemic on March 11, 2020.[3]

India reported the first case of this coronavirus disease (COVID-19) on January 30, 2020, in the state of Kerala in South India, where a student with a history of travel to Wuhan presented with respiratory symptoms. This was followed by two more similar cases on consecutive days.[4]

Initially lockdown was started in China to curb the spread of the disease where schools and colleges were shut until further orders and there were travel restrictions followed. The similar pattern was followed by other countries worldwide.

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Similarly, in India, the central government announced "Janata curfew" on March 22, 2020.[5] Converting it into a nationwide lockdown since March 24, 2020, continuing for a period of 21 days (Phase-1).[6] The lockdown was placed when the number of confirmed positive coronavirus cases in India was approximately 500.

On April 14, Prime Minister Narendra Modi extended the nationwide lockdown until May 3 (Phase-2), with a conditional relaxations after April 20 for the regions where the spread had been contained or was minimal.[7]

On May 1, the Government of India extended the nationwide lockdown further by 2 weeks until May 17 (Phase 3). There was relaxation as per the zones – red, green, and orange and the restrictions were done accordingly [Figure 1].[8]

As per May 22, data from state health departments show that with the addition of 6510 cases, there have been a total 124,525 confirmed cases with 69,140 active infections and 51,666 recoveries country wide. Fatalities increased by 148, to take the total death toll to 3720.[9]

Karnataka government followed similar lockdown pattern as instructed by the central government.

In Karnataka at the time of first lockdown (March 23), the total number of cases was around 108. At the end of the

#	Activity	Green	Orange	Red	Containmen
1	Travel- Air, Train, Metro	NO	NO	NO	NO
2	Inter-state Road Movement	NO	NO	NO	NO
3	Education Institutions	NO	NO	NO	NO
4	Hospitality- hotels, cinemas, malls	NO	NO	NO	NO
5	Worship & Large gatherings	NO	NO	NO	NO
6	Barbershop, spa	YES	YES	NO	NO
7	Coming out between 7 pm and 7 a	NO	NO	NO	NO
8	Age >65, <10, Pregnant - Outing	NO	NO	NO	NO
9	Medical Clinic, OPD	YES	YES	YES	NO
10	Auto, Taxi ,	1+1	1+1	NO	NO
11	4 Wheeler	1+2	1+2	1+2*	NO
12	2 Wheeler	1+1	1+1	1+0*	NO
13	Inter-district Bus	50%	50%	NO	NO
14	Intra-district Bus	50%	50%	NO	NO
15	Industrials with access control	YES	YES	YES	NO
16	Urban Industries	YES	YES	YES	NO
17	Urban in-situ construction	YES	YES	YES	NO
18	Urban single non/essential shops	YES	YES	YES	NO
19	E-com Essential goods	YES	YES	Yes	NO
20	Private and Govt (non-core)	YES	YES	33%	NO
21	Agri activiteis	YES	YES	Yes	NO
22	Bank & Finances	YES	YES	Yes	NO
23	Courier and Postal	YES	YES	YES	NO
24	Goods Traffic	YES	YES	YES	NO

Figure 1: Zone-wise restrictions during coronavirus disease 19 pandemic

first, second, and third phases of lockdown, the number of corona cases was 1463, 1755, and 4987, respectively. As of May 23, 2020, it was about 6654.[10]

The symptoms of COVID-19 commonly present as fever, cough, sore throat, fatigue, dyspnea, occasional diarrhea, and vomiting. It was seen in certain population such as the immunocompromised and the elderly that it can progress to acute respiratory distress syndrome (ARDS), sepsis, and multiorgan failure. Due to the lack of a vaccine or drug to treat this condition, the mortality rate was on the higher side.[11]

The World Health Organization announced that the spread of COVID-19 was also through droplets, fomites, and contacts just like SARS.[12]

Since there was a high risk of health care workers contracting this virus, when the lockdown came in place, there was advice to the doctors to continue only with emergency services and to shut regular outpatient departments, elective procedures, and admissions across the country until further orders.

Aim

The aim of the study was as follows:

1. To document the ophthalmic cases seen in a tertiary eye care center during the lockdown period from March 23 to May 23, 2020
2. To assess the impact of lockdown on ophthalmic practice.

METHODOLOGY

Since the lockdown, in the ophthalmology department in our institution as per the AIOS guidelines 2020 (COVID practice patterns), only emergency ophthalmic conditions were treated only after screening for COVID-19 symptoms were done. Screening was done in the casualty based on history and thermal screening.

COVID-19 screening questionnaire:

- Have you had any history of fever in the last 14 days?
- Have you had any respiratory illness such as cough or difficulty breathing in the last 14 days?
- In the past 14 days, have you or any household member had any contact with a known COVID-19 patient?
- Have you or any household member traveled to international area or to areas of suspected community spread in the last 14 days?
- Have you or any household member had history of exposure to COVID-19 biologic material?

If the patients temperature was more than 99.3 F on thermal screening and if they had positive history, they were subjected to further evaluation by the physicians.

In our department, all the elective procedures were deferred indefinitely, the OTs were shut and no admissions were undertaken.

Safety guidelines in the department –

a. The department had minimal personal on duty which included one senior faculty, one resident and a house surgeon who worked on rotation basis
b. Doctors used PPE's such as N95 mask, face shield, gloves, and cap
c. Slit lamps were equipped with temporary protective barriers
d. Procedures which required close contact such as direct ophthalmoscopy and retinoscopy were deferred
e. Frequent sanitization of equipment, patient seating area, and consultation rooms were done
f. Ophthalmic examinations undertaken in the outpatient department preceded with history taking, anterior segment torchlight examination of the eyes followed by slit lamp examination. If indicated, posterior segment evaluation was done with indirect ophthalmoscopy after dilating the pupil with appropriate cycloplegics.

RESULTS

A total of 160 patients were examined in time period of 2 months, that is, March 23, 2020–May 23, 2020, out of which 77 were male and 83 were female [Figure 2].

Viral conjunctivitis constituted 32.5% (52/160). Bacterial conjunctivitis constituted 12.5% (20/160). Allergic causes of red eyes constituted 13.75% (22/160).

Trauma to the eye constituted 22.5% (36/160). Follow-up cases including post-operative were 6.87% (11/160).

Out of total number of viral conjunctivitis cases which were seen, 59.61% were seen during the Phase 1 of lockdown, that is, March 23– April 14, 2020, 28.84% during Phase 2 of lockdown, that is, April 15–May 3, and 11.53% during Phase 3 from May 4 onward [Figure 3].

Out of total number of bacterial conjunctivitis, cases which were seen 35.5% were seen during Phase 1 of lockdown, 30% during Phase 2, and 35% during Phase 3 of lockdown.

Allergic conjunctivitis – Phase 1 – 31.81%, Phase 2 – 18.18%, and Phase – 3.50%.

Trauma to eye – Phase 1 – 2.7%, Phase2 – 38.88%, and Phase 3 – 58%.

Follow-up cases including post-operative – Phase 1 – 9.10%, Phase 2 – 0%, and Phase 3 – 90.90%.

Other cases which were seen –

- Blepharitis – 1
- MGD – 2

- Chalazion – 2
- Optic neuritis – 1
- Dacryocystitis – 3
- Inflamed pterygium – 2
- Inflamed pinguecula – 1
- POAG – 1
- PACG – 1
- HMC – 1
- Papilledema – 1
- Preseptal cellulitis – 1
- Anterior uveitis – 1
- Corneal ulcer – 1

DISCUSSION

Coronavirus is positive-stranded RNA viruses with a crown-like appearance under an electron microscope (corona is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. The subfamily Orthocoronavirinae of the Coronaviridae family (order Nidovirales) [Figure 4].[13]

Common human CoVs: HCoV-OC43, and HCoV-HKU1 (beta CoVs of the A lineage); HCoV-229E, and HCoV-NL63 (alpha CoVs). They can cause common colds and self-limiting upper respiratory infections in immunocompetent individuals. In immunocompromised subjects and the elderly, lower respiratory tract infections can occur.[13]

These cause epidemics with variable clinical severity featuring respiratory and extrarespiratory manifestations.[13]

The epidemic of unknown acute respiratory tract infection broke out first in Wuhan, China, since December 12, 2019, possibly related to a seafood market. Several studies suggested that bat may be the potential reservoir of SARS-CoV-2 as an emerging acute respiratory infectious disease, COVID-19 primarily spreads through the respiratory tract, by droplets, respiratory secretions, and direct contact.[14]

Based on current epidemiological investigation, the incubation period is 1–14 days, mostly 3–7 days. Moreover, the COVID-19 is contagious during the latency period.[15] It is highly transmissible in humans, especially in the elderly and people with underlying diseases.

As it is designated SARS-CoV-2, COVID-19 patients presented certainly similar symptoms, such as fever, malaise, and cough.[16] Most adults or children with SARS-CoV-2 infection presented with mild flu-like symptoms and a few patients are in critical condition and rapidly develop ARDS, respiratory failure, multiple organ failure, and even deaths.[17] SARS-CoV-2 is capable of causing ocular complications such as viral conjunctivitis in the middle phase of illness.

Possible theories include direct inoculation of the ocular tissues from respiratory droplets or aerosolized viral particles, migration from the nasopharynx through the nasolacrimal duct, or even hematogenous spread through the lacrimal gland.

Patients infected with SARS-CoV-2 can present with symptoms of conjunctivitis, including eye redness, ocular irritation, foreign body sensation, tearing, and chemosis. These symptoms have more commonly affected patients with severe systemic symptoms of COVID-19, though they can rarely present as an initial manifestation of the disease.[18]

Examination findings include those consistent with mild follicular conjunctivitis, including unilateral or bilateral bulbar conjunctiva injection, follicular reaction of the palpebral conjunctiva, watery discharge, and mild eyelid edema. As with other viral infections, ocular manifestations of COVID-19 are presumed to be self-limited and can be managed with symptomatic care.

During the Phase 1 out of the total number of cases, there were more cases of viral conjunctivitis followed by bacterial conjunctivitis and allergic conjunctivitis.

There were Less trauma cases and no workplace injuries in this period.

During Phase 2, the viral conjunctivitis cases remained more followed by more number of trauma to the eye cases followed by bacterial conjunctivitis and allergic conjunctivitis. There were no follow-up cases of pseudophakia seen.

Phase 3 trauma cases were mostly followed by allergic conjunctivitis followed by follow-up cases and bacterial conjunctivitis and allergic conjunctivitis.

Treatment protocols followed during the lockdown period in our outpatient department were as follows –

1. Viral conjunctivitis – Topical steroids, for example, prednisolone/loteprednol/fluorometholone were given with antibiotic cover, for example, moxifloxacin/gatifloxacin/tobramycin 4–6 times/day depending on the severity of the inflammation. Lubricants were also added for about 4–6 times/day
2. Bacterial conjunctivitis – topical antibiotics along with lubricants 4–6 times/day depending on severity
3. Allergic conjunctivitis – antihistamine eye drops, for

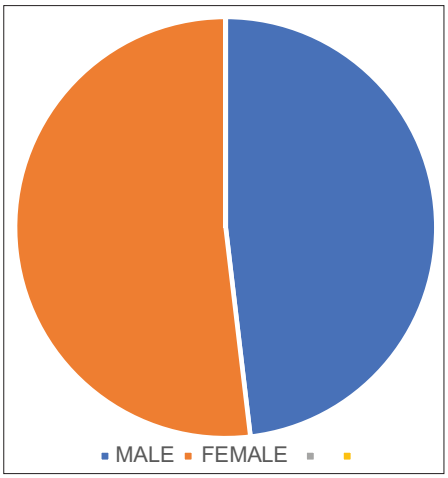

Figure 2: Gender distribution of the cases seen in the outpatient department during lockdown

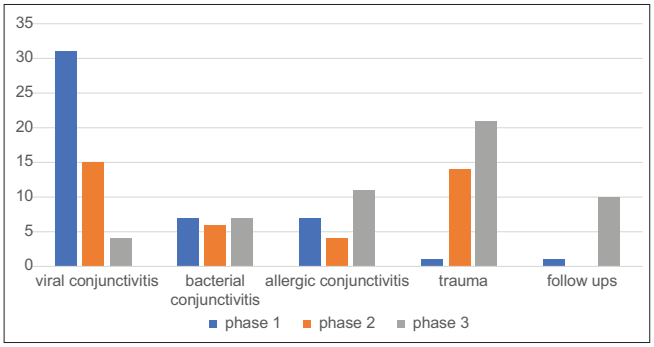

Figure 3: Number of cases according to the different phases of lockdown

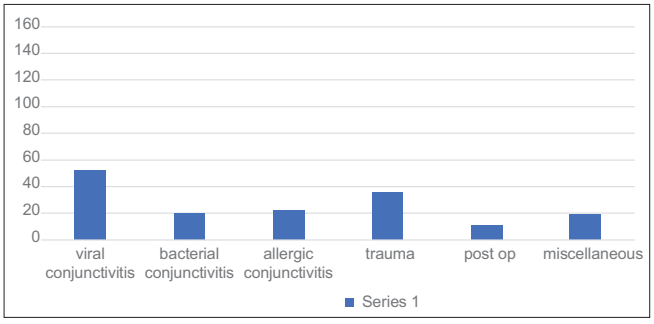

Figure 4: Types of cases visiting outpatient department during lockdown

example, olopatadine/bepotastine 2 times/day along with lubricants

In cases having vernal keratoconjunctivitis, immunomodulators such as tacrolimus or cyclosporine eye ointments were given 1–2 times/day.

4. Trauma – symptomatic treatment was given along with primary suturing done in cases where it was indicated taking adequate precautions under aseptic conditions.

As the lockdown was relaxed in different phases, trauma cases were more followed by follow-up cases which were very less in the first phase compared to second and third cases.

Due to non-availability of public transport during the initial phases on the lockdown (1 and 2), it could have been a contributory factor to the decrease in the number of cases visiting the outpatient department other than the fact that non-essential movements were restricted. As the public transportations gradually resumed in the latter half of the lockdown, there was a slight increase in the number of patients visiting the hospital.

The study done by Nair *et al.* stated that elective procedures such as cataract and refractive surgeries can be rescheduled to a later date while patients with sudden loss of vision, infections, and post-operative patients needed immediate care and intervention.[19]

CONCLUSION

Lockdown resulted in a decrease in the number of follow-up cases including post-operative cases to ophthalmology outpatient department.

Cases with infectious etiologies prevailed more during the lockdown mostly in majority during Phase 1 and Phase 2. Trauma cases spiked up during the second and third phases of lockdown due to relaxation given in lockdown period as work and day-to-day activities started resuming.

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Original Article

Significance of Magnetic Resonance Imaging of the Brain in Analyzing the Causes of Vertigo

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Abstract

Introduction: Vertigo is an incapacitating illness with a panorama of causes, ranging from benign to potentially life-threatening. The etiopathogenesis can remain elusive owing to the extensive differentials, which are usually tackled by a combination of clinical assessment and neuroimaging.

Objective: This study aims to investigate the role of magnetic resonance imaging (MRI) in the evaluation of causes of vertigo.

Settings and Design: This is a cross-sectional study of 100 patients conducted at the Department of Radiodiagnosis and Imaging, MGM Medical College and Associated Hospitals, Indore. MRI of 100 cases of vertigo were collected over 1 year and evaluated for a possible diagnosis. Variables were expressed as percentages, and statistical analysis was performed using SPSS v 24.0.

Results: MRI findings suggesting a probable cause of vertigo were seen in 79% of patients. These were broadly classified as central, peripheral, cervical, and others. Cervical spine abnormalities were the most common finding, seen in 35.44% cases, and categorized as cervical causes of vertigo. Pathologies involving the middle and inner ear comprised the peripheral causes and were the next most common abnormalities detected, accounting for 27.85% cases. Brainstem and cerebellar pathologies were bracketed as central causes of vertigo and accounted for 24.05% cases. Besides these, some MRI findings suggesting other plausible etiologies were grouped and accounted for 12.65% cases. There was a significant correlation between older age and an increase in central causes of vertigo. No gender variation was noted in vertigo patients in the present study.

Conclusion: This study indicates that MRI has a good diagnostic yield and can assess a multitude of pathological conditions in patients with vertigo. It can provide a probable cause of vertigo in most patients and accurately diagnose potentially life-threatening conditions needing immediate interventions such as strokes and intra-parenchymal bleeds.

Key words: Cervicogenic, Inner ear, Magnetic Resonance Imaging, Otogenic, Vertigo, Vestibulocochlear system

INTRODUCTION

Dizziness is a common complaint in medicine, with about 2.2% of patients consulting their physician per year for dizziness.[1] It is the ninth most common clinical symptom, third most common symptom among patients between the ages of 65 and 75 years, and the most common symptom among patients older than 75 years.[2] Patients may use an umbrella of terms to describe dizziness such as lightheadedness, vertigo, unsteadiness, disequilibrium, and so on. It is an alarming symptom for the patient and exasperating for physicians, as symptoms can be challenging to categorize owing to its subjective nature and a broad spectrum of differentials.[3]

Unlike other forms of dizziness, vertigo is characterized by the illusionary sensation of spinning, tilting, or translational motion. Vertigo is broadly classified based on etiology as central and peripheral vertigo. Central vertigo involves lesions of the brainstem and cerebellum such as vertebrobasilar ischemia or cerebellar stroke. These are relatively less common in presentation but can be life-threatening – for example, posterior fossa bleed. Peripheral vertigo involves the vestibulocochlear

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apparatus and is far more common and more severe than its central counterpart. Owing to their different natures, differentiating the central and peripheral causes is decisive to management.[4]

Diagnosis of vertigo can be challenging and often needs a thorough clinical assessment followed by neuroimaging. Computed tomography (CT) and magnetic resonance imaging (MRI) are two primary neuroimaging modalities used for the evaluation of vertigo. Both have their merits and demerits.

The purpose of this study was to assess the role of MRI in the evaluation of vertigo, specifically its utility in diagnosing the etiology of vertigo, such as central and peripheral causes.

MATERIALS AND METHODS

This was a hospital-based cross-sectional study done at the Department of Radiodiagnosis and Imaging, Mahatma Gandhi Memorial Medical College and Associated Hospitals, Indore, from July 2019 to July 2020. One hundred patients who underwent MRI for evaluation of vertigo were included in the study.

MRI brain was done as per vertigo protocol, and images were stored in a compact disc. Inclusion criteria were patients of age group 15–85 years with a chief complaint of vertigo. Patients with major complaints other than vertigo were excluded from the study.

MR studies were done by GE Signa Pioneer 3.0 T MR system with a dedicated head coil. The detailed MRI vertigo protocol included the following sequences: Axial T2, FLAIR, pre and post-contrast T1, DWI, 3D SWI, coronal T2, sagittal T1, 3D FIESTA in the posterior fossa, 3D TOF circle of Willis, and T2 sagittal cervical spine screening. Two observers independently analyzed MRIs to determine the cause of vertigo, and the results were grouped under four major categories according to their etiology, namely central, peripheral, cervicogenic, and others. Central causes included lesions of the brainstem and cerebellum; otogenic causes were grouped in the peripheral category. Cervicogenic causes were evaluated after excluding central and peripheral causes. All other causes not falling into either category were grouped separately as "others."

Data was analyzed using SPSS v 24.0. Variables were expressed as percentages, and Fisher's exact test was used to evaluate the association. Two-tailed $P < 0.05$ was considered statistically significant for all the tests.

RESULTS

Composition of the study group

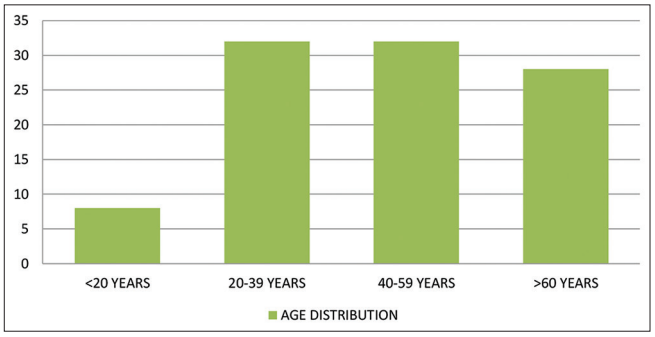
- One hundred cases of vertigo were included in our study, of which 48 (48%) were females and 52 (52%) were males
- Ages of patients in the study ranged from 13 to 83 years. The average age of our study group was 44.75 Years [Graph 1].

MRI abnormalities suggesting probable causes of vertigo were seen in 79 patients (79%).

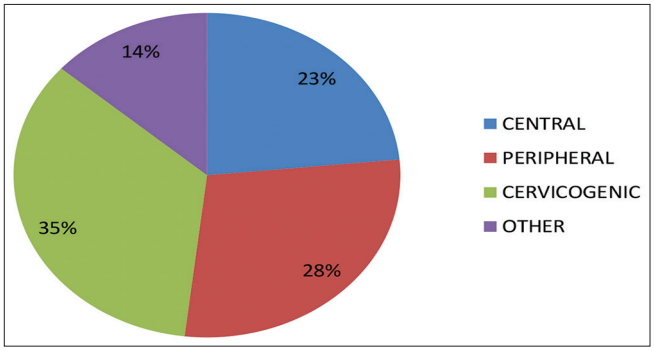
- Causes of vertigo were broadly grouped into four categories – central, peripheral, cervicogenic, and others. Cervicogenic causes were the most common, accounting for 35.44 % of cases, followed by peripheral causes, which constituted 27.85% of cases. Central causes were seen in 24.05 % of cases, and other causes constituted the remaining 12.65 % cases [Graph 2].

Impact of age on causes of vertigo

- There was a significant correlation between central causes of vertigo and increasing age ($P < 0.001$), with central causes of vertigo being the most common cause in patients of age >60 years



Graph 1: Age composition of the study population. The study population was homogeneously distributed in the range of 20–85 years. Patients <20 years constituted the least percent of the study group



Graph 2: Causes of vertigo in the present study. Cervicogenic causes were the most common causes of vertigo, followed by peripheral causes in our study

- Cervicogenic vertigo was rarely seen in patients of age <20 years, suggesting a possible association between cervical spondylosis and cervicogenic vertigo. [Graph 3].

Central Causes of Vertigo

- Acute infarcts involving the brainstem or cerebellum were the most common causes of central vertigo, accounting for 42.10% of all cases
- Neoplasms were the second most common cause constituting 27.78% cases. Brainstem glioma, acoustic schwannoma, CP angle meningioma, and CP angle epidermoid cyst were causes observed in this study
- Posterior fossa bleeds, a potentially life-threatening cause, were seen in 10.52 % cases
- Infective and inflammatory causes such as tuberculomas and neurocysticercosis accounted for 10.52% cases
- The primary cause of demyelination was multiple sclerosis, which was observed in 5.27% of cases
- A rare cause of central vertigo observed in this study was Lhermitte–Duclos disease, seen in 5.27% cases [Graph 4].

Peripheral Causes of Vertigo

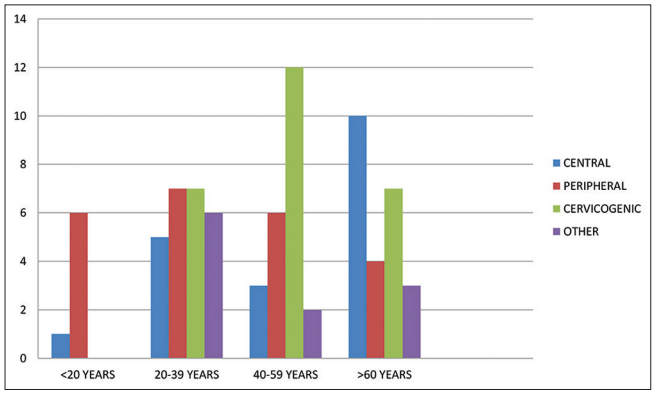
- The most common cause of peripheral vertigo observed in our study was ectatic vascular loops entering IAC, especially AICA, causing neurovascular conflict, accounting for 54.54% cases
- Otogenic infection/inflammation, which included vestibular neuritis, otitis media, and mastoiditis, accounted for 40.91% cases
- Endolymphatic hydrops was observed in 1 patient, constituting 4.54 % of peripheral vertigo causes [Graph 5]
- Grade I conflict of AICA in IAC was the most common form seen, accounting for 66.67% cases followed by Grade II, which comprised 25% cases. Grade III was the least common form, seen only in 8.34% cases [Graph 6].

Cervicogenic Vertigo

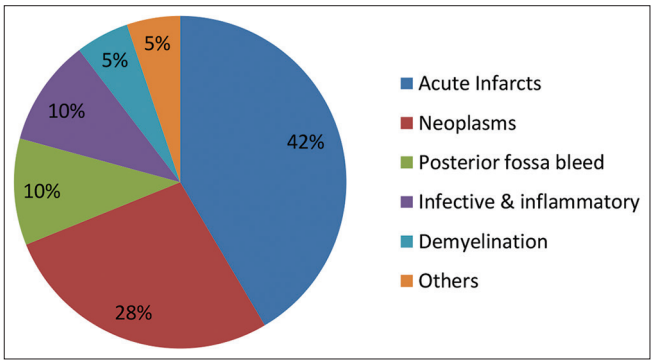
- Cervical spine pathologies were the most common MRI findings observed in our study, accounting for 35% cases. These comprised cervical spondylosis (64.28%), block vertebrae (17.85%), cervical spasm (10.71%), and craniovertebral junction (CVJ) anomalies (7.14%) [Graph 7].

Other Causes

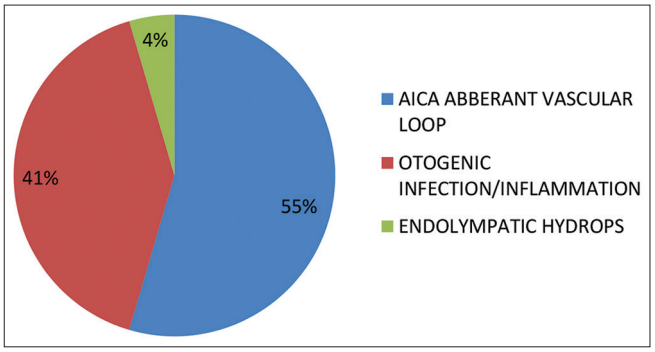
- Besides these three major causes of vertigo, some other MRI findings suggesting a probable cause were observed in 12.65 % cases, most common of these were vertebrobasilar artery anomalies seen in 6 patients (60%) [Graph 8]
- Unilateral hypoplastic vertebral artery was the most common vertebrobasilar circulation anomaly observed in the present study, accounting for 66.67% of cases [Graph 9]



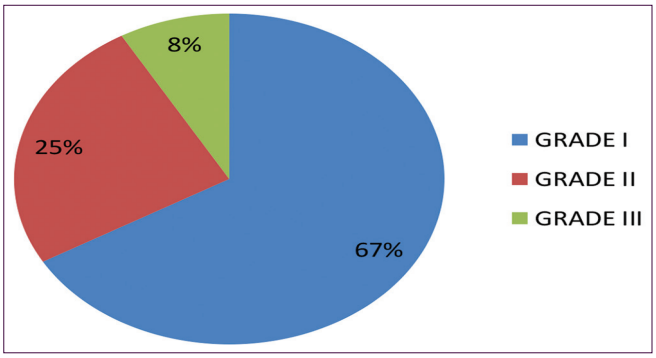
Graph 3: Impact of age on causes of vertigo. Cervicogenic causes were not observed in the age group of < 20 years. Central causes were the most common causes observed in the age group of 60 years and above



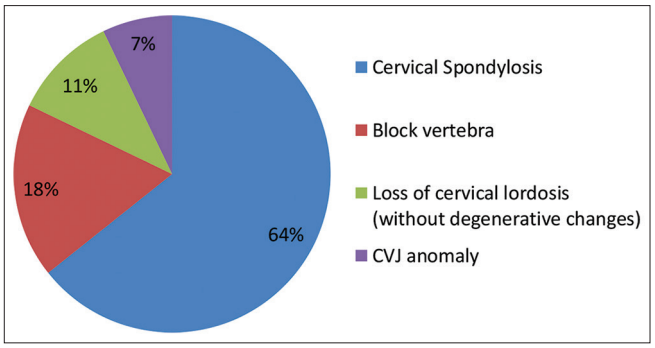
Graph 4: Magnetic resonance imaging (MRI) finding indicating central causes of vertigo. Acute infarcts were the most common MRI finding indicating central cause of vertigo observed in the present study, followed by neoplasms



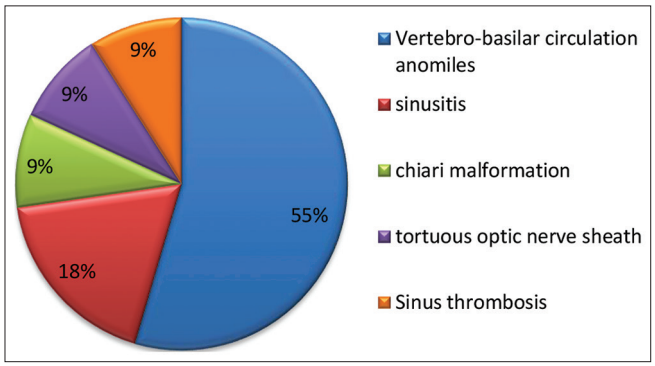
Graph 5: Magnetic resonance imaging (MRI) findings denoting peripheral causes of vertigo. Aberrant vascular loop of AICA was the most common finding among MRI findings denoting peripheral causes of vertigo, followed by otogenic infection/ inflammation



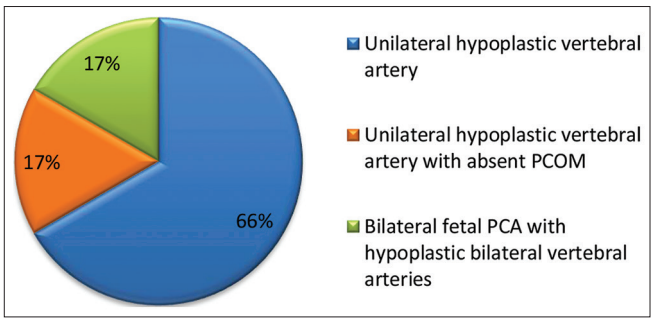
Graph 6: Grades of AICA neurovascular conflict in IAC in the present study. Grade I neurovascular conflict was most common followed by Grade II and Grade III, respectively



Graph 7: Magnetic resonance imaging (MRI) findings indicating cervical causes of vertigo. Cervical spondylosis was the most common MRI finding depicting cervical causes of vertigo



Graph 8: Magnetic resonance imaging findings in otherwise unclassified vertigo depicting a probable cause



Graph 9: Vertebrobasilar circulation anomalies observed in the present study

- Potentially life-threatening causes of vertigo requiring immediate intervention were found in 10 % cases in the present study. These included acute brainstem and cerebellar infarcts (80%) and posterior fossa bleeds (20%)
- Rare causes of vertigo in our study included Chiari Malformation, Lhermitte–Duclos disease, CP angle AVM, and cerebral venous sinus thrombosis.

DISCUSSION

Vertigo is a commonly encountered medical condition with an extensive spectrum of causes, ranging from essentially benign to potentially life-threatening. Owing to its plethora of etiologies, few of which are still not fully understood, it can often be a challenging diagnosis.

The prevalence of vertigo is estimated to be 1.8% in young adults, which increases to 30% in the elderly. Although initially purported to be more common in females, recent studies indicate a more gender-neutral distribution of vertigo.[5] Our study group comprised 52% males and 48% females, suggesting no significant gender variance.

Evaluation of vertigo usually entails thorough clinical assessment followed by laboratory tests and neuroimaging to reach onto a possible cause. Two significant neuroimaging modalities used in the evaluation of vertigo are CT and MRI. Head CT has the advantage of being immediately and widely available and may be used to rule out specific life-threatening causes such as posterior fossa bleed and acute cerebellar stroke. High-resolution computed tomography of the temporal bone is another modality which has the advantage of allowing detailed evaluation of bony labyrinth and can effectively diagnose specific middle ear and inner ear pathologies such as labyrinthitis ossificans, semi-circular canal dehiscence, and fractures in post-traumatic vertigo.[5,6]

Although CT provides a quick diagnosis, it is not very sensitive and has a low diagnostic yield in vertigo.[7] CT is also known to have low sensitivity for both posterior fossa pathology and for ischemic strokes (26% compared with 83% of MRI), which are a common cause of central vertigo and potentially life-threatening.[8]

With the advent of 3D CISS, the old dictum stating the use of CT for peripheral and MRI for imaging of central causes of vertigo also fails. The superior sensitivity of MRI and its lack of non-ionizing radiation make it a better modality for evaluating vertigo.[9,10]ACR appropriateness criteria also support this wherein CT scan for vertigo is rated 5 on a scale of 1–9, indicating it "may be appropriate," while MRI is rated 7, or "usually appropriate."[11]

Many studies have been performed on the diagnostic yield of MRI, which reinforce that diagnostic yield can be attributed to appropriate patient selection and appropriate clinical referral. Lawhn-Heath *et al.* concluded in their study on the role of neuroimaging in evaluating vertigo in the emergency department that MRI plays a key role in evaluating vertigo with appropriate case selection.[5] In their study on diagnostic yield and impact of MRI for acute ischemic stroke in patients presenting with vertigo, Kabra *et al.* concluded that the presence of predictors of acute ischemic stroke aid in patient selection for MRI, to increase diagnostic yield.[10] Likewise, in their study on the diagnostic value of MRI in acute vertigo of undetermined origin, Huang *et al.* concluded that the diagnostic yield of cranial MRI is low for vertigo of undetermined origin.[12]

In the present study, MRI showed some abnormalities suggesting a possible cause for vertigo in 79% cases. This can be attributed to proper patient selection and referral criteria. ACR appropriateness criteria are routinely used to assess patients needing further imaging based upon onset, duration, persistence, aggravating factors, and clinical testing.[11]

In our study, the MRI findings were grouped under four major categories according to their etiology, namely central, peripheral, cervicogenic, and others.

Central Vertigo

Epidemiological studies indicate that central causes are responsible for nearly one-fourth of cases of vertigo. In our study, central causes were implicated in 27.85% of cases, which agrees with the general population prevalence.[13] Central vertigo customarily has milder symptoms than peripheral vertigo and is not usually associated with hearing loss and tinnitus. Furthermore, ataxia is frequently present in central vertigo and rarely seen in peripheral vertigo. Although central vertigo has a milder presentation, pathology masquerading behind it usually has a more unfavorable prognosis than peripheral vertigo.[14]

The majority (42.1%) of central vertigo cases in the present study were due to acute infarcts involving the brainstem and cerebellum [Figure 1]. In their study on the differential diagnosis of stroke in an emergency department, Vanni *et al.* concluded that the most common causes of central vertigo were ischemic strokes, which is in keeping with the results of our study.[15] Acute strokes presenting with vertigo are often diagnostic pitfalls and may be missed, especially cerebellar strokes, which do not present with motor deficits.[16] MRI being the most sensitive imaging modality to diagnose acute strokes plays an integral part in their management. In their study on diagnostic yield and impact of MRI for acute ischemic stroke in patients presenting with vertigo, Kabra *et al.* reported the diagnostic impact of MRI on management to be 21%.[10]

Neoplastic lesions were the second most common cause of central vertigo in our study, accounting for 27.78% cases. The neoplasms noticed in our study were brainstem glioma, cerebellopontine angle masses such as acoustic schwannoma, epidermoid, and meningioma [Figure 2]. This is similar to the results of the study by Karatas on epidemiology, differentials, and common causes of central vertigo in which they listed acute infarcts and neoplasms as predominant causes.[13]

Vertigo also happens to be one of the most common clinical presentations in CP angle tumors. In their study on cerebellopontine angle tumors, Jawad *et al.* reported that the most common presentation of CP angle tumors was vertigo, followed by tinnitus.[17] Cacho-Díaz *et al.* performed a study on vertigo in patients with cancer. They concluded that vertigo accompanied by headache and ataxia in a cancer patient should prompt evaluation for cerebral metastasis.[18]

Posterior fossa bleeds involving the cerebellum were also among the causes of central vertigo observed in our study [Figure 3]. Although vertigo may be associated with posterior fossa bleed, it is not the most common symptom. Posterior fossa arteriovenous malformation near the cerebellopontine angle was a rare cause of central vertigo observed in the present study [Figure 4]. Argaet *et al.* have described one such similar case of cerebellar AVM, causing vertigo in their study.[19]

Tuberculomas and neurocysticercosis involving posterior fossa have been known to cause vertigo.[20] Rarely vertigo can be one of the earliest features of MS.[21] In our study, infective and inflammatory lesions, which included tuberculoma, neurocysticercosis, and multiple sclerosis, accounted for 15.79% causes of central vertigo [Figures 5 and 6].

One case of Lhermitte–Duclos disease was among the rare causes of central vertigo in our study[22] [Figure 7].

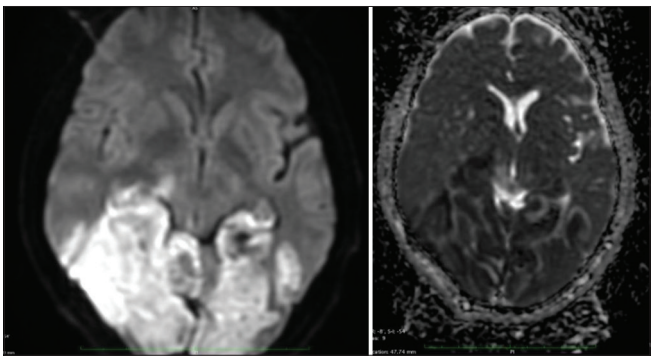


Figure 1: Diffusion-weighted magnetic resonance imaging images with corresponding ADC map showing a large posterior circulation infarct involving cerebellum and parieto-occipital cortex

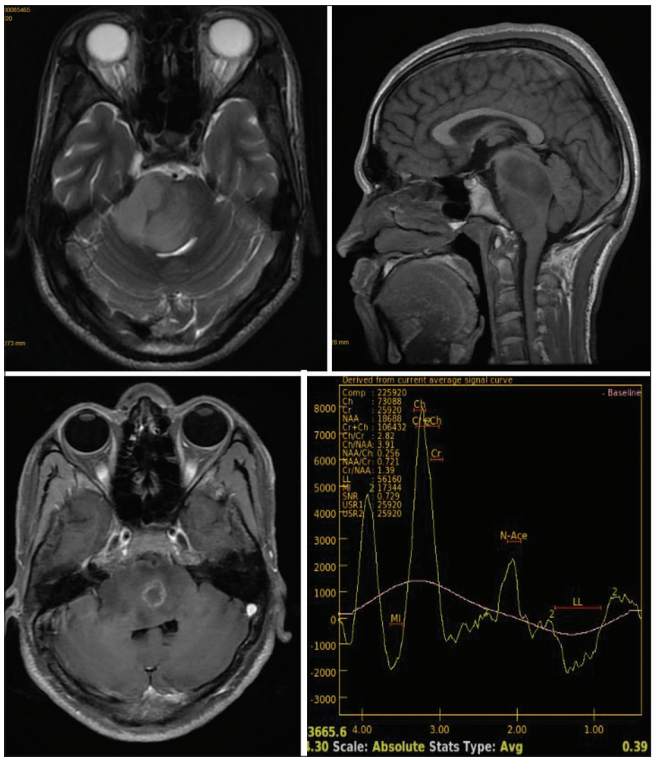


Figure 2: Axial T2, sagittal and axial T1 fat saturated pre and post contrast MR images showing a large T1 & T2 hypointense, heterogeneously enhancing lesion involving and expanding the brainstem. MRS shows choline peak, which is suggestive of brainstem glioma

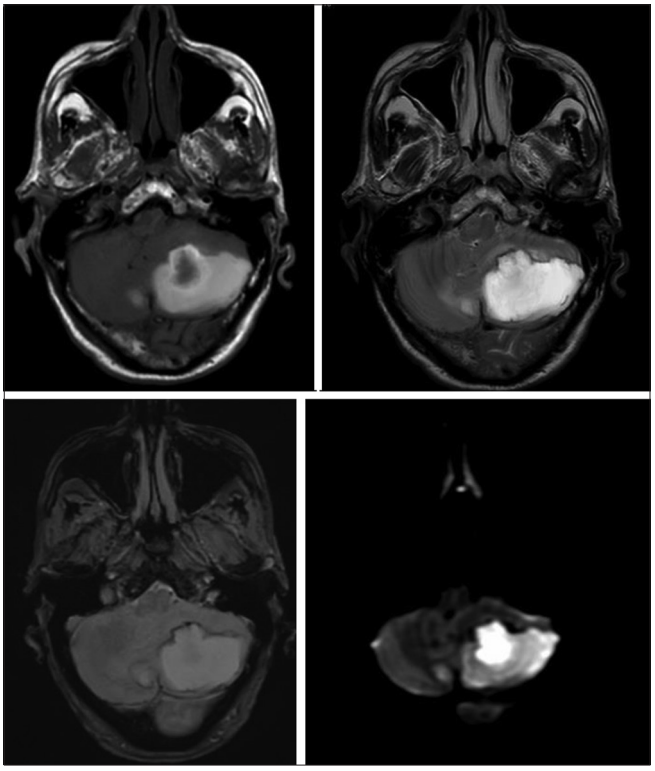


Figure 3: Axial FLAIR, T1, SWI and diffusion weighted MR images showing a large hyperintense lesion in the left cerebellar hemisphere with blooming on SWI and areas of restricted diffusion on DWI images, which is suggestive of subacute cerebellar hemorrhage

A significant correlation was found between central causes of vertigo and increasing age in the present study, with central causes of vertigo being the most common cause in patients of age >60 years. These findings are similar to the results of the study by Shahrami *et al.* on the epidemiology of vertigo, indicating an increased prevalence of central causes in patients aged 60 years and more.[23]

Peripheral Vertigo

Peripheral causes of vertigo were observed in 27.85 % cases. Although peripheral vertigo is very common, the lower incidence in our study may be because the most common cause of peripheral vertigo, which is benign positional paroxysmal vertigo, has no radiological abnormality. Furthermore, in our research, cervicogenic causes were grouped separately from peripheral causes, further lowering the number of cases.[24-26]

The most common peripheral cause of vertigo in our study was the aberrant vascular loop of AICA in IAC, which constituted 54.54% cases, followed by otogenic infection and inflammation, which accounted for 40.91 % cases [Figure 8]. Endolymphatic hydrops was the least common cause in our study, with only 4.54% cases. These findings are comparable to study on neuroimaging in vertigo by Katta in which they concluded cerebrovascular conflicts were one of the most common causes of peripheral vertigo.[27]

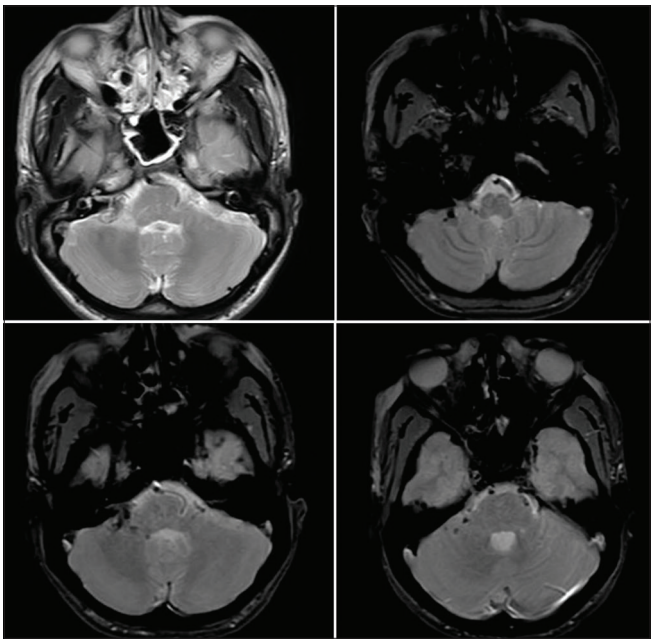


Figure 4: Axial T2 and SWI images showing an abnormal tangle of vessels in the right cerebellopontine angle cistern and inferior cerebellar peduncle – suggestive of arteriovenous malformation

The cerebellopontine angle contains AICA and VII and VIII cranial nerves in close proximity. AICA has a spectrum of normal variants, including variation in number, course,

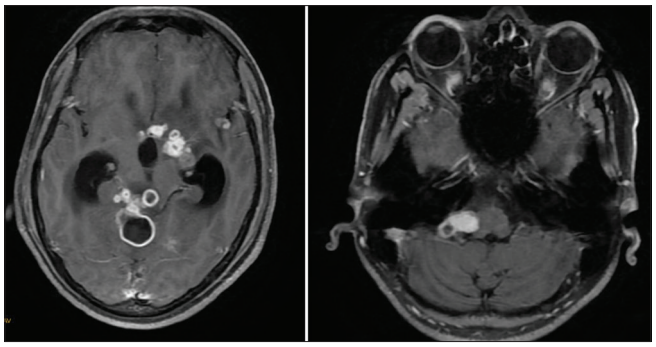


Figure 5: Post-contrast fat-saturated T1-weighted magnetic resonance images showing multiple intra- axial as well as extra-axial peripherally enhancing lesions involving brainstem, left temporal region, ambient cistern, and cerebellopontine angle in known case of central nervous system tuberculosis

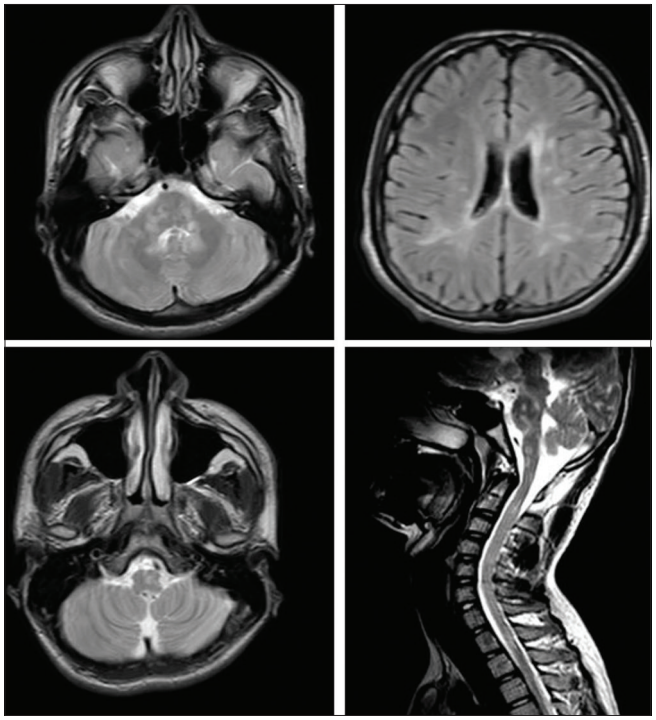


Figure 6: Axial T2 and FLAIR sections of brain and sagittal T2 section of cervicodorsal spine showing multiple variable-sized T2/FLAIR hyperintensities in a patient of multiple sclerosis

and aberrant looping. AICA can compress VIII cranial nerve at CP angle or inside IAC.[28,29] The grading of this neurovascular conflict is customarily done by Chavda classification. The Chavda classification grades the AICA vascular loops as follows: Grade I – when an AICA vascular loop borders the internal auditory meatus but does not enter the internal auditory canal, Grade II – when the loop insinuates itself into the internal auditory meatus but occupies 50% or less of the canal, or Grade III – when the loop occupies more than 50% of the canal.[30-32]

Grade I was the most common grade of AICA loop observed in the present study, accounting for 66.67

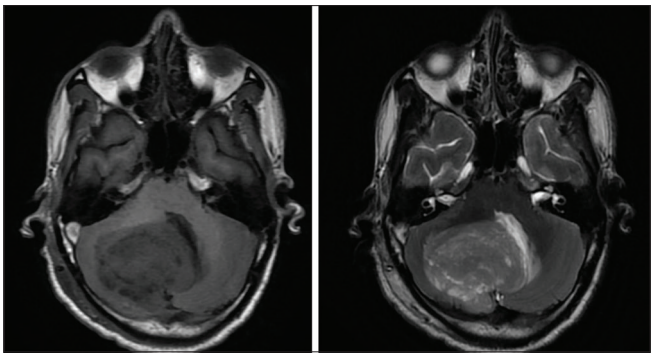


Figure 7: Axial T1 and T2 WI images of brain showing T1 hypointense and T2 hyperintense lesion in the right cerebellar hemisphere with widened cerebellar folia in disarray giving "tigroid appearance" – suggestive of Lhermitte–Duclos disease

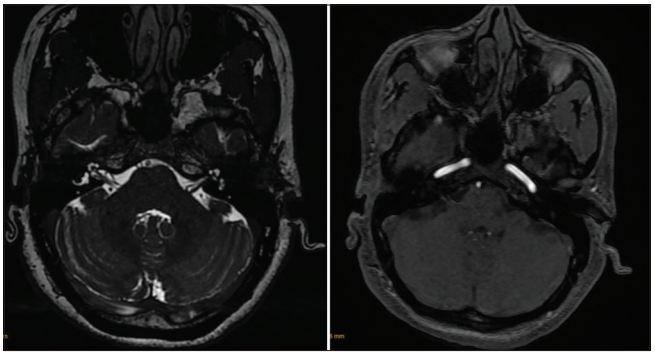


Figure 8: Axial 3D CISS and 2D TOF image showing an aberrant vascular loop of AICA traversing nearly 50 % length of IAC – suggestive of Grade II AICA neurovascular conflict

% cases, followed by Grade II, which comprised 25% cases. Grade III was the least common type accounting for 8.34% cases. These results are similar to findings of studies by Reka *et al.* and Kim *et al.* on the relationship between AICA variation and neurological symptoms, wherein, individually, they reported Grade I AICA loop as the most common variant followed by Grade II and III, respectively.[33,34]

Cervical Vertigo

Cervical vertigo is another perplexing entity. There are inconclusive data on its etiopathogenesis, but it is general agreement that its vertigo associated with various neck pathologies and provoked by a particular neck posture, no matter what the orientation of the head is to gravity. It is a poorly understood and controversial entity. Some studies advocate the inclusion of cervicogenic vertigo into peripheral vertigo, but some studies indicate otherwise, as the etiology is unclear.[35-37]

A few of the proposed etiopathogenesis mechanisms include abnormal sensory information from damaged joint receptors of cervical vertebrae, diseased cervical intervertebral discs, and tense neck muscle spindles, which

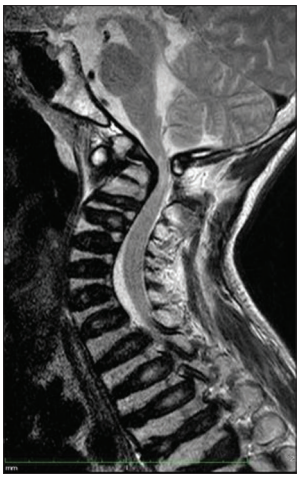


Figure 9: Sagittal T2-weighted magnetic resonance imaging image showing a smooth well-corticated ossicle superior to hypoplastic dens, suggestive of Os odontoideum. Visualized cervical and thoracic vertebrae are flattened craniocaudally indicating platyspondyly

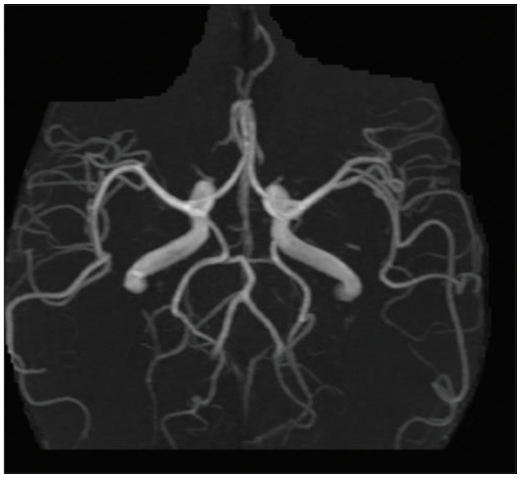


Figure 10: Magnetic resonance angiogram showing hypoplastic bilateral vertebral arteries with bilateral fetal posterior cerebral arteries

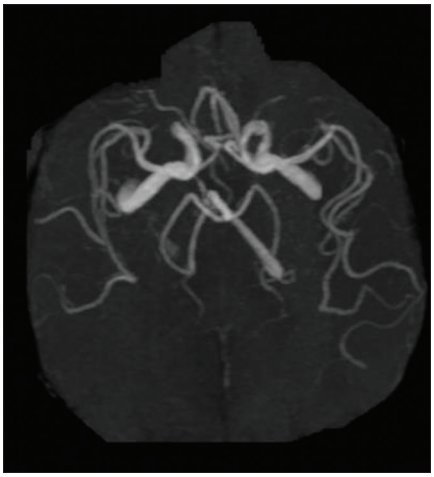


Figure 11: Magnetic resonance angiogram image showing hypoplastic right vertebral artery with absent bilateral posterior communicating arteries

are misinterpreted in the vestibular system; this mismatch resulting in vertigo.[38,39]

In keeping with these theories, the most common cause of cervical vertigo observed in our study was cervical spondylosis, which accounted for 64.28% cases, followed by block vertebrae, which were seen in 17.85% cases. The straightening of cervical spine, probably due to muscle spasm, was the third most common cause comprising 10.71% of cases. CVJ anomalies were the least common causes, accounting for 7.14% cases [Figure 9].

These findings are consistent with the study by Hain in which cervical spondylosis is implicated as one of the common causes.[40] Cervical causes were the most common radiological finding in our study, accounting for % cases. This is also similar to the results of a study by Rai *et al.* in which they reported cervical spondylosis as the most common finding in MRI of vertigo patients.[25]

Other Causes

Besides these three important classes, various other minor causes can be implicated in causing vertigo. Some of the critical MRI findings in these were vertebrobasilar anomalies, which were seen in 60 % of cases of other causes of vertigo.

It has been hypothesized that variations in vertebrobasilar circulation can cause transient brainstem or cerebellar ischemia and result in vertigo, much like transient ischemic attacks. Paksoy *et al.* concluded in their study that a significant association existed between vertigo and anomalies in the vertebrobasilar system. In keeping with this, variations in vertebrobasilar circulation were included in other causes of vertigo.[41] In our study, 60% of unclassified vertigo cases had vertebrobasilar system anomalies, most common of them being unilateral hypoplastic vertebral artery (66.67%). One patient had hypoplastic bilateral vertebral arteries and bilateral fetal posterior cerebral artery bilateral fetal posterior cerebral arteries [Figures 10 and 11].

In their research titled frequency of sinusitis in brain MRI in vertigo, Golshiri *et al.* described that sinusitis was present in 17% vertigo cases. In their study on vestibular characteristics of patients with chronic sinusitis, Brody-Camp *et al.* concluded that the pathophysiological relationship between sinusitis and vertigo is unclear and warrants further studies. In our study, in vertigo with undetermined cause, 20% of patients had sinusitis.[42,43]

In cases of the undetermined cause of vertigo, few other MRI findings were Arnold Chiari type I, cerebral venous sinus thrombosis, and tortuous bilateral optic nerve sheaths.[44-46]

CONCLUSION

Vertigo is a complex incapacitating illness with an umbrella of differentials tackled by a combination of clinical examination and neuroimaging. MRI plays a key role in the evaluation of vertigo as it can diagnose a spectrum of underlying pathologies and give a clue regarding the probable cause in most of the cases. It is especially important in assessing cerebellar and brainstem strokes, which can be easily overlooked in a head CT. All these collaborate to make MRI an essential tool in guiding the management of vertigo patients.

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Original Article

Cytology, Histology, and Imaging Correlation in the Plethora of Thyroid Lesions from a Tertiary Care Center

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Abstract

Introduction: Fine needle aspiration cytology (FNAC) has a pivotal role in evaluating the lesions of the thyroid. Although FNAC has distinct advantages, it has limitations too. This study was done to correlate the FNAC findings of thyroid lesions with thyroid imaging reporting and data systems classification on ultrasound and histopathological findings. We also evaluated the discordant cases and analyzed them.

Materials and Methods: Our study is a retrospective analysis of 179 cases of thyroid nodules over a period of 3 years from April 2016 to April 2019. The FNAC findings were reviewed. These data were compared with the histopathological and imaging findings and analyzed.

Results: Cytohistological correlation was done in 179 cases, 94 benign cases and 85 malignant lesions. The mean age of presentation of discordant cases was 43.2 years with male:female ratio of 1:3.8. Concordance was noted in 84% cases and discordance was noted in 15.6%, respectively. Reasons of discordance included sampling error in 11 (6.1%) cases, cystic nature of the lesion in 12 (6.7%) cases, and interpretation error/nature of the lesion in 5 (2.8%) cases. The sensitivity and specificity of FNAC was 58.3% and 100%, respectively. The positive predictive value was 100% and negative predictive value was 71.5%. Accuracy of FNAC in differentiating benign from malignant thyroid lesion was 79.6%.

Conclusion: FNAC of thyroid nodules provides the most accurate pre-operative diagnosis. It is a minimally invasive procedure and hence considered as a gold standard diagnostic tool in the evaluation of thyroid nodules. Nature of the disease, experience of the cytopathologist, and the understanding of certain limitations determine its diagnostic utility. Thus, the Bethesda system of reporting thyroid cytology should be meticulously followed to minimize these errors and a repeat FNAC asked for in discordant cases after a multidisciplinary team conference.

Key words: Bethesda system, Fine needle aspiration cytology, Follicular lesions, Papillary carcinoma, Thyroid lesions

INTRODUCTION

The incidence of clinically apparent thyroid swellings in the general population is 4–5%.[1] Thyroid lesions can present as a diffuse enlargement, solitary or multiple nodules. Fine needle aspiration cytology (FNAC) is a simple, safe, reliable, and cost-effective tool with a high degree of sensitivity and specificity for detecting malignancies.[2] It is considered the first line of investigation in the clinical evaluation of thyroid nodules. However, limitations of FNAC include technical factors (skills of the performing expert, inadequate sampling) and pathological factors (cystic lesions). We studied the spectrum of thyroid lesions and analyzed the cytohistological and histology-imaging discordance.

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OBJECTIVE

The objective of the study was as follows:

1. To study the spectrum of thyroid lesions
2. To correlate the FNAC findings with histopathology of excised specimens

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3. To study the imaging and pathological discordance in thyroid lesions.

MATERIALS AND METHODS

Our study is a retrospective analysis of 179 cases of thyroid nodules over a period of 3 years from April 2016 to 2019 from a tertiary care hospital. Ethical clearance was obtained (IEC No: CSP-MED/19/JAN/49/04). FNAC and histopathology slides were reviewed, double-blinded and reported by two independent observers. These data were documented and analyzed. Imaging findings were also reviewed and documented.

Inclusion Criteria

All patients who presented with thyroid swellings, irrespective of age, and who have undergone FNAC followed by surgery were included in the study. Exclusion criteria – patients in whom either one (FNAC/histopathology/Imaging findings) was not available were excluded from the study.

RESULTS

A total of 179 patients were included in the study, of which 142 were females and 37 were males with a male:female ratio of 1:3.8. Age of the patients ranged from 19 to 71 years, with a mean age of 43 years. Mode of the clinical presentation was either a nodule or a diffuse enlargement in front of the neck. Thyroid imaging reporting and data systems (TIRADS) classification was followed according to The American College of Radiology (ACR) to determine the risk of cancer in thyroid nodules.[3] According to the ACR classification, TIRADS 1 – Normal thyroid gland; TIRADS 2 – Benign lesion; TIRADS 3 – Probably benign lesions; TIRADS 4 – Suspicious lesions; TIRADS 5 – Probably malignant lesions; and TIRADS 6 – Biopsy proven malignancy.

Total thyroidectomy was performed for 87 cases, right hemithyroidectomy for 47 cases, and left hemithyroidectomy for 45 cases. By histopathology, 94(52%) cases were benign and 85 (47.4%) cases were malignant. Cytohistology correlation was seen in 151 (84%) cases and non-correlation was observed in 28 (15.6%) cases [Table 1]. Reasons for discordance were mainly due to inadequate sampling and cystic nature of the lesion.

Cytohistology correlation along with the radiological analysis was done for all the 28 cases of discordance. The mean age of presentation of discordant cases was 43.2 years with male:female ratio of 1:4.6. Out of 28 discordant cases, only 3 cases (10.7%) had undergone ultrasonogram (USG)-guided FNAC. On imaging, TIRADS 3 and 4 categories had the maximum discordance [Table 2]. Most malignant cases were misdiagnosed as Bethesda II category. Reasons of discordance included sampling error in 11 cases (6.1%), cystic nature of the lesion in 12 cases (6.7%), and interpretation error/nature of the lesion 5 cases (2.8%). Among the discordant cases, follicular lesions were noted in 16 cases (57.1%), papillary carcinoma in 9 cases (32.1%), papillary microcarcinoma in 2 cases (7.1%), and medullary carcinoma in 1 case (3.5%).

Table 1: Clinicopathological profile of the thyroid lesions

1. Bethesda category diagnosis	Number of cases	Percentage
II Benign	103	57.5
III Atypia of undetermined significance	5	2.7
IV Follicular neoplasm	6	3.3
V Suspicious for malignancy	17	9.4
VI Malignant	24	13.4
Suboptimal	7	3.9
2. Histopathology diagnosis	**Number of cases**	**Percentage**
Benign	85	57
Malignant	64	42
3. Age distribution	**Number of cases**	**Percentage**
<20 years	2	1
21–40 years	78	44
41–60 years	85	47
>60 years	14	8
4. Sex	**Number of cases**	**Percentage**
Males	37 cases	20
Females	142 cases	72

Below are three selected cases of discordance with valuable learning points.

Case 1 – 50 years female presented with a swelling in front of the neck, a TIRADS 3 lesion measuring 3.5 cm × 2.7 cm × 5.4 cm was noted on imaging. Ultrasound of the thyroid showed a well-defined wider than taller mixed solid cystic nodule with few macrocalcifications and increased internal vascularity. Nine milliliters of colloid were obtained. FNAC showed thyroid follicular epithelial cells in a background of thick and thin colloid, Bethesda II category. Final histopathological diagnosis was given as medullary carcinoma of the thyroid [Figure 1].

Case 2 – 36 years female presented with a solitary nodule, a TIRADS 3 lesion with cystic changes measuring 4.3 cm × 2.4 cm × 3.6 cm was noted on imaging. Ultrasound showed an ill-defined mixed solid cystic wider than taller nodule in the left lobe of thyroid with a macrocalcification. FNAC suggested a Bethesda II category lesion. Histopathological diagnosis was papillary carcinoma of thyroid, classic type [Figure 2].

Table 2: Analysis of discordant cases

Discordant cases number	Female	Male	Mean age	Sampling error	Cystic nature of the lesion	Others (Interpretation error)	TIRADS classification	Bethesda category
28	23	5	43.2	11 (6.1%)	12 (6.7%)	5 (2.8%)	TIRADS 3: (12/28) 42% TIRADS 4: (16/28) 57%	All cases belonged to Bethesda II category

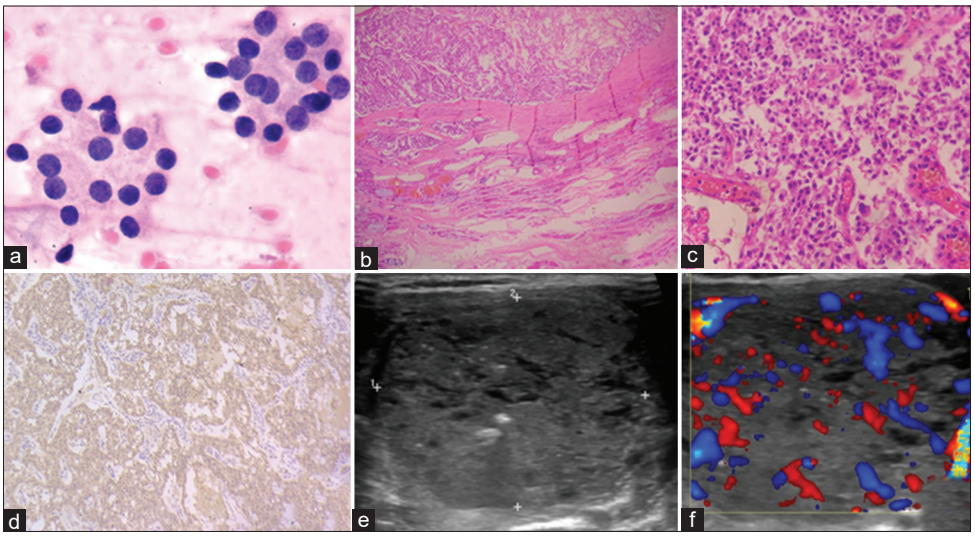

Figure 1: (a) ×40, fine needle aspiration cytology shows thyroid follicular epithelial cells in a background of thick and thin colloid. (b) H&E, ×4 shows sheets of tumor cells. (c) H&E, ×40 shows round, plasmacytoid cells in nests with fine stippled chromatin separated by capillaries. (d) IHC, ×4, synaptophysin positivity noted. (E and F) High-frequency ultrasound of thyroid shows a well-defined wider than taller mixed solid cystic nodule in the left of thyroid with few macrocalcifications and increased internal vascularity

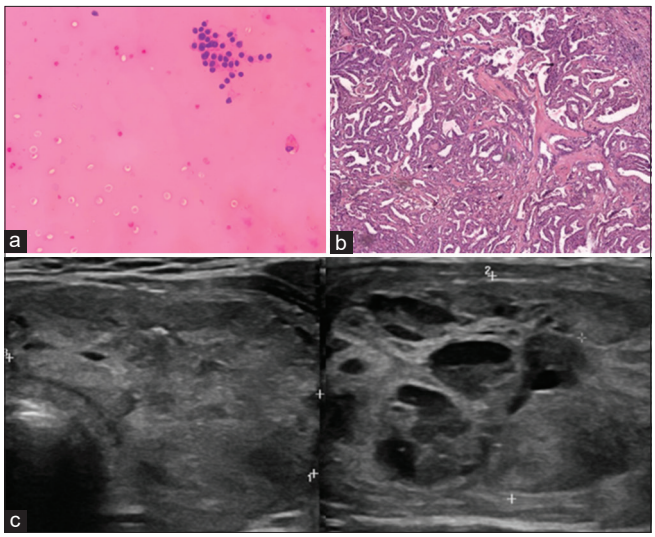

Figure 2: (a) ×10, fine needle aspiration cytology shows scattered thyroid follicular cells with cyst macrophages in background colloid. (b) H&E, ×10, tumor cells arranged in papillary pattern with nuclear features of papillary carcinoma. (c) Ultrasound of thyroid shows an ill-defined, mixed solid cystic wider than taller nodule in the left lobe of thyroid with a macrocalcification

Case 3 – 28 years male presented with a solitary nodule in the front of the neck. A TIRADS 3 lesion was noted with a cystic area within the nodule measuring 3.4 cm × 2 cm × 3 cm. Ultrasound showed a tall well-defined hypoechoic wider than taller solid nodule in the right lobe of thyroid with increased internal vascularity and no calcifications. FNAC showed thyroid follicular cells with few showing Hurthle cell change and hemorrhage, suggesting a Bethesda II category lesion. Histopathological diagnosis was given as follicular variant of papillary thyroid carcinoma (PTC) [Figure 3].

Statistical analysis was done using SPSS software. The sensitivity and specificity of FNAC in diagnosing malignancy was 58.3% and 100%, respectively. Positive predictive value was 100% and negative predictive value was 71.5%. Accuracy of FNAC in differentiating benign from malignant thyroid lesion was 79.6%.

For radiologically evaluated TIRADS category, the sensitivity and specificity was 59.7% and 100%, respectively. Positive predictive value was 100% and negative predictive value was 72.4%. Accuracy of TIRADS in differentiating benign from malignant thyroid lesions was 80.4%.

DISCUSSION

It is well-known that thyroid lesions are most common in middle-age females, similar to the observation in

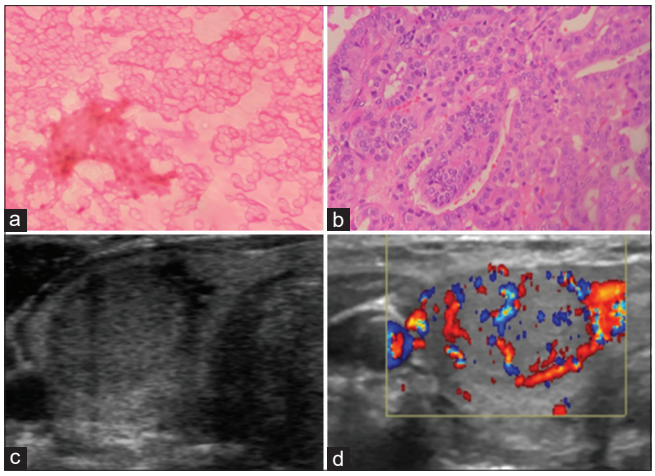

Figure 3: (a) ×10, fine needle aspiration cytology shows scant thyroid follicular cells with few showing Hurthle cell change in a background of hemorrhage. (b) H&E, ×40, microfollicles with tumor cells showing nuclear features of papillary thyroid carcinoma. (c and d) Ultrasound shows a tall well-defined hypoechoic wider than taller solid nodule in the right lobe of thyroid with increased internal vascularity and no calcifications

our study.[3] Thyroid lesions usually present with an asymptomatic swelling in the anterior part of the neck. It can present as a solitary nodule, multinodular or as a diffuse swelling. The vast majority of these nodules are non-neoplastic lesions or benign neoplasms.[3] The general protocol for the investigation of a thyroid nodule includes clinical examination, imaging modalities such as ultrasound, biochemical analysis including thyroid function tests with antibodies levels followed by FNAC diagnosis using The Bethesda system of reporting. In the case of a Bethesda IV category, surgical lobectomy is performed, Bethesda V category lesions are managed with a near-total thyroidectomy and Bethesda VI category lesions are managed with total thyroidectomy with or without neck dissection.[4]

FNAC of thyroid lesions is a safe, cost-effective, minimally invasive, simple out-patient procedure, hence considered as a gold standard for pre-operative assessment of patients with thyroid nodules.

TIRADS has been proposed for risk stratification of thyroid nodules. TIRADS 3 are probably benign nodules with a risk of malignancy of <5%. The risk of malignancy in TIRADS 4a (undetermined) and 4b (suspicious) is 5–10% and 10–80%, respectively.[5]

Reasons for discordance are mainly because of the error in sampling and the nature of the lesion (43%)[6] which is associated with an adverse outcome in patients with thyroid cancer and ultimately, it determines the treatment.

The diagnosis of follicular patterned lesions can be challenging in FNAC because of the overlapping features between benign and malignant lesions and is hence, considered to be a grey zone. Follicular spectrum of thyroid lesions includes follicular adenoma, follicular carcinoma, and follicular variant of PTC. The sole criteria for the diagnosis of follicular carcinoma are the demonstration of capsular or vascular invasion. Follicular carcinoma can be divided into minimally invasive (capsular invasion only) and angioinvasive carcinoma. Hence, the capsule has to be all embedded for accurate diagnosis in histopathology.[7] One more pitfall is that benign follicular nodules cannot be distinguished in FNAC from follicular carcinomas because the criteria to distinguish them are based upon histological evidence of capsular or vascular invasion which cannot be assessed in cytology.[8-10]

Adequacy in FNAC is based on cellularity criteria (6 clusters of 10 cells or 10 clusters of 6 cells).[4,11] Aspirates that contain only cystic fluid and erythrocytes are considered inadequate.

Sampling error may be the reason for discordance in papillary carcinoma and microcarcinoma. The occurrence of a cystic change with underlying malignancy in thyroid lesions is a common diagnostic pitfall in FNAC.[12-14] PTCs tend to undergo hemorrhagic and degenerative changes. Sampling of this area will result in a lesser number of cells and false interpretation of it to be a benign cyst.[15-17] Any recurrent cystic lesion should raise a strong suspicion for malignancy and should be treated accordingly. In such cases, USG-guided FNAC is suggested to accurately locate the lesion for a better diagnostic yield. The term papillary microcarcinoma is used when it is found incidentally and it measures <1 cm in diameter as defined by the World Health Organization.[18-20] There is a high chance of it being missed in FNAC because of the small size of the lesion. Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is an encapsulated or clearly delimited, non-invasive neoplasm with a follicular growth pattern and nuclear features of PTC. It is considered as a premalignant lesion in patients with RAS mutation. The diagnosis of NIFTP is made after complete resection of the lesion by the defined criteria.[21]

The reason for the false-positive diagnosis is the presence of diagnostic features of PTC even in benign conditions of thyroid such as adenomatoid nodule and Hashimoto's thyroiditis. Benign thyroid nodules with papillary hyperplasia can pose a diagnostic challenge not only in cytology but also in histopathology as it mimics classical PTC.[16,20]

In the current study, 3.9% aspirates were reported as inadequate compared to the study done by Nandedkar *et al.* which showed inadequate/nondiagnostic category in 26 cases (4.29% of total cases).[22]

Utility of core needle biopsy compared to FNAC is still debatable and results have been inconclusive. While its distinct advantages include identifying the architectural pattern and performing ancillary techniques; however, disadvantages include invasiveness of the technique with a risk of complications as well as failure to differentiate between follicular lesions.[23,24]

ACR TIRADS (TI-RADS) was established in 2017 based on the US features of thyroid nodules into five categories – Composition, echogenicity, shape, margins, and presence of echogenic foci. Each of these features was assigned individual points from 0 to 3 and the nodule's total point determines its risk of malignancy (TR1 – benign, TR2 – not suspicious, TR3 – mildly suspicious, TR4 – moderately suspicious, and TR5 – high suspicious). Depending on the diameter and the TR category of the nodules, further recommendations like the need for FNA biopsy short-term follow-up or no further action is recommended.[23] In our study, of the 28 cases that were discordant 12 cases were given TIRADS-3 and 16 cases were given TIRADS-4 on USG which were predominantly solid cystic lesions and subsequently advised for a cytology correlation due to their ultrasound features suspicious for malignancy. Except 3 patients, all other 25 discordant cases underwent FNAC without image guidance which resulted in sampling error and inadequate sample owing to the cystic nature of these nodules. Moreover, all these 28 discordant nodules which labeled as suspicious TIRADS-3/4 lesions on USG were malignant on histology.

CONCLUSION

Histopathological evaluation of thyroid nodules provides the most accurate method of diagnosis. FNAC is considered only as a screening tool and particular attention should be given to minimize the false positive and negative diagnosis. The Bethesda system of reporting should be followed to minimize these errors. Occurrence of cystic change in thyroid lesions is a common diagnostic pitfall in cytology. Hence, the possibility of neoplastic etiology should be considered in cystic lesions and these cases require USG-guided FNAC to ensure cellular adequacy, thus, preventing a sampling error. In suspicious cases, repeat FNAC/core biopsy is suggested for a confirmatory diagnosis. A benign FNAC diagnosis should be followed up with excision in case of imaging and pathology discordance. A multidisciplinary team discussion involving the surgeon, oncologist, radiologist, and pathologist is warranted in discordant cases for planning and instituting optimal management.

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Original Article

Dexmedetomidine Versus Labetalol in Controlling Emergence Hypertension in Craniotomy

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Abstract

Introduction: Emergence hypertension is a poorly understood yet notorious phenomenon, especially in neurosurgical cases. This may pave the way for deleterious complications leading to increased patient morbidity. The aim of this study was to compare dexmedetomidine and labetalol in controlling emergence hypertension in patients undergoing craniotomy.

Materials and Methods: We conducted a prospective, randomized, comparative study of 60 patients who underwent craniotomy. These patients were randomized into two groups. At the start of dural closure, Group D received intermittent i.v boluses of dexmedetomidine 0.1 mcg/kg every 3 min and Group L received intermittent i.v boluses of labetalol 0.04 mg/kg every 3 min if systolic BP was >20% of baseline or more than 140 mm of Hg. Hemodynamic parameters, cumulative dose of the drugs and sedation scores were determined.

Results: Significant effect in attenuating pulse rate, systolic, diastolic, and mean arterial blood pressure was observed in both groups with better reduction of blood pressures by dexmedetomidine and that of pulse rate by labetalol. Patients who received dexmedetomidine were found to have lower Richmond Agitation and Sedation Scores (RASS) than those who received labetalol. The mean dose of drugs used to achieve this was 18 mcg of dexmedetomidine and 12 mg of labetalol.

Conclusion: Dexmedetomidine was more effective than labetalol in controlling the blood pressure associated with the emergence phenomenon in patients undergoing craniotomy but caused more sedation.

Key words: Dexmedetomidine, Labetalol, Emergence hypertension

INTRODUCTION

Rapid and smooth emergence after craniotomy is a common practice, the goal of which is to permit early neurological examination. The most feared complication after intracranial surgery is the development of post-operative hematoma, the incidence being 0.8%–2.2%.[1] The surgical stress often leads to the emergence hypertension and may predispose to intracranial hematoma and cerebral edema.[2] Both may lead to cerebral hypoperfusion and brain injury.

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Recovery from general anesthesia and extubation is a period of intense physiological stress for patients. This is mainly caused by pain associated with the surgery and discomfort caused by the presence of endotracheal tube during awakening.

There are several post-operative physiological responses to stress, which include an increase in oxygen consumption, catecholamine levels in blood, blood pressure, and heart rate. Blood pressure and heart rate increase gradually toward pre-operative values or higher as the patient recovers from general anesthesia. Extubation causes a transient increase in these parameters due to tracheal and laryngeal stimulation. Shivering and pain are also among the main causes of these metabolic and hemodynamic changes and changes in cerebral blood flow and intracranial pressure. Pain is a key stress factor which increases post-operative oxygen consumption and release of catecholamines.

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Thus, anesthetic emergence should include the maintenance of respiratory and cardiovascular parameters. Emergence hypertension has an incidence of more than 90% in neurosurgical patients.[3] Hypertension during recovery from anesthesia and extubation is partly reduced by analgesia through a decrease in catecholamine release.[2] Some of the factors like pre-operative patient status and the surgical procedure does not remain under the control of the anesthesiologist. However, conditions such as post-operative hypothermia, severe pain, restlessness, coughing, and fighting the endotracheal tube seen during recovery are preventable.

Conventionally, non-anesthetic drugs such as β-blockers, calcium channel blockers, and lidocaine have been tried successfully to blunt the hemodynamic response during emergence and extubation.[4] These drugs have their own disadvantages. Labetalol, a combined selective alpha-1 adrenergic receptor blocker and non-selective beta-adrenergic blocker given by i.v bolus or continuous infusion, has been studied for the treatment of emergence hypertension. The overall response rate is 85–100%,[5] making labetalol an effective option to control emergence hypertension. However, its contraindications in asthma and congestive heart failure and significant bradycardia must be considered.[6]

Intravenous infusions of dexmedetomidine, a highly selective alpha-2 adrenergic agonist with sedative, anxiolytic, analgesic and hypotensive properties, have also been evaluated as an adjuvant to anesthesia for neurosurgery with desirable effects on hemodynamic parameters.[7,8] However, studies with intermittent boluses of dexmedetomidine rather than continuous infusion are yet to be documented.

In this study, we compare the effect of intermittent i.v boluses of dexmedetomidine and labetalol in attenuating emergence hypertension in patients undergoing craniotomy.

MATERIALS AND METHODS

The study was planned as a prospective, randomized, and double-blind study. After getting approval from the Institutional Ethical Committee and obtaining informed consent from the patients enrolled in the study, 60 patients of ASA I and II scheduled for craniotomy under general anesthesia were randomly allocated to one of the two following groups using the sealed envelope technique. Any patient who refused to give consent, who was of the age <18 or >65 years, ASA physical status >II, with impaired renal functions, uncontrolled hypertension, bronchial asthma, arrhythmias, congestive cardiac failure, Glasgow coma scale <12, requirement of post-operative ventilation, and history of allergy to the study drugs were excluded from the study.

At any point from the start of dural closure, should emergence hypertension occur, we planned to give intermittent boluses of i.v dexmedetomidine to patients in Group D and intermittent boluses of i.v labetalol for patients in Group L till the hemodynamic parameters normalized.

A careful pre-anesthetic evaluation was done. The patients were randomized on the day of surgery into two groups. Patients were kept nil per oral for 8 h before surgery. After shifting the patient to the operation theatre, two large-bore (18 G) intravenous cannulae were secured and normal saline was started at the rate of 4 ml/kg/h. Standard monitors such as pulse oximeter, noninvasive blood pressure, 3-lead electrocardiogram were connected, and pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and oxygen saturation (SpO_2) were recorded at that time.

Patients were premedicated with intravenous glycopyrrolate (0.2 mg) and fentanyl (1.5 mcg/kg). After adequate preoxygenation for 5 min, induction was achieved with i.v propofol (2 mg/kg) followed by i.v vecuronium bromide (0.1 mg/kg) to facilitate direct laryngoscopy and endotracheal intubation (high-volume/low-pressure cuffed endotracheal tube). The internal diameter of the endotracheal tube was 7 mm for women and 8 mm for men. All the patients were mechanically ventilated at a fresh gas flow of 1 L/min and anesthesia was maintained with isoflurane (minimum alveolar concentration 0.8–1.0) and vecuronium (0.01 mg/kg every 20–30 min) throughout the surgical procedure. Intraoperative analgesia was supplemented with incremental doses of fentanyl (1 mcg/kg) every hour. Intraoperatively, end-tidal CO_2 and urine output were also monitored. During mechanical ventilation, a respiratory rate of 12–16/min and tidal volume of 4–6 ml/kg were used, which were adjusted to maintain normocapnia and normoxia with oxygen saturation ≥ 98%. Ringer lactate and normal saline were used for the maintenance of fluid balance. Colloids, blood, and blood products were used as and when required.

From the start of dural closure, if at any point, the patient's systolic BP rose to > 20% of baseline value or 140 mm of Hg (whichever is higher), study drugs were administered over 20 s. Group D and Group L received intermittent boluses of i.v. Dexmedetomidine 0.1 mcg/kg and i.v labetalol 0.04 mg/kg, respectively, every 3 min until the desired hemodynamic response was achieved (reduction of Systolic BP to <140 mm of Hg or <20% of baseline value). Both the study drugs were prepared in identical

syringes and administered by a senior anesthesiologist not involved in the study.

At the end of the surgery, all anesthetic agents were discontinued, and patients were ventilated with 100% oxygen. Neuromuscular blockade was reversed with i.v neostigmine 0.05 mg/kg and i.v glycopyrrolate 0.01 mg/kg. Once the patient became conscious and responded to verbal commands, extubation was performed. After extubation, the patients were oxygenated with 100% oxygen for 5 min. The values of pulse rate, systolic BP, diastolic BP, and mean arterial pressure were obtained just before administration of the study drug, every 3 min from the time of administration of the first dose till extubation and every 3 min until 15 min after extubation. After extubation, all these patients were observed for sedation using Richmond Agitation Sedation Score (RASS).

Statistical Analysis

The data were analyzed with the help of IBM SPSS 22 for windows. Appropriate univariate and bivariate analysis for comparing two means were applied and Student's *t*-test was used to test the null hypothesis for continuous variables. Test of normality was done for all the continuous variables before applying parametric statistical methods. All means were expressed as mean ± standard deviation and proportions in percentage (%). $P < 0.05$ was considered statistically significant.

RESULTS

There were no significant differences in demographic data between the two groups with respect to the patients' age, body weight, ASA physical status, and duration of surgery. The pre-operative hemodynamic parameters such as Glasgow Coma Score, pulse rate, systolic, diastolic, and mean arterial blood pressures were comparable in both the groups [Table 1]. However, as far as pulse rate was concerned, at 9 min, 6 min, 3 min before extubation and 12 min, and 15 min after extubation, a significant difference was noted between these two groups, with labetalol achieving better control of pulse rate than dexmedetomidine [Table 2] [Figure 1].

With respect to systolic blood pressure, at 9 min, 6 min, 3 min before extubation, and for the entire 15 min after extubation, a significant difference was noted with dexmedetomidine achieving a better control than labetalol [Table 3] [Figure 2].

Significant differences in diastolic blood pressure were noted at 6 min and 3 min before extubation, with dexmedetomidine achieving a better control than labetalol [Table 4] [Figure 3].

Dexmedetomidine achieved better control of mean arterial pressure than labetalol, with significant differences at 9 min, 6 min, 3 min before extubation, and for the entire 15 min after extubation [Table 5] [Figure 4].

The median RAS score for patients in Group D was 0 (alert and calm) and for Group L was 2 (agitated) [Figures 5 and 6]. This shows that patients of Group D were more sedated than those of Group L. This can be attributed to the central mechanism of action of dexmedetomidine.

The median dose to achieve favorable hemodynamic control was only 18 mcg of dexmedetomidine and 12 mg of labetalol [Figure 7].

DISCUSSION

Emergence hypertension refers to the systemic surge of catecholamines that accompany a patient when he/she shifts from deeper to lighter plane of anesthesia. The chief instigator of this cataclysmic event is the activation of the sympathetic system, although Renin Angiotensin Aldosterone system activation and surgical manipulation of the brain have also been cited as causative factors. These are commonly ascribed causes of post-operative intracranial hematoma, which is a catastrophic complication that paves the way to increased morbidity and mortality of these patients. A pool of

Table 1: Demographic characteristics of patients

Characteristics	Group D Mean±SD	Group L Mean±SD	*P* value	Significance
Age (In years)	37.33±13.69	40.279.45	0.338	Not significant
Weight(In kg)	63.17±9.61	67.77±9.45	0.067	Not significant
Pre-Op Parameters				
GCS	13.77±1.19	4.27±1.01	0.086	Not significant
Pulse rate (per min)	79.47±10.10	82.00±8.92	0.307	Not significant
Systolic blood pressure (mmHg)	117.63±9.59	118.37±9.37	0.765	Not significant
Diastolic blood pressure (mmHg)	76.70±7.47	78.63±5.62	0.262	Not significant
Mean arterial pressure (mmHg)	90.54±7.31	91.88±5.40	0.359	Not significant
Duration of surgery (min)	204.17 ± 8.64	212.47 ± 6.39	0.781	Not significant

Table 2: Comparison of Pulse Rate

Time	Group Mean±SD	Group L Mean±SD	*P* value	Significance
9 min before	96.17±12.24	73.73±9.2	<0.0001	Significant
6 min before	97.37±11.24	72.47±5.13	<0.0001	Significant
3 min before	93.93±8.75	72.77±49	<0.0001	Significant
Extubation	90.4±7.98	91.7±7.68	0.523	Not significant
3 min	90.03±8.97	89.73±7.31	0.888	Not significant
6 min	89.83±8.27	88.07±663	0.315	Not significant
9 min	88.27±7.53	84.9±6.46	0.068	Not significant
12 min	86.87±7.64	81.83±6.05	0.006	Significant
15 min	85.77±7.24	77.9±5.1	<0.0001	Significant

Table 3: Comparison of systolic BP

Time	Group D Mean±SD	Group L Mean±SD	*P* value	Significance
9 min before	128.9±16.32	138.63±9.33	0.006	Significant
6 min before	119.13±16.49	134.3±8.45	<0.0001	Significant
3 min before	112.2±7.13	131.73±7.44	<0.0001	Significant
Extubation	126.8±6.4	128.7±6.69	0.266	Not significant
3 min	112.73±11.68	125.67±5.68	<0.0001	Significant
6 min	110.2±11.1	124.1±6.27	<0.0001	Significant
9 min	109.43±10.55	122.13±5.18	<0.0001	Significant
12 min	109.17±9.4	120.1±5.31	<0.0001	Significant
15 min	110.37±9.36	119.47±5.6	<0.0001	Significant

Table 4: Comparison of diastolic BP

Time	Group D Mean±SD	Group-L Mean±SD	*P* value	Significance
9 min before	79.17 ±11.77	83.57±5.54	0.069	Not significant
6 min before	72.83±10.81	82.87±5.79	<0.0001	Significant
3 min before	71±6.52	81.1±5.45	<0.0001	Significant
Extubation	80.13±5.32	78.97±5.18	0.39	Not significant
3 min	80.13±5.03	79.07±5.23	0.196	Not significant
6 min	79.2±5.01	78.5±3.61	0.537	Not significant
9 min	78.33±5.45	78.1±4.71	0.860	Not significant
12 min	77±4.68	75.9±3.98	0.330	Not significant
15 min	75.8±5.32	75.13±4.06	0.587	Not significant

Table 5: Comparison of mean arterial pressure

Time	Group D Mean±SD	Group L Mean±SD	*P* value	Significance
9 Min before	95.74±12.18	101.92±5051	0.014	Significant
6 Min before	88.27±11.58	100.01±5.43	<0.0001	Significant
3 Min before	84.73±4.95	97.98±4.79	<0.0001	Not significant
Extubation	95.69±4.2	95.54±4.24	0.805	Significant
3 Min	91.44±4.89	94.6±4.36	0.01	Significant
6 Min	89.53±4.92	93.7±2.96	<0.0001	Significant
9 Min	88.87±4.35	92.78±3.66	<0.0001	Significant
12 Min	87.72±3.9	90.63±3.28	0.003	Significant
15 Min	87.32±4.48	89±3.24	0.013	Significant

drugs is available for the anesthesiologists to control or prevent this notorious event, some examples of which are nicardipine, dexmedetomidine, labetalol, esmolol, lignocaine, and verapamil. Numerous alterations to anesthetic techniques, especially during emergence,

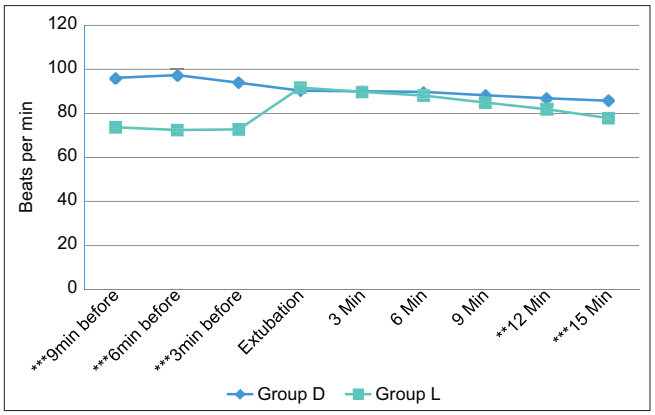

Figure 1: Comparison of Pulse Rate

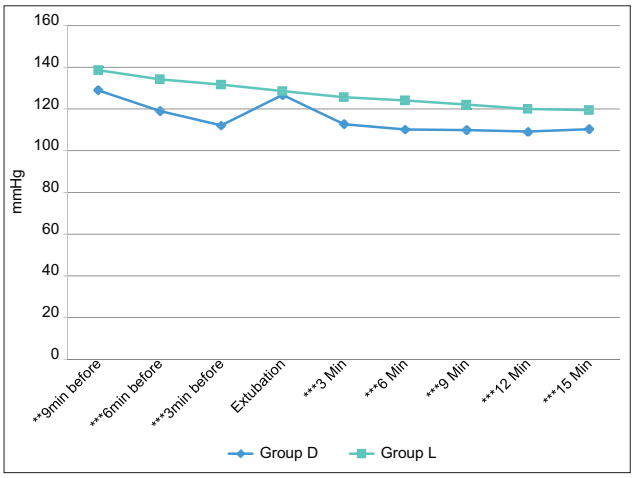

Figure 2: Comparison of systolic BP

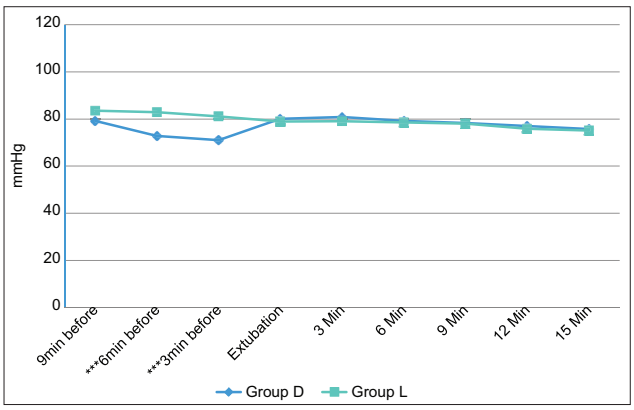

Figure 3: Comparison of diastolic BP

have been proposed to overcome the periextubation hypertensive response. These include titrated doses of short-acting opioids, continuing volatile anesthetics, and nitrous oxide until head dressing is over, extubating patients undergoing otherwise uncomplicated surgeries in deeper planes of anesthesia, etc. Besides pharmacological intervention, methods such as Bailey's maneuver are also handled by anesthesiologists to control emergence hypertension.

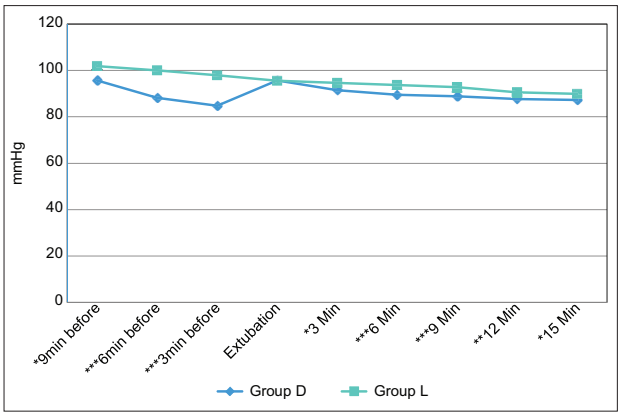

Figure 4: Comparison of mean arterial pressure

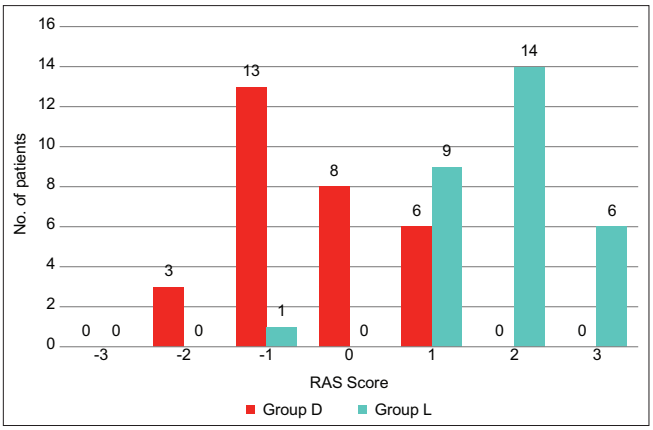

Figure 6: RAS score comparison

Richmond Agitation-Sedation Scale

	Target RASS Value	RASS Description
+4	Combative	Combative, violent, immediate danger to staff
+3	Very Agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive but movements are not aggressive or vigorous
0	Alert and Calm	
-1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening & contact **greater** than 10 seconds)
-2	Light Sedation	Briefly awakens to voice (eye opening & contact **less** than 10 seconds)
-3	Moderate Sedation	Movements or eye opening to voice (but **NO** eye contact)
-4	Deep Sedation	No response to voice, but has movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Figure 5: Richmond agitation sedation scale

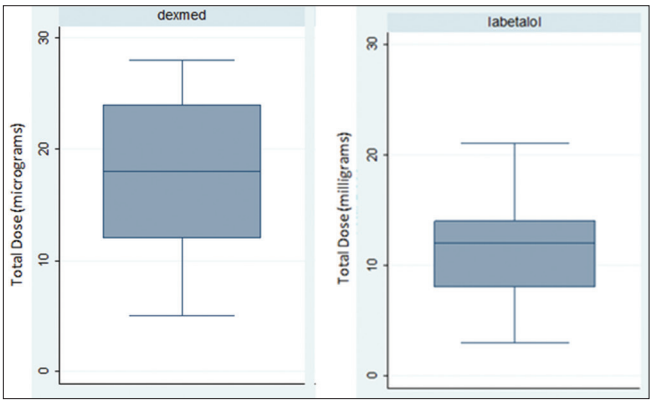

Figure 7: Total dose of the drug given

The present study was done to demonstrate the efficacy of dexmedetomidine and labetalol in controlling emergence hypertension in craniotomy. To the best of our knowledge, no comparative study between the hemodynamic effects of labetalol and dexmedetomidine (using intermittent boluses) on emergence from anesthesia during craniotomies is yet available.

The results of the present study were in accordance with those of Radwan *et al.*[9] who compared the efficacy of infusions of dexmedetomidine and labetalol in preventing emergence hypertension in patients undergoing craniotomy for supratentorial tumors. They studied 27 patients of ASA I-II who were scheduled for supratentorial craniotomy under general anesthesia, who were randomly allocated to one of three groups. At the time of dural closure, the group "dex" received dexmedetomidine infusion in a rate of 1 mcg/kg/h, group "labetalol" received labetalol infusion in a rate of 0.5 mg/kg/h, and group "control" received saline infusion at the same rate of dexmedetomidine and labetalol. Hypertensive episodes were managed with nitroglycerin at a dose starting from 1 mcg/kg/min if systolic blood pressure exceeded 25% of its preinduction value. It was concluded that dexmedetomidine infusion in a dose of 1 mcg/kg/h and labetalol infusion in a dose of 0.5 mg/kg/h started at dural closure had a significant effect in reducing the incidence and the extent of emergence hypertension without prolonging the time needed for extubation. There was more reduction of the systolic, diastolic, and mean arterial pressure in the dexmedetomidine group and of the pulse rate in the labetalol group in comparison with the other two groups. It should, however, be noted that our study used intermittent boluses of these drugs rather than continuous infusion. Furthermore, we differed from this study in such a way that the pharmacological intervention was started not as prophylaxis but as a treatment, meaning, the drugs were administered only when the emergence hypertension occurred. Another striking inference was that our median dose to achieve comparable hemodynamic control was only 18 mcg of dexmedetomidine and 12 mg of labetalol, which was notably lower than their median dose. The nil incidence of sudden hypotension and bradycardia can be attributed to the strikingly lower doses of both these drugs. Moreover, complications such as severe hypertension due to the peripheral alpha 2 receptor stimulation[10] in patients who received dexmedetomidine

were not observed as we refrained from giving the conventional initial bolus dose.

Furthermore, Ilhan *et al*.[11] studied in a double-blind prospective clinical study, the effects of fentanyl and dexmedetomidine as adjuvant agents in supratentorial craniotomies on the hemodynamic changes during perioperative period. Thirty patients undergoing intracranial tumor surgeries were divided into two groups. In one group ($n = 15$), dexmedetomidine was infused as a 1 mcg/kg bolus 10 min before induction of anesthesia and maintained with 0.4–0.5 mcg/kg/min during the operation, and fentanyl was given as a 2 mcg/kg bolus at induction. In the other group ($n = 15$), patients were given fentanyl 4 mcg/kg before induction and 0.02 mcg/kg/min as an infusion for maintenance of anesthesia. They concluded that dexmedetomidine controlled the hemodynamic changes better than fentanyl perioperatively, which supports the results of our study. The time and method of administration of dexmedetomidine, however, differed from that of our study.

Regarding the hemodynamic effects of labetalol, in a recent study conducted by Busara *et al*.,[12] which was an equivalence trial comparing labetalol and diltiazem in controlling emergence hypertension after supratentorial tumor surgery, the drugs were administered at a fixed dosage of 2.5 mg every 2–3 min to maintain systolic BP lower than 140 mmHg with a cumulative dose within 20 mg. The success rate of treatment with labetalol was equivalent to diltiazem (87.1% and 80.2%, respectively) ($P = 0.003$, 95% CI = 6.88 [−2.06–15.8]). There was no statistically significant difference on the dosage of drugs used or incidence of side effect (hypotension, bradycardia, heart block, and bronchospasm). Median doses of labetalol and diltiazem were 10 mg (2.5–20 mg) and 10 mg (2.5–20 mg), respectively. The median dose of labetalol in the abovementioned study is in concordance with that of our study, where the median dose of labetalol was 12 mg. Labetalol at this dose was not only found to be efficient in achieving the desired hemodynamic control but also was devoid of complications of beta-blockade such as bronchospasm and bradycardia.

A study by Kross *et al*.[13] compared the efficacy of the combination of enalaprilat/labetalol with that of enalaprilat/nicardipine to prevent emergence hypertension in craniotomies. Forty-two patients received enalaprilat 1.25 mg i.v at dural closure followed by either multidose nicardipine 2 mg i.v or labetalol 5 mg i.v to maintain the systolic BP below 140 mmHg. In the labetalol group, at closure of dura, the systolic, diastolic, mean arterial pressure, and pulse rate were 104 ± 9 mmHg, 75 ± 8mm Hg, 60 ± 8 mm Hg, and 84 ± 11 beats per min, respectively. The labetalol group experienced a progressive decrease in HR (14%) which is consistent with our findings. In the nicardipine group, at closure of dura, the systolic, diastolic, and mean arterial pressures were 109 ± 9 mmHg, 76 ± 8 mmHg, and 60 ± 8 mmHg, respectively. The nicardipine group experienced a higher incidence of hypotension and tachycardia than the labetalol group. This study is in agreement with the present study except that labetalol in the present study was given as a sole antihypertensive agent starting at dural closure as intermittent boluses of 0.04 mg/kg.

Although not studied, we strongly believe that the incidence of rebound hypertension and tachycardia after discontinuing these drugs can be significantly cut down with the significantly smaller doses used in our study. Cost-effectiveness will also be in our favor. From these findings, it can be stated that dexmedetomidine was better in controlling the systolic, diastolic, and mean arterial pressures and labetalol in controlling the pulse rate. Due to its central action, dexmedetomidine caused sedation in these patients, which helped in smooth extubation and did not prolong the duration of extubation.

CONCLUSION

Both dexmedetomidine and labetalol had favorable effects on hemodynamics during emergence from anesthesia. Dexmedetomidine achieved a better reduction in systolic blood pressure, diastolic blood pressure, and mean arterial pressure and labetalol in pulse rate. A higher degree of sedation was produced by dexmedetomidine, which facilitated smooth extubation.

Limitations of Our Study

A sample size of 60 cannot be projected overall patients. This study included only patients undergoing craniotomy in the supine position. It did not include patients who were positioned prone. Furthermore, patients undergoing neuroendoscopic procedures for tumor removal were not included. Hemodynamic monitoring did not include invasive blood pressure monitoring and cardiac output monitoring. Surgeries lasting more than 4 h were not included in this study.

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Original Article

A Review of Coronavirus Disease-2019 Prophylaxis, Treatments, and Prevention

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Abstract

Introduction: There is a new world health crisis threatening the public with the spread of Coronavirus Disease-2019 (COVID-19). Since December 2019, when Covid-19 emerged in Hunan seafood market at Wuhan, South China, and rapidly spread throughout the world, the virus outbreak has been declared a public health emergency of international concern by the World Health Organization (WHO).

Materials and Methods: We here summarize the current clinical characteristics data to guide potential COVID-19 about prevention, diagnosis, treatments, and prevention of COVID-19. In this review, the data were extracted from various Research Report WHO guidelines and other articles. It is important to warn readers that COVID-19 publishes new data almost every hour with respect to clinical symptoms, diagnosis, treatment approaches, and outcomes. The disease has caused various degrees of illness around the world.

Results: Patients typically experience fever, cough, sore throat, breathlessness, exhaustion, and malaise, among other symptoms. The illness is treated by general diagnosis, symptomatic treatment, antiviral medicine, oxygen therapy, and the immune system.

Conclusion: It is necessary to identify the potential cases as soon as possible and isolate the suspected people from the confirmed cases of COVID-19, to prevent the potential transmission of infection to other patients and health-care staff.

Key words: Coronavirus, COVID-2019, Respiratory syndrome, Hydroxychloroquine, Azithromycin, Passive immunization

INTRODUCTION

The SARS-CoV-2 pandemic and COVID-19 diffusion are an international public health emergency.[1] Coronaviruses are ribonucleic acid viruses. Importantly, the viruses can infect respiratory, gastrointestinal, hepatic, and central nervous systems in humans.[2] Infection with four of the most common strains of coronaviruses (HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1) usually results in mild, self-limiting infections of the upper respiratory tract.[3] Other coronaviruses, however, are associated with severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV).

Symptoms of infection are usually nonspecific and include fever, cough, and myalgia, with diarrhea, with or without the subsequent development of dyspnea.[4] Severe cases that include respiratory distress, sepsis, and septic shock have been increasingly reported.[5] One recent systematic review and meta-analysis reported ten observational studies of corticosteroid administration in 6458 influenza-affected patients.[6] The aim was to investigate the effectiveness of various therapies in COVID-19 patients.

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Hydroxychloroquine as Prophylaxis or Treatment

Chloroquine (CQ) is an affordable and fairly safe antimalarial used in India and other malaria-endemic countries for decades. Previous studies showed CQ to be highly effective *in vivo* for the treatment of avian influenza A (H5N1)[7] and *in vitro* against extreme coronavirus acute respiratory syndrome (SARS-CoV).[8,9] HCQ used for the treatment of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis has shown to be active against COVID-19 *in vitro*.[7]

Mechanism of Action

It prevents the fusion of the SARS-CoV-2 to host cell membrane[10] and blocks the release of SARS-CoV-2 viral genome.[11] HCQ also has immunosuppressive properties

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that can help to minimize the extreme COVID- 19 cytokine storm.[12,13] Although HCQ is relatively safe, it can lead, under adverse conditions, to cardiac disorders such as prolongation of the QT segment, which could lead to myocardial arrest and arrhythmia.[14]

Randomized Clinical Trial Data

Recent *in vitro* studies have shown that SARS-2CoV-2 replication can be inhibited by both CQ and HCQ.[11,10,15] Based on these encouraging *in vitro* data, CQ has been used to test, it is *in vivo* efficacy in multicenter clinical trials involving 100 COVID-19 patients in China. The study concluded that CQ decreased the inflammation of the lungs and shortened the duration of disease without significant adverse reactions.[16] The Chinese analysis of 62 patients found that HCQ shortened the time to recover from chronic conditions.[17]

Hydroxychloroquine and Azithromycin (AZM) Combination

RCT data for the combination of hydroxychloroquine and AZM are not available; however, several RCTs are ongoing.[18] Two case series were reported in France, one reporting benefit[12] and other no benefit.[19] At present, this combination should be used only in the setting of a clinical trial as routine use could lead to severe adverse events with QT prolongation.

Randomized Clinical Trial Data

In addition, two studies conducted in France have indicated that HCQ can reduce the viral load in COVID-19 patients, particularly in combination with AZM.[14,20] These encouraging preliminary studies should have guided the Indian Medical Research Council (ICMR) to recommend HCQ for chemoprophylaxis of asymptomatic health workers who treat suspected or confirmed COVID-19 cases and confirmed patient asymptomatic household contacts.[13] For asymptomatic health workers, the recommended dose is 400 mg twice on day 1, followed by 400 mg once every week for 7 weeks, while for asymptomatic household contacts, the duration is 3 weeks and has to be prescribed by a registered medical practitioner.[13] However, there is no previous research to support the use of CQ and HCQ as prophylaxis to COVID-19. Recently, the US Food and Drug Administration has authorized HCQ for emergency use to treat COVID-19 pneumonia.[21]

Lopinavir/ritonavir

Lopinavir/ritonavir is an approved drug for the treatment of HIV and has been shown to be effective against other novel CoVs such as SARS CoV-1 and MERS Co-V *in vitro*.[22,23] A recent studies indicated *in vitro* activity of lopinavir against SARS-CoV-2.[24]

Mechanism of Action

It inhibits 3-chymotrypsin-like protease enzyme, which is conserved in SARS-CoV-2.[25]

Randomized Clinical Trial Data

One well-done RCT involving 199 patients in China compared clinical outcomes among hospitalized patients with severe COVID-19 infection with lopinavir/ritonavir and standard of care.[26] While in the lopinavir/ritonavir community, the mortality was lower (19.2% vs. 25%) and the duration of the intensive care unit (ICU) stay was shorter (6 days vs. 11 days) relative to the standard of treatment, this was not statistically important. In a second study involving 86 patients with mild to moderate COVID-19 infection in China, lopinavir/ritonavir was contrasted with arbidol (also known as umifenovir) and the 2:2:1 standard of treatment.[27] The results indicated no benefit in clinical outcomes with lopinavir/ritonavir or arbidol compared to standard of care. Additional RCTs are ongoing.[28] At present, routine use of lopinavir/ritonavir is not recommended, and it should be only used in the context of clinical trial.

Major Adverse Effects

Major adverse effects of lopinavir/ritonavir are nausea, vomiting, diarrhea and hepatotoxicity.

Remdesivir

Remdesivir is an analog prodrug of intravenous adenosine nucleotide with activity against many RNA viruses, including SARS CoV-1 and MERS Co-V.[29] It has demonstrated *in vitro* activity against SARS-CoV-2 as well.[30]

Mechanism of Action

It inhibits the viral RNA-dependent RNA polymerase leading to premature termination of RNA transcription.[31]

Randomized Clinical Trial Data

One well-conducted double-blinded RCT from China examined the outcomes in patients with severe COVID-19 disease.[32] In this study, 237 patients were enrolled and randomly assigned to a remdesivir (158 patients) or placebo (79 patients). The primary outcome was the time before day 28 for clinical changes. Receiving remdesivir trials had a quicker duration of clinical progress than those receiving placebo in 10-day studies; however, it was not statistically relevant.[26] Another RCT carried out by the National Institute of Health in the United States announced the findings in a press release, but this research is not published in a peer-reviewed scientific journal.[32] Patients receiving remdesivir had a 31% quicker recovery time than those receiving placebo, according to the press release (median time to recovery 11 days with remdesivir vs. 15 days with placebo; $P < 0.001$). In addition, there was a trend for survival benefit (mortality rate of 8.0% in remdesivir group vs. 11.6% in placebo group [$P = 0.059$]).

There are several other RCTs ongoing.[33] On May 1, 2020, the United States Food and Drug Administration released an emergency use authorization for the use of remdesivir for the care of hospitalized COVID-19 patients, taking into account the findings of the United States National Institute of Health research.[34]

Major Adverse Effects

Major adverse effects of Remdesivir are nausea, vomiting and elevated liver enzymes.

Favipiravir

Favipiravir is an approved drug for the treatment of influenza A in Japan[35] and China[36] with activity against several RNA viruses with pandemic potential.[37]

Mechanism of Action

It inhibits the viral RNA-dependent RNA polymerase halting viral replication.[36]

Randomized Clinical Trial Data

Limited RCT data are available. In one RCT in China, 240 hospitalized patients with moderate-to-severe COVID-19 were randomized to favipiravir or arbidol.[38] There was no major difference in the primary outcome that was a 7-day clinical recovery rate (61% for favipiravir vs. 52% for arbidol; $P = 0.14$).[32] At present, there is insufficient evidence to recommend either for or against the use of favipiravir for COVID-19 treatment. At present, an RCT using favipiravir is planned in India.[39]

Major Adverse Effects

Major adverse effects of Favipiravir are nausea, vomiting, elevated serum uric acid levels, and elevated liver enzymes.

Other Antivirals

Arbidol (umifenovir) is an antiviral agent currently approved in Russia and China for the treatment and prophylaxis of influenza.[35,36] It did not show any benefit over the standard of care[27] or with other agents such as favipiravir in the RCTs which included arbidol;[27,28] however, other trials are ongoing ribavirin has been known to have antiviral activity and was suggested to be one of the possible agents against SARS-CoV-2, and several RCTs are underway.[40] Oseltamivir which is currently approved for the treatment of influenza has limited role in the treatment of SARS-CoV-2.[35]

Ribavirin Major Adverse Effects

Ribavirin major adverse effects are hepatotoxicity, hemolytic anemia, and teratogenicity.[35]

Adjunctive Therapies for Coronavirus Disease 2019

Some adjunctive therapies for supportive care are currently under investigation or are used off-label. These agents may target the virus (e.g., convalescent plasma [CP]) or modulate the immune response (e.g., interleukin (IL)-1 or IL-6 inhibitors) or anti-inflammatory agents (corticosteroids).

Immunoglobulin Therapy or Convalescent Plasma

CP is plasma collected from patients fully recovered from SARS-CoV-2 infection.[41] CP contains antibodies that could help clearing the free virus and the virus from the infected cells. A previous meta-analysis of observational studies showed a reduction in mortality with convalescent plasma or hyperimmune immunoglobulin among SARS-CoV-1 and severe influenza infection.[42]

Mechanism of Action

CP-derived antibodies can neutralize a virus by preventing replication or by binding without interfering with replication.[41]

Randomized Clinical Trial Data

RCT data are not available at present. In case series of two studies with 5[43] and 10,[44] severely ill COVID-19 patients showed promising results. The clinical status of all patients had improved approximately 1 week after transfusion. In addition, the neutralizing antibody titers of patients increased after breathing samples tested negative after transfusion. Many RCTs of CP for COVID-19 infections are underway in various countries.[45] At present, routine use of CP therapy is not recommended for the treatment of COVID-19 outside the clinical trial setting.

Major Adverse Effects

Potential major adverse effect of Immunoglobulin therapy are antibody-dependent enhancement of infection, transfusion-associated acute lung injury, and allergic transfusion reactions.[46]

Anticytokine Agents

Good amounts of data from various studies indicate that cytokine storm plays an important role in severe cases of COVID-19. Therefore, monoclonal antibodies directed against key inflammatory cytokines represent other potential class of adjunctive therapy for COVID-19 infection.[47]

Interleukin-1 and Interleukin-6 Inhibitors

SARS-Cov-2 infects the upper and lower respiratory tract and cause a mild or highly acute respiratory syndrome with a release of pre-inflammatory cytokines, including IL-1 β and IL-6.[48] Similarly, the Janus kinase (JAK) family of enzymes regulates signal transduction in immune cells, and thus, JAK inhibitors could block the cytokine release. Therefore, IL-1, IL-6, and JAK inhibitors could overcome the systemic inflammation associated with severe COVID-19 illness.[49]

Mechanism of Action

It inhibits the amplified immune response and cytokine release.[49]

Randomized Clinical Trial Data

At present, there is no RCT data examining the impact of IL-1, IL-6, and JAK inhibitors on COVID-19-infected patients. RCTs are underway for COVID-19 infection using Anakinra (Recombinant human IL-1 receptor antagonist), recombinant humanized anti-IL-6 receptor monoclonal antibodies (tocilizumab and sarilumab), and siltuximab (recombinant human-mouse chimeric monoclonal antibody that binds IL-6).[50,51] At present, routine use of these agents is not recommended for the treatment of COVID-19 outside the clinical trial setting.

Major Adverse Effects

Main risk of Interleukin-1 and 6 Inhibitors are serious bacterial infections including tuberculosis.

Interferons

Interferons belong to the cytokine family, which have antiviral effects; nonetheless, major interferon toxicities outweigh the possible benefit and are therefore not recommended for COVID-19 diagnosis or as adjuvant therapy.[35] At present, no RCT data as a monotherapy are available.

Major Adverse Effects

Hematological toxicities elevated liver enzymes, nausea, vomiting, and psychiatric problems.

Corticosteroids

Corticosteroids are currently not recommended as adjunctive therapy in patients with COVID-19, except in the case of RCT.[30] The rationale for such recommendation is based on observational studies in patients with SARS CoV-1 and MERS Co-V.

Mechanism of Action

Corticosteroid helps in decreasing the host inflammatory response in the lungs. However, patients with chronic diseases (such as primary or secondary adrenal insufficiency, rheumatologic diseases, asthma, and chronic obstructive pulmonary disease) on chronic corticosteroid therapy (oral or inhalational) should not discontinue the therapy.[30]

Major Adverse Effects

Including delayed viral clearance and increased risk of secondary infections, hyperglycemia, psychosis, and avascular necrosis.[35,52,53]

Coronavirus and Analgesics

Experimental animal studies are ambivalent concerning NSAIDs and paracetamol.

Randomized Clinical Trial Data

A systematic analysis found that rats diagnosed with influenza had an increased risk of mortality following analgesics/antipyretics (i.e., aspirin, paracetamol, and diclofenac).[54] Nonetheless, the same study found no evidence for a similar impact on humans, while criticism was made of the consistency of those studies.

Mechanism of Action

Human volunteers challenged with rhinovirus type[54] given ibuprofen, aspirin, and paracetamol showed that aspirin and paracetamol were associated with suppression of serum antibody and a trend for a prolonged time of viral shedding.[55] Aspirin increased the shedding of virus, but did not alter infection or disease levels.[56] Paracetamol prolongs the actual illness in experimentally infected patients with influenza A[57] and inhibits leukocyte function in *in vitro* experiments.[58]

India Situation

The Ministry of Health and Family Welfare (MoH&FW), Government of India, released their revised guidelines on clinical management of COVID-19 on March 31, 2020. The guidelines suggest that these drugs should be administered under close medical supervision with monitoring for side effects, including QT interval. This therapy is not recommended for children <12 years, pregnant, and lactating mothers.[59] The MoH and FW released an advisory (March 22, 2020) on the use of hydroxychloroquine as prophylaxis for SARS-CoV-2 infection based on the recommendation by the National Task Force for COVID-19 constituted by the Indian Council of Medical Research. The guideline calls for the placement of the following high-risk population with hydroxychloroquine under chemoprophylaxis for (i) asymptomatic health-care staff engaged in the treatment of suspected or confirmed COVID cases and (ii) asymptomatic household contacts with reported laboratory cases.[60] Many centers in different states of India are engaged in RCTs evaluating treatment, prevention, and adjunctive therapies for the management of COVID-19.[61] These clinical trials are mainly evaluating hydroxychloroquine and chloroquine in the prevention of new infection and adverse outcomes and effect of chloroquine in addition to standard therapy in COVID-19 patients. The World Health Organization's Solidarity trial involving four treatment options (remdesivir, chloroquine or hydroxychloroquine, lopinavir with ritonavir, and lopinavir with ritonavir plus interferon) comparing standard of care for hospitalized patients with COVID-19 infection is also ongoing.[61,62] Many other clinical trials include evaluating the effect of Ayurvedic and homeopathic agents on COVID-19 prevention, the efficacy of recombinant Bacillus Calmette-Guerin vaccine in reducing COVID-19 infection incidence and disease severity, and the efficacy and protection of convalescent plasma therapy in serious COVID-19 patients in several centers.[61]

Passive Immunization

PI is a method for obtaining immediate, short-term fortification in patients against infectious agents by adding pathogen-specific anticorps. These specific antibodies can bind to the pathogenic antigens and block their interaction with a cell receptor, which is extremely applicable to viral antigens which facilitate attachment to the target receptors.[63] The patient's body, after exposure to a viral infection, creates large multinational corporations to fight off the virus. Such antibodies in a recovered patient's blood can be obtained as convalescent plasma (CP) and transferred to a newly infected patient's blood where they can neutralize the pathogen, improve the patient's immunity and contribute to blood circulation enucleation in the patient after transfusion.[64] CP gets growing attention as a favored therapeutic tool after large-scale epidemics for several reasons: Collecting a large volume per session, repeated donations are feasible and without any effect on the donor's hemoglobin,[64] which seems to be an appealing approach in the case of COVID-19. There are currently about 1,159,953 patients who have survived and the number continues to grow, and we hope all of them will donate their plasma to end this pandemic. However, donor plasma should be screened for antibody activity and neutralization activity to provide a successful CP infusion. ELISA IgG may be a replacement for neutralization tests in a resource-limited situation.[65]

Safety and Preventive Measures for Dental Health Care Professionals on COVID-19

An alternative to relief symptoms should be provided to patients suspected or confirmed with COVID-19 infections, who need emergency dental treatment in case of tooth pain and/or swelling, antibiotics and/or analgesics. It will allow dental personnel time to prepare and provide dental care with both appropriate and preventive measures to prevent spread of infection. According to the British Medical Journal, the use of ibuprofen became banned on March 17, 2020, because of its interference with immune function. Acetaminophen is an analgesic drug of choice for treating patients diagnosed with COVID-19. The recommendation was endorsed by the World Health Organization (WHO) on March 18, 2020.[66]

In certain emergency cases such as dentoalveolar trauma and fascial space infection, dentists should be aware of the following recommendations:

- Use of disposable dental equipment for cross-contamination preventive measures is mandatory.
- Radiographs: Avoid intraoral radiographs as they can cause gag reflex or cough. Extraoral radiographs (e.g., panoramic radiograph or CBCT) should be done.[65] When intraoral imaging is required, double protections are performed on sensors to prevent cross-contamination.
- Rubber dam will be used for non-surgical endodontic treatment to reduce the splatter generation.
- Dental procedures that generate higher aerosol content, for example, should be avoided for ultrasonic instruments, high-speed handpieces, and three-way syringes.
- Suspected or reported cases of COVID-19 should be treated only in negative pressure rooms or in isolation rooms for airborne infection (AIIRs)[66] and not in routine dental practice.
- Coronavirus survival time is up to 9 days at room temperature on inanimate surfaces or objects, with a greater preference for humid conditions. Therefore, to avoid SARS-CoV-2 spread, dry conditions should be maintained. Recently, approved COVID-19 chemicals should be used for the disinfection.

CONCLUSION

The COVID-19 pandemic is an ongoing public health crisis for which effective therapeutic agents are urgently needed. At the time of writing this commentary, there is no peer-reviewed published evidence from randomized clinical trials of any pharmacological agents improving outcomes in COVID-19 patients. Globally, several clinical trials involving repurposed and novel pharmacological agents for the treatment of COVID-19 are ongoing and thus recommendations may change with new evidence. The positive results of remdesivir against COVID-19 are encouraging; however, the findings from other ongoing remdesivir trials will be critical in establishing its therapeutic efficacy against COVID-19 infection.

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Original Article

Assessment of Role Played by Pharmacists in Oral Health Care in Jammu – A Cross-Sectional Study

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Abstract

Introduction: Pharmacies are the frontline approach for delivering oral health care and the pharmacist should be able to discuss the appropriate dental products for a patient's oral health needs as well as know when referral to a dentist is needed.

Purpose: The purpose of the study was to determine the knowledge, attitude, and practice of pharmacist about oral health care and oral health products in Jammu.

Methodology: This cross-sectional study was carried out among pharmacists using self-administered, closed-ended questionnaire. Descriptive statistics were used for the data analysis. Statistical analysis was done using SPSS version 20.

Results: A total of 384 pharmacists were included in the study. Mean age was 43.2 ± 10.4 years. Among these, approximately 79% knew about a nearby dental clinic. Toothpaste was most common among the oral health-care product available in the pharmacies. Toothache was the most common pathology encountered by these pharmacists.

Conclusion: Community pharmacists play a major role in oral health care of the population. The present study revealed that majority of these pharmacists had no prior oral health training. Most of them were willing to give oral health care advice to the patients. Thus, proper and continuous oral health training of pharmacists can help to serve the oral health needs of the community.

Key words: Attitude, Knowledge, Oral health care, Pharmacist, Practice

INTRODUCTION

Oral health is important to general health and quality of life. Forty years ago, the American Dental Association stated, "The dentist and the pharmacist are partners in caring for oral health." In fact, the pharmacist sees more people with dental problems than the average dentist![1] Team working is now acknowledged as a key concept in the delivery of oral health care. The practice of community pharmacist has developed over years from traditional dispensing of medicine to more profound public and professional involvement in health care which is valuable to the community.[2] A survey of community pharmacists in Edinburgh, Scotland, in the fall of 2002, revealed that the pharmacist was asked at least one question every week about some oral health- related problem; nearly half of these questions were related to mouth ulcers or persistent soreness.[3]

India being a densely populated country with approximately 1.3 billion population, which is unevenly distributed in rural and urban areas. Jammu and Kashmir is geographically located in the Indian Himalayan Region (IHR), where Jammu district is located on the foothills of IHR. The hilly geography makes the accessibility to oral health care difficult. However, community pharmacies have been spread over the remotest areas of Jammu district. Pharmacies are the frontline approach for delivering oral health care and are easily accessible to the public. There are a variety of ways by which the pharmacist can take a frontline approach to oral disease prevention, identification, assessment, management, and referral.[3] These include

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promoting topical fluorides, especially fluoride toothpastes, encouraging effective oral hygiene practices, promoting healthy eating, encouraging use of dental services and preventive therapies, and giving parents and other family caregivers information, motivation, confidence, and the skills to prevent oral disease.[1] The pharmacist should be able to discuss the appropriate dental products for a patient's oral health needs and know when referral to a dentist is needed. He should be able to recognize the oral side effects of systemic medications, be familiar with the interactions between oral and general health, and counsel patients as needed.

While this is most often discussed in the context of members of the "dental team," this study provides a useful reminder of the potential contribution of healthcare professionals, beyond the confines of the surgery. Thus, this study was done to evaluate the role of pharmacist in dentistry.

The aim of the study was to evaluate the knowledge, attitude, and practice of pharmacist regarding oral health care and oral health products in Jammu district.

METHODOLOGY

A cross-sectional study was conducted on pharmacists in Jammu district, over a period of 2 months. A sample size of 384 was estimated. A pilot study was undertaken on 10% of the study participants to check the feasibility of pro forma and to improve the clarity and understanding of the questionnaire. They were not included in the study.

Informed consent was obtained from the pharmacists participating in the study before the start of the study. Stratified simple random sampling method was used to select the pharmacies. Jammu district is administratively divided into seven subdivisions, namely, Jammu South, Jammu North, R.S. Pura, Marh, Akhnoor, Chowki Choura, and Kour. A closed-ended pre-validated questionnaire[4] was distributed among pharmacists from all subdivision of Jammu. The questionnaire was divided into five sections: Section I: Comprised details regarding the vicinity of the dentist to the pharmacy, Section II: Comprised details regarding range of dental products stocked in the pharmacy, Section III: Comprised details regarding advice given by the pharmacist to customers regarding oral health, Section IV: Comprised details regarding pharmacist's source of information regarding oral health and oral hygiene, Section V: Focused on the dental patients attending the pharmacies; their number, common complaints, and advices sought out by them regarding dental problems.[4]

The collected data were thoroughly screened and entered into MS Excel spread sheets. Statistical Package for the Social Sciences (SPSS) version 20 was used to analysis the collected data.

RESULTS

The mean age of pharmacist was 43.2 years ± 10.41. Among 384 pharmacists, 311 (80.9%) were male [Figure 1]. Most of the pharmacists were diploma holders. About 3.6% of the pharmacist had master's degree [Figure 2]. About 357 (92.9%) pharmacies were owned by individuals, 22 (5.7%) belonged to a chain of pharmacies, and the rest were attached to hospitals [Figure 3].

Table 1 gives the details about the knowledge and attitude of pharmacists regarding oral health care and oral hygiene products. About 79.1% of the pharmacists who participated in the present study knew that there were dental clinics in their vicinity and among them only 60.5% knew their working timings. Most of the pharmacist (63.8%) recommended oral hygiene products based on their personal experience.

While assessing the attitude toward oral health care, 79.1% were interested of the participating pharmacists were interested in giving oral health care advice to patients [Figure 4]. When asked whether fluoride in toothpaste is

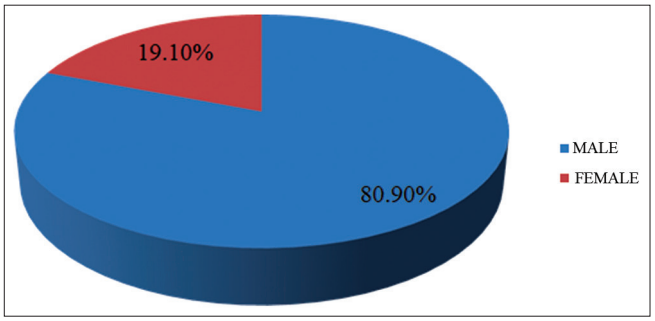

Figure 1: Distribution of study subject according to gender

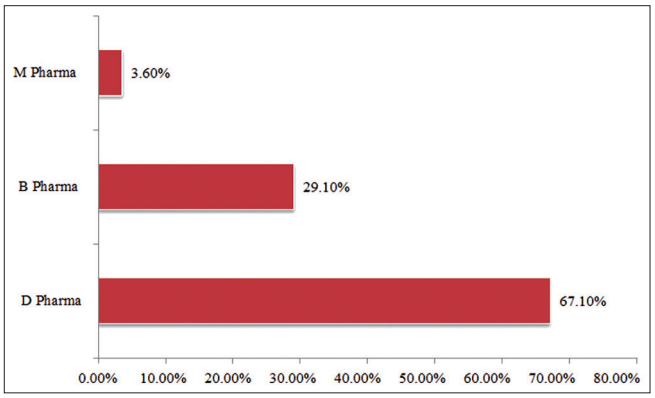

Figure 2: Distribution of pharmacist based on qualification

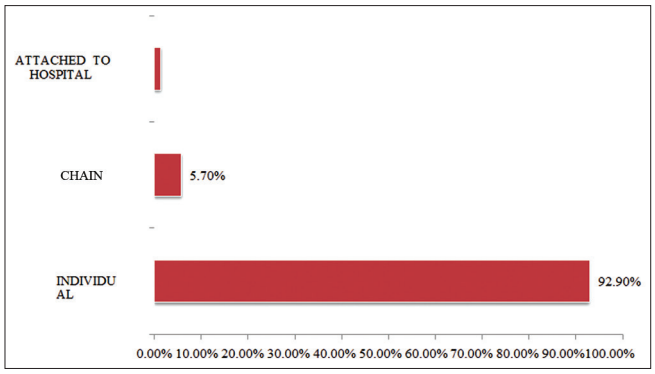

Figure 3: Distribution of type of pharmacy

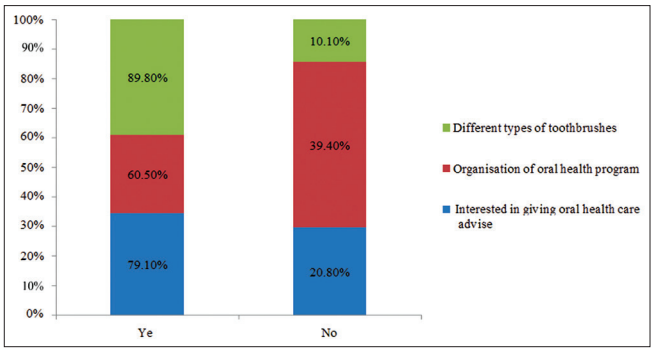

Figure 4: Distribution of study subjects according to knowledge and attitude

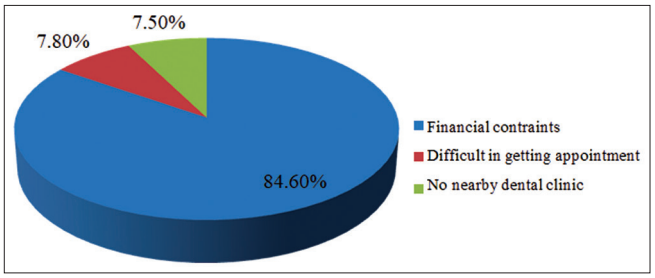

Figure 5: Distribution of study subjects according to knowledge and attitude

beneficial, nearly 89.8% of pharmacists were unaware of the benefits of fluoride in toothpaste [Table 1]. Most of the pharmacists (84.6%) feel that financial constraint is the reason for patient approaching the pharmacist instead of a dentist [Figure 5].

Most common oral health problem experienced by the participating pharmacist was toothache (83.1%) followed by bleeding gums and ulcers. Most of the pharmacies (75.3%) said that they experience <10 patients per day complaining about oral problems. Toothpaste is the most common dental product followed by toothbrush available in the pharmacies. About 70.3% of the participating pharmacists ask the patient to consult a nearby dentist after dispensing medications, 10.4% dispensed antibiotics and painkillers without any referral to a nearby physician or dentist. About 19.2% of pharmacists said that they just ask the patient to consult a nearby dentist, without dispensing medication [Table 2].

Table 1: Distribution of study subjects according to knowledge and attitude

Question	Options	Frequency (%)
Nearby dental clinic	a. Yes	304 (79.1)
	b. No	80 (20.8)
Working time of the dentist near your pharmacy	a. Yes	184 (60.5)
	b. No	120 (39.4)
Basis of recommendation of the oral hygiene products	a. Knowledge of product	46 (1.2)
	b. Personal experience	245 (63.8)
	c. Dentist opinion	89 (23.1)
	d. Advertisement	0 (0.0)
	e. Popularity of product	1 (0.2)
	f. Others	0 (0.0)
	g. All products are same	3 (0.7)
Do you think fluoride in toothpaste is beneficial?	a. Yes	34 (8.8)
	b. No	5 (1.3)
	c. Do not know	345 (89.8)

DISCUSSION

Pharmacists and pharmacy have a substantial role in the primary health-care system and hold a great potential to expand their role in oral health promotion.[5] Pharmacist being the frontline of health-care system, customers/patients frequently visit them to seek oral health advice. Excellent communication between a pharmacist and dentist is the best way to provide oral health care. Thus, this cross-sectional study was conducted to explore the knowledge, attitude, and practice of pharmacists on oral health care and oral hygiene products in Jammu district.

In the present study, more number of males (80.9%) was seen working as pharmacist in Jammu district. Similar results were seen in a study done by Gupta *et al.*[4]

In India, community pharmacies are either owned by a single person or attached to government and private hospitals. In addition, there are a chain of pharmacies running all over the country. In the present study, approximately 93% of the pharmacies were owned by individual pharmacists. Similar observations were seen in Gupta *et al.*[4] and Priya *et al.*[3]

Pharmacist being the first line access of the health-care system should know about the nearby dentist so that he/she can refer patient when needed. While assessing knowledge of the pharmacist, it was seen that about 79% of the pharmacist knew that there was a nearby dental clinic. Among them, only about 60% knew the working timings of the dentist. Similar observations were seen in study done by Priya *et al.*,[3] Gupta *et al.*,[4] Bawazir,[6] Hamissi and Hamissi,[7] and Maunder and Landes.[8]

Table 2: Distribution of study subjects according to practice

Question	Options	Frequency (%)
Health problems experienced	a. Toothache	319 (83.1)
	b. Gum problem (bleeding gums)	33 (8.5)
	c. Mouth malodor	9 (2.3)
	d. Ulcers	19 (4.9)
	e. Dental abscess	4 (1.0)
	f. Teething	0 (0.0)
Patients visiting pharmacy complaining about oral health problem	a. <10	289 (75.3)
	b. >10	95 (24.7)
Oral health products available in the pharmacy	a. ≤10%	84 (21.8)
	b. 10–20%	146 (38.02)
	c. >20%	154(40.1)
Different oral health-care products available in the pharmacy: (can tick more than one)	a. Tooth paste	381 (99.2)
	b. Toothbrush	350 (91.1)
	c. Mouthwash	230 (59.8.9)
	d. Dental floss	190 (49.4)
	e. Denture care products	120 (31.2.8)
	f. Others	47 (12.2)
Advice given to the patients	a. Ask to consult a nearby dentist, after dispensing medications	270 (70.3)
	b. Dispense medication (pain killer and antibiotic)	40 (10.4)
	c. Ask to consult a dentist without medication	74 (19.2)

Most of the pharmacists (63.8%) recommended the oral health products based on their personal experiences. Only 89 pharmacists out of 384 recommended the oral health-care products based on the dentist opinion. However, when asked about the benefits of fluoride in toothpaste, approximately 90% of the pharmacist did not know anything about fluoride. This observation shows that there is an immediate need of imparting oral health knowledge to the pharmacist. Regular meetings and seminars imparting oral health information should be conducted for the pharmacists. Interdisciplinary approach is the key to attain oral health care in the district. Further, this lack of knowledge can also be related to less number of pharmacists with master's degree. Approximately 67% of the pharmacists were diploma holders. Similar observations were seen in a study done by Gupta *et al.*[4] and Bawazir.[6]

Knowledge along with positive attitude toward imparting oral health care is very important. Hence, while assessing the attitude of the pharmacist, a total of 61% of the pharmacist expressed their interest in attending more courses or programs. This illustrates that pharmacists are an underused but are potential oral health-care resource. If the investment is put into their training, then they can reasonably be expected to undertake more responsibilities as oral health-care providers. Similar results were seen in studies done by Priya *et al.*,[3] Gupta *et al.*,[4] and Bawazir.[6] Most of the respondents (84.6%) said that financial constraints are the barrier to the patients visiting dental clinics. This is in accordance with other studies done by Gupta *et al.*[4]

Many people visit pharmacies looking for pain relief and medications to rid themselves of toothache, ulcers, and oral health problems.

The most common oral health complaint experienced by pharmacists in the present study was toothache (83.1%) followed by ulcers (4.9%). About 70.3% of the pharmacist recommended these patients to visit a dentist and they were supplied with medications for short-term pain relief. Similar results were seen in studies done by Priya *et al.*,[3] Gupta *et al.*,[4] Bawazir,[6] Maunder and Landes,[8] and Hamissi and Hamissi.[7] It is significant to note that although the most common recommendation of the pharmacist is "to see a dentist," few pharmacists had ever met the dentist nearby, did not know the working times of the dentist. Approximately 10% of the pharmacist dispensed the medications without recommending to the dentist. This might provide a temporary pain relief, but there can be misuse of the medication by the patient. Furthermore, short-term pain relief might mean that the patient will postpone consulting a dentist and, thus an opportunity to diagnose a disease in its early stage may be lost.

While assessing the practice, approximately 75% of the pharmacist said that <10 patients a day visit pharmacy complaining about oral health problem. Similar results were observed in studies done by Gupta *et al.*[4] and Bawazir.[6]

Most of the pharmacies stock a wide range of dental products such as toothpaste and toothbrush.

Assessment of the stocks revealed, nearly 40.1% of the pharmacies had >20% of the oral health products. Toothpaste and toothbrush were available in approximately 99% and 91% of the pharmacies. Similar results were seen in a study done by Gupta *et al.*[4] It is important to

conduct oral health education programs and courses for the pharmacist, so that the pharmacist can discuss the appropriate dental products for a patient's oral health needs and know when referral to a dentist is needed.

This study included a large sample size from different subdivisions of Jammu district. This provided a representative sample that can be generalized. The response rate was satisfactory. The results of the present study rely on self-reported data, thus the information may have been biased through over and underreporting due to social desirability.

Overall knowledge, attitude, and practice among the pharmacists in Jammu district were low. Increasing oral health diseases, along with unevenly distributed dentist in rural and urban areas requires interdisciplinary approach. Pharmacists have long served as the medication expert of the health-care team and, due to their knowledge and accessibility, are frequently approached by the public to answer health-related questions. However, pharmacists are an underutilized resource, and there is a definitive need to improve their training and access to information on available dental services.

The pharmacists exhibited negative attitude and inadequate self-care practices toward oral health. It can be speculated that the average oral health knowledge among pharmacists could be the main reason for such a finding.

Recommendations

1. There is a need for revisiting the pharmacy curricula for undergraduates and more collaboration with dental institutions
2. Tailored oral health programs and education courses should be conducted according to the needs of already established pharmacists
3. Stronger collaborations and interactions among pharmacists and dentists should be established including referral protocols.

CONCLUSION

Our findings suggest that overall knowledge, attitude, and practice of oral health care and oral hygiene products is low among pharmacist in Jammu district. Community pharmacists play a major role in referring and oral health promotions. Thus, collaborations between pharmacist and dentist and better oral health education and training programs may enhance their roles in oral health. This may help reduce the disparities in oral health among the residents of Jammu district.

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Original Article

Ocular Findings in Patients with Oculocutaneous Albinism: A Retrospective Study

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Abstract

Background: Oculocutaneous albinism (OCA) is a group of autosomal recessive disorders characterized by a reduction in melanin production in the skin and eye tissues. It is associated with a variable number of ocular morbidities which include foveal hypoplasia, nystagmus, refractive errors, iris transillumination defects, and strabismus. The purpose of this study was to determine ocular findings and visual status of patients with oculocutaneous albinism.

Materials and Methods: In the present retrospective study, we analyzed 30 case sheets of patients with OCA who had presented to our clinic over the past 2 years. Variables noted were best-corrected visual acuity (BCVA), type of refractive error, presence or absence of foveal hypoplasia, nystagmus, strabismus, iris transillumination defects, or any other ocular morbidity.

Results: Mean age of our study group was 21.66 years (range 5–45 years) with a male:female ratio of 1.3:1. We noted a high percentage of consanguineous marriages (73.33%). All patients had foveal hypoplasia, nystagmus (horizontal), and iris transillumination defects. Eighty percent of the patients had BCVA between 6/24 and 6/60. Astigmatism (with the rule) was the most common refractive error seen in 56.66% of the cases, followed by hypermetropia (33.33%) and myopia in 10% of cases. Strabismus was noted in 33.33% of the cases, the most common type being esotropia (70%).

Conclusion: OCA is associated with varied ocular manifestations, so it is important to screen these patients early in their lives so that appropriate rehabilitative measures are taken early improving the quality of life and better social and economic integration of these individuals. Moreover, given the genetic nature of the disease, consanguineous marriages in families with a history of OCA should only be done after proper genetic counseling.

Key words: Oculocutaneous albinism, Foveal hypoplasia, Refractive errors

INTRODUCTION

The term albinism is derived from the latin word "albus " meaning white.[1] Oculocutaneous albinism (OCA) is a group of autosomal recessive disorder characterized by a reduction in the production of melanin pigment in the structures of skin and eyes [Figure 1].[2] The deficiency of tyrosinase enzyme is responsible for the variable production of melanin in these patients. OCA is associated with variable number of ocular morbidities which include foveal hypoplasia, fundus hypopigmentation [Figure 2], iris transillumination defects, misrouting of the optic nerve fibers at the chiasm, nystagmus, reduced visual acuity, strabismus, photophobia, and refractive errors.[3,4]

The purpose of this study was to determine ocular findings and visual status of patients with OCA. Despite recent advances in medical care, there is no cure for OCA, hence making it even more important to detect various ocular abnormalities, especially refractive errors so that they can be treated at the appropriate time. Early interventions in this group can prevent visual disability later on in their life.

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MATERIALS AND METHODS

The present retrospective study was done at Vision Center (A complete Eye clinic) at Lal Bazar Srinagar, which is a registered eye clinic with the directorate of health services Srinagar J&K. We analyzed the clinical case sheets of patients with OCA who had presented to the clinic over the past 2 years. The diagnosis of OCA was based on clinical findings of hypopigmentation of skin and hair in addition to characteristic ocular finding.[5] Variables noted were visual acuity, type of refractive error, presence or absence of foveal hypoplasia, nystagmus, strabismus, and iris transillumination defects. The presence of any other ocular anomaly was also noted. Consanguinity of marriages was also noted in our study as OCA is a heritable disorder. Patients of <5 years age were excluded as it is difficult to obtain measurements of various variables from them.

The study adhered to the tenets of the Declaration of Helsinki and consents were obtained from patients/ parents. Data were analyzed using the Statistical Package for the Social Sciences (SPSS). A $P < 0.5$ was considered statistically significant.

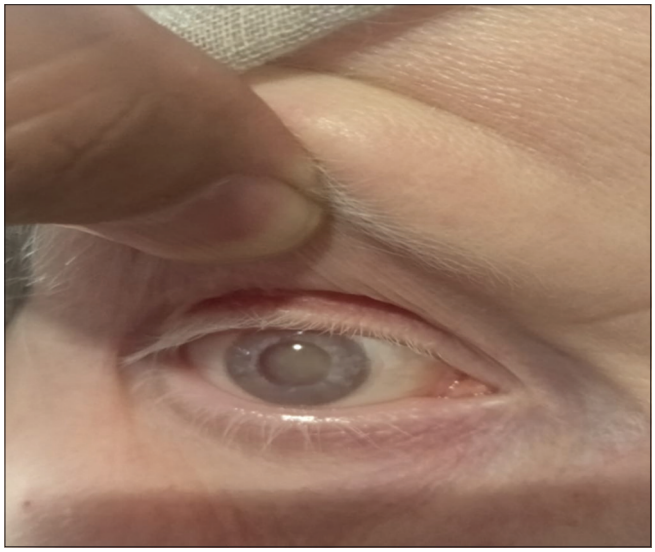

Figure 1: A case of OCA with mature cataract

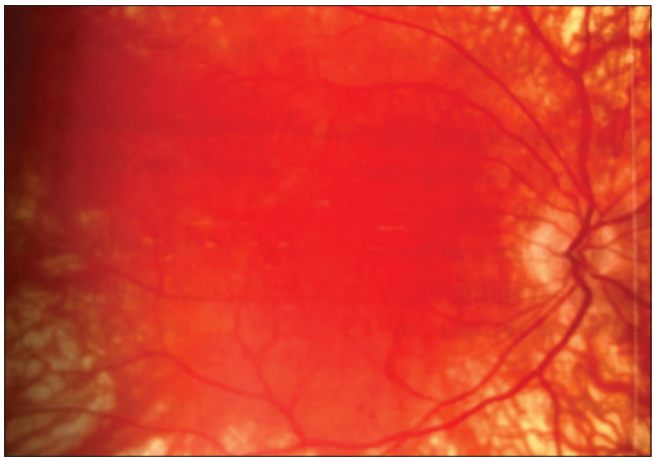

Figure 2: Fundus hypopigmentation and foveal hypoplasia

RESULTS

Data comprising 30 patients (60 eyes) were analyzed in our study. The mean age of our study group was 21.66 years with a range of 5 to 45 years. Out of the total 30 patients, 17 were male and 13 were female with a male:female ratio of 1.3:1. We recorded a high percentage (73.33%) of consanguineous marriages in our patients. All of our patients had typical characteristics of OCA which includes foveal hypoplasia, fundus hypopigmentation, iris transillumination defects, and nystagmus.

The visual status of the patients is depicted in Figure 3. Eighty percent of the patients had vision between 6/24 to 6/60. The distribution of refractive errors is shown in Figure 4. The most common refractive error in our study was astigmatism 56.66% (with the rule), followed by hypermetropia (33.33%) and myopia (10%).

Three of our patients had cataracts (one nuclear cataract, one mature cataract, and one had posterior subcapsular).

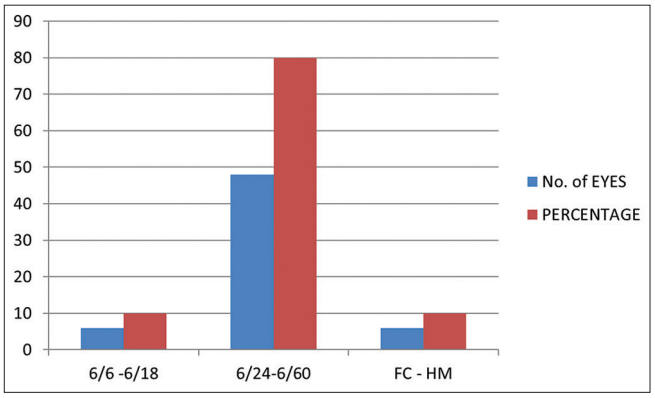

Figure 3: Visual status of patients with OCA

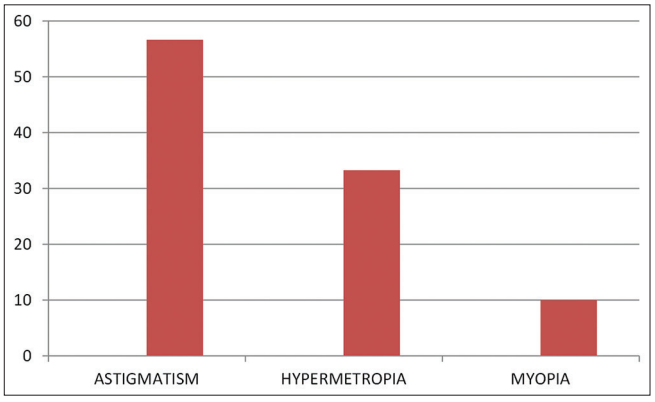

Figure 4: Astigmatism (56.66%) to be the most common refractive error

All of them underwent phacoemulsification with good post-operative results. One patient had keratoconus.

DISCUSSION

A total of 30 patients (60 eyes) of OCA were analyzed in our study, we found that the mean age of our study subjects was 21.66 years which is more than reported by some other studies.[6,7] This late presentation can be attributed to a lack of awareness of the disease and its associated ocular morbidities. The male:female ratio in our study was 1.3:1, which is comparable to other studies.[8]

One of the striking observations of our study was the high rate of consanguinity. Out of the total 30 patients, 22 patients had a history of consanguineous marriage (73.33%). This is close to the study done by Mohammed *et al.*,[9] in which 66.37% of patients had a history of consanguineous marriages. Another study done by Gamella *et al.*[10] also reported role of consanguineous marriages in OCA. All types of OCA are inherited as autosomal recessive disorders.[3,11] Thus, the presence of various types of carriers within different generations of a family is the cause of high prevalence of OCA in them. Consanguineous marriages markedly increase the chance of children developing OCA among parents who are themselves asymptomatic carriers, hence the need for carrier detection and genetic counseling in such families.

In our study, we found that 80% (48 eyes) had best-corrected visual acuity between 6/24 and 6/60 of Snellens chart [Figure 3]. The cause of this low vision was foveal hypoplasia, nystagmus, iris transillumination defects, and refractive errors. These findings were present in all of our patients. Foveal hypoplasia is one of the most significant vision limiting factors found in albinism.[1] The cause of foveal hypoplasia in OCA is thought to be related to decreased amounts of melanin in retinal pigment epithelial cells.[12] All of our subjects had horizontal nystagmus, the cause of which is foveal hypoplasia and misrouting of the optic nerve fibers.[4] Horizontal nystagmus has been reported by other studies[13] to be the predominant type of nystagmus in patients with OCA. Iris transillumination defects were seen in all subjects, cause of which is reduced melanin production in the iris as a result of which light reflected from retina is not filtered by iris due to which the iris appears pink in pigment deficient areas.[5] Iris transillumination defects are also the cause of photophobia which is the most common symptom of OCA[5,14] and is also the cause of disability glare resulting in decreased visual acuity. Strabismus was present in 33.33% of the cases, the most common type being esotropia accounting for 70% of the cases. The high prevalence of strabismus in OCA cases has been supported by other studies.[5,15] Misrouting of the optic nerve fibers due to incomplete pigmentation is one of the causes, the abnormalities of decussation result in a monocular representation of the visual field in each occipital cortex.[3] Abnormal visual cortex development has also been reported by some studies as a cause of strabismus in these cases.[16]

Refractive errors are common in OCA. We found astigmatism (with the rule) to be the most common refractive error in 56.66% of the cases. This is in agreement with various other studies.[4,6,8,14,17-19] Hypermetropia was present in 33.33% of the cases and myopia in 10%. Hence, it is very important that these refractive errors are detected and treated early in their life so that visual morbidities like amblyopia are prevented. The mean age of presentation in our study was 21.66 years, hence the need for awareness among people with OCA to get screened for any kind of refractive error early in their life. This will not only improve quality of life of these patients but also help in better social and economic integration in to the society.

CONCLUSION

OCA is a condition that is associated with various ocular manifestations. Given the fact there is no cure for the disease at present, it is imperative to screen these patients for refractive errors early in their lives. Moreover, given the genetic nature of the disease, consanguineous marriages in families with OCA should be avoided or done only after proper genetic counseling. Further, an effort should be made to increase the awareness of the disease which will help in better management of the ocular morbidities associated with OCA.

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Original Article

A Prospective Comparative Study to Evaluate the Susceptibility of Bacterial Strains Isolated from Patients with Respiratory Tract Infection to Cefpodoxime Plus Clavulanic Acid and to Amoxicillin Plus Clavulanic Acid

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Abstract

Respiratory tract infections (RTIs) are one of the major public health problems in India. Susceptibility tests conducted to ascertain the susceptibility of the isolated bacteria to various antibiotics and to identify emerging trends of antibiotic resistance are helpful for antibiotic selection for initiating empirical treatment while awaiting results of the culture and sensitivity. This study was conducted to evaluate the susceptibility of bacterial strains isolated from patients with RTIs, determined by *in-vitro* strip method, to amoxicillin plus clavulanic acid in comparison to cefpodoxime plus clavulanic acid in terms of the Minimal Inhibitory Concentration (MIC) values a hundred subjects of either gender more than 3 months age, with clinical diagnosis of RTI and having culture positive samples with either *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Haemophilus influenzae,* and/or *Moraxella catarrhalis* were considered. Primary efficacy endpoint was to compare MIC_{90} of the two antibiotics (cefpodoxime plus clavulanic acid and amoxicillin plus clavulanic acid) against these bacteria. Secondary efficacy endpoints were MIC_{50} of the two antibiotics and the geometric mean MIC of the two antibiotics. The MIC_{90} and MIC_{50} values of cefpodoxime plus clavulanic acid are found to be lower as compared to that of amoxicillin plus clavulanic acid for all four bacterial strains, that is, *S. aureus*, *S. pneumoniae*, *S. pyogenes* and *M. catarrhalis*. Further, the mean MIC values of cefpodoxime plus clavulanic acid are significantly lower in comparison with that of amoxicillin plus clavulanic acid for *S. aureus*. Pain and discomfort during collection of throat swab were adverse events recorded in the study.

Key words: Amoxicillin, Antibiotic resistance, Cefpodoxime, India, Respiratory tract infections

INTRODUCTION

Respiratory tract infections (RTIs) are one of the major public health problems and one of the leading causes of morbidity and mortality in both developed and developing countries. RTIs account for over 50 million deaths each year globally.[1] In fact, RTIs are one of the commonest types of infections affecting the Indian population, with prevalence rates ranging around 52%. Most of the RTIs are limited to the upper respiratory tract and only 5% involve the lower respiratory tract. As per the main locus of the infections, RTIs are categorized as – upper RTI (URTIs) and lower RTI (LRTIs). URTIs involve the nasal passages, pharynx, tonsils, and epiglottis, whereas LRTIs involve the bronchi and alveoli and include two serious conditions – acute bronchitis and pneumonia.[1,2] Some of these respiratory infections such as common cold, pharyngitis, and otitis media are more common among children and peak from infancy to 5 years.[3]

Paediatric RTIs are one of the most common reasons for physician visits and hospitalization. These infections present one of the major complaints in children and adolescents.[4] On an average, children below 5 years of

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age suffer about 5 episodes of acute respiratory infection per child per year, thus accounting for about 238 million attacks and about 13 million deaths every year in the world.[5] The child with recurrent respiratory infections presents a difficult diagnostic challenge. The recurrent respiratory infections in infants and children are among the most common causes of counseling and admission to the hospital. They are responsible for significant morbidity measured by school days lost.[6] Cough and cold lead to missed school days for children, this in turn leads to missed office days for working parents who need to stay at home to take care of their children.[7]

Physicians, in general, rely on clinical signs and symptoms to diagnose respiratory infections; the causative microbes are rarely identified. The uncomplicated URTIs are most likely caused by viruses. The viruses detected most frequently during acute RTI are human *rhinoviruses*, *paramyxoviruses*, *coronaviruses,* and *bocavirus*.[6] Bacterial URTIs are mainly caused by *Streptococcus*, *Klebsiella*, *Pseudomonas*, *Staphylococcus*, *Acinetobacter*, *Proteus*, *Enterobacter*, and *Haemophilus*. However, the responsible pathogens are usually un-identified in 50% of the patients despite of thorough diagnostic tests being carried out.[8] The choice of antibiotics in these cases is mostly empirical, usually based on the severity of illness, the known probabilities of the pathogens in specific geographical areas, resistance patterns of the most commonly implicated etiological agents, and associated co-morbidities.[8] The high disease and economic burden of RTIs call for evidence-based public health approaches, including a better understanding of causative microorganisms, for prevention and treatment of RTI.[9]

Guidelines on antibiotic choice for RTI are generally not consistent.[10] The main class of antibiotic prescribed are penicillins, cephalosporins, macrolides, and fluoroquinolones. In many countries, plain amoxicillin and other penicillins are recommended as first-line therapy for most children with acute infections; however, amoxicillin-clavulanate, which is a broad-spectrum antibiotic, is more popularly used. Broad-spectrum antibiotics for URTIs would be the ones with activity against clinically important colonizing flora beyond *Pneumococcus* (the primary target for the specified acute RTI) such as *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Staphylococcus aureus*. Apart from amoxicillin-clavulanate, the other commonly prescribed broad-spectrum antibiotics in RTI are the cephalosporins and macrolides.

Susceptibility tests determine a microbe's susceptibility/vulnerability to antimicrobial drugs by exposing a standardized concentration of organisms to specific concentrations of antimicrobial drugs. Susceptibility testing can be done for microbes. Antimicrobial Susceptibility Testing (AST) can be used for drug discovery, epidemiology, and prediction of therapeutic outcome.[11] First introduced in 1929, *in vitro* AST methods are considered to be the most valuable in determining the efficacy of antimicrobial compounds against various microorganisms.[12] In general, AST methods combine one or more antimicrobial agents with bacteria to assess bacterial growth. This testing is essential to determine the possible suitability of specific antibiotics on inhibiting the bacteria and/or to determine if the bacteria have developed resistance to certain antibiotics. The results of this test can be used to help select the particular antibiotics that can be expected to be most effective in treating an infection.

Accurate and appropriate susceptibility testing of microbes will guide the physician in choosing the antimicrobial agent for difficult-to-treat infections and ensure optimal effective patient-tailored therapy and avoid over-prescription. The results from susceptibility testing are reported as the MIC, which is defined by the lowest concentration of a drug in which no visible growth occurs. The MIC_{50} represents the concentration at which ≥50% of the isolates in a test population are inhibited; it is equivalent to the median MIC value. The tested microorganism is then classified as either clinically susceptible, intermediate, or resistant to the tested drug. The MIC_{90} represents the MIC value at which ≥90% of the strains within a test population are inhibited; the 90th percentile.

Bacteria have the capability to develop resistance to antibiotics at any time. This means that antibiotics which once could kill or inhibit their growth may no longer be effective. Numerous resistant strains of major pathogens are emerging and so susceptibility testing will surely help out to observe their pattern of growth. This also helps to keep under scrutiny the susceptibility pattern of the existing-prevalent microbial strains.

Combination of amoxicillin with clavulanic acid and cefpodoxime with clavulanic acid are two popular antibiotics that are used by the General Practitioners, ENT specialists, and pediatricians for the management of URTIs. Both are broad-spectrum antibiotics with demonstrated efficacy against various aerobic (Gram-positive and Gram-negative) bacteria and anaerobic bacteria. Table 1 lists the microbes that are shown susceptible to these antimicrobials.

The current study was planned to evaluate the susceptibility of bacterial strains isolated from patients with upper RTI to amoxicillin plus clavulanic acid as compared to cefpodoxime plus clavulanic acid with respect to MIC values, determined by *in-vitro* strip method.

Table 1: List of microorganisms that are shown susceptible to amoxicillin plus clavulanic acid and cefpodoxime plus clavulanic acid

Commonly susceptible microorganisms	
Amoxicillin plus clavulanic acid	**Cefpodoxime plus clavulanic acid**
Aerobic Gram-positive micro-organisms	
Enterococcus faecalis	*Staphylococcus aureus* (including penicillinase-producing strains)
Gardnerella vaginalis	Note: Cefpodoxime is inactive against methicillin-resistant *staphylococci.*
Staphylococcus aureus (methicillin-susceptible)	*Staphylococcus saprophyticus*
Coagulase-negative *staphylococci* (methicillin-susceptible)	*Streptococcus pneumoniae* (excluding penicillin-resistant strains)
Streptococcus agalactiae	*Streptococcus pyogenes**
Streptococcus pneumoniae	*Streptococcus agalactiae**
Streptococcus pyogenes and other	*Streptococcus agalactiae**
beta-hemolytic *streptococci*	*Streptococcus* spp. (Groups C, F, G)
Streptococcus viridans group	Note: cefpodoxime is inactive against *enterococci*
Aerobic Gram-negative micro-organisms	
Capnocytophaga spp.	*Escherichia coli*
Eikenella corrodens	*Klebsiella pneumoniae*
Haemophilus influenzae	*Proteus mirabilis*
Moraxella catarrhalis	*Haemophilus influenzae* (including beta-lactamase-producing strains)
Pasteurella multocida	*Moraxella* (Branhamella) catarrhalis
	Neisseria gonorrhoeae (including penicillinase-producing strains)
	Citrobacter diversus
	Klebsiella oxytoca
	Proteus vulgaris
	Providencia rettgeri
	Haemophilus parainfluenzae
	Note: Cefpodoxime is inactive against most strains of *Pseudomonas* and *Enterobacter*
Anaerobic micro-organisms	
Bacteroides fragilis	*Peptostreptococcus magnus**
Fusobacterium nucleatum	
Prevotella spp.	

*Safety and efficacy of cefpodoxime in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials

MATERIALS AND METHODS

The objective of this study was to evaluate the susceptibility of bacterial strains isolated from patients with upper RTI to cefpodoxime plus clavulanic acid as compared to amoxicillin plus clavulanic acid by *in-vitro* strip method. The study was conducted in compliance with the "National Ethical Guidelines for Biomedical and Health Research Involving Human Participants" issued by Indian Council of Medical Research, 2017 and in accordance with the ethical considerations laid down in Declaration of Helsinki, Fortaleza, Brazil (October 2013). The study/trial was conducted as a prospective, active-controlled *in-vitro* study in samples obtained from treatment-naïve patients suffering from RTIs. This was a study to compare MIC of two different antibiotic combinations and did not involve any treatment provided to the enrolled patients. As this was a study conducted to generate real-world data and to assess the antibiotic sensitivity scenario; hence, no formal sample size calculation was done. The patients enrolled in the study were treated by the physician/investigator as per his/her standard of care (routine clinical practice) and patients were not given any specific treatment as a part of this study. The Study Protocol and Patient Informed Consent Document (ICD) (in English and other applicable vernacular languages) were submitted to the applicable locally registered Institutional Ethics Committee before initiating the study at the site. The approval was received before the start of the study itself. Written informed consent was obtained before initiation of any of the study/trial-related activities on the ICDs from all patients willing to take part in the study. The patients who had provided their consent to participate in the study were then evaluated as per the inclusion/exclusion criteria. The main inclusion criteria were: (a) Patients of either gender more than 3 months, (b) patients with clinical diagnosis of RTI, and (c) patients or patient's legally acceptable representative willing to sign the ICD. The exclusion criteria were: (a) Patients who had taken antibiotics, antiviral agents, or interferon therapy in the past 30 days before enrolment into this study, (b) patients who were on immunosuppressive therapy, (c) patients who had taken any vaccine in the past 30 days, (d) patient who has participated in any other clinical study in the past 30 days, and (e) patients not willing to give a sample for analysis.

The two antibiotic combinations for which MIC was evaluated were:

- Antibiotic 1: Cefpodoxime plus clavulanic acid: Cefpodoxime/clavulanic acid Ezy MIC™ Strip (CPD) manufactured by HIMEDIA (Catalog No. EM138), capable of showing MICs in the range of 0.016 mcg/ml to 256 mcg/ml
- Antibiotic 2: Amoxicillin plus clavulanic acid: Amoxyclav Ezy MIC™ Strip (AMC) manufactured by HIMEDIA (Catalog No. EM003), capable of showing MICs in the range of 0.016 mcg/ml to 256 mcg/ml.

Ezy MIC™ Strips is a quantitative technique for determining the antibiotic susceptibility of a wide range of aerobic and fastidious organisms. The system comprises a predefined antibiotic gradient which is coated on a paper strip used to determine the Minimum Inhibitory Concentration (MIC), in μg/ml, of different antibiotic agents against a variety of microorganisms when tested on appropriate agar media under specific incubation conditions. As with other dilution methods, Ezy MIC™ Strip directly quantifies antibiotic susceptibility in terms of discrete MIC values. However, using a predefined, stable, and continuous antibiotic concentration gradient, MIC values observed using Ezy MIC™ Strip are more precise and reproducible results are obtained as compared to those from conventional procedures based on discontinuous two-fold serial dilutions.

Based on the clinical signs and symptoms, either of the samples was taken from the eligible patients: (1) Throat swab, (2) sputum, or (3) pus. Only one sample was taken per patient. The sample was collected following all requisite aseptic precautions and stored in wide-mouthed sterile bottles. These were then shipped to the diagnostic laboratory within 4 h of collection and processed in laboratory; sample culture was performed and the organism was identified.

If any of the six target bacteria were isolated from the sample collected (*Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Haemophilus influenzae,* and *M. catarrhalis*), antibiotic sensitivity testing was done using strip method and MIC was determined for two antibiotic combinations under study. The primary efficacy endpoint was MIC_{90} of the two antibiotics combination (cefpodoxime plus clavulanic acid and amoxicillin plus clavulanic acid) against the different bacteria isolated. The secondary efficacy endpoints were (1) MIC_{50} of the two antibiotics combination against the different bacteria isolated, (2) MIC of the two antibiotics combination against the different bacteria isolated, and (3) proportion of samples sensitive for the two antibiotics combination as per criteria laid down by Clinical and Laboratory Standards Institute (CLSI).

As no particular medication was provided to the patients enrolled in the study, safety evaluation of study medication stands not applicable. However, like any other clinical trial procedure, adverse events were anticipated at the time of sample collection. Adverse events if any occurring during the sample collection process were recorded. After receiving the case record forms (CRFs), the data were checked for inclusion and exclusion criteria and then evaluated for analysis. The patients were to be treated by the investigator as per the routine clinical practice.

The data collected from the CRFs were analyzed for demographics, efficacy, and safety outcome using GraphPad Prism Version 8.0.1(244). Data were presented as mean (95% confidence intervals)/geometric mean (95% confidence intervals) or number (percentage). Descriptive statistics were used for different variables at baseline. $P < 0.05$ was considered as statistically significant. Standard statistical tests (unpaired *t*-test for continuous variables/ log-transformed MIC data and Fischer's exact test for categorical data) were used to analyze the data obtained.

RESULTS

Clinical Phase

A total of 100 subjects having culture-positive samples with either of the six target bacteria (*S. pneumoniae*, *K. pneumoniae*, *S. aureus*, *S. pyogenes*, *H. influenzae,* and *M. catarrhalis*) were considered for analysis in the study. It was a single-center study and all the samples were collected by the investigator and his team from routine Outpatient Department/in-house subjects with a clinical diagnosis of upper RTI. No deviations to the study protocol were reported during the study.

The mean age of the subjects enrolled in the study was 34.5 (30.3–38.6) years. The youngest subject was 3 months old, while the eldest subject enrolled in the study was 79 years. Among these 100 subjects, 58 were male, while 42 were female. The number of subjects when grouped on the basis of age was as follows in Table 2.

Types of Samples and Distribution of Target Organisms

Among the 100 culture-positive samples subjected to MIC evaluation during the study, 41 were swab samples, 32 sputum samples, and 27 pus samples.

Table 2: Age-distribution of the enrolled patients

Age (years)	No. of subjects
<12 years	21
Between 13 and 18 years	4
Between 19 and 65 years	70
Above 65 years	5

Among the 100 culture-positive samples subjected to MIC evaluation during the study, the distribution of the 4 target organisms isolated was 48 for *S. aureus*, 25 for *S. pneumoniae*, 21 for *S. pyogenes,* and 6 for *M. catarrhalis*.

Determining MIC_{50} and MIC_{90}

The MIC_{50} represents the MIC value at which ≥50% of the isolates in a test population are inhibited; it is equivalent to the median MIC value. Given n test strains and the values y1, y2……yn representing a graded series of MICs starting with the lowest value, the MIC_{50} was the value at position nx0.5, as long as n was an even number of test strains. If n was an odd number of test strains, the value at position (n+1) ×0.5 represented the MIC_{50} value.

The MIC_{90} represents the MIC value at which ≥90% of the strains within a test population are inhibited; the 90th percentile. The MIC_{90} was calculated accordingly, using nx0.9. If the resulting number is an integer, this number represented the MIC_{90}; if the resulting number was not an integer, the next integer following the respective value represented the MIC_{90}.

Both MIC_{50} and MIC_{90} values are presented as concentrations on the standard AST dilution series.

Efficacy Results

All patients with a positive culture and subjected to antibiotic sensitivity testing were considered for inclusion in the efficacy analysis. The MIC results obtained for the two antibiotics were evaluated as per the cut-offs mentioned in the CLSI guidelines. These were divided into susceptible or resistant as per the below table adopted from CLSI guidelines M100 (2018).

The primary efficacy endpoint was to compare MIC_{90} of the two antibiotics (cefpodoxime plus clavulanic acid and amoxicillin plus clavulanic acid) against the different bacteria isolated. The MIC_{90} values for the two study antibiotics are presented in Table 3.

There were two secondary endpoints, one of the secondary efficacy endpoint of the study was the MIC_{50} of the two antibiotics (cefpodoxime plus clavulanic acid and amoxicillin plus clavulanic acid) against the different bacteria isolated. The MIC_{50} values for the two study antibiotics are presented in Table 4.

The other secondary efficacy endpoint of the study was the geometric mean MIC of the two antibiotics (cefpodoxime plus clavulanic acid and amoxicillin plus clavulanic acid) against the different bacteria isolated. The geometric mean MIC values for the two study antibiotics are shown in Table 5.

The third secondary efficacy endpoint of the study was the proportion of samples sensitive for the two antibiotics as per CLSI criteria. The samples have been rated as sensitive and resistant based on the cut-offs given in CLSI guidelines and defied in the study protocol. The details are given in Tables 6 and 7.

Safety Results

All patients enrolled in the study and whose sample was collected were considered for inclusion in the safety analysis.

A total of 4 adverse events were reported in 4 study patients. The most common events recoded during sample

Table 3: MIC_{90} values for the two study antibiotics

Organism	Amoxicillin plus clavulanic acid		Cefpodoxime plus clavulanic acid	
	MIC_{90} (mcg/ml)	CLSI "Resistant" breakpoint(mcg/ml)	MIC_{90} (mcg/ml)	CLSI breakpoint (mcg/ml)
Staphylococcus aureus	4	8	2	8
Streptococcus pneumoniae	2	≤2	0.5	≤0.5
Streptococcus pyogenes	3	NAv	0.75	NAv
Moraxella catarrhalis	0.75	≤4	0.75	NAv

Values represent the MIC at which ≥90% of the strains within a test population are inhibited. NAv: Not available

Table 4: MIC_{50} values for the two study antibiotics

Organism	Amoxicillin plus clavulanic acid		Cefpodoxime plus clavulanic acid	
	MIC_{50} (mcg/ml)	CLSI 'Resistant' Breakpoint(mcg/ml)	MIC_{50} (mcg/ml)	CLSI Breakpoint(mcg/ml)
Staphylococcus aureus	1	8	0.5	8
Streptococcus pneumoniae	0.19	≤2	0.094	≤0.5
Streptococcus pyogenes	0.5	NAv	0.125	NAv
Moraxella catarrhalis	0.064	≤4	0.032	NAv

Values represent the MIC at which ≥50% of the strains within a test population are inhibited. NAv – Not available

Table 5: Mean MIC of the two antibiotics against the different bacteria isolated

	Geometric mean MIC (mcg/ml)		
Organism	**Amoxicillin plus clavulanic acid**	**Cefpodoxime plus clavulanic acid**	***P*-value**
Staphylococcus aureus	0.73 (0.51–1.05)	0.41 (0.27–0.62)	0.04
Streptococcus pneumoniae	0.21 (0.11–0.42)	0.13 (0.08–0.20)	0.20
Streptococcus pyogenes	0.32 (0.15–0.70	0.14 (0.08–0.24)	0.07
Moraxella catarrhalis	0.10 (0.03–0.34)	0.05 (0.01–0.23)	0.44

Data presented as GMT (95% CI). *P*-values derived from unpaired 2 sample *t*-test with equal variance on log-transformed data

Table 6: Proportion of samples sensitive for the two antibiotics as per CLSI criteria

		Sensitivity as per CLSI criteria		
Organism	***n***	**Amoxicillin plus clavulanic acid (%)**	**Cefpodoxime plus clavulanic acid (%)**	***P*-value**
Staphylococcus aureus	48	42 (87.5)	44 (91.7)	0.74
Streptococcus pneumoniae	25	23 (92.0)	23 (92.0)	1.0

Data presented as n (%) *P*-values derived from Fisher's exact test

Table 7: Proportion of samples resistant for the two antibiotics as per CLSI criteria

		Resistance pattern as per CLSI criteria		
Organism	***n***	**Amoxicillin plus clavulanic acid (%)**	**Cefpodoxime plus clavulanic acid (%)**	***P*-value**
Staphylococcus aureus	48	6 (12.5)	4 (8.3)	0.74
Streptococcus pneumoniae	25	1 (4.0)	0 (0.0)	1.0

Data presented as n (%) *P*-values derived from Fisher's exact test

collection include pain and discomfort during the collection of a throat swab. No other adverse event was reported during the sample collection. All four events were judged as mild and resolved without any treatment.

DISCUSSION

Globally, respiratory infections are one of the major health problems and as per ones estimation, respiratory infections lead to over 50 million deaths per year.[8] As per a study conducted in 2019 to understand the rate and pattern of prescription of antibiotics in an out-patient setting, it was found that the majority (around 30%) of the antibiotic prescriptions were dispensed for acute upper respiratory infections, including cough and acute nasopharyngitis.[13] Further, the highest antibiotic prescription rates were observed in the children in the age group 0–4 years.[13]

RTI triggers inflammation and production of mucus, leading to nasal congestion, a runny nose, scratchy throat, and cough, which may last as long as up to 14 days. In pediatric patient practice, cough is seen to have continued for weeks after the upper respiratory infection has resolved.[14] Coughing in children can be distressing and can have a major impact on child's sleep, school performance, and ability to play.[7] Fever as high as 101–102° F is a very common feature in young children with acute respiratory infections. Other typical symptoms in children include decreased appetite, headache and body aches, lethargy, and a general feeling of illness (malaise), followed by either wheezing or stridor. Acute respiratory infections could further develop into otitis media or pneumonia. Further, in children predisposed to asthmatic conditions, RTI could often lead to an acute asthma attack.[14] This may be the reason that although the general clinical guidelines mention that the antibiotics should not be prescribed for the common cold and nonspecific URTIs,[15] general practitioners tend to take a cautious approach and prefer to initiate empirical treatment with a broad spectrum antibiotic rather than waiting for the results of culture and sensitivity.

A considerable percentage (>65%) of prescriptions is that of broad-spectrum antimicrobials such as amoxicillin-clavulanic acid, cephalosporins, macrolides, clindamycin, and piperacillin-tazobactam.[16] Both general physicians and pediatricians mainly prescribe cephalosporins, followed by fluoroquinolones, penicillins, and macrolides.[10,15]

Amoxicillin

Amoxicillin is semisynthetic penicillin that inhibits enzymes in the biosynthetic pathway of bacterial peptidoglycan, which in turn leads to weakening of the cell wall, followed by cell lysis and death. Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes. Combining with clavulanic acid

helps amoxicillin to exert a therapeutic effect against the bacteria resistant to amoxicillin alone.

Clavulanic Acid

Clavulanate potassium is structurally related to penicillin and possesses the ability to inactivate a wide variety of beta-lactamase enzymes, thereby preventing inactivation of the combining antibiotics, such as amoxicillin and cefpodoxime. Clavulanic acid alone does not exert any clinically effective antibacterial effect.

Cefpodoxime

Cefpodoxime paroxetil is a third-generation, orally-administered, broad-spectrum, and antibiotic of the cephalosporins class. While first- and second-generation cephalosporins could only be administered by intravenous or intramuscular injection, the development of third-generation cephalosporins that are broad-spectrum and can be administered orally has significantly increased their value in the management of RTIs. The presence of clavulanate potassium in cefpodoxime-clavulanic acid combination further extends the antibiotic spectrum of cefpodoxime to include many bacteria normally resistant to cefpodoxime alone.

The pathogens causing RTIs are susceptible to beta-lactam antibiotics that include penicillins and cephalosporins. The presence of bacteria producing beta-lactamase is a major cause of antibiotic resistance, and these can interfere with the action of beta-lactam antibiotics even when they are not the primary pathogens. The addition of clavulanic acid increases the spectrum and the susceptibility of amoxicillin and cefpodoxime. This is also observed in the present study where 44 (92%) of 48 samples of *S. aureus* were found to be sensitive to cefpodoxime and clavulanic acid combination and 42 (87%) of 48 samples of *S. aureus* were found to be sensitive to amoxicillin and clavulanic acid combination, whereas sensitivity of *S. pneumoniae* was found to be 92% for both antibiotic combinations. This high level of the sensitivity of two common bacteria which formed 73% of the samples collected for this *in vitro* study indicates a possible reason for the popular use of these antibiotics for empirical treatment of URTIs while awaiting the results of culture and sensitivity.

The widespread and repeated prescription of antibiotics, especially those with a broad-spectrum, is the single most important cause of the rise of drug resistance.[17] In prescribing the pragmatic antibiotic, clinicians should consider the following: (1) The site of infection and the organisms most likely to be colonizing that site, (2) knowledge/patient's medical history of any bacterial infections in recent past, and (3) the local geographical bacterial resistance patterns that are observed for important pathogens at most hospitals.[18]

When a pathogenic microorganism is identified in clinical cultures, AST is performed. AST measures the ability of a specific organism to grow in the presence of a particular drug *in vitro* and is performed using guidelines established by the CLSI[19] an organization that develops laboratory process standards through extensive testing and clinical correlation. To optimize an accurate microbiological diagnosis, clinicians should ensure that diagnostic specimens are properly obtained and promptly submitted to the microbiology laboratory, preferably before the institution of antimicrobial therapy.[20] The goal of AST is to predict the clinical success or failure of the antibiotic being tested against a particular organism. Data are reported in the form of MIC, which is the lowest concentration of an antibiotic that inhibits visible growth of a microorganism, and are interpreted by the laboratory as "susceptible," "resistant," or "intermediate," according to CLSI criteria. A report of "susceptible" indicates that the isolated microbe is likely to be inhibited by the usually achievable concentration of a particular antimicrobial agent when the recommended dosage is used for the particular site of infection.

Various testing methods are grouped based on their chronological development:[21] (1) Gold-standard clinical methods, (2) mechanical methods, (3) optical methods, (4) microfluidics and microdroplets methods, and (5) models of *in vivo* infection.

Gold standard methods are standardized by various organizations such as the Clinical and CLSI and the International Organization for Standardization (ISO). The interpretation of test results is, among others, standardized by the European Committee on AST (EUCAST).[22] A number of laboratory methods can be used to evaluate the *in vitro* antimicrobial activity.[11] The two basic principles on which these tests are established on are the disk-diffusion and broth or agar dilution methods.

In this study, the *in-vitro* strip method using the Ezy MIC™ Strip gradient technology, based on the combination of both the dilution and diffusion principles for AST, is utilized. This method involves unique MIC determination paper strip(s) which are coated with the two antibiotic combinations under study, namely, (1) cefpodoxime and clavulanic acid and (2) amoxicillin and clavulanic acid in a concentration gradient manner, capable of showing MIC's in the range of predefined gradient, when tested on appropriate agar media, following overnight incubation.

Ezy MIC™ Strips provides *in vitro* MIC values, which provide only a possible indication of pathogens potential in *in vivo* susceptibility. These values can be considered as a guide to therapy selection only after taking into

consideration several other factors and must be the sole decision and responsibility of the physician along with the clinical experience in treating the infection. These tests are comparable to the standards as per the given specifications and set of experiment standards as far as possible.

The widespread and repeated prescription of antibiotics, especially those with a broad-spectrum, can lead to antibiotic resistance and therefore, it has caused a lot of concern amongst regulators and clinicians. In India, key antibiotics are included in Schedule H1. Drugs included in Schedule H1 can only be sold with the prescription of a registered medical practitioner. Therefore, it is very important to regularly conduct such studies to continuously assess the susceptibility of various antibiotics and the MIC values to monitor emerging resistance patterns.

The results of this prospective, active-controlled *in-vitro* study of samples obtained from patients suffering from RTIs show that both the antibiotics, that is, cefpodoxime plus clavulanic acid and amoxicillin plus clavulanic acid are effective against the common respiratory pathogens, *S. aureus*, *S. pneumoniae*, *S. pyogenes*, and *M. catarrhalis* that were isolated from the isolated from the 100 patients with upper RTI, enrolled in this study, when respective MICs are compared against the CLSI 'resistant' breakpoint concentrations.

In this study, the MIC_{90} and MIC_{50} values of cefpodoxime plus clavulanic acid are found to be lower as compared to that of amoxicillin plus clavulanic acid for all the four bacterial strains, that is, *S. aureus*, *S. pneumoniae*, *S. pyogenes,* and *M. catarrhalis*. Further, the mean MIC values of cefpodoxime plus clavulanic acid are significantly lower as compared to that of amoxicillin plus clavulanic acid for *S. aureus*.

MIC values when compared with breakpoints provided in CLSI provide a fair estimate of the potential efficacy of these two antibiotics in URTIs caused by susceptible bacteria. However, there is a need to further substantiate these findings from this *in vitro* with clinical data. Further, such *in vitro* studies should be frequently planned in various geographies to assess the trend of microbial resistance against various antibiotics and antibiotic combinations. The results of these *in vitro* studies should be made available to the clinicians who can use the information on MIC to optimize the selection of the antibacterial and its dose considering the PK-PD data.

CONCLUSIONS

AST is done to measure the ability of a specific organism to grow in the presence of a particular drug *in vitro* and so, performed with a goal to predict the clinical success or failure of the antibiotic being prescribed against a particular organism. The results are reported in terms of Minimum Inhibitory Concentration(s), which is the lowest concentration of an antibiotic that inhibits visible growth of a microorganism, and are usually interpreted by the laboratory as "susceptible," "resistant," or "intermediate." In this study, the MIC_{90} and MIC_{50} values obtained for cefpodoxime plus clavulanic acid were found to be lower as compared to that of amoxicillin plus clavulanic acid for all the four bacterial, that is, *S. aureus*, *S. pneumoniae*, *S. pyogenes,* and *M. catarrhalis*. Further, the mean MIC values of cefpodoxime plus clavulanic acid are significantly lower as compared to that of amoxicillin plus clavulanic acid for *S. aureus*.

The susceptibility/sensitivity of a microbe toward a particular antimicrobial agent is better explained when MIC values obtained are assessed in conjunction with breakpoints provided in CLSI. This provides a fair estimate of the potential efficacy of the two antibiotics in URTIs caused by susceptible bacteria. Although there is a need to further corroborate these *in vitro* findings with real-world clinical data, the results from this study do indicate superiority or enhanced/better susceptibility of these bacterial strains to cefpodoxime plus clavulanic acid in comparison to amoxicillin plus clavulanic acid.

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Original Article

Morbidity Pattern, Mortality, and Its' Determinants among Inborn Neonates Admitted in Rivers State University Teaching Hospital

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Abstract

Background: The neonatal period is the most critical and vulnerable period of life. The survival of neonates does not only depend on the severity of the illness but also on the standard of care.

Purpose: The present study was carried out to determine the morbidity, mortality, and its' determinants among inborn neonates in the Rivers State University Teaching Hospital, Nigeria, as no study has been published in this regard.

Materials and Methods: It was a descriptive cross-sectional prospective study carried out from April 2019 to March 2020. Eligible inborn neonates admitted were consecutively recruited.

Results: Four hundred and sixty-eight neonates were admitted during the period of study. Males predominated 251 (53.6%) with a M:F ratio of 1.2:1. The most common clinical features were difficulty in breathing 208 (54.0%), yellow eyes 178 (46.2%), and fever 116 (30.1%). Probable sepsis 265 (58.9%), neonatal jaundice (NNJ) 229 (50.9%), prematurity 215 (47.8%), and hypoglycemia 101 (22.4%) were the most common morbidities observed. Three hundred and ninety-eight (85.0%) neonates were discharged home and 29 (6.2%) died. Difficulty in breathing, prematurity, hypoglycemia, birth asphyxia, severe anemia, and birth weight was significantly associated with mortality ($P < 0.05$). Males were about ×2 more likely to survive, while babies with normal Apgar scores were more than ×5 more likely to survive. Severe anemia 20.5%, birth asphyxia 13.0%, hypoglycemia 12.9%, seizure 12.0%, and difficulty in breathing 11.1% had the highest case fatality rates.

Conclusion: The most common morbidities among inborn neonates are probable sepsis, NNJ, and prematurity, with a mortality rate of 6.2%. Difficulty in breathing, prematurity, hypoglycemia, birth asphyxia, severe anemia, and birth weight is significantly associated with mortality. Improved obstetric and neonatal care is thus vital in the reduction of morbidity and mortality.

Key words: Inborn, Morbidity, Mortality, Neonates, Port Harcourt

INTRODUCTION

The neonatal period which represents the first 28 days after birth has been found to be the most vulnerable period of life.[1] World Health Organization estimates that of 130 million babies born yearly, about 4 million neonatal deaths occur, most (98%) occurring in developing countries.[2] Neonatal deaths account for about 2/3rd of infant mortality and 1/3rd of under-five mortalities worldwide.[3-5] It is important to note that a quarter to half of these deaths occurs in the 1st day of life and three quarter within the 1st week of life.[6] Ten countries, including Nigeria, constitute 75% of the world's neonatal deaths.[6]

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In spite of a global decline of the neonatal mortality rate, there is marked disparity across regions and countries.[6] Regionally, mortality is highest in sub-Saharan Africa (SSA) and South Asia, with estimated neonatal mortality rates of 27 and 25 deaths per 1000 live births, respectively, in 2019.[6] It is worthy of note that a child born in Sub-Saharan Africa is 10 times more likely to die in the neonatal period than a child born in developed countries, whereas a child born in South Asia is 9 times more likely to die.[6]

The neonatal mortality in Nigeria has shown a very slow reduction in the last decade, that is, from 38 per 1000

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live births in 2009 to 36 per 1000 live births in 2019.[7] There was only 1.5% reduction in the annual reduction of neonatal mortality rate between the years 2000 to 2018. The neonatal mortality rate also accounts for 31% of under-five mortalities.[8]

The morbidity pattern in neonates is a useful indicator of the availability, utilization, as well as effectiveness of maternal and child health services.[9] This pattern varies from place to place as well as overtime, even in the same location.[10] The survival of neonates does not only depend on the severity of illness but also on the standard of care provided.[11] High neonatal mortality rate, therefore, reflects poor health infrastructure and poor quality of care.

In developing countries, neonates die mainly from preventable causes such as infections, birth asphyxia, neonatal jaundice (NNJ), and prematurity, whereas in developed countries, mortality during this period is mainly due to unpreventable causes like congenital anomalies.[12]

The present study was, therefore, carried out in the special care baby unit (SCBU) of Rivers State University Teaching Hospital (RSUTH), Nigeria, to determine the neonatal morbidity pattern, mortality, and its' determinants as there is no published data in this regard. These neonatal morbidity and mortality rates, which are indicators of a country's socioeconomic status, will thus evaluate the efficiency and effectiveness of the health care system in Rivers State, Nigeria. This study will also generate baseline data for the formulation of policies in health care delivery.

MATERIALS AND METHODS

This hospital-based descriptive cross-sectional prospective study was carried out over a one-year period from April 2019 to March 2020 in the SCBU of the River State University Teaching Hospital. The RSUTH, a government-owned tertiary institution, is a 375-bedded hospital made up of the departments such as Paediatrics, Obstetrics and Gynaecology, Surgery, Internal medicine, Pathology, Radiology, Pharmacy, Physiotherapy, as well as Nursing departments. The pediatrics department consists of other specialties in addition to neonatology such as nephrology, endocrinology, infectious disease and immunology, hemoncology, pulmonology, cardiology, neurology and community, and social pediatrics. The hospital serves as a referral center for all the primary health centers in the 23 local government areas, general hospitals, and private-owned hospitals within the state and its environs. Patients are expected to pay out of pocket for services rendered except an insignificantly few number under the National Health Insurance Scheme (NHIS).

The SCBU is a 30-bedded unit, consists of an inborn and outborn section, and it is run by two consultant pediatricians, resident doctors with a nurse: Patient ratio of 6:1. The inborn section consists of 14 cots, seven functional incubators, a Resuscitaire/radiant warmer, and eight phototherapy machines, while the outborn section, which is much smaller, consists of six cots, a Resuscitaire/radiant warmer, three functional incubators, and four phototherapy machines. The unit also consists of two breastfeeding rooms for mothers of inborn and outborn babies, an office for the chief nursing officer, nursing relaxation room, and doctors call room. This unit does not provide intensive care services such as mechanical ventilation, total parenteral nutrition, and blood gas analysis, among others. Babies admitted into the inborn section are babies whose mothers had antenatal care (ANC) in RSUTH, Rivers state government-owned primary health care (PHC) centers, and general hospitals and delivery in any of these centers, whereas the outborn section admits all babies whose mothers did not undergo ANC in RSUTH, PHC or the government-owned general hospitals with/without delivery in RSUTH as well as babies from other health facilities in and around the state.

Ethical approval was sort from the RSUTH Health Research Ethics Committee and consent was obtained from parents/caregivers before recruitment into the study. Inclusion criteria were inborn babies whose parents gave consent while all outborn and inborn babies whose parents/caregivers did not give consent and brought in dead babies were excluded from the study.

A convenient sampling method was employed and babies admitted were consecutively recruited. All parents/caregivers of eligible babies admitted were meticulously clerked by a resident doctor, thoroughly examined, and diagnosis made clinically based on the protocol in the unit and where necessary with the support of laboratory and radiological findings. A pretested structured questionnaire was used to record information such as sex, age at presentation, birth weight, gestational age at birth, Apgar score at 1 and 5 min after birth, clinical features, mothers age, parity, mode of delivery, HIV status of mothers, and maternal level of education and occupation. Other information recorded was diagnosis made and outcome.

Diagnosis of probable sepsis was made for babies with suspected sepsis with a result of full blood count showing white blood cell count of the $>20 \times 10^9$/L or $<5 \times 10^9$/L or neutrophil count of >75% or <40%.[13] NNJ was diagnosed clinically with a serum bilirubin value greater than the normal on the nomogram for the baby's gestational age and weight. Birth asphyxia was diagnosed using Apgar score at 1 and 5 min and clinical manifestations. The

gestational age of the babies was calculated from the 1st day of the last menstrual period or ultrasonographic findings done in the 1st trimester of pregnancy. Hypoglycemia was defined as random blood sugar <2.6 mmol/L, while infants with birth weights ≥4.0 kg were defined as macrosomia regardless of their gestational age. Severe anemia requiring blood transfusion was defined as hematocrit level <31%. Prematurity was defined as liveborn neonates delivered before 37 completed weeks.

Sick babies were treated based on the unit's standard operation procedure. Babies were closely followed up until either discharged home, discharged against medical advice (DAMA), died, or referred to other centers for cases where desired services needed were unavailable in RSUTH.

Data were entered into a Microsoft Excel spreadsheet and thereafter analyzed using SPSS version 23. The results were presented in frequency tables, percentages, pie, and bar charts. Chi-square test of association and Fishers' exact test were carried out to determine if there were statistical significance in the association between outcome variables and the independent variables. Statistical significance was considered if $P < 0.05$ at 95% confidence interval. Forward regression was carried out to identify possible predictors of the outcome variable. Odds ratio and confidence intervals were generated which aided in describing the strength of the associations established between the outcomes and predictor variables.

RESULTS

Characteristics of Neonates Admitted

Four hundred and sixty-eight babies were admitted during the period of study. There were 251 (53.6%) males and 217 (46.4%) females with M:F ratio of 1.2:1. The majority, 447 (95.5%), presented within 24 h of life and were of 1st birth order 198 (42.3%). Most were of the gestational age of 37–42 weeks, 250 (53.4%) with a mean of 36.54 ± 3.56 weeks, while birth weights of 2.5–3.99 kg were most common 222 (37.2%) with mean of 2.81 ± 0.97 kg, Table 1.

Maternal Sociodemographic Factors

Most of the mothers were of age group 27–36 years 323 (69.0%) with a mean of 31.80 ± 5.37 years, multiparous 296 (63.7%), and had ANC in RSUTH 284 (60.7%). Four hundred and nineteen (89.5%) mothers had singleton gestation {419 (89.5%)}, with the predominant mode of the delivery being Caesarean section 356 (76.1%). Of 49 multiple gestations, 34 (69.4%) were twin, 12 (24.5%) triplet, and 3 (6.1%) were quadruplets. Majority of the mothers had tertiary education 244 (52.2%) and were mainly traders/artisans 197 (42.1%), Table 2.

Clinical Features of Neonates Admitted

The most common clinical features of neonates admitted in the SCBU were difficulty in breathing 208 (54.0%), yellow eyes 178 (46.2%), and fever 116 (30.1%), Figure 1.

Morbidity Pattern of Neonates Admitted

The most common morbidities in neonates admitted were probable sepsis 265 (58.9%), NNJ 229 (50.9%), prematurity

Table 1: Characteristics of neonates admitted

Variables	Frequency, *n*=468(%)
Sex	
Male	251 (53.6)
Female	217 (46.4)
Age at presentation (hours)	
≤24	447 (95.5)
>24	21 (4.5)
Birth order	
1st	198 (42.3)
2nd	126 (26.9)
3rd	73 (15.6)
≥4th	71 (15.2)
Gestational age (weeks)	
<37	215 (46.0)
37–42	250 (53.4)
>42	3 (0.6)
Birth weight (kg)	
<2.5	174 (37.2)
2.5–3.99	222 (47.4)
≥4.0	72 (15.4)

Table 2: Maternal sociodemographic factors

Variables	Frequency, *n*=468 (%)
Mother's age	
17–26	66 (14.1)
27–36	323 (69.0)
>36	79 (16.9)
Parity	
Primiparous	172 (36.8)
Multiparous	296 (63.2)
Place of ANC	
RSUTH	284 (60.7)
PHC	184 (39.3)
Type of pregnancy	
Singleton	419 (89.5)
Multiple	49 (10.5)
Mode of delivery	
SVD	112 (23.9)
CS	356 (76.1)
Mother's level of education	
No formal education	6 (1.3)
Primary	25 (5.3)
Secondary	193 (41.2)
Tertiary	244 (52.2)
Mother's occupation	
Civil/public servant	123 (26.3)
Traders/artisans	197 (42.1)
Professionals	30 (6.4)
Unemployed	118 (25.2)

ANC: Antenatal care, RSUTH: Rivers State University Teaching Hospital, PHC: Primary Health Care, SVD: Spontaneous vertex delivery, CS: Caesarean section

215 (47.8%), and hypoglycemia 101 (22.4%), while the least common was meningitis 7 (1.6%), Figure 2.

Outcome of Neonates

Of 468 neonates admitted into the SCBU, 398 (85.0%) were discharged home while 29 (6.2%) died. Thirty-three (7.1%) were DAMA and 8 (1.7%) were referred to other health facilities. Reasons given by parents/caregivers for discharging their babies against medical advice were financial constraint 20 (60.6%), tired of the hospital environment 5 (15.2%), father's decision 4 (12.1%), and no reason given 4 (12.1%), Figure 3.

Determinants of Mortality among Neonates Admitted

The determinants of mortality in inborn neonates admitted were difficulty in breathing, prematurity, hypoglycemia, birth asphyxia, severe anemia, and birth weight ($P < 0.05$), Table 3.

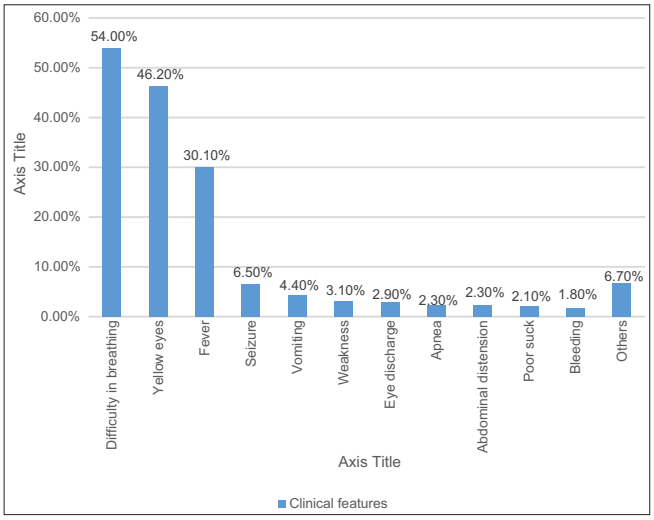

Figure 1: Clinical features of neonates admitted

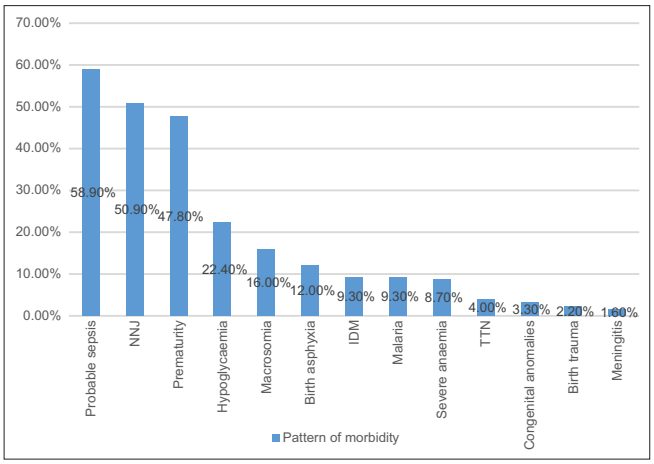

Figure 2: Morbidity pattern of neonates admitted. IDM: Infant of diabetic mothers, TTN: Transient tachypnea of the newborn

Factors Associated with Outcome among Neonates Admitted

Males were close to ×2 more likely to survive than the females, while babies with normal Apgar scores were more than ×5 more likely to survive than those with low Apgar scores. Gestational age, temperature at presentation, mode of delivery, and birth weight were significantly associated with mortality ($P < 0.05$), Table 4.

Case Fatality Rates (CFR) of Clinical Features and Morbidities

The CFR was highest in neonates with severe anemia, 20.5% followed by birth asphyxia 13.0%, hypoglycemia 12.9%, seizure 12.0%, and difficulty in breathing 11.1%.

Table 3: Determinants of mortality among neonates admitted

Variables	Mortality		*P*-value
	No {*n*=439(%)}	Yes {*n*=29(%)}	
Clinical features			
Difficulty in breathing	185 (42.2)	23 (79.3)	<0.0001*
Yellowness of the eyes	165 (37.6)	13 (44.8)	0.437
Fever	112 (25.5)	4 (13.8)	0.187
Seizure	22 (5.0)	3 (10.3)	0.196
Weakness	10 (2.3)	2 (6.9)	0.166
Morbidities			
Probable sepsis	250 (56.9)	15 (51.7)	0.699
NNJ	217 (49.4)	12 (41.4)	0.401
Prematurity	146 (33.3)	20 (69.0)	<0.0001*
Hypoglycemia	88 (20.0)	13 (44.8)	0.002*
Macrosomia	56 (12.8)	2 (6.9)	0.560
Birth asphyxia	47 (10.7)	7 (24.1)	0.028*
Malaria	41 (9.3)	1 (3.4)	0.500
Severe anemia	31 (7.1)	8 (27.6)	0.0001*
Congenital abnormalities	14 (3.2)	1 (3.4)	1.000
Birth trauma	9 (2.1)	1 (3.4)	0.476
Meningitis	5 (1.1)	2 (6.9)	0.064
Birth weight (kg)			
<2.5	149 (33.9)	25 (86.2)	
2.5–3.99	220 (50.1)	2 (6.9)	<0.0001*
≥4.0	70 (15.9)	2 (6.9)	

*Statistically significant

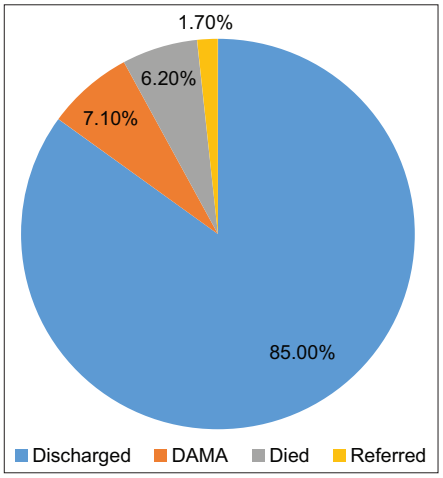

Figure 3: Outcome of neonates

Table 4: Factors associated with outcome among neonates admitted

Variables	Mortality		*P*-value	OR (95% CI)
	No {*n*=439(%)}	Yes {*n*=29(%)}		
Sex				
Male	241 (54.9)	10 (34.5)	0.033	1.8 (0.70–4.39)
Female	198 (45.1)	19 (65.5)	-	-
Gestational age (weeks)				
<37	189 (43.1)	26 (89.7)		
37–42	247 (56.3)	3 (10.3)	<0.0001	
>42	3 (0.7)	0 (0.0)		
Apgar score				
≥7	390 (88.8)	20 (69.0)	0.015	5.3(1.39–19.95)
0–3	24 (5.5)	4 (13.8)	0.963	1.0(0.15–6.16)
4–6	25 (5.7)	5 (17.2)	-	-
Temp at presentation (°C)				
<36	196 (44.0)	25 (86.2)	0.018	0.2(0.07–0.78)
≥36	246 (56.0)	4 (13.8)	-	-
Mode of delivery				
SVD	95 (21.6)	17 (58.6)	0.002	0.3(0.05–1.66)
CS	344 (78.4)	12 (41.4)	-	-
Maternal HIV status				
Positive	15 (3.4)	3 (10.3)	0.093	
Negative	424 (96.6)	26 (89.7)		
Pregnancy complications				
Yes	240 (54.7)	21 (72.4)	0.062	0.062(0.23–1.68)
No	199 (45.3)	8 (27.6)	-	-
Birth weight (kg)				
<2.5	149 (33.9)	25 (86.2)	0.018	0.2(0.04–0.74)
2.5–3.99	220 (50.1)	2 (6.9)	0.257	3.1(0.44–22.73)

The least CFR was observed in neonates with macrosomia 2.8% and malaria 2.4%, Table 5.

DISCUSSION

Evaluating the morbidity pattern and mortality in neonatal units is integral in measuring the quality of health care services rendered and as such identifies deficiencies in the system. This would provide a framework on which interventions are designed to improve the outcome of newborns.

In the present study, there was a male preponderance in the ratio of 1.2:1. Similar findings were observed in all other studies in Nigeria,[14-20] Pakistan,[21] Ghana,[22] India,[23-25] and Bangladesh.[26] This observation is not surprising as gender has been found to be a significant predictor of health and development in children with boys showing greater vulnerability.[27] It has also been observed that the male gender is more likely to be born premature and tends to have more neonatal complications.[28]

More term babies were admitted into the SCBU in the present study as also observed in some Indian studies.[23,24] This was, however, at variance with the study in Ghana[22] and Bangladesh[26] were preterm babies dominated. This difference could be due to the difference in geographic locations as well as varying disease pattern.

Table 5: Case fatality rates of clinical features and morbidities

Variable	Total	Mortality	CFR (%)
Difficulty in breathing	208	23	11.1
Fever	116	4	3.4
Seizure	25	3	12.0
Probable sepsis	265	15	5.7
NNJ	229	12	5.2
Prematurity	215	20	9.3
Hypoglycemia	101	13	12.9
Macrosomia	72	2	2.8
Birth asphyxia	54	7	13.0
Malaria	42	1	2.4
Severe anemia	39	8	20.5
Congenital abnormalities	15	1	6.7
Birth trauma	10	1	10.0

About three-quarters of neonates were delivered via Caesarean section. A similar finding was also documented by Hussain[21] in Pakistan. In contrast, Okechukwu and Achonwa[20] in Abuja Nigeria, Verma *et al.*,[23] Saini *et al.*[25] in India, and Tajkia *et al.*[26] in Bangladesh documented SVD as the predominant mode of delivery. This variance in the mode of delivery could be because of the different health facilities' standard operating procedures as well as varying pregnancy and fetal complications.

Probable sepsis was the most common morbidity observed in neonates admitted in the SCBU in the present study

followed by NNJ and prematurity. These three morbidities were the most common also reported in India.[24] In Jigawa state,[14,15] Jos[17] Nigeria, Pakistan,[21] and Bangladesh,[26] neonatal sepsis and prematurity were observed to be the most common morbidities. A previous study in Port Harcourt[29] carried out 5 years before the present study and in India,[25] neonatal sepsis, NNJ, and severe birth asphyxia were the most common morbidities documented, whereas in Delta state[19] in Nigeria and Ghana,[22] birth asphyxia and prematurity were the leading morbidities. In addition, NNJ, prematurity, and birth asphyxia were the most common morbidities observed in Zaria, Nigeria.[30] Interestingly, a study done in Calabar,[29] Nigeria, more than a decade earlier revealed birth asphyxia, neonatal tetanus, and sepsis as the most common morbidities. Another study done in Benin city,[31] Nigeria, also reported neonatal tetanus as one of the most common morbidities observed. Neonatal tetanus which was once common morbidity in Nigeria is very rare in recent times because of the gains of immunization and increased awareness in the utilization of ANC services as well as increased hospital deliveries. This varying morbidity observed is not surprising as disease pattern varies from place to place and from time to time even in the same locality. It is pertinent to note that only inborn babies were recruited in the present study as opposed to all other studies cited where both inborn and outborn were considered as this could also contribute to the difference in the morbidity pattern. Regular auditing of neonatal units is thus advocated. This is critical in assessing the quality of care provided, identifies deficiencies in the system, and assists policymakers in effective planning.

The mortality rate of inborn neonates in the RSUTH of 6.2% was comparable with the 6.4% reported among inborn babies in Zaria,[18] Nigeria. It was, however, lower than the 8.93%, 9.73% documented in Ghana[22] and India,[24] respectively, but much lower than most other studies in Nigeria,[14-16,19,20,29,31,32] India,[23-25] and Pakistan.[21] It was, however, higher than the 3.9% documented in Bangladesh.[26] The lower mortality reported in the present study could be attributable to the fact that only the inborn babies were included, unlike all the other studies[14-16,19,20-25,29,31,32] where both inborn and outborn babies were studied. It is pertinent to note that studies carried out in Kano[18] and Benin city,[31] Nigeria showed that mortality in the inborn babies was significantly much lower than that of the outborn. This could be attributable to late presentation of sick babies to the hospital, lack of ANC, harmful traditional practices, and lack of skilled attendance among women delivered at home or by unqualified persons. The high mortality observed in the developing countries could be due to lack of manpower and poor infrastructural development as is the case with the present neonatal center which does not have neonatal intensive care units and unavailability of mechanical ventilators, parenteral nutrition, and blood gas analyzers, among other very important equipment important for neonatal care and survival.

Prematurity, probable sepsis, and NNJ were the leading causes of mortality among inborn neonates in Port Harcourt. Prematurity being the leading cause of death was also observed by Also and Gwarzo[14] in Jigawa state, Toma *et al*.[17] in Jos, Hussain[21] in Pakistan, Verma *et al*.,[23] Kotwal *et al*.,[24] and Saini *et al*.[25] in India. These findings were, however, at variance with the study by Abdullahi[15] in Jigawa state and Ekwochi *et al*.[16] in Enugu, Nigeria, who documented birth asphyxia as the most common cause of mortality, while Ugwu[19] in Delta state, Nigeria, documented neonatal sepsis as the most common cause. In addition, Tette *et al*.[22] in Ghana reported hypoglycemia as the most common cause of mortality. These differences could also be attributed to the varying geographic locations, maternal and fetal risk factors, and the availability of quality infrastructure and care. It is, however, worthy of note that the leading causes of death in these studies were preventable and as such the importance of improved obstetric care and neonatal care cannot be overemphasized.

Difficulty in breathing, prematurity, birth asphyxia, hypoglycemia, severe anemia, birth weight, as well as gestational age, temperature at presentation and mode of delivery were observed to be significantly associated with mortality. Thus, improved antenatal and obstetric care, early diagnosis as well as prompt and provision of standard neonatal care will reduce morbidity and mortality from these disease conditions.

Surprisingly, mortality was 2 times more in the female gender than the males in the present study. A similar finding of more mortality in female gender was also documented in India.[25] This was at variance with most other studies carried out in Jigawa state,[15] Enugu[16] and Jos[17] Nigeria, where the mortality rate was higher in males, although they were not statistically significant. The reason for this difference could not be ascertained.

Neonates with normal Apgar score were more than 5 times more likely to survive than those with a low Apgar score in the present study. This is not surprising as birth asphyxia was observed in the present study to be significantly associated with mortality and documented by Abdullahi[15] to have the highest CFR in Jigawa state in Nigeria. Improvement in the obstetric care and standardized neonatal care with a well-equipped neonatal care unit will reduce the occurrence as well as the survival of asphyxiated babies.

Eighty-five percent of neonates admitted were discharged home in the present study. This was comparable with the

84.9% and 86.0% reported in Jigawa state[14] and Zaria,[30] Nigeria, respectively. It was, however, higher than the 70.0%, 77.0%, 78.5%, 78.9%, and 78.6% in India,[23] Jigawa,[15] Abuja,[20] Kano[18] Nigeria, and Bangladesh,[26] respectively, but lower than the 90.07% documented in Jammu and Kashmir in India.[24] These different rates could be attributable to the difference in the quality of care provided.

The DAMA in the present study of 7.1% is comparable with the 6.0% and 5.3% reported in Jigawa state,[15] Nigeria, but higher than 3.2%, 1.5%, and 0.2% reported in Kano,[18] Jigawa[14] Nigeria and India.[24] DAMA is usually as a result of poverty and ignorance as observed in the present study where close to two-thirds of the reasons given for DAMA were financial constraints and the other reasons being tired of the hospital environment and father's decision. Massive enrolment into the NHIS would thus drastically reduce the DAMA rate as parents/caregivers would not need to pay out of pocket.

Severe anemia had the highest CFR of 20.5% in the present study followed by birth asphyxia (13.0%) and hypoglycemia (12.9%). This is not surprising as these three morbidities were significantly associated with mortalities. It is, however, surprising that although prematurity was the most common cause of mortality in the present study, its' CFR was much lower, 9.3%. This was also the case for probable sepsis (5.7%) and NNJ (5.2%). In Jigawa state,[14] CFR was highest in neonatal tetanus (42.8%) followed by prematurity (20.4%) and severe birth asphyxia (16.3%). In this study, severe anemia had a much lower CFR of 14.3% when compared with the present study. Similar findings, like the latter study, were observed in Benin,[19] Nigeria. Birth asphyxia and prematurity had the highest CFRs of 26.78% and 21.81% in Pakistan[21] and 9.4% and 4.3% in Bangladesh.[26] In India, however, meconium aspiration syndrome and congenital abnormalities had the highest CFRs accounting for 33.3% and 23.1%, respectively. Thus, the establishment of well-equipped neonatal intensive care units with adequate man-power will reduce drastically the CFRs of various disease conditions in the newborn and as such reduce neonatal morbidity and mortality rates.

CONCLUSION

The most common morbidities among inborn neonates in the RSUTH are probable sepsis, NNJ, and prematurity with a mortality rate of 6.2%. Causes of death are preventable, with the leading cause being prematurity followed by probable sepsis and NNJ.

Difficulty in breathing, prematurity, birth asphyxia, hypoglycemia, severe anemia, birth weight as well as gestational age, temperature at presentation, and mode of delivery are significantly associated with mortality. Male gender and neonates with normal Apgar score are close to 2 times and more than 5 times more likely to survive, respectively. CFRs are highest with severe anemia followed by birth asphyxia and hypoglycemia.

Improved obstetric care, provision of standard neonatal care with well-equipped neonatal intensive care units, and adequate manpower will thus reduce morbidity and mortality in the neonatal period.

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Original Article

A Study to Compare "change" in Auditory and Visual Reaction Time After Administration of Caffeine in Medical Students

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Abstract

Introduction: The present study is a comparative study of the changes seen in auditory reaction time (ART) and visual reaction time (VRT) in 1st-year medical students after the administration of caffeine present in coffee.

Purpose: This study is aimed at comparing how the ART and VRT are affected after caffeine present in coffee is administered to them.

Materials and Methods: The study was conducted on 42 male and 35 female 1st-year medical students. The 77 students were not regular coffee drinkers and were tested for changes in auditory and VRTs after the administration of caffeine present in coffee.

Results: It was found that the change in either ART or VRT did not differ significantly ($P > 0.05$) in either gender after the administration of caffeine.

Conclusion: No significant differences in change were observed between ART and VRT post caffeine intake in either gender. In both gender changes in ART and VRT were comparable after the intake of caffeine.

Key words: Auditory reaction time, Caffeine, Coffee, Visual reaction time

INTRODUCTION

Reaction time (RT) is the time that elapses between a person being presented with a stimulus and the person initiating a motor response to the stimulus. It involves the reception of stimuli by sense organ, conduction of information through the nerve to brain, and from brain to muscle contraction and movement. It is thus a simple and effective method of studying central neuronal processing and is a simple method of determining sensory-motor association, performance, and cortical arousal. Apart from the time required for sensory-motor association, this is the time required by the brain for perceptual decision making and motor planning.[1] RT depends on age, sex, fatigue, fasting state, sleep, and stress.

In daily life, one has to respond to various situations immediately and as the RT indicates the time taken by an individual to react to an external stimulus, it can be important in the case of various activities that are carried out on a day to day basis. These activities can be both of "Auditory" as well as "Visual" in nature. Auditory ones could be like a response to a phone call, a door bell, whistle of pressure cooker or even may be a "cry of help." Visual ones could be like responding to traffic signals, "Driving and changing lanes," maneuvering a fighter plane, responding to enemy fire, or even preventing an accident from occurring. Thus, they could just be normal routine activities or could also extend to crucial ones pertaining to life and death.

Caffeine is one of the most commonly used substances found in everyday beverages such as tea and coffee. It is an alkaloid compound and is actually a bitter substance

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found in coffee beans, cocoa beans, and many other plant products. The scientific name for caffeine is 1,3,7-trimethylxanthine.[2] Caffeine is known to stimulate the central nervous system. Mild cortical stimulation appears to be beneficial, resulting in more clear thinking and less fatigue. Caffeine in low doses is capable of causing desirable improvement of physical and cognitive functions. The usage of caffeine is also considered to be addictive in nature. Daily use of caffeine is known to cause some sort of dependence for this substance in the form of nervousness, headache, and irritation.[3] But used judiciously within limits, it is known to have many beneficial effects. The USFDA considers a moderate intake of caffeine to be "SAFE." Safe doses of caffeine are considered to be around 300 mg/day in an adult.[4,5] Beneficial doses of caffeine which increased motor and mental performances range to about 65–130 mg of caffeine in a single take.[6]

Studies done on caffeine by Bullock and Gilliland[7] on the auditory modality have shown speeding up of the sensory component of brainstem auditory evoked potentials. This finding suggests that caffeine keeps the auditory sensory pathways alert, probably at the brainstem level.

Similarly, studies done by Tharion *et al.*[8] on both auditory and visual stimuli showed caffeine to significantly ignore distracting or irrelevant stimuli, thus helping the subjects focus more on the task, thereby giving rise to improved RTs. Furthermore, studies done by Lorist *et al.*[9] showed the effect of caffeine in reducing visual RT (VRT) by stimulating the input and output stage of the information processing system.

After considering the studies done on the effects of caffeine, there remains no uncertainty that caffeine improves the RTs in both the visual as well as the auditory scales. However, we as researchers were curious to know if caffeine affects auditory and visual modalities differently. Hence, we decided to check how the administration of caffeine fared comparatively on the improvement in VRT and ART on the male and female subjects and thus have tag on information about the effects of caffeine present in a standard cup of coffee.

MATERIALS AND METHODS

The study was conducted in Grant Government Medical College on 42 male and 35 female 1st-year medical students. Entire batch was requested to enroll for the study. However, those who turned up for the study, on their own, were considered for the study. Informed consent of the subjects and approval from the institutional ethics committee was taken to conduct the study. The study was conducted in the Department of Physiology when the authors were posted there.

The subjects being 1st-year medical students were mostly of the same age range. Habitual coffee drinkers were excluded from the study to discard the effects of caffeine dependence. Too obese or too lean subjects were excluded from the present study. Studies done on the female subjects were done after excluding their menstrual and premenstrual period.

The coffee sachets from a well-known coffee brand were taken. We considered the fact that beneficial dose of caffeine for increased mental and motor performance is about 65–130 mg of caffeine.[6] Hence, 2 g of coffee powder was used to make one cup of coffee, which contained around 63 mg of caffeine, thereby bringing the caffeine content to near ideal doses.

Both the male and the female medical students were tested for RT "before" and 30 min "after" the intake of coffee, considering that the effects of caffeine are known to be more pronounced within the 1st h of coffee intake.[10] RT measurements were done in the form of auditory RT (ART) and VRT.

RT apparatus (Anand Agencies, Pune) was used for the study. It has a built-in 4 digit chronoscope and displays accuracy of 1 ms. Recordings were taken in the morning time. Subjects were instructed to come with routine normal breakfast. Recordings were taken "before" and 30 min "after" the intake of a standard cup of coffee as mentioned before. ART was recorded for auditory beep sound stimulus and VRT for red light stimulus. To avoid the effect of lateralized stimulus, the subjects were given visual and auditory stimuli from the front. They were instructed to respond with their dominant hand as soon as they perceived the visual or auditory stimulus. Subjects were given adequate exposure to get acquainted with the working of the apparatus before starting with the actual test.[11,12]

Calculation and Result

The present study had data generated from 42 male and 35 female students. Data obtained for ART and VRT was presented as mean ± SD. These data comprised ART and VRT done in the male and female subjects "before" and 30 min "after" consumption of caffeine. The motive was to find out what "changed" more, ART or VRT after caffeine usage. Hence, the data obtained "before" and 30 min "after" consumption of caffeine for ART was compared with similar data obtained for VRT in both genders. Statistical analysis for the study was done using

the popular software GraphPad prism 5 software. Paired and unpaired *t*-test used for comparing the data between the ART and VRT change. $P > 0.05$ was considered non-significant.

Results are summarized in Tables 1-3:

Data were analyzed separately for both male and female subjects. In both cases, there was a significant decrease found in ART as well as VRT after caffeine intake ($P < 0.05$), but on comparing the changes obtained between ART and VRT after caffeine intake, the result was not found to significant ($P > 0.05$) in either of the gender.

DISCUSSION

Caffeine in one of the world's most widely used psychoactive substance. However, the use of caffeine is legal and widely accepted, unlike other psychoactive substances. Caffeine is most commonly consumed by humans as coffee brewed from the extract of beans of coffee plants. The USFDA lists caffeine as a "Multiple purpose generally recognized as safe food substance."[13] The widespread consumption of coffee in the absence of a clear definition of physiological and behavioral spectrum of action has continued to stimulate research. Mental performance where speed, endurance, or vigilance was required showed reported benefits from caffeine intake.[14] Evidence for the behavioral effects of caffeine is well documented in the literature. It is associated with increased subjective alertness. Ingestion of caffeine within physiological limits caused the subjects to experience a decrease in fatigue, lesser drowsiness, enhanced wakefulness, more concentration or reduced distraction, and increased energy.[9,15]

The effects of caffeine were seen to improve the RTs in both the visual as well as the auditory scales. Studies done by Bullock and Gilliland[7] on the auditory modality have shown speeding up of the sensory component of brainstem auditory evoked potentials. This finding suggests that caffeine keeps the auditory sensory pathways alert, probably at the brainstem level.

Similarly, studies done by Tharion *et al*.[8] on both auditory and visual stimuli showed caffeine to significantly ignore distracting or irrelevant stimuli, thus helping the subjects focus more on the task, thereby giving rise to improved RTs. Furthermore, studies done by Lorist *et al*.[9] showed the effect of caffeine in reducing VRT by stimulating the input and output stage of the information processing system.

While comparing two types of stimuli, plenty of studies maintain the fact that VRT was more than ART.[16-19] This can be attributed to the number of synapses in the visual pathway as compared to the auditory pathway. Vision takes 20–40 ms to travel in the visual pathway,[20] while sound takes just 8–10 ms to travel in the auditory pathway.[21,22] Thompson *et al*.[23] has documented that the mean RT to detect visual stimuli is approximately 180–200 ms, whereas for the sound, it is around 140–160 ms. Consequently, since the auditory stimulus reaches the cortex faster than the visual stimulus, the ART is faster than the VRT. Shelton and Kumar[24] also concluded that simple RT is faster for auditory stimuli compared with visual stimuli and auditory stimuli have the fastest conduction time to the motor cortex along with fast processing time in the auditory cortex. Such studies support the evidence that ART is faster than the VRT.[25]

However, the above findings are contradictory to the studies done by Shenvi and Balasubramanian,[26] who therein state that the auditory pathway is more polysynaptic than the visual pathway. At each synaptic junction, there is a modest (0.1–0.5 ms) and somewhat variable synaptic delay and therefore the conduction time is greater from the cochlea to the auditory cortex.[26,27] Again another research done by Yagi *et al*.[28] shows that RT to visual stimuli is faster than to auditory stimuli.

From the previous studies, it is clear that ART as well as VRT both decrease after administration of caffeine. It was also seen in most of the studies that ART is less than VRT. With this prior knowledge, we, therefore, conducted this study to check whether it was ART or was it VRT which was affected more by the administration of caffeine. This thought led us to the present study and led us to understand that caffeine influenced both ART as well as VRT equally.

Table 1: Comparison of changes in ART and VRT after caffeine intake in males and females. Data obtained was presented as mean±SD

Reaction time	Males (*n*=42)			Females (*n*=35)		
	Before caffeine	After caffeine	Difference in mean	Before caffeine	After caffeine	Difference in mean
ART (ms)	243.45±10.43	231.52±12.38	11.93±7.84	243.03±10.35	228.80±11.32	14.23±9.12
VRT (ms)	200.21±7.77	186.57±12.01	13.64±9.03	199.84±10.22	183.01±11.60	16.83±7.53
	Unpaired *t*=0.91			Unpaired *t*=1.28		
	P>0.05			*P*>0.05		

Table 2: Comparison of ART on 42 male and 35 female medical students "before" and "after" intake of caffeine. Data obtained was presented as mean±SD

Subjects	ART before caffeine	ART after caffeine	*P*-value
Males (*n*=42)	243.45±10.43	231.52±12.38	<0.01
Females (*n*=35)	243.03±10.35	228.80±11.32	<0.01

ART: Auditory reaction time

Table 3: Comparison of VRT on 42 male and 35 female medical students "before" and "after" intake of caffeine. Data obtained was presented as mean±SD

Subjects	VRT before caffeine	VRT after caffeine	*P*-value
Males (*n*=42)	200.21±7.77	186.57±12.01	<0.01
Females (*n*=35)	199.84±10.22	183.01±11.60	<0.01

VRT: Visual reaction time

No differences were observed in our study for the decrease in RT post caffeine consumption in either gender for ART and VRT. Similar studies seem to not have been done till date, so corroboration of our data with other studies was difficult at this juncture. Future studies as and when undertaken could obviously compare with our data and thus validation obtained.

RT depends on several factors, that is, arrival of the stimulus at the sensory organ, conversion of stimulus to a neural signal by sensory organ, transmission and processing of neural signal, muscular activation, soft tissue compliance, and the selection of an external measurement parameter. The study done by Lorist *et al.*[9] supported the view that caffeine increases cortical arousal and perceptual sensitivity and that stimulating effect of caffeine was mainly located at input and output stages of the information processing. Caffeine did not seem to affect central processing. The main differences in ART and VRT, as pointed before, involved various polysynaptic pathways from the receptor organ to the brain. That, coupled by the fact that caffeine hardly has a role to play in affecting central processing, it had not affected either VRT or ART differentially. This seems to be the most probable rationalization for not deriving any significant differences between changes in ART and VRT post caffeine intake in our study.

CONCLUSION

In this study, ART as well as VRT decreased in both gender after intake of caffeine, but no significant differences in change were observed between ART or VRT post caffeine intake in either gender. The present study thus sheds light upon the fact that the administration of caffeine improves ART and VRT to an equal extent in either gender. In a lighter note, it also shows that both males and females can gain equally on RT for many auditory and visual tasks after the judicious intake of caffeine in the form of tasty beverages like coffee.

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Original Article

A Prospective Study of the Incidence of Upper Gastrointestinal Lesions and Bleed in Burn Injuries – An Endoscopic Evaluation in a Tertiary Care Hospital

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Abstract

Introduction: Acute gastroduodenal ulceration (Curling's ulcer) is the most life-threatening gastrointestinal complication that can follow thermal burns. Prospective, serial endoscopic evaluation is the best method to know the exact location and incidence and behavior of these lesions, and also the influence of medication on such lesions.

Aim of the Study: The aim of the study was to study the incidence of the upper gastrointestinal lesions and bleed in patients with burns and to observe the influence of PANTOPRAZOLE and SUCRALFATE on the lesions.

Materials and Methods: A total of 70 patients were taken into this study and grouped into two of 35 each of pantoprazole and sucralfate. Ethical committee Reg No: SS 15080312.

Statistical Analysis System: The analysis was performed by Proposition test, Chi-square test, and Fisher's exact test. "*P*" < 0.05 was considered significant.

Results and Discussion: About 44.28% of the patients had lesions on endoscopy. Erosions were the common lesions at 77.41%. About 48.75% of patients had lesions in the pantoprazole group and 40.0% had lesions in the sucralfate group. About 51.42% patients had burns between 41% and 50% TBSA. Among them, 58.33% had lesions.

Conclusions: Incidence of lesions has a direct relation to the percentage of burns. There is no significant difference in the incidence between pantoprazole and sucralfate group. Sucralfate has a better healing of lesions and also helped in preventing erosions from progressing to ulcers than pantoprazole.

Key words: Endoscopy, Lesions, Pantoprazole, Percentage of burns, Sucralfate

INTRODUCTION

Acute gastroduodenal ulceration (Curling's ulcers) is the most life-threatening gastrointestinal complication that can follow thermal burns.

Curling's ulceration of the stomach and duodenum is due to a decrease in mucus production by the stomach and is related to the magnitude of the burn. Gastrointestinal erosions occur within 5 h of injury in 80% of all patients with severe burns. These erosions cause only minor upper gastrointestinal bleeding, but within 72 h many of these may progress to frank gastrointestinal ulcerations (Curling's ulcer) result in major hemorrhage. Although not common, perforation and hemorrhage are always potentially fatal complications. Prophylactic treatment with antacids or H_2-receptor antagonists has dramatically reduced the incidence of gastrointestinal bleeding in many burn units. Disruption of gastric mucosal barrier and increased gastric acid secretion is primarily implicated as causes of gastrointestinal lesions in burns patients.[1] Successive and serial upper gastrointestinal endoscopic evaluation is a good method to know the exact incidence and behavior of these lesions, and also helps in

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observing the influence of medication on such lesions. To determine the effectiveness of gastric acid neutralization and their efficacy in prevention of gastrointestinal lesions and clinical complication of the selected drugs, burn patients were randomly divided between sucralfate and proton pump inhibitor (PPI) therapy.

The symptoms of gastrointestinal lesions vary from pain and tenderness to pressure on the epigastrium, to improper digestion and vomiting. When ulceration ensues, the stools are dark and bloody. In very acute instances, either hemorrhage or perforation may be the initial sign, and there may be no symptoms at all. In addition to the local pathology, there are inevitable systemic and constitutional complications characterized primarily by pain and shock. The first concern in management of these lesions is to prevent formation of these lesions and avoid complications.

Sucralfate

Sucralfate is composed of sucrose octa sulfate and aluminum hydroxide, which dissociates in the acid environment of the stomach and is polymerized to a viscous sticky substance that binds to the proteinaceous exudate usually found at ulcer sites.[2] Sucralfate prevents hydrogen ion back-diffusion, protects the ulcer against pepsin and bile, and therefore promotes ulcer healing. Apart from formation of a protective physical barrier there is stimulation of mucosal defense and reparative mechanisms related to stimulation of local Prostaglandin E_2 and Prostaglandin I_2 production.[3]

Pantoprazole

Pantoprazole is a PPIs. Under acidic conditions in parietal cells, the sulfhydryl bond irreversibly inactivates the pump, rendering it incapable of secreting gastric acid. PPIs s inhibit both histamine induced and vagally mediated gastric acid secretion.[3]

MATERIALS AND METHODS

A prospective study is undertaken over a period of 26 months with 70 patients included in the study. These patients were divided into two equal groups of 35 each: Group I (Pantoprazole) and Group II (Sucralfate). Ethical committee clearance and consent from the patients were taken. Burn patients after admission were assessed for percentage and those with burns between 15% and 55% are taken into study group with following inclusion and exclusion criteria.

Inclusion Criteria

The following criteria were included in the study:

- Patients presenting with burns of 15%–55%,
- Both genders
- Ages between 18 and 60 years.

Exclusion Criteria

The following criteria were excluded from the study:

- Patients under 18 years and above 60 years
- Habitual alcoholics and smokers
- Pregnant women
- Those with facial/respiratory burns
- Chemical burns
- Those with history of acid peptic disease, or significant medical illnesses.
- Group I: These patients were given injection pantoprazole at a dose of 40 mg intravenously once daily from the time of admission
- Group II: These patients were given syrup sucralfate at a dose of 2 g every 4th hourly from the time of admission orally or through nasogastric tube.

All the patients were followed up with clinical symptoms and their regular assessment. Serial endoscopies were done in selected patients at an interval of 2 weeks till the lesions healed if noted on initial endoscopy.

RESULTS

Relationship of Percentage of Burns to Number of Patients

The study group comprised 70 patients. The patients with burns between 15% and 55% were taken in to study. Among the 70 patients, 13 (18.57%) patients had burns of 15–30%, 21 (30.0%) patients were admitted with burns of 31–40%, and 36 (51.42%) patients had burns of 41–55%.

On doing upper gastrointestinal endoscopies in these patients in the 1st week of burns, lesions were noted in 31 patients out of the study group of a total of 70 [Figure 1].

The Incidence of Endoscopic Lesions

Diagram 2 shows the incidence of lesions in this study. During this study, endoscopies were started in the 1st week of burns among the selected patients in each group. Lesions were noted in 31 patients out of the study group of a total of 70 [Figure 2].

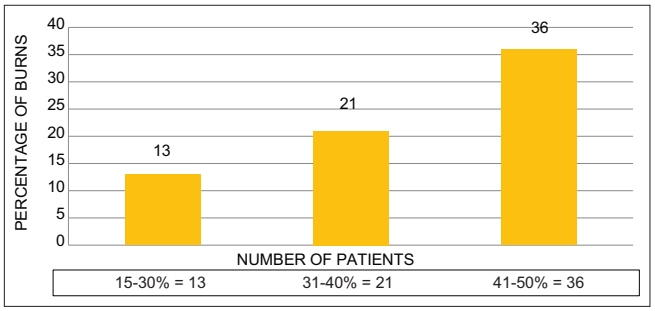

Figure 1: Relationship of percentage of burns to number of patients

Relation of Percentage of Burns to Lesions

Among the 13 patients admitted with 15–30% burns, two (15.38%) patients had endoscopic lesions. In 21 patients admitted with 31–40% burns, eight (38.09%) patients showed lesions on endoscopy and of the 36 patients admitted with 41–55% burns, and 21 (58.33%) patients had endoscopic lesions [Table 1].

The "*P*" value here is 0.022 which is significant.

Incidence of Lesions in Each Group

In Group I (Pantoprazole, n = 35), endoscopic lesions were seen in 17 (48.57%) patients. In Group II (Sucralfate, n = 35), endoscopic lesions were seen in 14 (40%) patients. "*P*" = 0.631 is not significant [Table 2].

Relationship of Percentage of Burns to Lesions in Each Group

Among 13 patients admitted with 15-30% burns, two (14.28%) patients of Group II (Sucralfate) had endoscopic lesions. In 21 patients admitted with burns of 31-40%, five (29.41%) patients of Group I (Pantoprazole) and three (21.42%) patients of Group II (Sucralfate) had endoscopic lesions. And of the 36 patients admitted with 41%–55% burns, 12 (70.58%) patients in Group I (Pantoprazole) and nine (64.28%) of Group II (Sucralfate) had endoscopic lesions [Table 3].

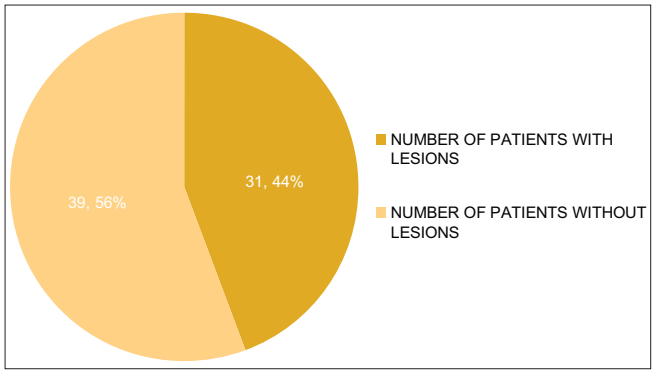

Figure 2: The incidence of endoscopic lesions

Table 1: Relation of percentage of burns to lesions

Percentage of burns	Number of patients	Number of patients with lesions	Percentage
15–30	13	2	15.38
31–40	21	8	38.09
41–55	36	21	58.33

Table 2: Incidence of lesions in each group

Group	Total number of patients	Patients with lesions	Percentage
Group I (pantoprazole)	35	17	48.57
Group II (sucralfate)	35	14	40.0

Type of Endoscopic Lesion (n = 31)

The study was done in 70 patients with burns, of which 31 patients had endoscopic lesions. Twenty-four of the 31 (77.41%) patients had erosions on endoscopy, and seven of 31 (22.6%) patients developed ulcers [Table 4].

Relationship between Age, Percentage of Burns, and Lesions

Maximum number of burn patients, 46 of 70 (65.71%), was in the age group of 18–30 years. Furthermore, most of the lesions, (erosions-18+ulcers-3), 21 of the 31 (67.74%) are noted in this age group [Table 5].

Type of Lesions in Each Group

Erosions (n = 24): Among the 24/70 (77.41%) patients who had only erosions on endoscopy during this study, 11 of the 35 (31.43%) patients of Group I (Pantoprazole) showed erosions, while in a total of 35 patients in Group II (Sucralfate) 13 (37.14%) patients had erosions.

Ulcers (n = 7): During this study, we noticed ulcers in seven out of 70 (22.6%) patients on endoscopy. These ulcers were seen in six (17.14%) patients out of 35 in Group I (Pantoprazole), while only one (2.86%) patient out of 35 in Group II (Sucralfate) developed ulcer. "*P*" = 0.094 shows that there is no significant association between erosions and ulcers among groups [Table 6].

Site of Endoscopic Lesions in Upper Gastrointestinal Tract

Erosions (n = 24): Of the 24 (34.28%) patients who had erosions on endoscopy, 4.28% patients had erosions in esophagus, 24.28% patients had them in stomach, and 5.71% patients had erosions in duodenum.

Ulcers (n = 7): Among the total 70 patients who underwent endoscopies, seven (10%) patients had ulcers. None was in esophagus. In 2.85% patients, ulcers were seen in stomach. And in five 7.14% patients, ulcers were in duodenum [Table 7].

Healing of Lesions

In Group I (Pantoprazole) of the 35 patients, 17 (48.57%) patients had endoscopic lesions in the form of erosions and

Table 3: Relationship of percentage of burns to lesions in each group

Groups	Number of patients with lesions	Number of patients with lesions in each percentage range of burns		
		15%–30% (*n*=13), *n* (%)	31%–40% (*n*=21), *n* (%)	41%–55% (*n*=36), *n* (%)
Group I (Pantoprazole)	17	-	5 (29.41)	12 (70.58)
Group II (Sucralfate)	14	2 (14.28)	3 (21.42)	9 (64.28)

ulcers. In 14 patients, that is, 82.35% the lesions healed in 4 weeks. However, it took 6 weeks for the lesions to heal in three, that is, 17.64% of patients.

In Group II (Sucralfate), of the 35 selected patients, 14 patients had endoscopic lesions. Nine (64.28%) patients showed healed lesions in 4 weeks at serial endoscopies. However, in five (35.71%) patients it took 6 weeks to heal the lesions [Table 8] $P = 0.413$. "*P*" value states that the association between lesions and healing time is not significant.

Incidence of Endoscopic Bleed

A total of four in 70 (5.71%) patients showed evidence of endoscopic bleed.

In Group I (Pantoprazole), three (3/35) patients, that is, 8.57% had evidence of endoscopic bleed. While only one (1/35) patient 2.85% from Group II (Sucralfate) showed bleeding on endoscopy [Table 9] $P = 0.60$ There is no significant association between groups and bleeding lesions on endoscopy.

Type of Bleeding Lesions in Each Group

Bleeding erosions: In a total of 13 patients who had erosions from Group II (Sucralfate), one patient with erosion, that is 7.69%, showed bleeding on endoscopy. In Group I (Pantoprazole) one out of 11 (9.09%) patients with erosions had bleeding.

Bleeding ulcers: Of the six patients who had ulcers in Group I (Pantoprazole), two patients, that is, (2/6) 33.33% patients had bleeding from the ulcers on endoscopy [Table 10] $P = 0.333$, there is no significant association between bleeding erosions and bleeding ulcers among groups.

Incidence of Clinical Bleed

Only one patient 2.85% out of 35 patients in Group I (Pantoprazole), presented with hematemesis and melena.

Table 4: Type of endoscopic lesion

Total number of patients	Number of patients with lesions, *n* (%)	Erosions, *n* (%)	Ulcers, *n* (%)
70	31 (44.28)	24 (77.41)	7 (22.6)

Table 5: Relationship between age, percentage of burns, and lesions

Age group	Number of patients, *n* (%)	Range of burn percentage	Type of lesion
18–30	46 (65.71)	20–45	Erosions - 18, Ulcers - 3
31–45	17 (24.28)	27–48	Erosions - 4, Ulcers - 4
46–60	7 (10)	20–50	Erosions - 2, Ulcers - 0

DISCUSSION

Stress-related mucosal damage (SRMD) is an erosive process of the gastroduodenal mucosa that occurs with abnormally high physiologic demands such as burns. Within hours of the onset of critical illness, macroscopic mucosal damage is apparent as subepithelial petechiae. Endoscopic evidence of stress gastritis occurs within 24 h of admission to an intensive care unit and may progress rapidly to erosive ulceration.[3]

Superficial mucosal erosions are asymptomatic but become symptomatic with exposure of superficial vessels presenting as hematochezia, melena, hematemesis, and bloody or coffee ground aspirates. Clinically significant bleeding is caused by deep ulceration into the submucosa and muscularis propria where erosion of larger vessels occurs, producing hemodynamic changes.

The rate of overt bleeding from SRMD varies between 0.1% and 39% in patients not receiving prophylaxis. Clinically significant bleeding from SRMD is associated with increased morbidity, lengthened hospital stays, and mortality rates >50%.[3]

To avert morbidity and mortality associated with clinically significant bleeding from SRMD, current recommendations are to provide stress ulcer prophylaxis with an antacid,

Table 6: Type of lesions in each group

Group	Total number of patients (*n*=70)	Patients with lesions (*n*=31), *n* (%)	Erosions (*n*=24), *n* (%)	Ulcers (*n*=7), *n* (%)
Group I (pantoprazole)	35	17 (48.57)	11 (31.43)	6 (17.14)
Group II (sucralfate)	35	14 (40.0)	13 (37.14)	1 (2.86)

Table 7: Site of endoscopic lesions in the upper gastrointestinal tract

Type of lesion	Total number of patients, *n* (%)	Esophagus, *n* (%)	Stomach, *n* (%)	Duodenum, *n* (%)
Erosion	24 (34.28)	3 (4.28)	17 (24.28)	4 (5.71)
Ulcer	7 (10)	-	2 (2.85)	5 (7.14)

Table 8: Healing of lesions

Group	Number of patients with lesions	Lesions healing in 4 weeks, *n* (%)	Lesions healing in 6 weeks, *n* (%)
Group I	17	14 (82.35)	3 (17.64)
Group II	14	9 (64.28)	5 (35.71)

Table 9: Incidence of endoscopic bleed

Group	Patients with lesions	Number of bleeding lesions on endoscopy, *n* (%)	Number of lesions which did not bleed
Group I	17	3 (8.57)	14
Group II	14	1 (2.85)	13

Table 10: Type of bleeding lesions in each group

Group	Patients with lesions	Bleeding erosions, *n* (%)	Bleeding ulcers, *n* (%)
Group I	17	1 (9.09)	2 (33.33)
Group II	14	1 (7.69)	-

a histamine2-receptor antagonist, or sucralfate.[3] PPIs maintain intragastric pH ≥4 for prolonged periods and have few adverse effects.

PANTOPRAZOLE is a PPIs acting on gastric parietal cells inhibiting acid hypersecretion.

SUCRALFATE is aluminum magnesium suspension which coats the gastric mucosa and protects it from the adverse effects of acid hypersecretion.

During this study, the earliest endoscopy was done on 4th day and erosion was observed appearing as early as 4th day after burns. It was also noted that as the percentage of total body surface area of burns increases, the number of patients who develop endoscopic lesions has increased. Pruitt' *et al* revealed similar findings that the incidence of Curling's ulcer increased with increasing burn percentage.[4]

The youngest patient was 18 years old while the oldest was of 56 years. Upper gastrointestinal lesions were found in nearly half of the study group that is 31 patients out of a total of 70 patients. All the patients with lesions were followed up with serial endoscopies at 2 weeks interval. The incidence of lesions in this study is 44.28%. Kumar and Sudhakar[5] in their study reported an incidence of 45.7%.

More number of burn patients, 46/70 (65.71%), were in the age group of 18–30 with21/31 (67.74%) showing lesions. Although the range of TSAB is similar to those of age group between 46 and 60, the more number of patients can be ascribed to the suicidal burns in this group compared to accidental cause in elderly.

The clinical presentation of the patients with lesions was upper abdominal pain and discomfort, sometimes with hematemesis and coffee colored aspirates from nasogastric tube. Once the treatment is started in each group, symptoms decreased. Lesions appeared in the groups in the form of either erosions or ulcers. In pantoprazole group, incidence of lesions was 48.57% and in sucralfate group the incidence is 40%.

The incidence of lesions in Group II (Sucralfate) was only marginally less than Group I (Pantoprazole) which can be explained for the reason that PPIs are effective in decreasing acid hypersecretions when started early in treatment. Sucralfate, on the other hand, effectively coats and protects the mucosal layer thus preventing the hyperacidity due to burns from further damaging the ischemic areas due to shock. However, the patient compliance in adhering to the dose quantity and frequency is of also significant for efficacy of the drug.

Common lesion observed was erosion, seen in a total 77.41% of 70 patients of which 31.43% were in pantoprazole group while 37.14% of sucralfate group had lesions. Ulcers were seen in 10%, most of them in duodenum, six in pantoprazole group, and one in sucralfate group. From this study, we could asses that though erosions were seen most in sucralfate group, very few progressed to ulcers. This enabled us to conclude that sucralfate is efficacious in preventing erosions from progressing to Curling's ulcers.

Observations regarding healing of lesions were that all the lesions took between 4 and 6 weeks to heal. Most of them healed by 4 weeks that is 82.35% of Group I and 64.28% of Group II. In 17.64% of Group I and 35.71% from Group II it took 6 weeks for the lesions to heal. Although the PPIs have revolutionized the treatment of acid peptic disorders and also as prophylactic drug in stress induced upper gastrointestinal lesions, this study could not conclude significant difference in the data between pantoprazole and sucralfate. Moreover, the superiority of one over the other is not clearly established.

An overall of four patients in the two groups had bleeding from the lesions, three from Group I and one from Group II. These bleeds were seen on 8th day in 51% burns patient, on 11th day in patient with 45% burns, and on 15th post burns day in patient with 48% burns. Two were erosions that bled and one was from ulcer. Only one patient in Group I (pantoprazole) showed clinical signs of bleed and presented with hematemesis and coffee ground aspirates from nasogastric tube.

In this study, there were three deaths out of 70 patients (4.28%). Sepsis is a major cause of death in burn patients. Inadequate volume replacement in the presence of hypovolemia and shock with or without sepsis is known to cause ischemia of the bowel mucosa[6] which leads to translocation of bowel pathogens into the systemic circulation causing septicemia and multiorgan failure. Early and vigorous fluid resuscitation plays an important role in the prophylaxis of ischemic mucosal injury and stress ulcers.

The "*P*" values of percentage of the burns to the number of patients with lesions are significant 0.022 which asserts the finding made by Kirksey and Pruitt[7] that Curling's ulceration of the stomach and duodenum is the most prevalent problem and is related to the magnitude of the burn. Furthermore, "*P*" = 0.018 of common site of lesion being stomach in the upper gastrointestinal tract is significant with similar observation made in another study.

CONCLUSIONS

The conclusions drawn from this study are as follows:

1. The study results have revealed a significant association between percentage of burns to the number of patients
2. Incidence of the upper gastrointestinal lesions has a direct relation to the percentage of burns. Incidence of lesions increases with the increase in total body surface area of burns (15–30% had two patients with lesions, 31–40% had eight patients with lesions, and 41–55% had 21 patients with lesions)
3. The incidence of lesions in this study is 44.28%. The lesions appeared as early as 4 post-burn day
4. Erosions 24/31(77.41%) were the most common lesions observed than ulcers 7/31 (22.6%)
5. Adult population of age 18–30 years are commonly affected with burns (65.71%) and gastrointestinal lesions are also commonly seen (67.74%) in them
6. The lesions which bled on endoscopy are more in pantoprazole group 3/17(8.57%) than in sucralfate group 1/14(2.85%)
7. Erosions were predominantly seen in stomach 17/70 (24.28%) and ulcers frequented 5/70 (7.14%) in duodenum
8. There is a difference in the incidence of lesions in pantoprazole group 17/35 (48.57%) and sucralfate group 14/35(40.0%)
9. The superiority of one drug over the other in preventing occurrence of lesions is not established
10. Sucralfate showed a better healing of lesions and also helped in preventing erosions from progressing to ulcers than pantoprazole
11. There was less number of patients with ulcers in sucralfate group 1/7 (2.85%) than pantoprazole group 6/7 (17.14%).

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Original Article

Percutaneous Transpedicular Biopsy in Patients with Tuberculosis of Spine – How to Increase the Diagnostic Yield

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Abstract

Background: Tuberculosis (TB) is one of the oldest diseases known to humankind, with evidence of its existing dating to over 4000 years ago. Spinal TB is the most common site of skeletal TB, amounting to half of skeletal TB. It is usually diagnosed clinicoradiologically magnetic resonance imaging (MRI) which has been the imaging modality of choice as it has been able to detect the earliest changes. Laboratory diagnostic tests such as histopathology, TB Gene X pert, culture, and sensitivity (TB Bactec) are used to assess bacteriology and sensitivity pattern, especially with the rise in multi-drug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), with the growth of *Mycobacterium* in culture specimens obtained from the infected tissue considered to be the single most confirmatory test of spinal TB, and hence considered the gold standard method. However, a negative culture or delay in the setting of resistant strains may lead to neurological deficits or deformity. Overall positive culture yields from abscess sites using core needle biopsies in previous studies, which is 50–83%. Our study aims to assess the efficacy of percutaneous transpedicular biopsy and Gene X pert for the diagnosis of TB of the Spine. Furthermore, we propose systematic area-specific biopsy and laboratory sampling of the affected vertebra (Abscess area), paradiscal region, and a relatively non affected part of the involved vertebra, which will help us understand the area-wise yield.

Materials and Methods: A total of 15 cases with clinical and/or radiological features suggestive of TB of spine were selected for the study. After obtaining an informed consent, the cases were subjected to area-specific percutaneous transpedicular biopsy. Multiple systematic area-wise transpedicular biopsy (abscess area – Area 1, paradiscal partially affected area – Area 2, and area of hyperintensity on MRI – Area 3) were taken. Three samples from obtained from each patient, which were subsequently sent for Gene Xpert and TB culture analysis. Statistical analysis used was IBM SPSS STATISTICS VERSION 20.

Results: The patient age ranged from 14 to 72. The mean age was seen to be 41.4. Nine out of the 15 (60%) subjects were male and six female (40%). Sensitivity of Gene Xpert for Area 1, 2, and 3 was found to be 100% each, specificity of gene Xpert for Area 1, 2, and 3 was found to be 90%, 100%, and 87.5%, respectively. Positive yield for Area 1 was 38.46%, Area 2 was 69.25%, and Area 3 was 53.89% *P* value for comparison of yield between Areas 1 and 2 which was found to be 0.122 (statistically not significant). *P* value for comparison of yield between Areas 1 and 3 was found to be 0.440 (statistically not significant). Erythrocyte sedimentation rate values ranged from 34 to 66, with a mean of 49.47 and standard deviation of 9.015. C-reactive protein values of all patients universally were seen to be positive.

Conclusion: Area specific percutaneous transpedicular biopsy for TB of spine is a good promising modality of investigation in TB spine since it can give a quick definitive diagnosis, by means of Gene Xpert. The accuracy of Gene Xpert can be high since it has shown to have a high sensitivity and specificity. Furthermore, MDR-TB can be diagnosed at an early stage, and appropriate chemotherapy can be initiated.

Key words: Gene Xpert percutaneous Transpedicular biopsy, Tuberculosis of spine

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INTRODUCTION

Tuberculosis (TB) is one of the oldest diseases known to humankind, with evidence of its existing dating to over 4000 years ago.[1-3] Extrapulmonary TB incidence is around 3%,[4] of which 10% contribution is by Skeletal TB. Spinal TB is the most common site of skeletal TB, amounting to

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half of skeletal TB.[5,6] Clinical picture is very variable, and it depends on the severity and duration of the disease, site of the disease, and the presence of complications such as abscess, sinuses, deformity, and neurological deficit.[7] It is usually diagnosed clinicoradiologically. Magnetic resonance imaging (MRI) has been the imaging modality of choice as it has been able to detect the earliest changes. Gadolinium-enhanced MRI further helps in differentiating TB from other causes of infective spondylodiscitis.[8,9] Laboratory diagnostic tests such as histopathology, TB gene Xpert, culture, and sensitivity (TB Bactec) are used to assess bacteriology and sensitivity pattern, especially with the rise in multi-drug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), with growth of Mycobacterium in culture specimens obtained from the infected tissue considered to be the single most confirmatory test of spinal TB, and hence considered the gold standard method.[10] However, a negative culture or delay in the setting of resistant strains may lead to neurological deficits or deformity. Overall positive culture yields from abscess sites using core needle biopsies in previous studies, which is 50–83%.[11]

Our study aims to assess the efficacy of percutaneous transpedicular biopsy and gene Xpert for the diagnosis of TB of the spine. Furthermore, we propose systematic area-specific biopsy and laboratory sampling of the affected vertebra (Abscess area), paradiscal region, and a relatively non-affected part of the involved vertebra, which will help us understand the area wise yield.

MATERIALS AND METHODS

Our study was prospective cross-sectional study conducted at orthopedic ward and outpatient department of a tertiary care hospital. Informed consent was taken from all the subjects enrolled. The following was the inclusion criteria – all patients clinicoradiologically (clinical examination, X-Ray, and MRI) diagnosed TB spine cases (thoracic and lumbar). The exclusion criteria were as follows patients with biopsy-proven malignancy and fracture spine. Three areas of vertebrae were biopsied – abscess/area of granulation tissue [Area 1]. Area of osteomyelitis, partially [Area 2], area showing hyperintensity on MRI [Area 3] [Figure 1]. Each of the sample (from Area 1, 2, and 3) was subjected to histopathology, ZN staining, TB Gene Xpert, and Culture and Sensitivity (TB Bactec). Each of this sample was blinded for the pathologist and laboratory technician. The positive outcome was – presence of acid-fast bacilli and/or granulomas (non-caseating or caseating) and/or positive culture growth.

Statistical Analysis

Primary data were collected in paper-based pro forma, and the data were then entered in Microsoft Excel spreadsheets. Statistical analysis was done on IBM SPSS STATISTICS VERSION 20. Means were compared using an independent sample *t* test. Categorical data were plotted using column charts and pie diagrams. Mean values represented by column charts are added with error columns representing actual standard deviation in plus and minus values. $P < 0.05$ was taken significant. $P < 0.01$ was considered highly significant. Receiver operating characteristics (ROCs) curves were plotted to assess the performance of a diagnostic test over the range of possible values of a predictor variable. The area under an ROC curve provided a measure of discrimination to compare the performance of two or more diagnostic tests.

Percutaneous transpedicular biopsy procedure was as follows – After thoroughly explaining the whole procedure to the patient and after obtaining informed consent, the patient was admitted for a single day for the procedure.

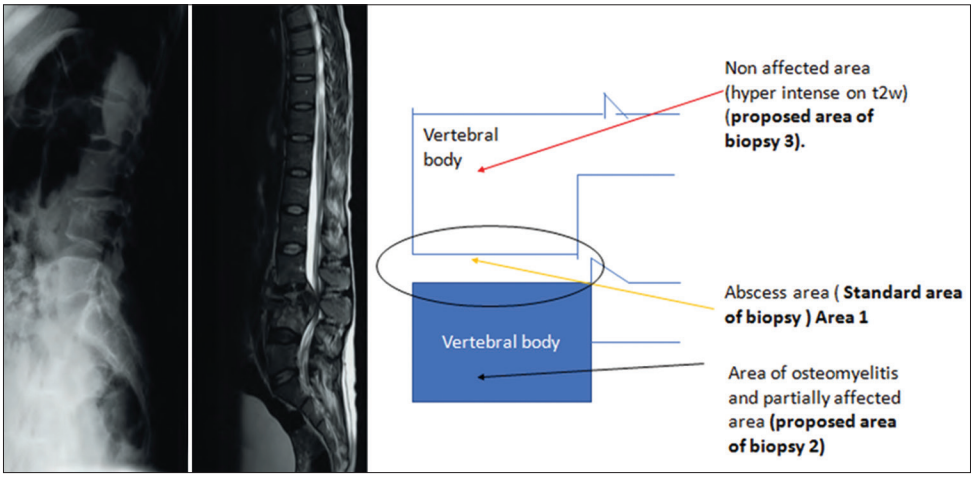


Figure 1: Area specific biopsy

Lignocaine sensitivity test was at least done 30 min before undertaking the procedure. The patient was made to lie prone on a radioluscent operating table, and their vitals were monitored with an anesthetist stand-by.

Planning was done beforehand so as to determine Areas 1, 2, and 3 of biopsy, based on presence of abscess, adjacent area with partial osteomyeltic involvement, and area of hyperintensity, respectively. Scrubbing of the back was done with iodine scrub solutions, followed by painting and draping the biopsy area under all aseptic precautions.

With the use of an image intensifier, the landmarks for the pedicles of the required vertebrae were marked with a sterile skin marker. Local infiltration with 2% lignocaine was given at the biopsy sites. After adequate anesthesia was attained, a small stab incision was taken on the skin, corresponding to the level, slightly lateral to the lateral border of the pedicle. A 10- gauge Jamshedi Needle (J-Needle), with the stylet *in situ*, was introduced through the stab incision to the surface of the pedicle, just medial to its lateral border. Once the position of the J-Needle was confirmed on both lateral and anteroposterior (AP) views such that it was at the center of the pedicle on the lateral view, and just medial to the lateral border on AP view, the J-Needle was advanced very carefully by providing controlled axial and rotational force to the needle. Advancement of the needle was duly monitored with periodic image intensifier images. Once the needle appeared to be reaching the medial wall of the pedicle on AP view, the lateral view confirmed that the J-Needle had traversed the pedicle and was now entering the vertebral body.

After just entering the vertebral body, the stylet was removed, and only the trocar was advanced. Once the needle covered at least 3/4th of the vertebral body, a 20 cc syringe was connected to the back end of the J-Needle and aspirated to collect any liquid content.

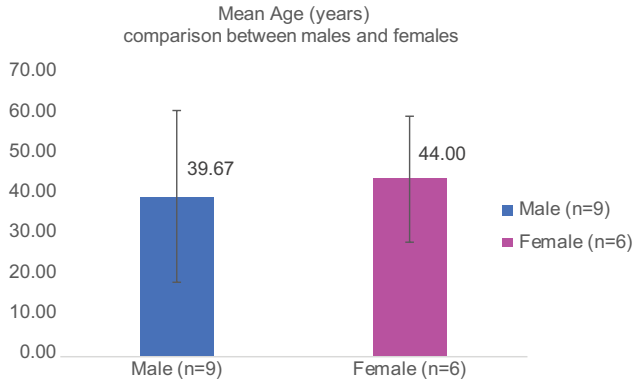
The needle was then rotated at this position a few times to ensure sample gets completely entrapped within the needle before slowly withdrawing it out. The stylet was reintroduced into the trocar, and the sample obtained was collected in a Gene Xpert container under aseptic precautions. These steps were then repeated two more times to obtain samples from the other 2 areas to be biopsied. All collected samples were then immediately sent to the Revised National TB Control Program (RNTCP) approved TB Laboratory, after filling out the appropriate forms.

Blinding was ensured at 3 levels – the personnel carrying the samples to the laboratory for analysis, the technician receiving the sample at the laboratory, and the technician undertaking Gene Xpert, culture, and histopathology.

RESULTS

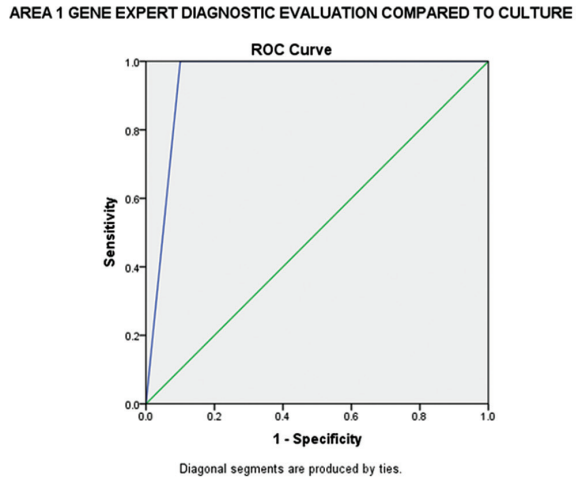
A total of 15 subjects were taken for the study. Their ages ranging from 14 to 72. Mean age was seen to be 41.4, with a standard deviation of 18.681.

Nine of the subjects were male and six were female. The mean age of males was found to be 39.67 with a standard deviation of 21.172. The mean age of female was 44.00 with a standard deviation of 15.697. The standard error mean was 7.057 and 6.408, respectively.

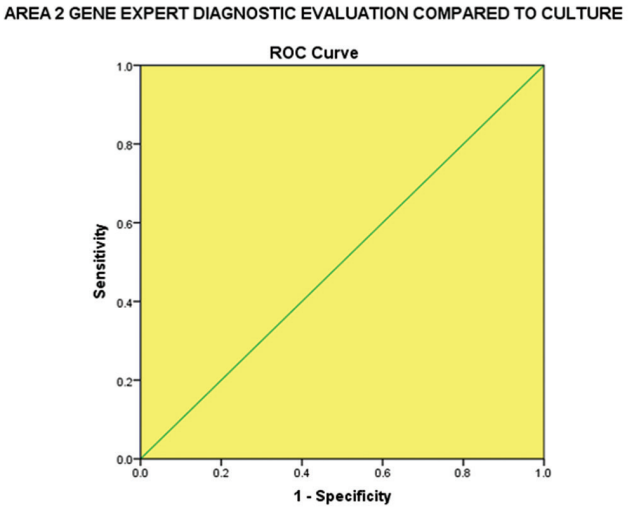


Considering TB culture as the gold standard test,[10] the sensitivity and specificity of Gene Xpert was calculated for each of the areas. These were evaluated using an ROC curve.

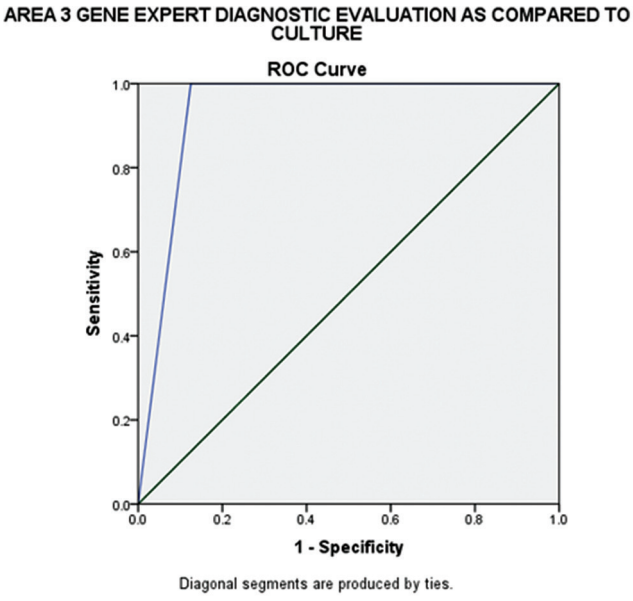
For Area 1, it as seen that it had a 100.00% sensitivity with a 95% CI of 47.82% to 100.00%. Specificity was seen to be 90.00%, with a 95% CI of 55.50% to 99.75%. A positive likelihood ratio of 10 was with a 95% CI of 1.56–64.20. The negative likelihood ratio was 0.



For Area 2, it as seen that it had a 100.00% sensitivity with a 95% CI of 66.37–100.00%. Specificity was seen to be 100.00% as well with a 95% CI of 54.07–100.00%.



For Area 3, it as seen that it had a 100.00% sensitivity with a 95% CI of 59.04–100.00%. Specificity was seen to be 87.50%, with a 95% CI of 47.35–99.68%.



Area under the Curve

The positive yields of Gene Xpert between Area 1 with that of Areas 2 and 3 were compared. It was seen that Area 1 had a yield of 38.46%, Area 2 had a yield of 69.25%, and Area 3 had a yield of 53.89%. Comparison of yields between Areas 1 and 2 gave a $P = 0.122$ (not significant), and that of Areas 1 and 3 gave $P = 0.440$ (not significant).

Erythrocyte sedimentation rate (ESR) values of all patient were compared. A minimum value of 34 was obtained and a maximum of 66. Mean was seen to be 49.47 with a standard deviation of 9.015.

Qualitative CRP analysis was done in all 15 patients. It was seen that all 15 patients had a positive CRP, giving a valid percent and cumulative percent of 100%

Total white blood cell counts were compared in both men and women. In men, a minimum value of 4200 and a maximum of 7800 was seen. Mean was seen to be 6177.78, with a standard deviation of 1068.78.

In women, a minimum value of 5600 and a maximum of 7600 was seen. Mean was seen to be 6425, with a standard deviation of 744.84 (Tables 1-14).

DISCUSSION

In our study, which was conducted over the course of 2 years, a total of 15 patients were enrolled and biopsied. As mentioned, nine of which were men and six women. This correlates with previous studies showing higher incidence and prevalence of TB in men as compared to women, as seen in a study done by Horton *et al.*[12] In this study, which was a systematic review and a meta-analysis, this generalized trend was seen all over the world, including India. This was accounted for due to an increased risk of exposure in men, in general, as well as neglecting to present at an early stage due to socio-economic responsibilities.

There was no specific age group that was found to be affected more than the others. Subjects ranged from ages as young as 14 to as old as 72. This further emphases on the importance of need of better, faster, and more effective modalities for early and accurate diagnosis and subsequent treatment since no age in particular seems to be affected preferentially, and spine seems to cause significant burden on all age groups, in an endemic country such as India.

A generalized consensus of the inflammatory biochemical parameters, namely, ESR and CRP, in our study showed correlation with existing literature[13,14] to the fact that these parameters are raised in the case of TB spine, as all 15 of our study patients showed abnormally high values for both. However, since both parameters are relatively non-specific for the disease itself, their role in diagnosis by itself is close to nil. Also, what needs to be kept in mind is the role of serial monitoring of patients on medical management on a long-term basis. A serial decrease in these parameters would indicate success of therapy. On the contrary, no change, or even increase of these parameters would suggest the clinician look for a possibly more sinister cause, such as MDR/XDR TB, or even perhaps a non-tuberculous or non-infectious pathology.

MDR-TB is that which is resistant to INH and rifampicin. Primarily, it occurs due to improper treatment, but resistant strains can also be communicable. Extensively drug-resistant TB (XDR-TB) is when there is resistance to INH and rifampicin, along with resistance to any fluoroquinolone and at least one injectable second-line anti-TB drugs.[15,16]

Pawar *et al.* suggested the following five predictors for successful outcome in MDR-TB: (1) Progressive clinical improvement at 6 months following chemotherapy, (2) radiographic improvement during treatment, (3) disease with strains that are resistant to < 3 anti-tubercular treatment drugs, (4) use of <4 second-line drugs in treatment, and (5) no changes of regimen during treatment.[17] In 2009, the term "totally drug-resistant tuberculosis" for TB strains that showed *in vitro* resistance to all first and second-line drugs tested was proposed by Velayati *et al.*[18]

Transpedicular biopsy was done as a daycare procedure in all of our subjects. Samples were obtained using stainless steel J-Needles. We found that size 10 and 11 gauge J-Needles gave the best yield in an adult, as the needle bore was sufficiently wide, both for aspirating contents and obtaining a biopsy. All samples were sent for Gene Xpert.

In our study, we primarily assessed the efficacy of Gene Xpert as compared to the TB culture, which is the Gold Standard for diagnosis.[10] We also assessed which areas, with respect to the MRI findings, were giving the best yield of bacilli for diagnosis.

On analyzing our data, we found a sensitivity and specificity of more than 85% in all three areas of biopsy across all the subjects. This is in line with existing literature,[19-21] which gives further credibility to the test. Since Gene Xpert is endorsed by the WHO[19]] and is recommended by RNTCP,[22] and the test requires 2 h to give a result,[23] a quick diagnosis can be achieved with minimal intervention by means of percutaneous transpedicular biopsy. TB culture methods, even newer ones such as BACTEC culture, on the other hand, require at least 2 weeks to give a definitive result.[24] Added of advantage of Gene Xpert over other modalities of diagnosis is that it can determine the presence of rifampicin resistance by detecting the presence of rpoB gene, which confers rifampicin resistance to the bacilli.[25] This can prove to be a huge factor in decreasing the morbidity and mortality associated with MDR TB since in most cases in India, MDR TB is usually suspected only when first-line antituberculous treatment (AKT) seems to show no improvement or there happens to be clinical worsening. By this time, the patient could have already had a significant effect on their disability-adjusted life year. An early diagnosis of MDR TB could mean earlier initiation of second-line drugs. This could be vital in minimizing the complications that may arise due to a late diagnosis.

A total of three biopsies were taken from each subject. First sample was taken from the abscess/diseased area, as is the usual protocol.[26] Second sample was taken from the adjacent vertebrae and a third sample from vertebra showing hyperintense signal on MRI. The abscess area has usually shown to give a yield of around 50–83%.[11]

In a study done by Watt and Davis[27] to assess yield in spinal TB, it was found that the overall positive TB culture rate was 59%, when the sample was taken from the abscess site (Area 1). In our study, we found that the abscess site gave a positive yield of only 38.46% of the samples. However, the adjacent vertebrae (Area 2) gave a positive yield of 69.25% and the area of hyperintensity gave a positive yield of 53.89% (Area 3). On assessing the statistical significance of these findings, Area 1 versus Area 2 gave $P = 0.122$ and that of Area 1 versus Area 3 gave $P = 0.440$, which would suggest statistical insignificance. However, since the sample size was small for this study, and the fact that numerically Areas 2 and 3, in general, showed a higher yield, it would be safe to suggest that a study with a possibly bigger sample size, over a longer duration of time, conducted perhaps

Table 1: Age descriptive

	N	Minimum	Maximum	Mean	Standard deviation
Age (years)	15	14	72	41.40	18.681

Table 2: Frequency distribution of age

Age (years)	Frequency	Percent	Cumulative percent
14	1	6.7	6.7
18	1	6.7	13.3
21	1	6.7	20.0
29	1	6.7	26.7
30	1	6.7	33.3
31	1	6.7	40.0
32	1	6.7	46.7
34	1	6.7	53.3
44	1	6.7	60.0
54	2	13.3	73.3
60	1	6.7	80.0
62	1	6.7	86.7
66	1	6.7	93.3
72	1	6.7	100.0
Total	15	100.0	

Table 3: Comparison of mean age

Gender	N	Mean	Standard deviation	Standard error mean	*P*
Age (years)					
Male	9	39.67	21.172	7.057	0.676
Female	6	44.00	15.697	6.408	

Table 4: Diagnostic evaluation of AREA 1 gene expert compared to culture

Statistic	Value	95% CI
Sensitivity	100.00%	47.82–100.00%
Specificity	90.00%	55.50–99.75%
Positive likelihood ratio	10	1.56–64.20
Negative likelihood ratio	0	

Table 5: Test result variable(s): AREA 1 Gene Expert

Area	Standard error[a]	Asymptotic significance[b]	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
0.950	0.060	0.006	0.833	1.000

Table 6: Diagnostic evaluation of AREA 2 gene expert compared to culture

Statistic	Value	95% CI
Sensitivity	100.00%	66.37–100.00%
Specificity	100.00%	54.07–100.00%

Table 7: Test result variable(s): AREA 2 Gene Expert

Area	Standard error[a]	Asymptotic significance[b]	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
1.000	0.000	0.001	1.000	1.000

Table 8: Diagnostic evaluation of AREA 3 gene expert compared to culture

Statistic	Value	95% CI
Sensitivity	100.00%	59.04–100.00%
Specificity	87.50%	47.35–99.68%

Table 9: Test result variable(s): AREA 3 Gene Expert

Area	Standard error[a]	Asymptotic significance[b]	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
0.938	0.072	0.005	0.795	1.000

Table 10: Comparison of Gene Xpert Yield between areas 1 and 2

	Area 1	Area 2	*P* value
Positive yield	38.46%	69.25%	0.122

over multiple tertiary care centers at once, could give more convincing evidence to prove that Areas 2 and 3 would give a better yield.

Table 11: Comparison of Gene Xpert Yield between areas 1 and 3

	Area 1	Area 3	*P* value
Positive yield	38.46%	53.89%	0.440

Table 12: ESR values

Test	N	Minimum	Maximum	Mean	Standard deviation
ESR (MM/HR)	15	34	66	49.47	9.015
Valid N (list-wise)	15				

ESR: Erythrocyte sedimentation rate

Table 13: C-reactive protein (CRP) values

	CRP values				
		Frequency	Percent	Valid percent	Cumulative percent
Valid	positive	15	100.0	100.0	100.0

Table 14: Total white blood cell count (WBC)

		N	Minimum	Maximum	Mean	Standard deviation
WBC (no/microliter)	Men	9	4200	7800	6177.78	1068.78
	Women	6	5600	7600	6425	744.84

What can be safely assumed, though, is that percutaneous transpedicular biopsy can serve as a good diagnostic investigation. It confers multiple advantages over other modalities of diagnosis. Since each sample is sent for histological confirmation, over-diagnosing and unnecessary treatment with AKT for TB spine could be avoided. The use of Gene Xpert helps give a quick result and also helps determine if there is resistance to first-line drugs, and hence, second-line therapy can be initiated earlier. The procedure by itself is low risk, as it is done under local anesthesia.

In addition, a percutaneous transpedicular biopsy would be superior to a CT-guided biopsy since CT imaging would not show any involvement in adjacent vertebrae. These areas might prove to be hyperintense under an MRI scan. A pre-operative planning using an MRI scan, followed by transpedicular biopsy from multiple areas, as mapped under the MRI, could possibly give a better yield, as opposed to that from a CT-guided biopsy.

CONCLUSION

In summary, percutaneous transpedicular biopsy is a good modality of investigation in TB spine since it can give a quick definitive diagnosis by means of Gene Xpert. The accuracy of Gene Xpert can be considered to be high since

it has shown to have a high sensitivity and specificity when considering TB culture as the gold standard. Furthermore, MDR TB can be diagnosed at an early stage and appropriate chemotherapy can be initiated.

With respect to determining which area of biopsy would give a better yield for diagnosis, probably more studies with a larger sample size and a larger demographic will have to be conducted to give a definitive and a statistically significant answer. However, results found in this study which would suggest that biopsy of adjacent areas as opposed to the diseased area could have promising results.

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Original Article

Prevalence and Risk Factors for Latent Tuberculosis Infection among Children in Contact with Smear-Positive Tuberculosis Cases in a Tertiary Care Center, South Tamil Nadu

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Abstract

Background: Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically active tuberculosis (TB). Knowledge of the prevalence of LTBI among children gives an understanding about the transmission of disease. Identification of risk factors associated with TB infection and treatment of the same among children reduce the chance of progression of tubercular infection to full blown disease.

Materials and Methods: This hospital-based cross-sectional study was done using a standard questionnaire and tuberculin skin test (TST) to evaluate the prevalence and risk factors for LTBI among children over 3 months of age and <72 months of age who were in contact with the smear-positive TB patient. Questionnaire used collected information on the socioeconomic status, household characteristics, index case characteristics, contacts anthropometric details, and proximity and activities of contact with the index case.

Results and Conclusions: Among the 104 children who were contacts of smear-positive index TB cases, 31 children (29.8%) had TB infection as assessed by TST. Relationship and proximity of the contact with the index case have a strong association for transmission of the TB infection. Bacterial load in the sputum of the index case and the number of lung zones involved in the chest X-ray of the index case are directly proportional to the risk of transmission of the infection.

Key words: Latent tuberculosis infection, Risk factors for tuberculosis, Smear-positive tuberculosis, Tuberculin skin test, Tuberculosis

INTRODUCTION

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest active tuberculosis (TB). As there is no "gold standard" test for LTBI, the global burden is not known with certainty; however, up to one-third of the world's population is estimated to be infected with *M. tuberculosis*.[1] In developing countries, the burden of TB infection and disease is much more compared to developed and Western nations. Despite modern treatment and health education to public, children are rarely investigated for TB. The proposed reason is difficulty in diagnosing in younger age group and children are mostly non-infectious. Additional reason is poor contact tracing in developing countries due to poor resources.

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Children mostly acquire infection from adults who are in their close proximity. TB infection among children has been considered as a marker of recent ongoing transmission in the communities.[2] Therefore, knowledge of the prevalence of TB infection among children gives an idea about the transmission of disease among the general population. Identification of risk factors for TB infection among

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children is very important in planning and reducing the burden of disease in the society.[3]

This study aims to find the prevalence and risk factors for TB infection among children who are in contact with adult smear-positive cases.

Aim of the Study

The aims of the study were as follows:

1. To study the prevalence of LTBI among household contacts aged 3 months and 72 months of smear-positive TB patients.
2. To identify the possible risk factors for transmission among household contacts and children.

MATERIALS AND METHODS

This is a hospital-based cross-sectional study which was done for a period of 12 months (July 2018–June 2019). The study population were household contacts of smear-positive TB patients being treated at district TB cell, Government Rajaji Hospital, Madurai, Tamil Nadu.

Any asymptomatic child over 3 months of age and ≤72 months of age in household contact with confirmed sputum-positive TB patients who are receiving treatment at district TB cell, Government Rajaji Hospital, Madurai, were included in the study. Household contacts who show symptoms or signs of TB were excluded from the study.

A standard questionnaire was generated and data were obtained from hospital records and interview with the index case. The questionnaire had details of the relationship with contact, duration of symptoms in the index case, their sputum load, and chest X-ray findings.

For children included in the study, information on age, sex, bacillus of Calmette and Guerin (BCG) status, nutritional status (by Indian Academy of Pediatrics [IAP] classification), activities spend by the contact with the index case, and proximity of the child with the index case were taken into account. The first-degree relation implies parents and siblings of the contact child who are sputum positive. The second-degree relation implies any other family member who is sputum positive.

Any symptoms suggestive of TB, namely, cough more than 2 weeks, evening rise of temperature, hemoptysis, loss of weight, and appetite were considered as significant symptoms in index case. Duration of symptoms was calculated from the onset of first symptom to the start of the antitubercular treatment. For the purpose of this study, the presence of these symptoms was categorized into ≤30 days and >30 days.

Sputum load in the household contact with confirmed sputum-positive TB is described as the amount of TB bacilli found in the oil immersion field when stained by Ziehl–Neelsen technique shown in below:

Smear grading	Number of bacilli in fields
+	1–99 bacilli/100 fields
++	1–9 bacilli/field
+++	10 or more bacilli/field

For the purpose of this study, radiologic findings of lung field in X-ray were divided into six zones, three in each lung (namely, upper, middle, and lower zones). The index cases were divided into two groups with Group 1 involving three or less zones and Group 2 involving more than 3 zones.

Family size or the household size is calculated by the no. of members in the family who live, eat, and sleep in the same house. It's divided into two groups with Group 1 comprising of a family with more than 4 members and Group 2 comprising of a family with four or less members.

The socioeconomic status of the family was calculated using the modified Kuppuswamy scale. For the convenience of this study, the socioeconomic class was divided into two groups, namely, Group 1 comprising Classes IV and V and Group 2 comprising Classes I, II, and III.

History of BCG administration to the contact was enquired. In addition, the child's left upper arm was examined for the presence of BCG scar. The contact children were classified into three groups, Group 1 – BCG administered with scar present, Group 2 – BCG administered but no scar, and Group 3 – BCG not administered.

The body weight of the child was measured using digital weighing machine, and nutritional status was calculated and classified based on IAP classification.

Activities of the contact with the index case were classified into three categories, namely, occasional, part of the day (<half a day in contact), or most part of the day (more than half a day).

Proximity of the contact child with the index case during sleep was categorized into three groups, namely, Group 1: Sleeps in the same house but not in same room, Group 2: Sleeps in the same room but not in same bed, and Group 3: Sleeps in the same bed.

An informed oral consent was obtained from the index case/guardian of the contact before the beginning of the interview, explaining the study and after completion of

the interview, the tuberculin skin test (TST) was done for the contact child.

TST

TST was given to the childhood contacts at the TB cell, Government Rajaji Hospital, Madurai, by a trained personal. The test was performed by giving intradermal injection of 0.1 ml of purified protein derivative (PPD) containing five tuberculin units PPD-RT 23 into the volar (ventral) surface of the forearm, in the long axis of the forearm using a short 26 gauge tuberculin syringe. A wheal of 6–10 mm in diameter was taken as successful administration. The test was read after 72 h both by palpation technique and ballpoint technique. An induration of size 10 mm or more at 72 h was taken as positive for TST.

OBSERVATIONS AND RESULTS

Out of 1239 cases diagnosed as smear-positive TB at TB cell, Government Rajaji Hospital, Madurai, 176 cases from the city limits were started treatment in TB cell. Out of these cases, 78 cases had contacts of children between 3 months and 72 months of age. Of them, 4 cases refused to join the study. One hundred and four contacts of the remaining 74 cases were brought to TB cell and after obtaining the informed consent from the contacts (parents), participated in our study.

We found that among our study population in the age of 3 months and 72 months, around 29.8% of household contacts of smear-positive index, TB cases had TB infection as assessed by TST. Among the 31 positive children, 19 were male and 12 were female. The mean age group among the contact children was 40 months [Tables 1 and 2].

The index case was a 1st-degree relation to 58.1% (18/31) infected contacts and 28.8% (21/73) of the non-infected contacts. Of the 104 contacts studied, 39 (37.5%) children had their first-degree relation as their index case of which 18 (46%) showed a positive TST test ($P < 0.04$) [Table 3].

Of the total 31 positive children, 80.6% (25/31) had contact with the index case whose symptoms were more than 30 days and 19.4% (6/31) had a contact with symptoms which were < 30 days. Among 73% of children whose contact had symptoms for more than a month, 33% showed a positive TST ($P = 0.25$) [Table 4].

Smear 3+ was present in 51.6% (16/31) of cases of infected contacts and 13.7% (10/73) of cases of non-infected contacts. Of the total contacts studied, 25% of children had contact with a smear 3+ positive patient and of them 61.5% had a positive TST ($P < 0.001$) [Table 5].

Table 1: Sex distribution of the contacts

Total contact cases	Mantoux positive	Mantoux negative
Male	19	40
Female	12	33
Total	31	73

Table 2: Age distribution of the contacts

Age group (in years)	Total	Mantoux positive	Mantoux negative
Between 3 months and 1 year	8	3	5
Between 1 and 2 years	9	4	5
Between 2 and 3 years	27	3	24
Between 3 and 4 years	16	7	9
Between 4 and 5 years	22	8	14
From 5 years up to 6 years	22	6	16
Total	104	31	73

Table 3: Correlation of Mantoux positivity to the relationship of the child to the index case

Relation of the children	Mantoux result		Total (%)
	Positive (%)	Negative (%)	
1st degree	18 (58.1)	21 (28.8)	39 (37.5)
2nd degree	13 (41.9)	52 (71.2)	65 (62.5)
Total	31 (100)	73 (100)	104 (100)

($P<0.04$)

Table 4: Duration of symptoms in the index case and the influence on Mantoux test on the contacts

Duration of the symptoms	Mantoux result		Total (%)
	Positive (%)	Negative (%)	
≤30 days	6 (19.4)	22 (30.1)	28 (26.9)
More than 30 days	25 (80.6)	51 (69.9)	76 (73.1)
Total	31	73	104

($P=0.25$)

Table 5: Correlation between sputum load in index case and Mantoux positivity in contacts

Sputum load	Mantoux result		Total (%)
	Positive (%)	Negative (%)	
1+	2 (6.5)	31 (42.5)	33 (31.7)
2+	13 (41.9)	32 (43.8)	45 (43.3)
3+	16 (51.6)	10 (13.7)	26 (25)
Total	31	73	104

($P<0.001$)

Chest X-ray shadows involving three or more zones were present in 51.6% (16/31) of index cases of infected contacts and 9.6% (7/73) of non-infected contacts. Of the total 23 contacts, whose index cases had an X-ray shadow of three or more zones, 70% of them showed a positive Mantoux test ($P < 0.001$) [Table 6].

Among the infected contacts, 71% (22/31) belong to a family with more than 4 family members and among the non-infected contacts, 65.8% (48/73) come from a family with more than 4 family members ($P = 0.604$).

Of the 70 contacts, who belong to a family size of more than 4, 31% of them had a positive Mantoux test.

About 54.8% (17/31) of the infected contacts and 46.6% (34/73) of the non-infected contacts belong to a lower economic status of society (Classes IV and V according to modified Kuppuswamy's scale).

About 33% of the total 51 children who came from lower socioeconomic status tested positive for TB infection ($P = 0.4$).

BCG scar was absent in 38.7% (12/31) of the infected contacts and 9.6% (7/73) of the non-infected ones. It was seen in 61.3% (19/31) of the infected and 90.4% (66/73) of the non-infected children. Among children with a BCG scar, 22% showed a positive TST whereas in children without a scar, 63% showed a positive TST ($P < 0.001$) [Table 7].

Among the infected contacts, 58.1% (18/31) had Grade 1 malnutrition and 38.7% (12/31) and 3.2% (1/31) of them had Grades 2 and 3 malnutrition, respectively. Only 24% of the children with Grade 1 malnutrition showed positive test for TB infection whereas 45% of children with Grade 2 or 3 malnutrition turned out to be Mantoux positive ($P = 0.103$) [Table 8].

Nineteen out of 31 infected children gave a history of sleeping in the same bed with the sputum-positive index case whereas among the non-infected children, 28.8% (21/73) gave a similar history ($p < 0.004$). Among the 40 contacts who had slept in the same bed with the index case, 47% of children had a positive Mantoux test.

Around 35.5% (11/31) of the infected children gave a history of spending most of their day with the index case, whereas among the non-infected, 26% gave a similar history [Table 9]. Among the 30 contacts who had spent most of their day with the index case, 37% of children had a positive Mantoux test. In children who spent occasional activity or part of their day with the index case, 27% showed a positive test.

Table 6: Chest X-ray features of the patient and influence on the child Mantoux

Chest X-ray zones	Mantoux result		Total (%)
	Positive (%)	Negative (%)	
±3 zones	15 (48.4)	66 (90.4)	81 (77.9)
>3 zones	16 (51.6)	7 (9.6)	23 (22.1)
Total	31	73	104

($P<0.001$)

Table 7: Association of BCG status and Mantoux result

BCG status	Mantoux result		Total (%)
	Positive (%)	Negative (%)	
BCG administered and scar present	19 (61.3)	66 (90.4)	85 (81.7)
BCG administered but no scar	6 (19.4)	2 (2.7)	8 (7.7)
Not administered	6 (19.4)	5 (6.8)	11 (10.6)
Total	31	73	104

($P<0.001$). BCG: Bacillus of Calmette and Guerin

Table 8: Association of nutritional status and Mantoux result

Nutritional status	Mantoux result		Total (%)
	Positive (%)	Negative (%)	
Grade 1	18 (58.1)	57 (78.1)	75 (72.1)
Grade 2	12 (38.7)	14 (19.2)	26 (25)
Grade 3	1 (3.2)	2 (2.7)	3 (2.9)
Total	31	73	104

($P=0.103$)

Table 9: Time shared by the contact with the index case

Time shared	Mantoux result		Total (%)
	Positive (%)	Negative (%)	
Occasional	2 (6.5)	8 (11)	10 (9.6)
Part of the day	18 (58.1)	46 (63)	64 (61.5)
Most of the day	11 (35.5)	19 (26)	30 (28.8)
Total	31	73	104

($P=0.543$)

DISCUSSION

Even in the era of modern medicine, TB is still a major health problem. It has been predicted that if at least 70% of new cases of smear-positive TB are diagnosed and treated and 85% of them are cured, TB transmission will decline by 7–11% per year.

Close contacts of smear-positive TB are at risk of being infected. Identification of risk factors for TB transmission as well the proportion of TB infection among the family contacts is important to evaluate ongoing TB transmission.

Our study demonstrated that among the study population in the age of 3 months and 72 months, around 29.8% of household contacts of smear-positive index TB cases were TB infected as assessed by TST. Among the 31 positive

children, 19 were male and 12 were female. The mean age group among the contact children was 40 months. The result is comparable with the various studies done in India.[4-7]

Our study shows that those children whose index cases are first-degree relatives are at a greater risk of developing the infection. Similar outcome has been shown in studies done by Tornee *et al*.,[8] Lienhardt *et al*.,[9] and Talay *et al*.[10] This can be explained by the fact that most children spend most of their time with parents.

In our study, it is found that the duration of symptoms of index case does not have a statistically significant association with the risk of infection in contacts. In our study, 21.4% of children who's index case showed symptoms ≤30 days showed positive Mantoux result when compared to 33% in children whose index cases had symptoms more than 30 days.

Bacterial load and the involvement of lung in the chest X-ray zones of the index cases showed a linear relationship with the risk of developing TB infection. Those children whose index cases had 3+ smear showed increased TST positivity (61.5%) when compared to children whose index case had smear of 2+ (28.8%) and 1+ (6.0%). About 69.5% of children whose index case had a chest X-ray with involvement of more than 3 lung zones had a positive tuberculin test when compared to 18.5% positivity in children whose index case X-rays had ≤3 lung zones involvement. It is comparable with the studies done by Tornee *et al*.,[8] Lienhardt *et al*.,[9] and Talay *et al*.[10]

The association between TB and socioeconomic factors has been reported in many studies. In our study, we did not find an association between risk of TB infection and socioeconomic status and household size.

However, many studies in the globe have shown association between socioeconomic status and the risk of TB infection [8,9,11] This difference in result may be attributed to smaller sample size and information bias by the index case.

Our study demonstrated a significant association between the presence of BCG scar and TB infection. In our study, 61.3% of contacts with BCG scar showed a positive result, whereas 38.7% of contacts without scar had a positive TST result. This result is similar to the study done in India by Miret *et al*.[12]

In our study, all the contact children belonged to the malnourished group according to IAP classification based on weight for age. As ours is a government run hospital, most of the patients attending this health-care facility belong to lower socioeconomic status. Of the 104 contacts, 24% with Grade 1 malnutrition showed positive tuberculin test, whereas 45% of children with Grade 2 or 3 malnutrition turned out to be tuberculin test positive. As all the contact children of the study were malnourished, we could not compare the risk of TB among normal child and malnourished child.

Proximity of the contact with the index case, especially during sleep at night, is directly proportional to the risk. Our study showed 35.5% of infected contacts gave a history of spending most of their day with the index case. This result was found to be statistically insignificant. In terms of proximity with the index case, 61.3% of the infected contact gave a history of sleeping in same bed with the sputum positive index case, whereas among the non-infected contact, 29% gave a similar history. These observations were similar to studies done by Lienhardt *et al*.[9] and Karima *et al*.[11]

Limitations of the Study

There were several limitations in this study, namely, study design, convenient sampling technique, and relatively small sample size.

Cross-sectional nature and convenience sampling technique based on hospital selection led to the limitation that the source cases are not fully representative of the TB population in the community.

This study lacked a true "gold standard" test for the diagnosis of TB infection and we are not able to make unequivocal assessments of the sensitivity and specificity of the tuberculin test.

We could not visit the subject's house to carry out observations on family details and socioeconomic status due to limited time and workforce. Moreover, questions on economic status could have been felt sensitive by some interviewees who may not have provided the right answers. The above-mentioned limitations may have led to information bias.

Recall bias occurred when interviewees who are the source cases, fear that they are the cause for disease transmission in the family. They might not give true answers about their contact with the children at home. Hence, the final conclusion based on their answers may have resulted in false-positive or false-negative results.

CONCLUSIONS

We found the prevalence of TB infection in children who are in household contact with smear-positive TB patients

at 29.8%. From the study, we could infer that active contact tracing and identifying the presence of TB infection among the contacts will play an important role in the control of TB. Making TST mandatory to all contacts of sputum smear-positive patients will enable to identify more LTBI of children and with ensuring treatment completion among them, the emergence of drug resistance TB and reservoir TB infection in the community could be prevented. Also ensuring that the diagnosed children complete their full course of treatment will prevent emergence of drug resistance TB and decrease the reservoir of TB infection in the community.

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Original Article

Risk of Cardiovascular Disease in Rheumatoid Arthritis Patients

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Abstract

Introduction: The chronic systemic autoimmune disease with an uncertain etiology affecting about 1–2% of the general population is inflammatory arthritis, which involves rheumatoid arthritis (RA), ankylosing spondylitis, and psoriatic arthritis. CV risk factors (e.g., hypertension, dyslipidemia, smoking habits, and diabetes) are more common in patients with inflammatory arthritis.

Aim: The aim of the study was to study the risk of cardiovascular diseases in RA patients.

Materials and Methods: This prospective hospital-based study was done to study the risk of cardiovascular diseases in RA patients. A total of 60 patients diagnosed with RA were enrolled in this study. Informed consent was obtained from the study population, and all the demographic data, history, all laboratory investigations were made, and the results were analyzed statistically and discussed.

Results: A total of 60 patients were included in this study in that females were 48 and males were 12. Mean age group was 44.21 years, mean duration of RA was 12.2 ± 4.28, mean CDAI score among them is 23.08 ± 11.14. Metacarpophalangeal, proximal interphalangeal joint, and wrist joints are the most commonly involved joints among the study population. Anemia occurs more common in our study population, followed by lymphocytosis, thrombocytopenia, thrombocytosis, dyslipidemia, and hypertriglyceridemia. ESR and CRP are increased in many of the patients in our study population. ECG changes show that 15 patients had left axis duration, followed by other changes. Echo cardiograph shows that 44% had VSDD, followed by other problems such as LVSD, PF, and so on.

Conclusion: From this study, we concluded that there is a significant relationship between variation in ejection fraction and clinical disease activity index score, and there is a strong correlation between left ventricular systolic dysfunction and clinical disease severity index score.

Key words: Cardiovascular diseases, CRP, ESR, Lymphocytosis, Rheumatoid arthritis

INTRODUCTION

The disorder contributes to the deterioration of the bone and cartilage in multiple joints, most possibly caused by constant inflammatory burden and leads to chronic inflammatory arthritis, including RA and ankylosing spondylitis and arthritis.[1] This disease destroys cartilage and bone. This disease leads to bone destruction and cartilage in various joints. In all these diseases, there is also a two- to three-fold rise in CV risk in RA, comparable to people living in diabetes mellitus, as data from the previous decadence has accumulated, chronic inflammatory arthritis patients are at greater risk for CV disease as well.[2,3] The previous studies reported up to twice an increase in CV prevalence over all these diseases in combination.[4-6]

Inflammatory arthritis patients are more likely to have a high prevalence of CV risk factors (such as hypertension, dyslipidemia, cigarette smoking, and diabetes).[7] Inflammation has shown to influence specifically microcirculation (which also precedes hypertension),[8,9] adverse changes to the lipid composition (and thereby causing dyslipidemia)[10,11] and to deteriorate insulin sensitivity leading to insulin resistance.[12,13] However, the

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risk factors for excessive risk of CV are not clarified in the patient of inflammatory arthritis alone. Moreover, in a patient with inflammatory arthritis, new risk factors for CV may improve the CV disease risk prediction.

Research has shown that from early endothelial dysfunction or lipid deposition to atherosclerotic plaque build-out and its eventual rupture can also affect all stages of the atherosclerotic phase, which eventually leads to thrombosis.[14] However, it is not yet completely understood how the CV disease occurs in chronic inflammatory arthritis.

A significant and potentially useful method for assessing the risk of subclinical CVs is non-invasive imagery of vessel walls. Many non-invasive therapies for vessel alterations linked to early pre-clinical atherosclerosis have been established. Because of the crucial role of inflammation in atherosclerosis production, in particular, for patients with inflammatory arthritis, the effects of anti-inflammatory treatment on the risk of CV in such patients will logically be investigated. The current anti-inflammatory weapons contain several other anti-inflammatory drugs, which have numerous mechanisms for reducing inflammation.[15] Tumor necrosis factor (TNF-) alpha-blockers are the most recent in the areas of rheumatology, which inhibits TNF-alpha, which is an essential pro-inflammatory cytokine for inflammatory arthritis and atherosclerosis.

Table 1: Distribution of study parameters

S. No	Study parameters	Mean values
1	Age	44.21 years
2	Duration of RA	12.2±4.28
3	CDAI score	23.08±11.14

Table 2: Risk factors

S. No	Risk factor	No. of patients	Percentage
1	Anemia	40	66
2	Lymphocytosis	10	16
3	Thrombocytosis	3	5
4	Thrombocytopenia	11	18
5	Dyslipidemia	10	16
6	Hyper triglyceridemia	4	6
7	Raised ESR	59	98
8	Raised CRP	34	56

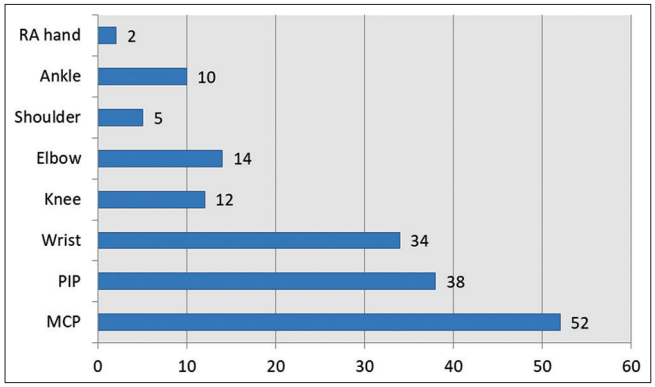

Figure 1: Joint involvement

Aim

The aim of the study was to study the risk of cardiovascular diseases in rheumatoid arthritis (RA) patients.

MATERIALS AND METHODS

This prospective observational study was conducted in the Department of General Medicine at Ramanathapuram Headquarters hospital from 2019 August to 2019 December. A total of 60 patients diagnosed with RA were enrolled in this study. Informed consent was obtained from the study population, and all the demographic data were obtained from the patients. All the medical history, complete blood examination, total cholesterol level, ESR, CRP values, and other laboratory investigation were obtained from the patients. ECG and echocardiography images were also obtained from the patients. The results were analyzed statistically and discussed.

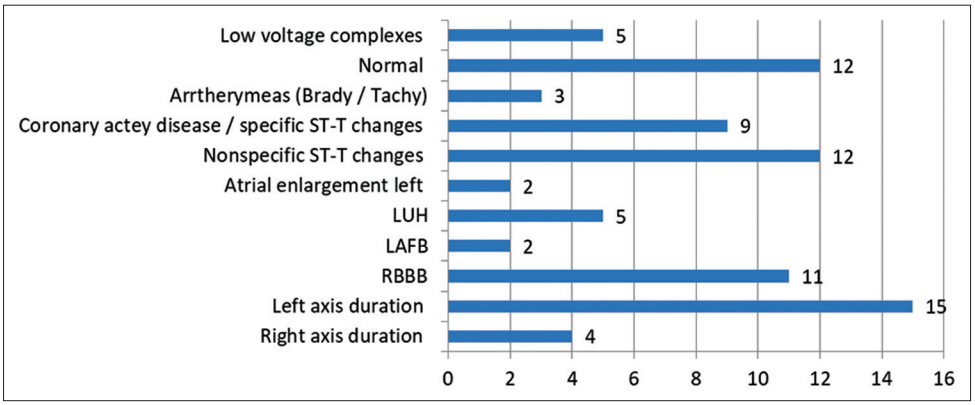

Figure 2: ECG changes in the study group

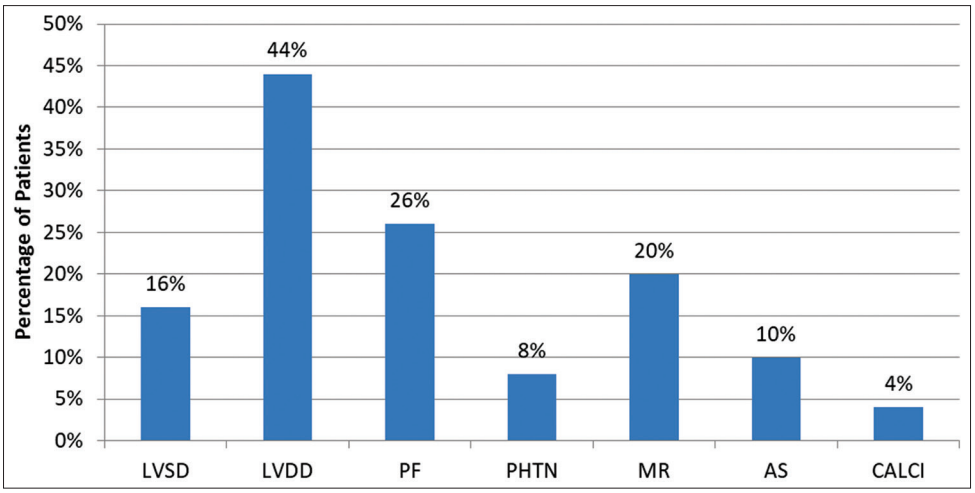

Figure 3: Distribution of echo radiograph

RESULTS

A total of 60 patients were included in this study in that females were 48 and males were 12. Mean age group was 44.21 years, mean duration of RA was 12.2 ± 4.28, mean CDAI score among them is 23.08 ± 11.14 [Table 1].

Fifty-two patients had RA involved in MCP, 38 patients in PIP, 34 patients in the wrist, 14 patients in the elbow, 12 patients in the knee, ten patients in Ankle, five patients in the shoulder, and two patients in RA hand [Figure 1].

Forty patients had anemia, ten patients had lymphocytosis, three patients had thrombocytosis, 11 patients had thrombocytopenia, ten patients had dyslipidemia, four patients had hyper triglyceridemia, 59 patients had raised ESR, and 34 patients had raised CRP [Table 2].

Fifteen patients had left axis duration, 12 patients had normal ECG, 12 patients had nonspecific ST-T changes, 11 patients had RBBB, nine patients had specific ST-T changes, five patients had low voltage complexes, five patients had LUH, four patients had right axis duration, three patients had arrhythmias, and three patients had LAFB [Figure 2].

Ten patients had LVSD, 26 patients had LVDD, 16 patients had PF, five patients had PHTN, 12 patients had MR, ix patients had AS, and two patients had CALCI [Figure 3].

DISCUSSION

CVD is the world's leading cause of death. The prevalence and incidence of CVD are rising alarmingly on the American continent. It is anticipated by the World Health Organization that the number of CVD-related deaths in the area between the 2 years 2000 and 2020 will rise by more than 60 percent if preventative steps are not taken.[16] Persons living in developing countries, for example, inappropriate styles of life, have more risk factors leading to a higher CVD death rate. To avoid CVD, it is, therefore, critical that healthy behaviors be encouraged among the general public and in patients with early diagnoses of RA.

In our study, there is a significant relationship between variation in ejection fraction and clinical disease activity index score (r= 0.412, P=0.001). There is a strong correlation between left ventricular systolic dysfunction and clinical disease severity index score ($P < 0.0001$).

The amount of lipid level has a paradoxical link to CAD risk in RA, as lower levels of lipid are correlated with more severe systemic inflammation, which, in turn, has a greater risk of CAD.[17] In RA inflammation seem to also alter the structure and function of lipoproteins[18] serum amyloid A increased heart disease load in patients with RA is related to increased inflammatory markers, such as CRP, erythrocyte sediment, rheumatoid factor, and anti-citrullinated protein antibodies.[19] A serum amyloid A increased load borne by HDL, and apolipoprotein A-I decreased, affecting typical anti-atherogenic effects of HDL and inducing a pro-atherogenic action.[20] Rheumatoid factor and antinuclear antibodies have been associated with heart disease and overall mortality, even in patients without rheumatic diseases.[21] Cisternas *et al.*[22] evaluated cardiovascular risk factors in Chilean patients with RA and reported a prevalence of 46.4% for CVD.

CONCLUSION

From this study, we concluded that there is a significant relationship between variation in ejection fraction and clinical disease activity index score, and there is a strong

correlation between left ventricular systolic dysfunction and clinical disease severity index score.

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Original Article

Risk Factors of Myocardial Infarction in Pre and Postmenopausal Women

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Abstract

Introduction: The leading cause of death of women, whatever their race or ethnicity, is cardiovascular disease, which accounts for one in three women. Myocardial infarction (MI) has multifactorial pathogenesis with variable inflammatory, atherosclerotic plaque eroded or ruptured, vasoconstriction, and thrombosis.

Aim: The aim of the study was to studying the risk factors of acute MI between women before and after menopause.

Materials and Methods: This research was a prospective clinical study in which 21 premenopausal women and 35 postmenopausal women (PMW) were enrolled who had a MI. The profile of the risk factor and the angiographic results was compared for the two classes.

Results: A total of 56 female patients were included in this study in that 21 patients were premenopausal, and 35 were PMW. The most common symptom is typical chest pain. In the premenopausal group, 14 patients were in the age group between 35 and 44 years and the postmenopausal group, 16 patients were in the age group between 51 and 60 years, accounting to 45%. The most common infarction in postmenopausal patients is the anterior wall MI, also common in inferior wall MI patients. Left ventricular dysfunction in the premenopausal population is 14.29% and postmenopausal group 40%. In the postmenopausal community, mortality was 8.57 percent.

Conclusion: From this study, we concluded that the risk factor of acute MI is highly prevalent among the PMW compared to premenopausal women. Similarly, the mortality rate was also high among the PMW compared to premenopausal women.

Key words: Coronary artery disease, Menopause, Myocardial infarction

INTRODUCTION

Unlike in the rest of the world, the incidence of coronary artery disease (CAD) is rising in India and is alarming because it becomes increasingly prevalent amongst younger age groups.[1] During this century, the primary cause of death and disability has been cardiovascular disease in women of every ethnic and racial group. Cardiovascular disease incidence in women rises sharply with age. Indian women are frequently affected by coronary heart disease. This could be due to social influences, lack of exercise, diet, frequent birth, and anemia. This could be due to religious, social, environmental, and economic factors; they seek medical advice late. After acute myocardial infarction (MI), they undergo further complications and mortality.

The measurement of acute cardiovascular syndrome has not been carried out for premenopausal women, even though it was the most important killers of women within the age group and outpaced even breast cancer.[2] In the postmenopausal women (PMW) who are all significant predictors of cardiovascular occurrences are BMI, physical inactivity, metabolic syndrome, hypertension, and diabetes mellitus (DMs) increase. Women differ in many ways, from men in cardiovascular anatomy and physiology. The chests, heart, and various structures of the body and distribution of fat are relatively smaller. Your cardiovascular system is designed to meet great pregnancy and birth requirements.

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CA mortality exceeds the death rate among women of all ages.[3] Still, in PMW, the key cause of death[4] is no doubt a multifactor cardiovascular risk and a variety of factors are involved. Still, the protective effects of female sex hormones, particularly estrogenic ones, are a factor that has been attributed to this discrepancy.[5] The increased rate of CAD in PMW seems partly linked to the loss of safety provided by endogenous estrogen. Type II DMs is a significant risk factor for MI and CAD.[6-8] This result is confirmed by a drastic rise in CAD among women in surgical menopause.[9] In comparison, hypertension and hyperlipidemia and a higher body mass index are found at higher levels after menopause.[10] Menopause is associated with a rise in blood pressure (BP) and a decrease in physiological night-time PB fall.[11] Furthermore, diabetic patients have increased vascular load and have abnormal of 24 h BP profiles.[12] These factors may be a factor in raising the risk of cardiovascular events in diabetic PMW.

The practice of coronary therapy is now better suited to reducing morbidity and mortality than other areas of cardiovascular medicine.[13] New treatments for acute MI are being tested, not just to prove their safety and efficacy but also to ensure their cost-effectiveness and quality of life.

Aim

The aim of the study was to studying the risk factors of acute MI between women before and after menopause.

MATERIALS AND METHODS

This prospective observational study was conducted in the Department of General Medicine at Ramanathapuram Headquarters hospital from 2019 August to 2019 December in 21 premenopausal women and 35 PMW who had a MI. The profile of the risk factor and the angiographic results was compared for the two classes. There have been registered clinical submissions, risk factors, vitalities, Killip functional classification, and ECG. Serial ECG, biochemistry routine, and other laboratory procedures needed have been performed. Results are analyzed and discussed in the following statistics.

RESULTS

Fifty-six females, 21 premenopausal and 35 PMW were included in this analysis [Table 1]. Typical chest pain is a common symptom. The chest pain lasts from 3 to 48 h for hospitalization. The maximum occurrence of MI in the premenopausal population is between 35 and 44 years. The postmenopausal category comprises 16 cases out of 35 patients, with a maximum event of MI between 51 and 60 years, which represents 45%. The most common infarction in postmenopausal patients is the anterior wall MI, also common in inferior wall MI patients [Table 2]. In postmenopausal cases, DM found 45.71% and premenopausal 38.10%. Among women premenopausal, 38.10% had high total cholesterol and 40.0% had high total postmenopausal cholesterol. Hypertension was observed in 33.33% of premenopausal women and 31.43% of PMW [Table 3]. About 23.81% and 22.86% of women in premenopausal and postmenopausal were found to be obese. Left ventricular dysfunction in the premenopausal population is 14.29% and postmenopausal group 40%. In the postmenopausal community, mortality was 8.57 percent [Table 4].

DISCUSSION

The annual occurrence of cardiovascular disease varies according to menopausal age. More significant loss of physical functioning in PMW leads to greater weight gain, insulin resistance, and hypertension. Weight gain is primarily due to central obesity which is related to waning of estrogen development. Changes in the lipid profile

Table 1: Distribution of the study group

Study group	No. of patients
Premenopausal group	21
Postmenopausal group	35

Table 2: Distribution of site of MI

Site	Anterior wall	Inferior wall	Anteroseptal	Lateral wall
Premenopausal group				
Frequency	12	6	3	0
Percentage	43.75%	40.62%	15.62%	0%
Postmenopausal group				
Frequency	18	8	8	1
Percentage	52.94%	23.52%	22.05%	2.63%

Table 3: Distribution of risk factors

Risk factors	Premenopausal group		Postmenopausal group	
	Frequency	Percentage	Frequency	Percentage
DM	8	38.10	16	45.71
HTN	7	33.33	11	31.43
Hyperlipidemia	8	38.10	14	40.00
Obesity	5	23.81	8	22.86

Table 4: Distribution of complication

Complication	Premenopausal group		Postmenopausal group	
	Frequency	Percentage	Frequency	Percentage
LV failure	3	14.29	14	40.00
Death	0	0.00	3	8.57

during the menopausal process are contributory risk factors to CAD in perimenopausal women. There is an elevated incidence of other risk factors such as DMs, hypertension, and metabolic syndrome in the postmenopausal era and is well related to increased risk of CAD.

In the majority of our sample, symptoms of chest pain were common. The common MI symptoms of McCance and Huether (1998) are chest pain, seizure, chest pain, nausea pain, diaphoresis, shortness of breath, or radiation to the nose, jaw, back, and left-arm.[14]

In our study, both premenopausal women and PMW majority had diabetes. No differences were found in blood glucose, and insulin levels among premenopausal and PMW in a study done in the Netherlands by Peters *et al*. and Manson *et al*. in Nurses' Health Study found that diabetes was associated with a marked increase in MI.[15,16]

The critical, independent factor in connection with deteriorated risk factors for cardiovascular disease was central obesity following menopause. Ley and Lees found a marked increase in android fat and a decrease in android fat in PMW.[17] In a study by Gower *et al*.; it was found that PMW had greater total body fat, summed central skin folds, and estimated intra-abdominal fat than premenopausal women.[18] The highest-level cardiovascular disease risk factor among menopausal women was high BMI stated by Green *et al*.[19] in his study.

In a cross-sectional study by Peters *et al*., no difference in systolic and diastolic BP was found between before and after menopause.[15]

Chang *et al*. found that PMW had total cholesterol and LDL-C than premenopausal women in their research in Chinese women.[19]

CONCLUSION

From this study, we concluded that the risk factor of acute MI is highly prevalent among the PMW compared to premenopausal women. Similarly, the mortality rate was also high among the PMW compared to premenopausal women.

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Study of Healthcare-associated Infection in Intensive Care Units of a Rural Medical College

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Abstract

Introduction: Healthcare-associated infection (HCAI) is a leading infection in the management of intensive care unit (ICU) patients, which causes a high economic burden for the patient's relatives and prolongs the stay of the patients in ICU. In this rural medical college, with the limited resources, we could control the infection in many cases with first-line antibiotics instead of second-line antibiotics used by the other authors worldwide.

Aim: The aim of the study was to study the healthcare-associated infection in ICU.

Materials and Methods: Samples collected were analyzed routinely and real-time polymerase chain reaction assay was also done outside the lab for early detection of organism. We took samples from the white coat pockets of staff nurses and the site of peripheral intravenous catheter insertion. Along with we insisted the HCW to follow the protocol and procedures strictly as per the infection surveillance team.

Conclusion: To conclude, adherence and to follow the stipulations laid by the Infection Control Committee and careful monitoring yielded good response and brought down the HCAI and health care cost.

Key words: Healthcare-associated infection, Intensive care unit, *P.aeruginosa*, infection, hand hygiene

INTRODUCTION

Healthcare-associated infection (HCAI) is defined as the infection which has developed in patients after 48 h or within 30 days of admission.[1]

HCAI some label it as a nosocomial infection is a challenging task in treating patients in intensive care unit (ICU). Among the vulnerable infection which we come across during this study were *Pseudomonas aeruginosa*, *Acinetobacter baumannii* (AB), *Staphylococcus*, resistant type of *Escherichia coli*, *Klebsiella*, etc., some important infections to mention.[2]

Prof. Dr. Semmelweiss, a Hungarian obstetrician in 1847, was the first to describe an HCAI and provide an intervention to avert its spread through "hand hygiene," which still holds good as proclaimed by WHO in Geneva in 2005–2006 as "Clear care is safe care."[3]

P. aeruginosa sometimes may be an opportunistic infection, a leading cause of death as it is present in 5–20% of hospitalized patients, so it can be endogenous or exogenous.[4] The risk of acquired HCAI is a recognized problem in hospital worldwide. However, knowledge of HCAI and adherence to the stipulated protocol may bring down the incidences.

This study involves a few observations made in this hospital ICUs, including late-onset sepsis (LOS) in low birth weight infants in NICU and other ways and means of transmission of infection.

Multiple study and references made by Haque *et al.*, in 2018[2] (70 related articles) indicate that the type of adverse events affecting hospitalized patients is adverse drug reaction, HCAI, and surgical complications. This small study was confining to HCAI that too in a limited area of Health Care in our MICU and NICU.

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Aim

The aim of the study was to study the healthcare-associated infection in ICU.

MATERIALS AND METHODS

The study was done in this Mount Zion Medical College Hospital with 550 inpatients beds, 8 MICU beds, 6 PICU beds, and 8 SICU beds. The study was approved by the local ethics committee.

After unsuccessful infection control by conventional antibiotics and recurrence of the same infection isolates, we decided to carry out (with limited resources) some possible methods of analysis and investigations and following the international guidelines, which yielded some reliable results and are compared with the already published articles. It was up to our satisfaction and encouragement in this rural medical college setup.

In the period from January 2018 to November 2019, all consecutive patients hospitalized in the ICU, samples from many sites such as blood samples, urinary catheters, ventilators, pharyngeal, perianal areas swabs, peripheral intravenous catheter sites, and environmental sites such as tape water, washbasins, and samples from the white coat pockets of staff nurses of MICU and NICU were collected and sent for analysis.

Hand hygiene techniques and surface contacts of healthcare workers also done.

For patients with prolonged stay in the ICUs, multiple samples (one every week until ICU discharge) were collected for isolate recovery.

Samples from coat pockets of nurses in MICU and NICU with the sterile pieces of cloths attached – one polyester and other polyester cotton blend on their dominant hand pockets were collected with aseptic precautions.

We also surveyed a single bed step-down observation room near MICU from where a recurrent infection of *P. aeruginosa* was isolated after the transfer of patients from MICU, who were not infected with *P. aeruginosa* previously.

Real-time polymerase chains reactions (PCR) assay was done in a few selected patients (done outside labs) for rapid detection of organism, especially for *Acinetobacter baumannii* colonization.

RESULTS

With available resources and under financial constraints, our study was limited to 200 patients and 300 samples since few patients needed another assay during review. This was good for tabulation and financial implications.

Of these, 300 isolates – *P. aeruginosa* was recovered from 126 isolates [Figure 1]. Fourteen patients from the single bedded step-down room near MICU have also grown isolates of *P. aeruginosa*. Eleven samples grow with AB in the conventional methods, but it was for 20 samples in the PCR assay, reinforcing the real-time PCR assay is reliable and fast in getting the reports.

We observed hand wash technique also few days at the beginning of the study. Hand wash with soap and water (60%) as well as alcohol gel (43%) was done. Before wearing gloves, nobody has done a hand wash, whereas it was 60% hand wash after removing the gloves. Gloves play an essential role in reducing the risk of infection transmission. Auxiliary nurses performed had hygiene on 51% occasions compared with 27% by the regular nurses.

In spite of adherence to the protocols stipulated, there was a report of isolation of PA in the single bedded step-down room. Hence, tape water was sent for isolation of organism which revealed the growth of *P. aeruginosa*. Remedial works were done; still, there were isolates of PA intermittently, after which we installed PAIL end filter as done by Garvey *et al.*, which yielded good results of negative for *P. aeruginosa*.

High touch surfaces such as patient bed care, equipment, charts, and tables in the workstation all handled by the staff nurses. They observed the protocol we stipulated, but the housekeeping staffs though we educated them, minimally followed the hand hygiene and surface contact techniques. May be due to low education qualification and understanding, we hope so. 50% of the time, they are the ones spreading infections from one bed to another, sometimes from outside also.

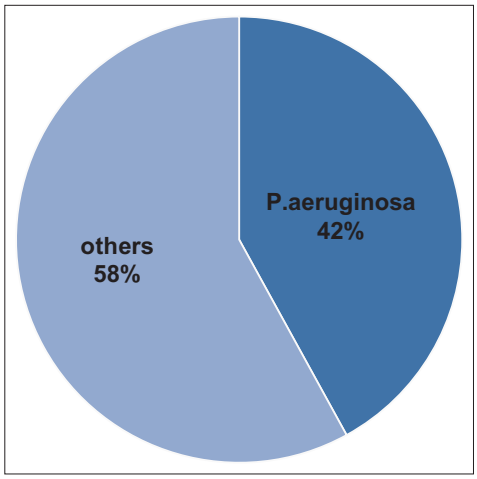

Figure 1: Distribution of *Pseudomonas aeruginosa*

Since it was a financially affecting task, without putting further efforts in this category of people, we advised the supervisors of housekeeping and staff nurses in MICU to watch strictly the housekeeping staff and to insist for adhere to aseptic techniques – after which there was a reduction of cases of *P. aeruginosa* infection.

Fifty samples from pharyngeal and perianal regions and urinary catheters were sent for microbiological investigations, which yielded *A. baumannii*. Because of multiple sites of infections, we sent it for conventional culture and sensitivity and real-time PCR outside our lab. Urinary samples also grow with multidrug-resistant organisms such as PA/AB/Kleb/*E. coli*.

Some 24 patients developed phlebitis of the PIVC. Samples taken from the catheter inserted sites and the area around the catheter were sent for culture. After strict instructions regarding the PIVC insertion and at the end of the baseline period, there was a significant reduction in the PIVC associated SAB infection rate.

Results of 10 each batch of samples from the coat pockets of staff nurses, which showed the bacterial load was higher in 8 batches (80%) in the polyester cotton blend fabric than on the polyester fabric 4 (20%). The organism was *Staphylococcus* spp., *P. aeruginosa*, *Klebsiella* spp., *E. coli,* and vancomycin-resistant *E. coli*.

Reports from NICU (9 samples) which show infant born <32–34 weeks of gestation who presented with sepsis. 71% with *S. aureus* and 3% coagulase-negative (CoNS) organisms was identified.

DISCUSSION

P. aeruginosa is a ubiquitous and important opportunistic pathogen in the health care setting, particularly those with the impaired host or mucosal immunity. It is found in a wide range of moist, nutrient-limited environments, may colonize hospital and domestic water taps, sinks, drains, toilets, and showers. *P. aeruginosa* forms biofilms that allow the persistence of microorganism in the water system for long periods. Once infected, it may remain in the same room for months together and cause continuous transmission. This helps to explain why high colonization rates of the hospital water system have been seen.[5]

Nosocomial *P. aeruginosa* outbreaks have been reported as associated with the water sources. Other potential routes of transmission include cross-infection, for example, patient to patient, carriage on the hands of HCW, and through contaminated medical equipment.

Transmission of *P. aeruginosa* through water and hand wash basin taps matters in NICU-supported by disinfection and replacement of high-risk plumbing parts which grew positive for *P. aeruginosa*. Between February 2019 and June 2019, we recovered isolates mainly from sink taps, floor taps, and damaged corners of a plastic rubber mattress in front of the bathroom door. During this period aromatic cleaning solution was used which was inappropriate for inert surface cleaning. Corrective infection control measures were implemented, including (i) revision of the disinfection protocol, (ii) drying of water surfaces on mattress after disinfection, and (iii) replacement of all sink taps in MICU and NICU.

There was no infection in other areas. Hence, a new cleaning method adopted using a cloth impregnated with antiseptic solution cleaned first from the sink tap down the outlet of the sink once only in a modification to the suggestion of Garvey *et al.*, using three separate cloth which was costlier in our economic situation.[6]

HCAI caused by multidrug-resistant AB also reported, which was continue to be an important problem. Multiple study including Blanco-Lobo *et al.* study described a low sensitivity of the conventional method for detecting *A. baumannii* colonization, so we preferred RT-PCR assay of rapid detection. Real-time PCR proved positive results within 3 h as claimed by Blanco *et al.* when compared with the conventional culture and sensitivity which took nearly 48–72 h.[7]

An observation study in accordance with the King *et al.*, a study involving healthcare workers assigned in 3 shifts with three nurses, three ANMS, and three cleaning staffs each in the shift in rotation for a specified period of study (1 month) which was a good model for this study and supportive for even to detect small mistake which was corrected very easily.[8] As usual, they touched all the surfaces during routine work in the MICU such as BP recording, equipment cleaning, distribution of meals, distribution of medications, and injection, among other works in the MICU.

Hand hygiene was observed, noting type of aseptic used (soap and water and alcohol-based solution) use of antiseptic before and after removal of gloves and swabs from high touch surfaces such as table surfaces, case record and the results are recorded. All subconsciously developed the hand hygiene practice, possibly after the education of the technique.

Regarding peripheral intravenous cannulae, infections with *S. aureus* resulted in morbidity and mortality and increased the cost of health care. Hence, we formulated

a program including healthcare worker education, removal of unnecessary catheters, removal of PIVC at or before 72 h, standard chart for phlebitis assessment, recording of the name of the staff nurse who inserted the cannula, date and time of insertion, hand hygiene practice, with an alert for out of hospital PIVC insertion, and those inserted in suboptimal conditions. Uniformity was maintained in this, including the phlebitis scoring system. Daily observation of the phlebitis scoring being followed till now.

With this multidisciplinary involvement which ensured to improve infection control in PIVC. The fact that improved process technique rather than a reduction in device use was associated with improved outcome. The compliance of the above program consistently brought down the infection rate to a significant level more than 85%. Some claimed impregnated sponge dressing for vascular catheters in addition to above-programmed care.

Wearing a white coat signifies a means of identification, professionalism, and cleanliness of the staff and protects the individuals against body fluids and other contaminants. However, it poses a problem by the transmission of contaminants to the peers, patients, and environmental surfaces in the health care facility.

Sepsis occurs one in every five of low birth weight infants worldwide. LOS due to *Staphylococcus capitis* occurred in low birth weight infants almost alternate days in our NICU recently with 10–15% mortality. Hence, we received a request from our NICU to combine with the evaluation of causes and containment of LOS along with our ongoing surveillance in our NICU. LOS was primarily with CoNS Staphylococci. Methicillin resistance and vancomycin resistance are reported worldwide and mortality was more with *S. aureus* than CoNS.[9]

In our NICU, SA capitis was the dominant organism involved and the response also surprisingly above to our expectation because of the strict compliance and knowledge of sepsis in LBW infants by our staff. After adherence to our surveillance and corrective measures as in MICU, LOS mortality became nil till the end of the study.

Follow-up Screening

After the implementation of infection control standards in the MICU on every 3 months intervals, the patients treated for NCI were reviewed with culture report of samples and nobody reported a positive PA infection or any other organism.

In the MICU step-down room same 3 months interval culture from already positive sites were analyzed; the incidence of PA isolates from MICU step-down room sample decreased from 14 isolates to zero only at the end of the study. PIVC-associated SAB events also decreased from 24 samples to 1 at the end of the study.

CONCLUSION

Double locus sequence typing method of *P. aeruginosa* was convenient and a straightforward tool for identifying *P. aeruginosa* species types. Importance of water sampling, clinical surveillance, molecular identification of species, identifying the source such as water taps, the rubber matte in front of the toilet facilities and education of healthcare workers in following in handwashing technique, insertion of PIVC technique, analysis of the type of fabric and colonization are an eye-opener to us. There was a remarkable outcome in controlling the NCI in MICU and other investigated areas. LOS infection in very LBW infant and SC-related LOS was found to be associated with severe morbidity and mortality.

Recommendation

The revised recommendation in PIVC dressing impregnated with povidone-iodine which is freely available in our setup instead of chlorhexidine for the vascular catheter in ICU yielded a good response.

A large portion of nosocomial infection is preventable with the increased infection control methods and compliance of regulatory guidelines and will bring down the infections to a large extent.

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Cross-sectional, Case Cohort, Observational Study to Assess Drug Utilization of Rosuvastatin, Clopidogrel, and Aspirin Fixed-dose Combination in Indian Patients with Stable Acute Coronary Syndrome – R-GOLD Study

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Abstract

Background: Atherosclerotic cardiovascular disease is one of the most common causes of mortality and morbidity globally. As cardiovascular diseases are usually having multiple mechanisms in their pathogenesis and frequent presence of co-existing risk factors, the choice and role of fixed dose combinations (FDCs), whenever suitable, are advised with rationality.

Objective: The objective of this study was to assess the prescription pattern of fixed-dose drug combinations (FDCs) of rosuvastatin, clopidogrel, and aspirin in Indian patients with the acute coronary syndrome (ACS) and in post-coronary intervention. This study was also aimed to evaluate the prevalence of comorbid conditions and co-prescribed drugs with FDC of rosuvastatin, clopidogrel, and aspirin.

Subjects and Methods: RGOLD was a cross-sectional and observational study in which total of 13,410 patients with ACS and post-coronary intervention were enrolled across India from Jul-2018 to Jul-2019 and data were collected retrospectively. Patient information, including demography, medical history, and treatment details, was collected retrospectively by 457 clinicians using a structured data collection form. Our primary aim was to assess cardiac medication use at discharge, defined as dual antiplatelet therapy (aspirin and P2Y12 inhibitor) and statin therapy as FDC.

Results: Baseline demographics, mean age 57.7±11 years, gender 76.7% males and 23.3% females, mean height 163.9±9.9 cm, and mean weight 73.1±11.7. Most patients were having a family history of ACS (66.6%) and risk factor of high blood cholesterol (55.9%). Most patients (41.9%) were prescribed FDC of rosuvastatin, clopidogrel, and aspirin for the treatment of unstable angina/ACS. Rosuvastatin 10 mg+ clopidogrel 75 mg+ aspirin 75 mg dose (77.6%), 1–3 years (41.8%) of treatment duration, and evening time of dosing (51.2%) of FDC of rosuvastatin, clopidogrel, and aspirin were observed to be common among study patients. Hypertension (72.6%), diabetes (51.8%), and obesity (33.6%) were common comorbid conditions, while anti-hypertensive drugs (75.5%), anti-diabetic drugs (46.9%), and lipid-lowering drugs (41.4%) were commonly co-prescribed drugs for comorbid conditions.

Conclusion: Usage pattern of FDC of rosuvastatin, clopidogrel, and aspirin for the treatment of ACS and in post-coronary intervention can be well defined by this study concluding rosuvastatin 10 mg plus, clopidogrel 75 mg plus, and aspirin 75 mg dose, 1–3 years treatment duration and evening time of dosing as common practice. Hypertension was common comorbid conditions, while anti-hypertensive drugs were commonly co-prescribed drugs for comorbid conditions.

Key words: Acute coronary syndromes, Clopidogrel and aspirin, Fixed-dose combinations of rosuvastatin, Observational study

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INTRODUCTION

The care of patients presenting with acute coronary syndromes (ACS) has changed dramatically over the past several years, with the latest treatment guidelines adopting an aggressive approach using early coronary angiography in conjunction with the use of multiple pharmacologic agents.

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ACS represents a continuum of acute myocardial ischemia, spanning from acute transmural infarction with ST-segment elevation to unstable angina (UA) characterized by minimal myocardial ischemia. Ischemic heart disease is the leading cause of death globally. India has the highest burden of coronary artery disease (CAD). The CAD has resulted in 3 million deaths annually, accounting for 25% of all mortality in India.[1]

The pathophysiology of ACS in most patients involves atherosclerotic plaque rupture with superimposed thrombus development resulting in limitation or interruption of coronary blood flow. Thrombin and platelets play a fundamental role in thrombus formation, resulting in ACS.[2]

The goal of health care providers in managing patients with this type of ACS is to treat within the 1st h of the onset of symptoms.[3] Percutaneous coronary intervention (PCI) can restore flow of blood into the myocardium in more than 90% of patients if performed by a skilled provider at a proficient PCI facility with a "door-to-balloon" time of <90 min.[4-6]

Anti-thrombotic therapy is the cornerstone of treatment for patients with ACS. It has four components: (1) Anti-platelet therapy includes oral anti-platelet agents such as aspirin, clopidogrel, ticagrelor, or prasugrel, intravenous anti-platelet drugs (glycoprotein IIb/IIIa inhibitors). (2) Anticoagulant therapy includes unfractionated heparin, low molecular weight heparins, fondaparinux, and bivalirudin. (3) Fibrinolytic drugs include streptokinase, t-PA, and reteplase tenecteplase.[1] (4) Long-term therapy with statins (for at least 1 year) has been shown to reduce the risk of heart attack, stroke, and all-cause mortality in patients with and without established coronary heart disease (CHD).[7]

ADP binding to the platelet P2Y12 receptor plays an important role in platelet activation and aggregation, amplifying the initial platelet response to vascular damage. The antagonists of the P2Y12 receptor are major therapeutic tools in ACS. Clopidogrel is an ADP receptor antagonist, selectively and irreversibly inhibits ADP receptor and prevents platelet activation. It is widely used in ACS or recent myocardial infarction (MI).[8]

Several lipid-altering therapies have been shown to benefit patients at risk for CHD, lowering of low-density lipoprotein (LDL) cholesterol with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, rosuvastatin has shown the most striking results. Lowering of LDL-C levels is thought to be the main beneficial effect of statin treatment; although, effects on HDL-C and other lipoproteins also play a role.[9]

Current guidelines recommend dual antiplatelet therapy that includes aspirin and the platelet P2Y12 ADP receptor antagonist clopidogrel after PCI. Statin use after PCI improves safety and effectiveness.[10] A recent meta-analysis of six randomized clinical trials concluded that statin therapy reduces the risk of MI after elective PCI, but not necessarily mortality or repeat revascularization.[11]

Large-scale randomized clinical trials have supported the use of early coronary angiography in high-risk patients with ACS, as well as the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) as an effective treatment in patients with CAD and especially those hospitalized with ACS.

The prevalence rate of risk factors for CVD has been rapidly rising within India. The annual number of deaths from CVD in India is projected to rise from 2.26 million (1990) to 4.77 million (2020). As cardiovascular diseases are usually having multiple mechanisms in their pathogenesis and frequent presence of co-existing comorbidities, clinicians have to prescribe multiple drugs. Multiple drug therapy is associated with poor patient compliance and adherence to treatment, so practically, it is not a successful strategy. Thus, concomitant use of two or more drugs as fixed-dose combinations (FDC), whenever suitable, is advised with rationality. Rational use of drugs as defined by the World Health Organization (WHO) depends on making the correct diagnosis and prescribing appropriate drugs in adequate doses.[12]

Globally more than 50% of drugs are prescribed, dispensed, or sold inappropriately. The market is flooded with fixed-dose ratio combinations of various drugs, though only a few FDCs are rational combinations and are approved by the world health organization. Irrational prescription of drugs has become common in clinical practice due to a lack of knowledge about drugs and also unethical drug promotion. Irrational use of drugs can lead to the high cost of medical treatment, increased incidence of adverse drug events and drug misuse.[12]

Hence, this non-interventional, retrospective, cross-sectional, and observational drug utilization study was planned with an objective to assess the usage pattern of Rosuvastatin, clopidogrel and aspirin combination treatment in ACS cases undergoing elective coronary intervention from multiple sites in India.

SUBJECTS AND METHODS

Review Process

All ethical approvals required for the study was obtained before the start of the trial. The protocol and data

collection form (DCF) were reviewed and approved by a central independent institutional ethics committee. Four hundred fifty-seven outpatient settings or clinics located across India participated in this observational study.

This study was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonisation–Good Clinical Practice guidelines while ensuring patient confidentiality during transcription of the patient records on the DCFs provided for the study. This was a retrospective drug utilization study conducted with the analysis of the accessed successive completed records as per the study protocol which is reviewed and approved by IEC while redacting the patient identifiers for the transcription of the data variables.

Patient Population and Recruitment

Patients enrolled in this study had to be at least 18 years old and alive at the time of hospital presentation, be admitted for ACS as a presumptive diagnosis (i.e., have symptoms consistent with acute ischemia), and have at least one of the following: UA, non-ST-elevation MI (NSTEMI), and STEMI who can undergo either PCI or CABG.

All patients who met all of the following criteria were considered for enrollment in the study: (A) Male or female patients 18 years and above (B) patients diagnosed with ACS and post-coronary intervention and treated with FDC of rosuvastatin, clopidogrel, and aspirin [Figure 1].

Study Design

This was a cross-sectional study in patients prescribed FDC of rosuvastatin, clopidogrel, and aspirin for the treatment of ACS and post-coronary intervention across India to evaluate the pattern of utilization. This study was conducted between Jan-2018 to Jul-2018 and data were collected retrospectively.

Details of the Study Products

Rosuvastatin 10 mg/20 mg + aspirin 75 mg + clopidogrel capsules 75 mg was prescribed for the treatment of ACS, MI, stroke, and angina.

Data Collection

To ensure the enrollment of an unbiased population, the first 30–50 consecutive patients (depending on each site's patient throughput) were recruited from each site per month.

A total of 457 clinicians participated in the study from different regions of India to collect large patient population data. All participating clinicians were provided paper-based data collection form (DCF) by sponsor. All DCFs were filled by respective doctors based on the data available with their medical records and completed DCFs were collected by the sponsor. Once completed DCFs were collected, they were converted from paper to electronic form with manual data entry. With the completion of data entry, data quality checks were performed by different logic checks and extreme/missing values. After ensuring quality of the data, it was further considered for the analysis. Data transcription and analyses were carried out by an independent agency after redacting patient identifiers.

Statistical Analysis

This drug utilization surveillance study was conducted with a sample size of 15,000 cases as retrospective cohort analyses of the prescription records containing FDC of rosuvastatin, aspirin, and clopidogrel from 457 centers across India. Per protocol analyses for 13,410 cases were carried out while assessing the records for complete details on baseline demographics, rosuvastatin/aspirin/clopidogrel FDC posology, common adverse drug reaction rate, and clinical indication as UA, NSTEMI, and STEMI before undergoing intervention as PCI or CABG.

Descriptive statistics were employed to describe the demographic variables while the continuous and categorical

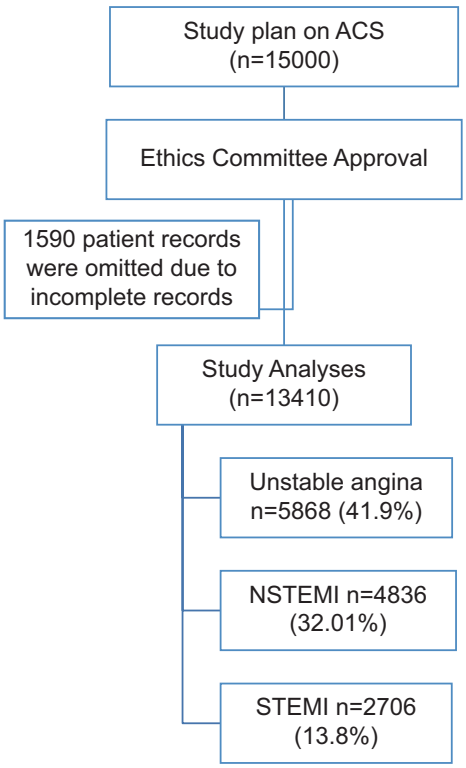

Figure 1: Patient disposition chart for cases receiving fixed-dose combination of rosuvastatin/aspirin/clopidogrel with diagnosis of stable acute coronary syndrome

variables were analyzed with appropriate statistical methods utilizing Students's T and Fischer's exact test.

All statistical analyses were performed using validated SPSS software (version 20, SPSS Inc., Chicago, Ill., USA.

RESULTS

A total of 13,410 patients with a diagnosis of UA or NSTEMI or STEMI were included in this analysis. However, missing values for a particular parameter were excluded and hence sum of all categories of any one characteristic may not come up to this number. As missing values vary with variables, total number will be different for different variables. Percentage mentioned in the results is valid percentages (excluding missing values).

Usage Pattern

Five thousand eight hundred sixty-eight (41.9%) patients were prescribed FDC of rosuvastatin, clopidogrel, and aspirin for UA, while 4836 (32.0%) and 2706 (13.8%) patients were prescribed it for NSTEMI and STEMI, respectively. Nine thousand five hundred five (77.6%) patients were prescribed 10 mg+75 mg+75 mg dose of FDC of rosuvastatin, clopidogrel, and aspirin, while 2738 (22.4%) patients were prescribed 20 mg+ 75 mg+75 mg dose of FDC of rosuvastatin, clopidogrel, and aspirin. Five thousand four hundred forty-four (41.8%) patients were having a treatment duration of 1–3 years, while 4756 (36.5%), 2146 (16.5%), and 680 (5.2%) patients were having treatment duration of <1 year, 3–5 years and >5 years, respectively. Six thousand five hundred nineteen (51.2%) patients were prescribed FDC of rosuvastatin, clopidogrel, and aspirin at evening, while 4036 (31.7%) and 2182 (17.1%) patients were prescribed it at morning and at afternoon, respectively. Summary of the usage pattern of FDC of rosuvastatin, clopidogrel, and aspirin is mentioned in Table 1 and Figure 2.

Table 1: Usage pattern of FDC of rosuvastatin, clopidogrel, and aspirin

Characteristic	Parameters	*n* (13410)	%
Indication	Unstable angina	5868	41.9
	NSTEMI	4836	32.0
	STEMI	2706	20.2
Dose (mg)	Rosuvastatin/aspirin/ clopidogrel: 10+75+75	9505	77.6
	Rosuvastatin/aspirin/ clopidogrel: 20+75+75	2738	22.4
Onset of therapy (years within diagnosis)	<1	4756	36.5
	1–3	5444	41.8
	3–5	2146	16.5
	>5	680	5.2
FDC administration	Morning	4036	31.7
	Afternoon	2182	17.1
	Evening	6519	51.2

FDC: Fixed-dose combinations

Demographic distribution

A total of 13,410 patients were enrolled in the study, of which 3068 (23.3%) were female and 10,112 (76.7%) were male. 0.5% patients were below 30 years of age while the frequency of patients in 30–44 years, 45–60 years, and >60 years age category was 10.5%, 50.8%, and 38.2%, respectively, and mean age, weight, and height of the study population were 57.7 years, 73.1 kg, and 163.9 cm, respectively. Summary of demographic distribution is shown in Table 2.

Patient Characteristics

Seven thousand eight hundred (66.6%) patients had a family history of ACS. Seven thousand four hundred ninety-eight (55.9%) patients had high blood cholesterol as a risk factor, while 5398 (40.3%), 4228 (31.5%), and 3475 (25.9%) patients had a risk factor of smoking, alcohol, and physical inactivity, respectively. Summary of the distribution of patient characteristics is mentioned in Table 3.

Prevalence of Other Comorbid Conditions

Nine thousand seven hundred forty-two (72.6%) patients were having hypertension as comorbid conditions, while 6950 (51.8%), 4505 (33.6%), and 324 (2.4%) patients were having diabetes, obesity, and chronic kidney disease CKD, respectively.

Summary of distribution of comorbid conditions is mentioned in Table 4.

Drugs Co-prescribed with Rosuvastatin, Clopidogrel, and Aspirin FDC

Ten thousand one hundred nineteen (75.5%) patients were prescribed anti-hypertensive drugs for comorbid condition, while 6295 (46.9%), 5548 (41.4%), and 1659 (12.4%) patients were prescribed anti-diabetic drugs, lipid-lowering drugs, and anti-coagulants, respectively. Summary of distribution of co-prescribed drugs is mentioned in Table 5.

DISCUSSION

In 2000, Wald *et al.* first proposed the use of FDC therapy for CVD prevention in the form of polypill. FDCs have many potential advantages like improved patient compliance and adherence to treatment as well as more efficacy, minimal side effects, and low cost of therapy.[13] A meta-analysis by Bangalore *et al.* showed that FDCs improve medication compliance.[14]

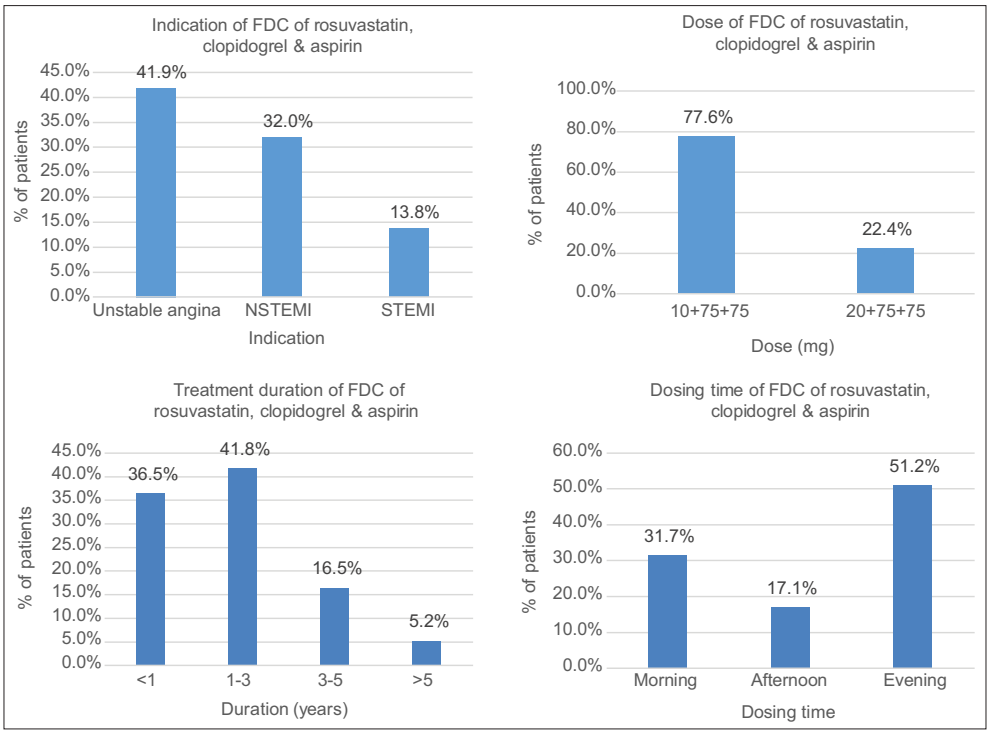

Figure 2: Usage pattern of fixed-dose combinations of rosuvastatin, clopidogrel, and aspirin

Table 2: Demographic distribution

Characteristic	Parameters	*n*	%
Total study population		13410	100
Gender	Female	3068	23.3
	Male	10112	76.7
Age group (years)	<30	59	0.5
	30–44	1311	10.5
	45–60	6332	50.8
	>60	4756	38.2
Age (years)	Mean (SD)	57.7 (11.0)	
Weight (kg)	Mean (SD)	73.1 (11.7)	
Height (cm)	Mean (SD)	163.9 (9.9)	

Table 3: Patient characteristics

Characteristic	Parameters	*n*	%
Family history of ACS	Yes	7800	66.6
	No	3917	33.4
Risk factor (modifiable/nonmodifiable)	Dyslipidemia	7498	55.9
	Smoking	5398	40.3
	Alcoholic	4228	31.5
	Physical inactivity	3475	25.9
	Others	40	0.3
	None	1719	12.8

Table 4: Other comorbid conditions

Comorbid conditions		*n*	%
Comorbidity	Hypertension	9742	72.6
	Diabetes	6950	51.8
	Obesity	4505	33.6
	Chronic kidney disease	324	2.4
	Any others	138	1.0
	None	1487	11.1

Table 5: Co-prescribed drugs

Co-prescribed drugs		*n*	%
Co-prescribed drugs	Anti-hypertensive	10119	75.5
	Anti-diabetic drugs	6295	46.9
	Lipid-lowering drugs	5548	41.4
	Anti-coagulants	1659	12.4
	Anti-obesity	1349	10.1
	Others	265	2.0

Another study also supports the use of FDCs in the treatment of CVD, combination pharmacotherapy at low doses is likely to be more efficacious than high dose with a monotherapy. FDCs treat different ailments in the same patient at the same time and with one pill.[15] Another study published by Gari *et al.* in 2019 in Indian population shows that rosuvastatin+aspirin+clopidogrel combination is prescribed in 23% of CAD/diabetes, 33.33% CAD/diabetes/hypertension, 19% for CAD/hypertension, and 13% in CAD patients.

This observational study was the first of its kind in India to analyze the utilization pattern of FDC of rosuvastatin, clopidogrel, and aspirin for the treatment of ACS and post-coronary intervention. Demographic distribution, prevalence of other comorbid conditions, and co-prescribed drugs were also evaluated in this study. Higher proportion of male patients (76.7%) as compared to

females (23.3%) was observed in this study. Most patients (61.3%) were between 30 and 60 years of age with mean age, weight, and height for the study population of 57.7 years, 73.1 kg, and 163.9 cm, respectively.

Most patients were having a family history of ACS (66.6%) and risk factor of high blood cholesterol (55.9%). Most patients (41.9%) were prescribed FDC of rosuvastatin, clopidogrel, and aspirin for the treatment of UA. Rosuvastatin 10 mg+ clopidogrel 75 mg+ aspirin 75 mg dose (77.6%), 1–3 years (41.8%) of treatment duration, and evening time of dosing (51.2%) of FDC of rosuvastatin, clopidogrel, and aspirin were observed to be common among study patients.

Hypertension (72.6%), diabetes (51.8%), and obesity (33.6%) were common comorbid conditions, while anti-hypertensive drugs (75.5%), anti-diabetic drugs (46.9%), and lipid-lowering drugs (41.4%) were commonly co-prescribed drugs for comorbid conditions.

Strength and Limitation of Study

This was a cross-sectional observational study to understand the clinical role, usage, or positioning for the FDC of rosuvastatin/aspirin/clopidogrel in real-world outpatient settings for patients with stable post-ACS or UA cases wherein the use of FDC with a low-intensity statin can be explored further following at least 3 months of the intervention can be explored further through confirmatory randomized trials.

CONCLUSION

Multifactorial etiology of CVD justified the use of FDCs to increase treatment adherence as well as improve medication compliance by reducing the pill burden of patients. Usage pattern of FDC of rosuvastatin, clopidogrel, and aspirin for the treatment of ACS and in post-coronary intervention can be well defined by this study concluding usage of rosuvastatin 10 mg plus, clopidogrel 75 mg plus, and aspirin 75 mg dose, 1–3 years treatment duration, and evening time of dosing as common practice. Dyslipidemia was common comorbidity in only half of the cases, thereby highlighting the benefit or clinical role of statin for their complementary effects with the recommendation to reach new lipid targets or goal in such a high-risk population.

Further studies are needed to validate the efficacy and safety of FDCs involving low-intensity statin in stable cases of ACS patients who may have undergone elective surgery or intervention for revascularization, which is not included in the current study.

DISCLOSURE

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AUTHORSHIP

All named authors meet the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

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Sukumar gudiyatham; k. Manojkumartirupattur; v ramakrishna rao chennai; sandeep kumar muzaffarpur; hetal patel karcheliya; rakesh m patel khergam; anand d katageri gulbarga; sachin g j, gulbarga; amit k shahvadodara; jaimin r shahvadodara; amol agarwal,ahmedabad; madhuker kapoorlucknow; sanjay arora,lucknow; sanjeev k sidana jaipur; dheeraj vermajaipur; kapil virpariya rajkot; a. Vamsidhar kadapa; vivek bangamtirupati; rameshwar bishnoi bikaner; viral b mehtajamnagar; ankur agarwal gandhidham; praveenkumar r jarag satara; l srichandran chennai; p sukumarchennai; sathya narayana dbangalore; jai babu,whitefield; jaya kumar pmysore; n suryaprakash bangalore; kiran shankar u bangalore; j shankerranchi; p c runnu ramngarh; prasad m. R,.Belgaum; vaibhav b patil belgaum; santosh vastradhubli; sanjay tandonlucknow; naveen jamwal lucknow; d. N. Apparow hyderabad; srinath v ssecunderabad; sameer pekhale nashik; sagar subhash more nashik; mayur punjabi pimpalgaon; vikrant v vijan nashik; haresh v patel patan; r r dhoot ahmednagar; giri gajendra ratan ahmednagar; sriram r bangalore; hara prasad lyelahanka; varma k y n palakol; bala murali krishna kbhimavaram; rajasekharn k coimbatore; anant saxenau d a i p u r; pinank r merjunagadh; vishnu varthan b coimbatore; c j selvakumarcoimbatore; ramraj g coimbatore; anand h poptani rajkot; sameer r dumirnavi mumbai; nitin n bote mumbai; naren u revar mumbai; paresh r bhajiyawala surat; viral kumar tandel surat; s balamuruganchennai; m. Sathya murthi chennai; mukulesh guptalucknow; amit chaudhary lucknow; yogesh m jain mumbai; r k saraogi kolkata; kamlesh prashnani veraval; jeevraj singh choudhary ratangarh; ambarish satwik new delhi; sanjeev thareja gwalior; atul kasliwal jaipur; aziz khan nagpur; arulnallasamy t pkangayam; dilip balani indore; ashish damor,dhar; ashish sharma khargone; n s vaish indore; angshu bhattacharya jamshedpur; partho p chowdhury jamshedpur; k k verma jabalpur; amal kanti sen jabalpur; asit khannaghaziabad; sumit kumar ghaziabad; rajeev kumar gupta meerut; pradeep jain meerut; arif wahab new delhi; pramod kumar nagar kota; bhanwar ranva ajmer; pramod kumar sharma new delhi; krishna surya devara venkata rao tenali; sunil v malgi mumbai; abhay mane yerwada; krishnakumar c salem; thulasi nsalem; a k saxena varanasi; jigyasu singh varanasi; baskaran v,thanjavur; a ansari nagapatinam; sanjay gupta new delhi; greesh manwani new delhi; mohit luthra new delhi; r m chhabra,new delhi; bajrang gulabsinh dube latur; shitalkumar r gatagat latur; mohana arjon neelam guntur; prashanth kulkarni hyderabad; shamshad ali new delhi; sudhanshu sekhar parida new delhi; ravinder kumar new delhi; s a afazalpurkar pen; vivek redkar malvan; anshul gupta aligarh; sanjay singhal aligarh; n b srivastava rishikesh; ajay sharma dehradun; dhinakaran t,madurai; j p vignesh chennai; kalyanaraman k cuddalore; arun g chennai; sathish dev mathur; k shunmuga sundaram chennai; amit sharma mumbai; yogesh aher bhosri; arati ambarish shahade pune; k a bharti pune; ameer patil mumbai; prashant s rane mumbai; kantibhai p patel himatnagar; narendra p chaudhari visnagar; chetan bhagwat chaudhari jalgaon; soumyojit saha kolkata; jotideb mukhopadhyay kolkata; saswata mukherjee kolkata; s c sarma dibrugarh; mary c lalnuntluangi, aizawl; bijush difeosa silchar; narendra chandra das udaipur; sagnik mukhopadhyay kolkata; abhijit sarkar kolkata; rakesh sarkarkolkata; sumit khotick burdwan; dibyajyoti guptaburdwan; sumit banerjee burdwan; raman raj asansol; kaushik surkolkata; arun kumar saha behrampore; naveen agarwal siliguri; achintya narayan ray siliguri; aniruddha ghosh siliguri; hamid md ali,berhampur; subhro chakaraborty kolkata; manish chandra mukul patna; madan prasad patna; ranjan kumar senberhampur; m nageswar berhampur; bharat chandra samal balasore; sanjay kumar giri balasore; laxmidhar roulcuttack; antaryami sahoo jajpur; chittaranjan nayak cuttack; pradipta kumar nayak cuttack; sovitendu kabi bhubaneswar; hariballav mahapatra bhubaneswar; brijesh mukherjee rourkela; lalit kumar pradhan sonepur; soumitra das kolkata; sampat jainkolkata; sujoy panchadhyayee kolkata; sudhir bhattacharyakolkata; dipankar chakrabortykolkata; anindya mukherjee ,kolkata; sanjoy seal kolkata; paramartha bhattacharya serampore; sujay kumar mahinta hooghly; ajay pandey mumbai; pranjal deori

dibrugarh; varun kumar ranchi; manish kumar patna; rakesh kumar patna; a shankar narayananthane; pravin r giri mumbai; ajay k garg mumbai; pritesh punjabi mumbai; siddharth ashok sheth mumbai; pradnya m nagle,kandivali; anand ambesange mumbai; bikash rai das,guwahati; deepak s rajani mumbai; saumen chaudhuri agartala; chandan modak guwahati; aqeel huseini malbari mumbai; ishtiaq ahmed,moradabad; balaji p m hyderabad; mithun hastirchandigarh; ajesh goel yamunanagar; arun kochar mohali; gurpeet singh bhatia chandigarh; karun behal mohali; manjunath r,bangalore; rajesh kishan rao bangalore; y balaji adoni; pradeep sukumar yalla rajahmundry; kiranmayi alla vijayawada; siva kumar nadella eluru; birinder singh paul ludhiana; sonu sharma,bhatinda; gurowinder singh amritsar; ravikumar aluri,hyderabad; p sreenivasulu kurnool; rohan gupta jammu; gurjeet singh jammu; munish khurana jalandhar; parminder darshan singh jalandhar; ajay pal singh amritsar; sanjeev kumar mittal ludhiana; mithun p chakravarthy rajahmundry; vijaya bhaskara rao visakhapatnam; nageswararao .Anakapalle; dinesh b mysore; sunil kumar s mysore; amalaselvam a,bangalore; kumar s bangalore; rohit mody bhatinda; dharmendra kumar new delhi; virendra jain new delhi; ravi kumar g visakhapatnam; siva kumar d visakhapatnam; nandakishore n pattar thane; sandip fulpagare thane; shahul e a hameedramanathapuram; shankar p madurai; ravisankar s soundian aruppukottai; aravazhi r theni; susmitha yvijayawada; siva kumar dv vijayawada; prakash b r k tiruvuru; eshan gupta,agra; praveg goyal agra; pawan kumar mehta purnea; tanveer ahmad kishanganj; gautam bhandari jodhpur; y alamanchi sadasiva rao vijayawada; n.P s savoikar chicalim

; Rajesh g bhatkurse mapusa; mahkar singh khari noida; ram bilas goyat hisar; sunil kumar jalodia hisar; gautam singh new delhi; madhusudan yemul mumbai; shirish gandhi akluj; amit joshi sangli; ummer k kozhikode; sajeer k.T perintal,manna

;Sagar mandlik nashik; shalivahan v patanshetti jath; arun v bahulikar pune; rushikesh maheswri r nanded; ravindra bilolikar nanded; r p shukla allahabad; anubha srivastav allahabad; deepak bhandari indore; sunil sharma dewas; sanjay shrivastava khandwa; muthukumaran r pondicherry; d selvaraj tuticorin; a. Mohammed meeran tenkasi; jayasheelan m r mysore; rajendra n s mysore; lalith kumar jain bangalore; darshan k jotangiya dholka; kiran hania bharuch; jay n vyas bharuch; mitul patel deesa; p s shinde alibag; kashinath dixit bangalore; praveeen kumar brahmavar; vijaykumar shet k p udupi; santosh k singhal gwalior; hiten n barot,ahmedabad; prabhakar c koregol bangalore; pratik sarvaiya,ahmedabad; vishal mehra ambala; prashant s chaudhary,aurangabad; ajay v rotte aurangabad; indraneel basuvaranasi; srinivas k chennai; darshan mehra bareilly; rashmit g pandya ahmedabad; jeethender jain kala hyderabad; r sreekanth reddy hyderabad; r.V sreekanth reddy nandyal; laxmana swamy p n n kurnool; ashutosh kumar thakur,nellore; bhaskar k rao hyderabad; kirti m mistry mumbai; vikas kataria,new delhi; manish kumar jain faridabad; sanjay pruthi dombivali; pankaj patil mumbai; s v deshpande mumbai; ganesh rathod,mumbai; amol s nanaware mumbai; bhadresh mangukiya,surat; vivek prakash aggarwal gurgaon; paresh v borkar ponda; chetan l velani mumbai; satheesh balakrishnan,thiruvalla; sajit varghese thiruvalla; jeyapal v,trivandrum; prakash n nair trivandrum; jossy chacko kollam; girish m mangalore; ambana gowda bangalore; aditya s chowti,bangalore; rajesh yadav mumbai; rohit deshpande mumbai; abdul hannan mumbai; showjad mohmmed chavakkad; anoop gopinath palakkad; sandeep unnikrishnan palakkad; anand m k,thrissur; chandrashekar g warangal; mallikarjun rao,hanamkonda; anjith vupputuri guntur; rama jagannadha rao narayanasetty visakhapatnam; prabhakar rao visakhapatnam; raghu m s mysore; vashisth das bangalore; bashir naikoo,srinagar; asif p bhojani mumbai; k k goyal faridabad; anirban ash kolkata; anwar jamal kolkata; agnibha maiti,howrah; siddhartha mani kolkata; shahid haider kolkata; soumik chaudhuri kolkatas; b bhattacharya kolkata; tanmoy majee kolkata; b p chakravarty guwahati; ashish h sarwate,thane; ghanshyam v patel surat; vimal kumar garg ujjain; pradeep t v davanagere; venkatesh b.P davanagere; umesh kohli faridabad; amar nath gupta kanpur; a k trivedi kanpur; harpreet singh kalra patiala; jo josephcochin; atul m shinde ambejogai; subir sahabarasat; avijit kumar ghosh belgharia; s sarkar kharagpur; aniruddha ghorai kolkata; v srinivasan trichy; rahul vasudeo jawle,bhusawal; shyna a patil kagal; ekam kumar ranchi; nilakantha mishra bhubaneswar; nishant debta bargarh; deepak kumar parhi bhubaneswar; ravi kumar a vijayawada; shefali a karkhanis thane; shardul k kothary mumbai; thulasidharan n k,calicut; pankaj s mistry mumbai; dhiraj das guwahati; m das,cooch behar; srikanth evuru tenali; blessan varghese kaloor; i rahman,raipur; kamala kant bhoi raipur; roy k thomaskannur; nirmal parmar ahmedabad; dhaivat s desai ahmedabad; hitesh patel ahmedabad; s k sahu hyderabad; deepak

p telavane mumbai; ramesh k chirala; kolli kranthi kishor vijayawada; ravi kumar m,hyderabad; m vikas hyderabad; peraiah chowdary guntur; abhijeet adgaonkar akola; nitin m virwani akola; ravindra chaudhary akola; kalpesh talati ahmedabad; satyendra kumar a rajahmundry; srinivas k c m l sakinetipalli; rahul aror,new delhi; b v nagabhushana rao visakhapatnam; m malleswara rao kasibugga; srinivas n hyderabad; pavan kumar g reddy hyderabad; ravi kanth a hyderabad; uday nath shahi,new delhi; arup kumar jas burdwan; amit khandelwal udaipur;mukesh chaudhary ahmedabad; k p joshi dehradun; zakia a khan,bhiwandi; r c sharma indore; h c khandelwal ratlam; anil jagat janjgir; k k agrawal bilaspur.

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Original Article

Retinal Damage in Type II Diabetic Patients in First Ocular Examination – An Observational Study

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Abstract

Introduction: Diabetes is a life-threatening disease and is also associated with other complications. Diabetic retinopathy is a condition that may result in serious visual disturbances or even vision loss. The complications of DR are best treatable when diagnosed early.

Aim: The aim of the study was to assess the incidence of DR and the extent of retinal damage at the time of first ocular examination in diabetic patients.

Materials and Methods: An observational study was carried out in the Department of Ophthalmology, Dindigul Medical College Hospital from July 2019 to December 2019, among 25 outpatients who had type II diabetes mellitus.

Results: About 28% of the patients had DM >5 years and 72 had DM <5 years. The mean age of the patients was 64.52 years. About 16% (4 patients) of the diabetic patients had symptoms of retinopathy at the time of the first ocular examination.

Conclusion: Incidence of type II DM related DR is 16% and the duration of DM plays an important role in the occurrence of DR. Periodic screening can prevent the disease progression and prevent any complications. About 12% of the patients had early retinal damage at the time of first ocular examination and lifestyle changes must be made for better glycemic control. Awareness must be spread among ophthalmologists to do an eye examination when the patient is diagnosed with DM.

Key words: Diabetes mellitus, Ocular surface changes, Proliferative retinopathy, Retinal damage, Retinopathy

INTRODUCTION

Diabetes mellitus (DM) has epitomized worldwide and more than 69.1 million cases of diabetes have been reported in India, according to a 2015 report. The International Diabetes Federation (IDF) and World Health Organization (WHO) estimate that this rate may cross one billion in the near future.[1] Diabetic retinopathy (DR) is a specific complication of type I and type II diabetes and studies show that around one-third of the patients present with DR at the time of diagnosis of type II DM. DR is a neurovascular complication that is most frequently associated with blindness in patients of age group 20–74.[2]

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DR often presents with no early signs or symptoms and it is mandatory that patients diagnosed with type II DM must undergo an initial comprehensive eye examination by an ophthalmologist to diagnose any disease at an early stage to avoid progression and complications.[3]

Diabetes is a condition where the body is unable to use and store glucose. This leads to hyperglycemia and causes damage to all the organs, including eyes. With time, the small blood vessels of the retina are damaged and they leak blood and other fluids, causing the retinal tissue to swell, ultimately ending up in blurred and cloudy vision.[4] Two types of DR exist proliferative diabetic retinopathy (PDR) and non-proliferative diabetic retinopathy (NPDR). NPDR is the initial disease stage where the symptoms are mild or non-existent. PDR is the advanced disease stage where the retina is deprived of oxygen and neovascularization takes place in the retina and vitreous that clouds the vision.[5,6]

Poor glycemic control can profoundly inflict the development and progression of DR by stimulating the

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polyol pathway, glycation of enzymes, hemodynamic changes, and activation of renin-angiotensin aldosterone pathway.[7] This observational study was conducted to assess the incidence of DR and the extent of retinal damage at the time of first ocular examination in diabetic patients.

Aim

The aim of the study was to assess the incidence of DR and the extent of retinal damage at the time of first ocular examination in diabetic patients.

MATERIALS AND METHODS

This hospital-based observational study was conducted Department of Ophthalmology, Dindigul Medical College Hospital, from July 2019 to December 2019. All patients registered in eye OPD with DM were taken into consideration for evaluation and 25 patients were selected for purposive sampling. The patients were divided into two groups, the first group who had <5 years of diabetes and group 2 who had more than 5 years of diabetes. All patients above age 20 and with Type II DM were included in the study and examined by an ophthalmologist. Patients not willing to participate in the study and patients with DM and who were not examined by the ophthalmologist were excluded from the study. All ophthalmological findings recorded by the ophthalmologist were documented as:

1. Mild NPDR,
2. Moderate NPDR, and
3. Severe NPDR.

The collected information was tabulated and analyzed using statistical software.

RESULTS

The medical records of 25 study patients were viewed and the patients were divided into two groups. Eighteen patients (72%) were in the first group and had <5 years of diabetes and group 2 had 7 patients (28%) with more than 5 years of diabetes. The mean age of the patients was 64.52 years. Figure 1 depicts the incidence of DR among the study participants. About 16% (4 patients) of the diabetic patients had symptoms of retinopathy at the time of first ocular examination and 84% of the patients had no DR [Figure 2]. With regards to disease staging, 3 patients (12%) had mild non-proliferative DR and 1 patient (4%) had moderate NPDR. There were no patients with severe NPDR [Figure 3]. Therefore, 16% of the patients with more than 5 years of type II diabetes and with a mean age of 64.52 years have DR at the time of first ocular examination.

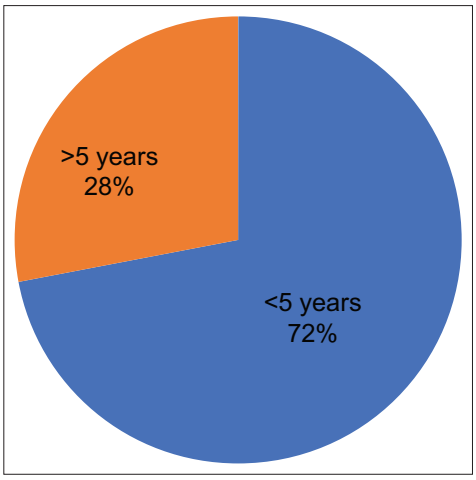

Figure 1: Distribution of duration of diabetes

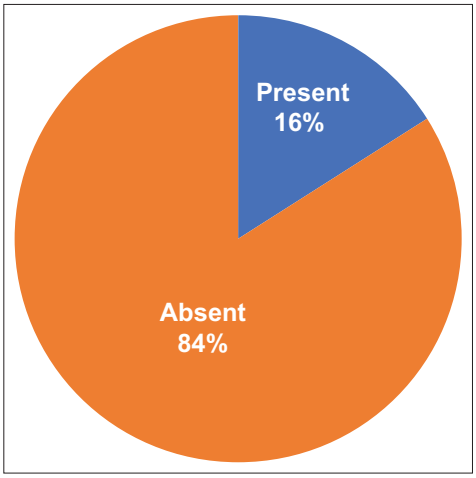

Figure 2: Incidence of retinopathy

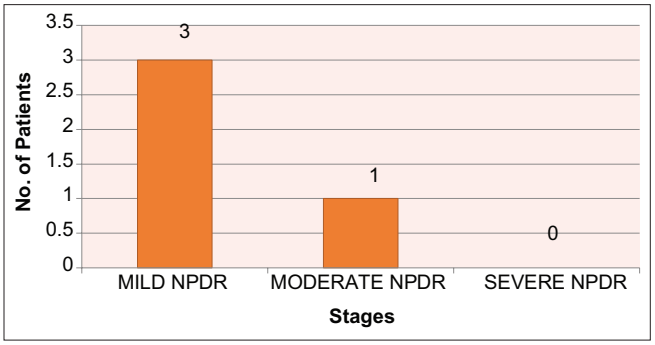

Figure 3: Stages of retinopathy

DISCUSSION

Diabetes is a potentially dangerous and life-threatening disease and it is also associated with other complications. Diabetic retinopathy is one such condition what the patients may not even realize and it may result in serious visual disturbances or even vision loss. The complications of DR are best treatable when diagnosed early.[8,9] The

retina is the light-sensitive inner lining of the back of the eye and an increase in blood glucose level could damage the retina's blood vessels. The blood vessels thicken, leading to blood and fluid leaks and finally lead to vision loss.[3] The incidence of DR is continuously increasing in the South Indian population and the prevalence is estimated to be from 12% to 22.4%. According to this study, the incidence of DR in patients with type II DM at the time of first ocular examination is 16%, which correlates with the study report by the National Urban Diabetic Society and AIOS DR eye screening study conducted in the year 2014.[10]

The prevalence of diabetes is also more among patients with age >60 years and the prevalence of DR increases from age 40. The prevalence of DR varies worldwide between countries; it may range from 17% in Switzerland to 52% in the United Kingdom.[11] The duration of diabetes is an important predictor of the extent of retinal damage and the risk of DR increases with the number of years the patient has lived with DM. Several studies have confirmed that the duration of the disease is the strongest factor for the development of DR.[12,13] In our study, too, the symptoms of retinopathy were observed in patients who have had diabetes for >5 years. Hence, patients diagnosed with type II DM must also be screened for signs of retinal damage as they fall under high-risk category. Proliferative and non-proliferative types are the two classifications of DR. In NPDR, microaneurysms cause a fluid leak into the retina leading to swelling of the macula. In PDR, there is retinal ischemia and neovascularization, which causes to cloud the vision. There can also be retinal detachment and scar tissue formation ending up in glaucoma.[14]

The ocular surface changes associated with type II DM may be reduced tear production, damage to corneal epithelium, poor tear film quality, and degeneration of corneal nerve fibers. In our study, the patients were diagnosed with early-stage non-proliferative DR at their first ocular examination. About 12% of the patients had mild NPDR and 4% had moderate NPDR. According to our study results, early screening is essential to prevent the complications of DR. The number of cases of DM is increasing in recent years due to changes in lifestyle and lack of awareness. Proper awareness among the patients and doctors can help to prevent the progression of the disease and also reduce the burden of DM related retinopathy.

CONCLUSION

Incidence of type II DM related DR is 16% and the duration of DM plays an important role in the occurrence of DR. Periodic screening can prevent the disease progression and prevent any complications. About 12% of the patients had early retinal damage at the time of first ocular examination and lifestyle changes must be made for better glycemic control. Awareness must be spread among ophthalmologists to do an eye examination when the patient is diagnosed with DM.

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Original Article

Dry Eye Syndrome in Patients with Type II Diabetes Mellitus: An Observational Study

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Abstract

Introduction: Dry eye syndrome (DES), also known as Keratoconjunctivitis sicca, is a major eye condition requiring medical care. Type II diabetes mellitus (DM) is the most common cause for dry eye. The symptoms may vary from redness, irritation, foreign body sensation, and stinginess to visual disturbances.

Aim: The aim of the study was to associate the relationship between Type II diabetes and DES.

Materials and Methods: Hospital-based observational study was carried out in the Department of Ophthalmology, Government Theni Medical College Hospital, among 100 patients. All the patients who reported to the OPD with symptoms of dry eye and with Type II diabetes were included in the study. Patients who were not willing to participate, not having Type II DM and who were on other medications were excluded from the study.

Results: Among the 100 patients who were involved in this study, the prevalence of DES was 56%. About 32% of the patients were above 60 years and 26% of the patients with hypertension (HT) showed symptoms of dry eye. DES was also more common among smokers than non-smokers.

Conclusion: The prevalence of DES is more common in patients with Type II diabetes and the risk of developing DES increases with age. HT along with DM is a risk factor for dry eye.

Key words: Diabetes mellitus, Dry eye syndrome, Keratoconjunctivitis sicca, Lacrimal function unit, Ocular dryness

INTRODUCTION

Dry eye syndrome (DES), also known as Keratoconjunctivitis sicca, is caused by progressive dysfunction of the lacrimal and meibomian glands that are associated with aqueous tear production. It is associated with ocular discomfort, stinging, irritation, dryness, foreign body sensation, redness, and visual disturbances and is the most common reason among the general population to seek eye-care.[1] Diabetes mellitus (DM) is the most widely accepted reason for the development of DES. Although DES is one of the major eye conditions among the general population, studies have shown that its prevalence is high among diabetics.[2] Patients with DM have low corneal sensitivity and low reflex-induced tear secretion, both of which could lead to DES. There is also a strong biological evidence suggesting the relationship between DM and DES.[3,4]

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Several studies have reported the association between diabetes and DES, but the results of inter-population studies have been conflicting.[5] DES is also more prevalent in patients with advanced stages of diabetic retinopathy. High glycemic index affects the anterior and posterior chambers of the eye, leading to decreased tear production. The global diabetic epidemic is on the high rise, according to an estimate by international diabetic federation and the prevalence of symptomatic and asymptomatic DES is 54%.[6,7] Although DES is a complication of DM, their associations are not confirmed. This observational study was conducted to assess the association between DM and the risk of occurrence of DES.

Aim

The aim of the study was to associate the relationship between Type II diabetes and DES.

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MATERIALS AND METHODS

A hospital-based observational study was conducted in the Department of Ophthalmology, Government Theni Medical College Hospital. All the patients registered in the outpatient department during the study period and who had DM were taken into consideration for evaluation of DES. A total of 100 patients were selected and purposive sampling was carried out. The study protocol was approved by the Institutional Ethics Committee and informed consent was collected from all the participants. Patients who were not willing to participate, not having DM, or with Sjogren's syndrome, rheumatoid arthritis, and other connective tissue disorders, patients on antihistamines, antidepressants, beta-blockers, OCPs, long-term anti-glaucoma medications, and patients who underwent recent ocular surgery were excluded from the study. All the patients selected for the study underwent routine investigations and were subjected to dry eye questionnaire. Schirmer's test was used to find whether the eye produces enough tears to keep it moist. The collected information was tabulated and analyzed using standard statistical software.

RESULTS

Out of the 100 patients involved in the study, 56 patients had DES.18% of the patients were between the age group 40 and 50 years. Of which only 6% had symptoms of dry eye, whereas 32% of the patients above 60 years had a prevalence of 32% DES [Table 1]. This shows that DES is more common with increasing age. 38% of the male patients had DES while only 18% of the females had the disease [Table 2]. Forty-two patients had comorbid conditions like hypertension (HT) and 12 patients had ischemic heart disease, of which 26% and 8% had symptoms of dry eye, respectively [Table 3]. The prevalence of DES was more among smokers (10%) than the non-smokers (2%) in our study [Table 4].

Table 1: Distribution of patient's age

Age	Dry eye	
	Yes	No
40–50 years	6	12
50–60 years	18	12
Above 60 years	32	20

Table 2: Distribution of gender

Gender	Dry eye	
	Yes	No
Male	38	29
Female	18	15

Table 3: Distribution of comorbidity of study patients

Comorbid	Dry eye	
	Yes	No
HT	26	16
IHD	8	4
CTD	4	0

Table 4: Distribution of smoking history of study patients

Smoking history	Dry eyes	
	Yes	No
Smokers	10	2
Non-smokers	2	10

DISCUSSION

DM is likely to increase the risk of ocular diseases and the prevalence of DES is more in patients with poor glycemic control than the healthy population. DM causes dysfunction of the epithelial barrier and lacrimal function unit (LFU).[8] The LFU protects and maintains the tear film and the functions of the cornea, conjunctiva, lacrimal gland, Meibomian gland, eyelids, sensory, and motor nerves. The Meibomian glands secrete lipids, the lacrimal gland secrete aqueous, and the conjunctiva and cornea secrete mucin, which are the three layers of the human tear film that is responsible in maintaining the normal physiological functions of the ocular surface.[9,10] Any damage to LFU may lead to tear deficiency or evaporative dry eyes.

Patients with Type I or Type II DM have a risk of developing LFU dysfunction and corneal epithelial abnormalities. Increased serum HbA1C levels can predispose to impaired function of the epithelial barrier and the corneal complications of hyperglycemia may include superficial punctuate keratopathy, corneal ulcers, and erosions. Studies have also shown that hyperglycemic have low tear secretion and tear breakup time test.[11] Poor glycemic control can also lead to abnormal tear dynamics, especially triggering of the polyol pathway. This activates aldose reductase, an enzyme associated with DES and which causes intracellular accumulation of sorbitol that can lead to cellular edema and structural damage to the lacrimal gland.[12,13] Moreover, diabetes induces the reduction of goblet cells that are responsible for mucin production. Mucin contributes to the hydrophilic nature of the ocular surface and a reduction in mucin can lead to tear instability.

In our study, the prevalence of dry eye was 56%, which is similar to many other study findings. The study by Moss *et al.* and Yazdani *et al.* demonstrated the correlation of dry eye with increasing age and our study also confirmed

the same. Diabetic males are at higher risk of developing DES when compared with females.[14] Our study findings also conclude that the risk of DES is more in patients with DM and co-existing HT. Smoking is also another factor that may increase the chances of the occurrence of DES in patients with type II DM.

Insulin is essential for the proliferation of acinar lacrimal gland and corneal epithelium. In hyperglycemia, where there are low insulin levels, there is oxidative stress in the lacrimal cells.[15] The glucose levels are also increased in the tears of patients with an elevated expression of advanced glycation end product modified proteins. Inflammation and immunity play an important role in the pathogenesis of DES and hyperglycemia includes an inflammatory cascade that kindles the immune responses of the LFU. Early diagnosis and treatment are critical to avoid any serious complications. Artificial tears may temporarily improve the symptoms. NSAIDs and topical steroids are administered to reduce inflammation and pain of DM associated DES.[16]

CONCLUSION

The prevalence of DES is more in patients with type II DM. More attention should be paid to DM associated DES since it is the most common diabetic complication in eye disorders in recent years.

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