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Publishing Details

Publisher Name: International Research Organization for Life & Health Sciences (IROLHS)

Registered Office: L 214, Mega Center, Magarpatta, Pune - Solapur Road, Pune, Maharashtra, India – 411028. Contact Number: +919759370871.

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International Journal of Scientific Study

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International Journal of Scientific Study
March 2022 • Vol 9 • Issue 12

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March 2022 • Vol 9 • Issue 12

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Case Report

Intracerebral Hemorrhage as Isolated Complication in Coronavirus Disease 2019 Patient: A Case Report

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Abstract

Human coronaviruses have neuroinvasive capacities and may be neurovirulent by two main mechanisms: Viral replication into neuronal or glial cells of the brain or autoimmune reaction with a misdirected host immune response In the present study, we present clinical presentation and imaging finding in a coronavirus disease 2019 (COVID-19) patient who presented as a rare isolated complication of severe intracranial hemorrhage to our institution, which has not been reported till date, in our knowledge. A 64-year-old patient presented with the complaints of headache and altered mental status. CT brain reflected multiple cerebral, left thalamic, and medullary hemorrhages. Antiphospholipid antibodies, IgM beta2 glycoprotein antibodies, and COVID antibodies came out to be positive. Contrast enhanced magnetic resonance (CEMR) was performed to rule out the other complications of COVID. CEMRI depicted multiple cerebral hemorrhages, involving the left thalamus, cerebellar hemispheres, and medulla. Hence, the patient got infected with COVID-19 at some point of time but remained asymptomatic and now presented with late complication of COVID as multiple cerebral and cerebellar hemorrhages.

Key words: Case report, COVID-19, Intracerebral hemorrhage, Neurovirulent

BACKGROUND

Due to the unprecedented times, the world witnessed the pandemic with the surge of coronavirus disease 2019 (COVID-19). Recent reports have highlighted the relationship between COVID-19 and cerebrovascular disease (CVD). Although, ischemic CVD has been validated to be a hypercoagulable state characterized by micro- and macrovascular thrombotic angiopathy,[1,2] is more common and is described in literature,[3-6] reports on hemorrhagic CVD in these patients are limited and occasional.[7-10] The paper presents the clinical presentation and imaging finding in a COVID-19 patient who presented as a rare isolated complication of severe intracranial hemorrhage (ICH) to our institution, which has not been reported till date, in our knowledge.

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

Human coronaviruses have neuroinvasive capacities and may be neurovirulent by two main mechanisms [11-13] Viral replication into neuronal or glial cells of the brain or autoimmune reaction with a misdirected host immune response.[14]

CASE PRESENTATION

On put date, the neurology department of our hospital reported a 64-year-old patient with the complaints of headache and altered mental status. Classic Framingham risk factors such as advanced age, being male, and pre-existing illnesses of diabetes mellitus, which are well-established risk factors for vascular degenerative changes, were present. The patient was not on any form of anticoagulation therapy. There was no history of recent or remote head trauma.

On physical examination, the following observations were made:-spontaneous response to eye opening (E4), no response to painful stimulus (M1), and no verbal response (V1), that is, glasgow coma scale of 6 and a fever of 100.3 F.

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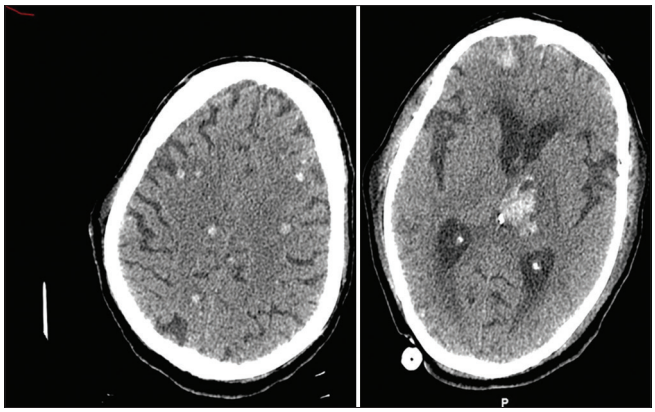

Figure 1: Non contrast computed tomography head shows multiple foci of cerebral hemorrhages, also involving the left thalamus

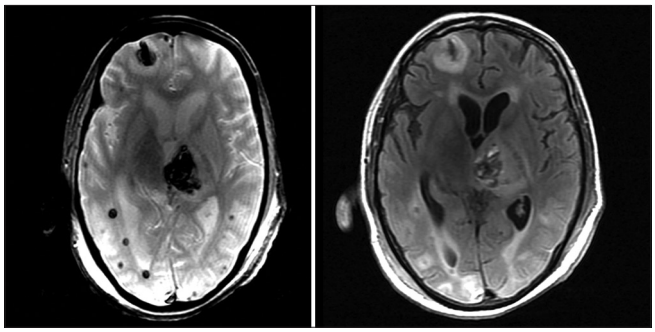

Figure 2: GRE and FLAIR images of the brain taken at the level of basal ganglia shows multiple cerebral hemorrhages

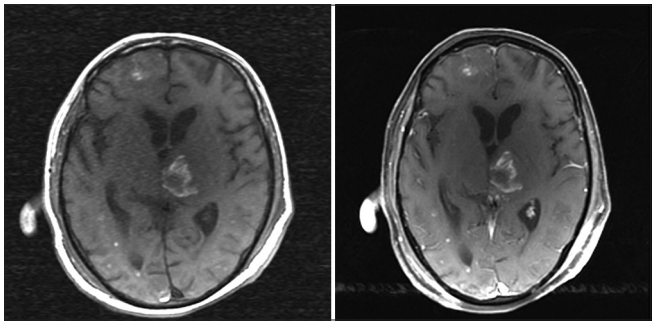

Figure 3: Pre- and post-contrast T1W images shows multiple foci of intracerebral hemorrhages with no post-contrast enhancement

Furthermore, laboratory investigation of complete blood count and COVID antigen was sent, and also head non contrast computed tomography (NCCT) was conducted.

The complete blood work showed thrombocytopenia and deranged coagulation profile. NCCT brain reflected multiple cerebral, left thalamic and medullary hemorrhages. The COVID antigens were negative.

In view of deranged coagulation profile, vasculitis workup, antiphospholipid antibodies (APLA), and IgM beta2 glycoprotein antibodies were ordered, and the result came out to be positive. Because of ongoing COVID-19 pandemic and positive APLA, COVID antibodies and NCCT chest were performed. CT chest came out to be normal while antibodies were positive. Hence, the conclusion drawn was as follows:- The patient got infected with COVID-19 at some point of time but remained asymptomatic and now presented with late complication of COVID as multiple cerebral and cerebellar hemorrhages as observed on NCCT [Figure 1].

Contrast enhanced magnetic resonance imaging (CEMRI) was performed to rule out the other complications of COVID. CEMR depicted multiple cerebral hemorrhages, involving the left thalamus, cerebellar hemispheres, and medulla [Figures 2 and 3]. No abnormal meningeal/parenchymal enhancement on post-contrast scans was found.

DISCUSSION

The common imaging findings across all the articles is acute infarction that is prognostic marker of a poor result in COVID-19[15] hospitalized patients seconded by diffuse white matter abnormality, consistent with leukoencephalopathy, with parenchymal microhemorrhages. Isolated ICH was noted in the above case reported by us with no associated infarction, white matter changes, and abnormal parenchymal enhancement.

COVID-19 can have association with a type of leukoencephalopathy which is particularly characterized by the presence (existence) of microhemorrhages. This might be a consequence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) CNS infection or a secondary effect of a generalized COVID-19 (such as hypercoagulability).[16]

As observed and speculated by Nicholson *et al.*,[17] multifocal, predominantly petechial hemorrhages in patients with COVID-19 may have resulted from diffuse thrombotic microangiopathy, which has previously been reported to cause similar abnormalities[18] and can also lead to PRES.[19]

Relatively, high percentage of neurologic involvement can be accounted by neurotropism of coronavirus.[20,21] In addition, other explanations shouldn't be secluded: Wide expression of the angiotensin-converting enzyme 2 (ACE2) receptor on endothelial cells in the brain.[22,23] This has been showed by few studies available and can activate a cytokine storm that recruits macrophages and causes inflammatory reactions similarly as vasculitis. Moreover, there is possibility that ICH may be linked with arterial hypertension catalyzed by binding pf ACE2 receptors with SARS-CoV-2 and thrombocytopenia.[24,25]

From the recent study conducted by Cheruiyot,[26] hemorrhage involving multiple cranial compartments was reported in 14 cases (9.5%). Single compartments were involved in the rest, with intraparenchymal hemorrhage being the most common variety (62.6%), followed by sub-arachnoid hemorrhage (15.0%), subdural hemorrhage (11.6%), and intraventricular hemorrhage(1.4%).

CONCLUSION

Although neurological complications such as acute infarction and diffuse white matter abnormality are relatively common among COVID-19 patients, case of isolated ICH is rare. Early identification of patients at risk of developing ICH, particularly with comorbid conditions, may be important to improve outcomes.

AUTHORS CONTRIBUTIONS

JA conceived the study, participated in its design and coordination, drafted the manuscript, and carried out the radiological results. GS participated in the study design and helped in drafting the manuscript and radiological results. JPS participated in the study design and helped in drafting the manuscript and radiological results. AJS participated in the study design and helped in drafting the manuscript and radiological results. AU participated in the study design and helped in drafting the manuscript and radiological results. MC participated in the study design and helped in drafting the manuscript and radiological results.

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How to cite this article: Anand J, Singh G, Singh JP, Sidhu AJ, Uttam A, Chhabra M. Intracerebral Hemorrhage as Isolated Complication in Coronavirus Disease 2019 Patient: A Case Report. Int J Sci Stud 2022;9(12):1-3.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Case Report

Genital Tuberculosis: A Common Disease Revisited

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Abstract

Tuberculosis is a common global disease, with a high prevalence rate in India. Genital tuberculosis in females affects fallopian tubes, uterine endometrium, ovaries, cervix, uterine myometrium, and vagina/vulva. It can lead to infertility, menstrual irregularity, and pregnancy loss in women. Here, we present a case of 52 years old, female patient who presented with chronic pain abdomen and post-menopausal bleed. Patient underwent hysterectomy. Although gross appearance of endometrium and cervix did not show significant pathology, microscopy revealed the granulomatous lesion in endometrium, cervix, and fallopian tubes.

Key words: Cervix, Common, Endometrium, Fallopian tubes, Genital, Tuberculosis

INTRODUCTION

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis, which is a major public health problem.[1] Tuberculosis can be categorized into pulmonary and extrapulmonary forms based on the affected organs. Female genital tuberculosis accounts 5–24% in India, 5% in world.[2] Most commonly secondary to pulmonary tuberculosis, rarely it has a primary etiology.[3] Tuberculosis is as an important etiological factor for infertility in countries with high prevalence of tuberculosis.[4]

CASE DETAILS

A 52 years old woman, nulligravida with post-menopausal status of 6 years presented to gynecology department with chronic pain abdomen and post-menopausal bleed. On examination: Per abdomen was soft, non-tender. Per vaginal examination - cervix was firm and bled on touch and bilateral fornices were free and non-tender. Ultrasound scan showed a subserosal fibroid with left adnexal mass, probably a neoplastic etiology and minimal pleural effusion. Hysterectomy was performed. We at histopathology unit received the following specimen of uterus cervix with bilateral fallopian tubes.

On gross examination, uterus was atrophied with hypertrophied cervix [Figure 1]. External surface of uterus noted two subserosal fibroid. External surface and cut surface of cervix was unremarkable. Cut surface of fallopian tube showed lumen occluded with gray-white material [Figure 2].

Microscopic examination revealed, a thinned walled endometrium with few endometrial glands lined by columnar epithelium, occasional glands were dilated and lined by flattened epithelium. Stroma was compact to spindly with foci of epithelioid granuloma with lymphocytes and langhan's types of giant cells [Figure 3]. Endocervix showed endocervical glands lined by columnar epithelium, ectocervix showed foci of ulceration with numerous well-formed non-caseating epithelioid granulomas, lymphocytes, and langhan's types of giant cells [Figure 4]. Bilateral fallopian tubes show obliteration of lumen by necrotic material [Figure 5].

A diagnosis of genital tuberculosis was made on the basis of histopathological examination.

DISCUSSION

In India, tuberculosis is the major cause of infertility especially in reproductive age group, commonly affecting the fallopian tubes.[5] The majority of patients are

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

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Figure 1: Uterus cervix with bilateral fallopian tube

Figure 2: Fallopian tube with gray-white material

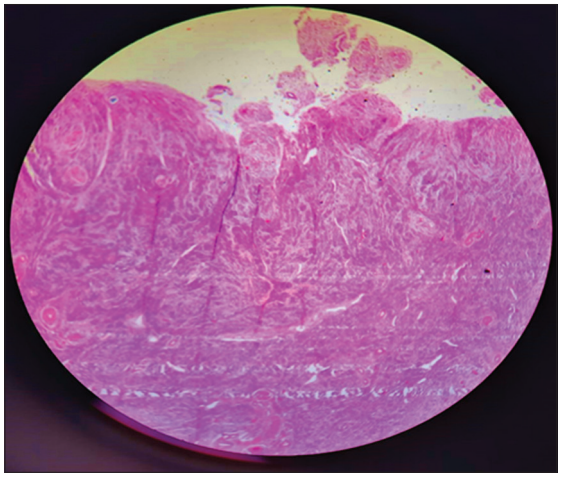

Figure 3: Section from endometrium showing multinucleated giant cell

asymptomatic, but patients also have the following symptoms such as oligomenorrhagia, menorrhagia, dysmenorrhea, dyspareunia, abnormal vaginal discharge, and chronic pain abdomen.[6] Frequent sites of involvement

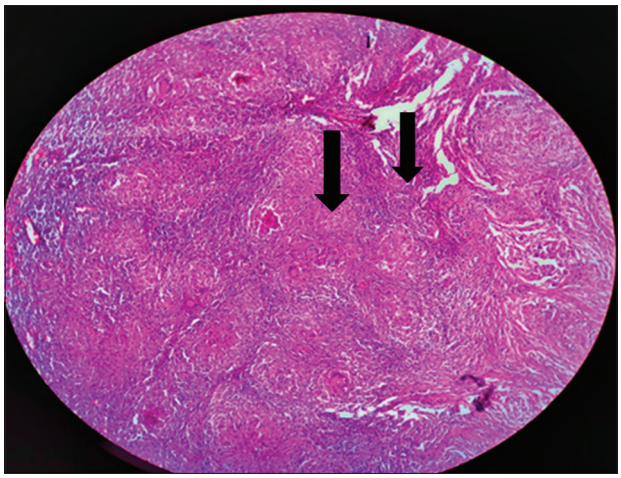

Figure 4: Section from cervix showing well-formed granulomas

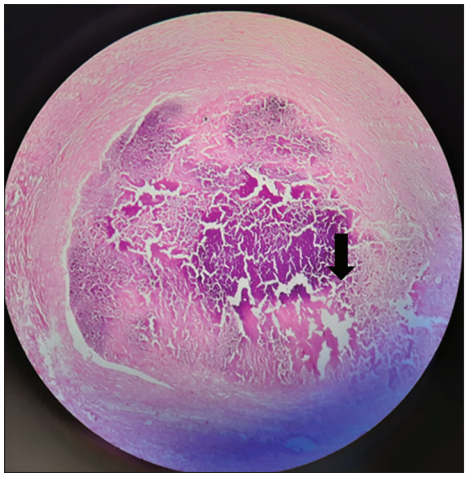

Figure 5: Fallopian tube showing necrotic material

are fallopian tubes (95–100%), endometrium (50–60%), ovaries (30%), cervix (5–15%), myometrium (2.5%), and vagina/vulva (1%).[7] The diagnosis is usually made on the basis of histopathological examination and serological diagnosis is done by enzyme-linked immunosorbent assay and polymerase chain reaction.

CONCLUSION

Diagnosis of tuberculosis is difficult clinically as most of the patients are asymptomatic, and it can mimic carcinoma in post-menopausal age groups.[8] Tuberculosis must be included in differential diagnosis, usually from the areas where it is commonly seen.

In this scenario, the clinical investigation tools such as ultrasound, computed tomography, dilation and curettage, hysterosalphingography, colposcopy, and biopsies from endometrium/cervix can play a significant role in the preliminary diagnosis. Histopathological examination with

the routine stains of hematoxylin and eosin can provide us with a definitive diagnosis.[9] Follow-up of the patient for any other organ/tissue involvement must be done. Early diagnosis can lead to early treatment.[10]

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How to cite this article: Choudhary S, Suba G, Rajesh S, Shilpa SJ. Genital Tuberculosis: A Common Disease Revisited. Int J Sci Stud 2022;9(12):4-6.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Case Report

Giant Cell Tumor of Distal Femur Treated with Resection Arthrodesis and Custom Made Intramedullary Nail Along with Tibia Slide and Fibula Graft: A Case Report and Review of Literature

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Abstract

Introduction: Giant cell tumor of the bone has been defined by the World Health Organization as a locally malignant tumor. The surgical treatment varies from a simple intralesional curettage to wide/*en block* resection. The surgical challenge faced is preventing recurrence of the lesion and at the same time providing with a painless functional limb.

Case Report: We report a giant cell tumor (GCT) of the distal femur in a 32-year-old female who underwent resection arthrodesis with the help of a custom-made interlocking nail with tibia slide graft and fibula strut graft.

Discussion: The aim in surgical treatment of GCT of bone should be to prevent recurrence. Recurrence rate with wide resection has been reported as low as 0–5%. Chances of revision surgery in a young patient with endoprosthetic reconstruction are higher than with arthrodesis.

Conclusion: Arthrodesis provides a painless, stable, and functional limb after *en block* resection.

Key words: Giant cell tumor, Wide resection, Arthrodesis

INTRODUCTION

Giant cell tumor (GCT) of the bone is a locally aggressive benign osteolytic tumor which was first described by Cooper and Travers in 1818.[1] The incidence of GCT of bone varies considerably between Western and Asian population, being 3–8% in former group and nearly 20% in the later group.[2] It accounts for 5% of primary bone tumors and 15% of benign bone tumors.[3] GCT is an epiphyseal long bone tumor and has more predilection for distal femur, proximal tibia, and distal radius. It is an osteolytic lesion and histologically shows osteoclast-like giant cells interspersed with vascular stroma.[4] It is seen in age group of 20–40 years and predominantly in males, with a male-to-female ratio of 1.27–1.77:1.[5] GCT was classified clinic-radiologically both by Enneking and later by Campanacci *et al.* These classifications were designed to define the extent of surgery for complete tumor excision.[6] Treatment, thus, includes intralesional curettage, extended curettage with adjuvants and high-speed burr and wide resection. Recurrence rate with wide resection is lower (0–5%) as compared to curettage alone (25–50%).[6] Bone tumors have been treated in the past with resection arthrodesis and have been declined after newer joint preserving options have been available. Arthrodesis was indicated when an extensive resection was required, and joint surfaces could not be preserved, but limb was neurologically intact.[7]

We report a case of a 32-year-old female with obesity who was diagnosed with GCT of the bone and treated with resection arthrodesis with a custom-made intramedullary nail and tibia slide and fibula grafts. The evidence base and clinical details are discussed.[8]

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

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CASE PRESENTATION

A 32-year-old female presented to the outpatient clinic with complains of pain and swelling over the left knee. The pain has been present since a year and was controlled with non-steroidal anti-inflammatory medications, but she found it increasingly difficult to walk since 2 months. She had no medical comorbidities; however, she was moderately obese with a BMI of 32. Clinical examination revealed a globular swelling over the distal thigh. There was tenderness on palpation around distal femur and joint line. Overlying skin was normal. Range of motion of the left knee was painful and restricted. There was no neurovascular deficit. Radiographs of her left knee [Figure 1] showed an osteolytic lesion of the left distal femur with cortical break and extension into soft-tissue posteromedially. She also underwent magnetic resonance imaging [Figure 2] which showed the soft-tissue extension. Further, confirmation was made after core needle biopsy. The tumor was graded according to Campanacci Grade as Stage III GCT with radiological and histological evidence. The surgical options, including wide resection and endoprosthetic reconstruction and resection arthrodesis, were considered. The surgical options were discussed in detail with the patient. Although endoprosthetic reconstruction would give a more functional joint, the patient wanted to resume fieldwork in farm which involves heavy physical labor. Hence, taking her BMI and occupation into consideration, the decision was made to proceed with resection arthrodesis. Wide resection of the tumor was performed [Figure 3]. Bone gap was measured to be 10 cm, and tibia graft was calculated as double of the bone gap plus 3 cm to make up for the joint space and prevent limb shortening. Tibia graft was taken along with non-vascular fibula strut graft from the same side. Custom-made interlock nail was introduced through the piriform fossa and extended distally into the tibia and locked with proximal and distal screws. Tibial graft was slided over the defect along with the fibula graft and stabilized with locking plate anterolaterally. Graft was covered with overlying vastus after drain insertion. Post-operative immobilization was obtained with knee immobilizer. Histology of resected specimen showed features suggestive of high-grade GCT. Radiograph of the limb was taken on 2nd post-operative day [Figure 4]. Post-operative period was uneventful, and the patient was advised to remain non-weight-bearing for 3 months. The patient underwent physiotherapy from 1st post-operative day and started mobilizing with help of walker on 2nd post-operative day. Partial weight-bearing was initiated after 12 weeks and full weight-bearing after 6 months. The patient was able to return to work in 8 months from the surgery, she was followed up to 3 years and showed no recurrence or complications.

Figure 1: Radiograph of the left knee showing lytic bone lesion involving the distal femur with characteristic soap bubble appearance with break in cortical continuity posteromedially

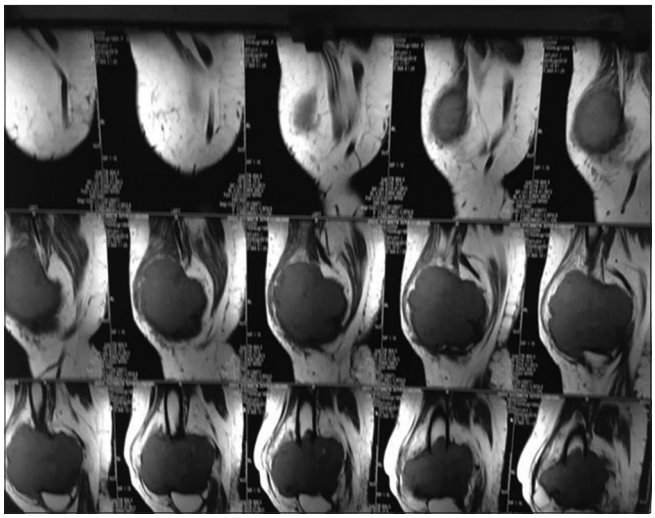

Figure 2: MRI left distal femur

DISCUSSION

Giant cell tumor is an aggressive benign bone tumor with higher incidence in the third decade of life. These tumors have been known to have high local recurrence rates.[4] Klenke *et al*., in a review of 118 GCT patients, concluded that age at diagnosis was the predictor of recurrence rates regardless of status of the lesion and the surgical modality taken to treat it.[3] In another study by Kivioja *et al*., they concluded that age and surgical margins are prognostic factors of local recurrence.[9] According to a large multicentric study on GCT of bone done in China, it was found that GCT around the knee was found more commonly in men. They also found the recurrence rate of GCT to be higher in patients between 20 and 39 years of age and those treated with intralesional curettage.[10] The GCT of the bone is associated with 1–4% benign pulmonary metastases. In spite of GCT being a benign tumor, it can cause significant destruction of bone and

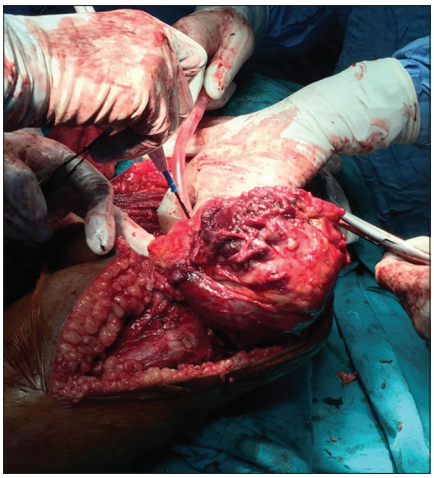

Figure 3: Intraoperative photograph after *en block* resection of the lesion from distal femur along with muscular attachments

Figure 4: Post-operative X-rays showing interlocking nail *in situ* with autologous bone graft reinforced with locking compression plate

could present as a challenge to surgeons specially in pre-articular areas. The aim of the surgeon is to completely excise the tumor, preserve limb function, and prevent any local recurrence.[11]

Campanacci graded these lesions on the basis of their radiological appearance. Grade III was designated to those lesions which had permeated growth and soft-tissue extension without any reactive bone shells limiting the lesion.[12]

The primary aim while treating a primary bone tumor should always be complete surgical removal of the lesion. Preservation of limb function and planning of reconstructive procedures is secondary and changes should be made according to the demands of tumor excision.[13] Surgical resection is the standard surgical treatment for GCT of bone. Intralesional curettage is favored in cases, where the lesion is benign and is Grade I/II. *En block*/wide resection has been advocated as the modality of treatment, as the recurrence rate is low and the recurrence-free survival rate has been reported between 84% and 100%.[13] Although *en-block* resection provides the best cure for GCT, joint reconstruction poses as a challenge to the surgeon and thus irrespective of the lesion being primary or recurrent , reconstruction of the joint surface is important.[14] This can be achieved with either megaprosthesis joint replacement or biological reconstruction.[15] The ideal reconstruction after an *en block* resection is still a matter of debate. Wide surgical resection is indicated when there is extensive bone destruction, recurrence or when the reconstruction is difficult to do after intralesional curettage.[16] The recurrence rate with wide (*en block*) resection is as low as 0–5%. Prosser *et al*. found that the recurrence rate of the 137 patients who had curettage alone varied with Campanacci grades, being only 7 % in patients of Grades I and II, but 29% in Grade III patients.[6] Chen *et al*. concluded that as knee joint is a weight-bearing joint, the amount of subchondral bone involved by the lesion is a valuable prognostic factor and found that the mean area of articular surface involvement in patients who underwent resection was 68.2%.[17]

Knee arthrodesis in tumor excision is mainly indicated when after resection of tumor joint surface cannot be preserved. Reconstructions by arthrodesis have declined, as a variety of techniques involving expandable endoprosthesis and biological reconstruction by freezing, autoclaving or irradiation, are present to preserve the function of the joint. Endoprosthesis reconstruction incurs high cost, which requires good muscular reconstruction.[18] In a young patient with a good remaining life span, endoprosthesis reconstruction will require multiple surgeries as the implant life will be significantly shorter than the patient's life span.[19] Ahmed *et al*., in his case report, desarthodesed a knee after 40 years of arthrodesis with patient having a functional painless limb for 39 years after arthrodesis for GCT of distal femur.[20] Gitelis *et al*. compared the results of *en bloc* resection of GCT (n = 20) and intralesional excision with adjunctive local insertion of methyl methacrylate or phenol (n = 20). They reported only one recurrence in the intralesional surgery group. There were no recurrences in the patients who had an *en bloc* resection. [21] Tuteja *et al*. showed the advantages of using a dual autologous vascular fibular graft along with knee arthrodesis after resection of GCT and found that they showed good union at recipient site and lesser complications in filling femoral defects. He

concluded that resection arthrodesis with dual fibular graft offers limb reconstruction as an alternative to amputation, providing a stable and functional limb in aggressive and recurrent GCT around the knee joint.[22] Campanacci and Costa reported 92% union rate in 26 patients treated with resection of GCT around the knee and stabilized with long intramedullary nail. They reported infection as the main complication occurring in five of their patients.[23]

In our case, we aimed at giving the patient a stable joint that would allow her to return to her occupation at the earliest. Endoprosthetic replacements require lifestyle modifications as well as prospects of the patient undergoing multiple surgeries are also high. In addition with obesity and high physical labor involved, there are high chances of early wear and revision. We believe that although endoprosthetic replacement is an attractive option, tumor grading, patient's occupation, socioeconomic status, and post-operative expectations that must be considered. Arthrodesis was considered due to the above reasons and has shown to give satisfactory functional outcome in up to 3-year follow-up.

CONCLUSION

Stage III GCT has higher incidence of recurrence and *en block* resection is advised to prevent recurrence. Resection arthrodesis with intramedullary nail and autologous bone graft provides a painless and functional limb and allows the patient to perform strenuous activities.

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How to cite this article: Lal AK, Srivastava N, Gupta S. Giant Cell Tumor of Distal Femur Treated with Resection Arthrodesis and Custom Made Intramedullary Nail Along with Tibia Slide and Fibula Graft: A Case Report and Review of Literature. Int J Sci Stud 2022;9(12):7-10.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Case Report

Nodular Fasciitis: A Diagnosis of Exclusion

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Abstract

Nodular fasciitis (NF) is an infiltrative or pseudosarcomatous fasciitis. It is a benign, self-limiting fibroblastic, and myofibroblastic proliferative process. It is a rare benign neoplasm most commonly affecting the soft tissues of upper extremity followed by trunk, head, and neck. Since it is an infrequent lesion, it is a diagnostically important lesion, because excision is usually the mainstay treatment. Although clinical history, examination, and imaging are important, histopathological diagnosis is the key for making the diagnosis in such lesions. It is one of the most under-diagnosed lesions and can be confused with many other lesions. Here, we present a case of a 42-year-old female patient who presented with swelling over the right side of the forehead since 2 months which gradually increased in size to the present size. A clinical diagnosis of lipoma was made and the tumor was excised for further investigation. Grossly, it was a single irregular gray white to gray brown bit of tissue measuring 0.6 × 0.5 × 0.5 cm. Microscopy showed fibroblasts of varying size and shape arranged in short bundles and fascicles with oval pale staining nuclei with prominent nucleoli. Characteristic feathery pattern was observed. The stroma showed hyalinized areas and focal myxoid areas. Few giant cells and mononuclear inflammatory cells were noted. To differentiate it from neural tumors, immunohistochemical study with S-100 and epithelial membrane antigen was done, which was negative. Smooth muscle actin showed positivity. In conclusion with the above features, NF was reported.

Key words: Epithelial membrane antigen, Feathery pattern, Fibroblasts, Forehead, Myofibroblasts, Nodular fasciitis, S-100, Smooth muscle actin, Underdiagnosed

INTRODUCTION

Nodular fasciitis (NF) is an infiltrative or pseudosarcomatous fasciitis. It is a benign, self-limiting fibroblastic, and myofibroblastic proliferative process. Most of these lesions are solitary. It was first described in 1955 by Konwaler and Weiss.[11] It can occur at any age, but most often seen in young and middle-aged adults between third and sixth decades of life with no sex predilection.[2] It is a rare benign neoplasm most commonly affecting the soft tissues of the upper extremity followed by trunk, head, and neck. It usually involves subcutaneous tissue or fascia, but can be rarely seen in intramuscular location.[3]

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

CASE DETAILS

Here, we are presenting a case of a 42-year-old female patient who presented to the surgical outpatient department with a swelling over the right side of the forehead since 2 months which gradually increased in size to the present size. A clinical diagnosis of lipoma was made and the tumor was excised for further investigation. We, at histopathology unit, received the soft-tissue mass labeled as lipoma for processing.

Gross [Figure 1]

Single irregular gray white to gray brown bit of tissue measuring 0.6 × 0.5 × 0.5 cm. Entire tissue was processed. The slides were stained with routine hemotoxylin and eosin.

Microscopy [Figures 2 and 3]

Sections showed fibroblasts of varying size and shape arranged in short bundles and fascicles with oval pale staining nuclei with prominent nucleoli. Characteristic feathery pattern was observed. The stroma showed hyalinized areas and focal myxoid areas. Few giant cells and mononuclear inflammatory cells were noted. Mild mitotic activity presents.

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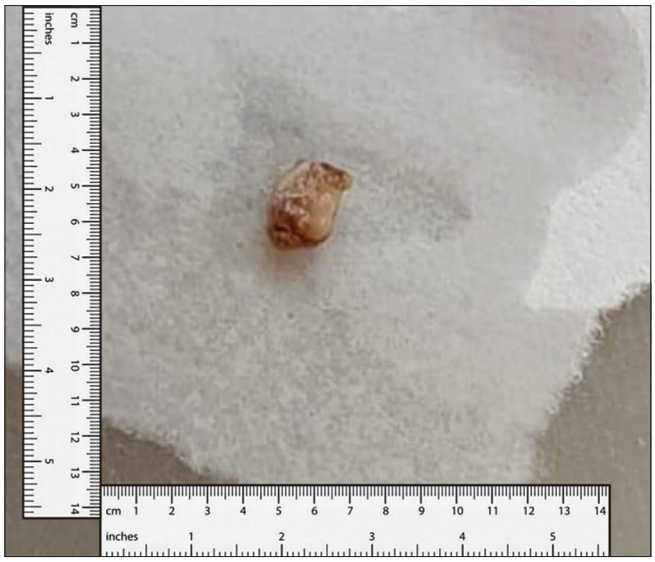

Figure 1: GROSS- Irregular gray white to gray brown bit of tissue

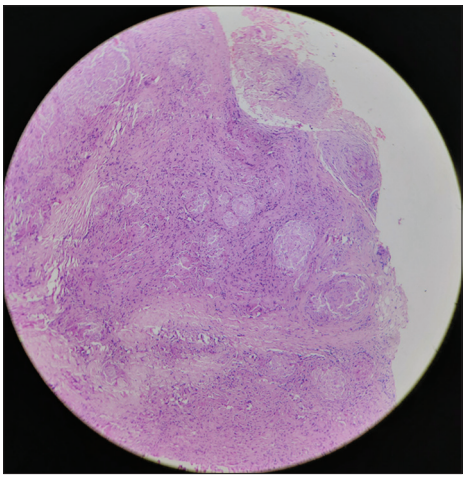

Figure 2: (Low power view) – shows fibroblasts arranged in short bundles and fascicles

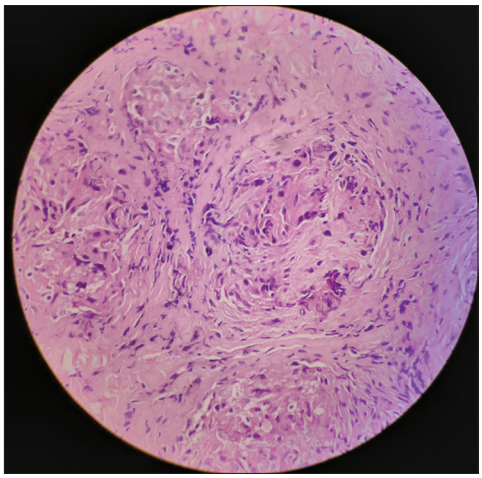

Figure 3: (High power view) – Fibroblasts showing the characteristic feathery pattern

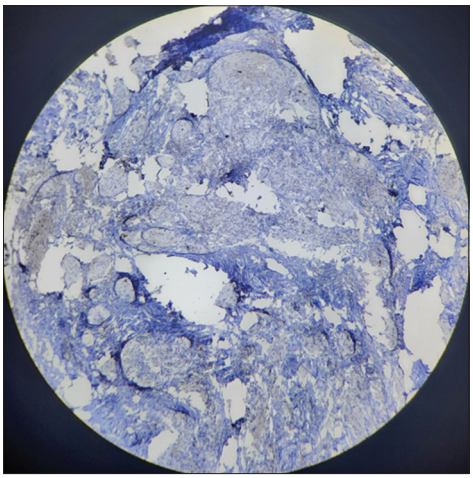

Figure 4: Immunohistochemistry with S-100 was negative

A diagnosis of NF was made.
To differentiate it from neural tumors, immunohistochemical study with S-100 [Figure 4] and epithelial membrane antigen was done, which was negative [Figure 5].
Smooth muscle actin showed positivity [Figure 6].
In conclusion with the above features, NF was reported.

DISCUSSION

Pathologically, NF has been described as a solitary, well-demarcated, and unencapsulated lesion which may be locally infiltrative and rapidly growing nodule usually of less than 3 months duration.[2,3,4,5] It tends to be mostly centered in fascia extending to sub cutaneous fat in an irregular manner but can also be dermal, subcutaneous, deep fascial, intermuscular, intramuscular, and intravascular.[2,4] It is one of the most under-diagnosed lesion and can be confused with spindle cell sarcoma, fibromatosis (desmoid tumor), fibrous histiocytoma, proliferative fasciitis, benign nerve sheath tumors, lipoma, dermatofibroma, fibrosarcoma, and pleomorphic adenoma because of similar features such as short history, rapid growth, marked infiltration, and somewhat similar histopathological picture.[3,6,7,8] The etiology is still unknown even after quite, a good number has been reported worldwide. It is considered to occur due to unusual proliferation of myofibroblasts, for which trauma or inflammatory process has been implicated as triggering factor.[3,7] Since it is an infrequent lesion, it is usually a neglected entity in the evaluation of benign tumor lesion.[9,10,11]

Immunohistochemical studies show negative staining for desmin, H-caldesmon, and nuclear localization of beta catenin and positive staining for vimentin and alpha-smooth muscle actin.[2]

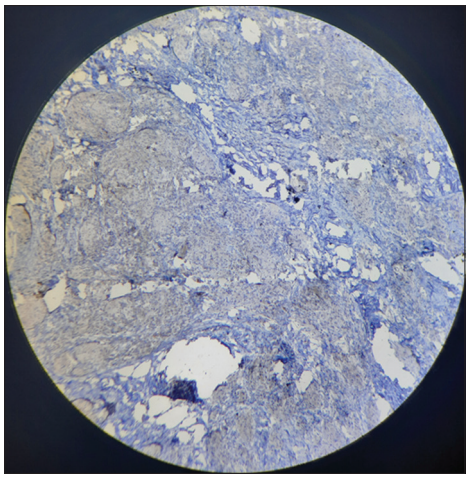

Figure 5: Immunohistochemistry with epithelial membrane antigen was negative

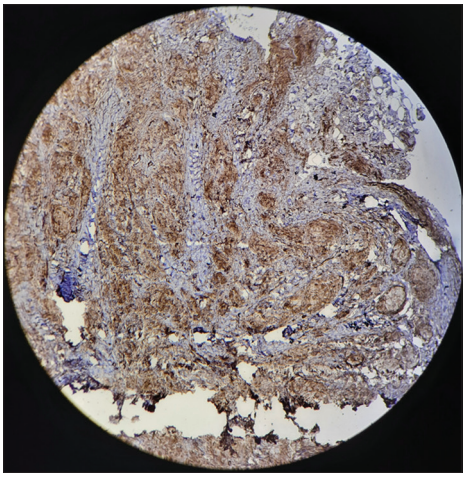

Figure 6: Immunohistochemistry with smooth muscle actin showed strong positivity (×10)

CONCLUSION

NF is an uncommom,but diagnostically important lesion and excision is usually the mainstay treatment. Although clinical history, examination, and imaging are important, histopathological diagnosis is the key for making the diagnosis in such lesions. Awareness about NF and its benign nature is essential to avoid misdiagnosis and inappropriate aggressive treatment of the patient.[3,7]

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How to cite this article: Choudhary S, Suba G, Shilpa SJ, Rajesh S. Nodular Fasciitis: A Diagnosis of Exclusion. Int J Sci Stud 2022;9(12):11-13.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Case Report

Sciatic Nerve Bifurcation and Its Implication in Posterior Approach of Total Hip Replacement: A Rare Case Report

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Abstract

Introduction: The Sciatic nerve is the widest nerve of the body. It consists of two components, the tibial and the common peroneal. This components are derived from the ventral rami of L4 to S3 spinal nerves of the lumbosacral plexus. Sciatic nerve exits pelvis through the greater sciatic foramen below the piriformis muscle and descends down between the greater trochanter of the femur and ischial tuberosity of the pelvis toward the knee. The purpose of this study is to identify the course and variations in branching pattern of the sciatic nerve which may lead to various clinical manifestations, complication, and care that should be taken during total hip replacement.

Case Report: A 60-year-old male came with pain in right hip since 6 months. X-ray PBH was done and showed Grade 4 arthritis. Patient was planned for total hip replacement. Patient was kept in floppy lateral position. Incision was taken from shaft of femur directing towards posterior side through greater trochanter. We observed Variation in sciatic nerve at this level and carefully pulled it away from the surgical site. Postoperatively, neurology was evaluated and showed no neurovascular deficit.

Conclusion: It is important to be aware of anatomical variation in sciatic nerve during a surgical intervention in the gluteal region so as to reduce the risk of injuring these nerves which are more susceptible to be injured.

Key words: Bifurcation of the sciatic nerve, Posterior approach, Sciatic nerve, Tibial and common peroneal nerves, Total hip replacement

INTRODUCTION

Sciatica is a Greek word derived from "Ischiadichus" and hence it is called as ischiadic nerve. The sciatic nerve is the widest nerve of the body, having two components, tibial and the common peroneal, both of which initially form a common trunk from the lumbosacral plexus. The tibial part is formed from the ventral branch of ventral rami of L4 to S3 spinal nerves. The common peroneal part is formed from the dorsal branches of ventral rami of L4 to S2 spinal nerves.[1] It usually exits from the pelvis through the greater sciatic foramen below the piriformis muscle and goes down between the greater trochanter of the femur and ischial tuberosity of the pelvis, at the posterior aspect of the thigh, it divides into the tibial nerve and common peroneal (fibular) nerves at a varying level proximal to the knee. At proximity it lies deep to the gluteus maximus muscle, resting first on the posterior ischial surface with the nerve to the quadratus femoris lying between them. It descends posterior to the obturator internus, the Gemeli, and quadratus femoris muscle, separated by the quadratus femoris from obturator externus muscle and the hip joint. On medial aspect, it is accompanied by the posterior femoral cutaneous nerve and the inferior gluteal artery. On

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

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descending course, it lies posterior to adductor magnus and anterior to the long head of biceps femoris. It represents to a line drawn from just medial to the midpoint between the ischial tuberosity and greater trochanter to the apex of the popliteal fossa. As the sciatic nerve has significant anatomical variation in its course, topography and level of division, the unpredictability of this can lead to inadvertent damage intraoperatively, and special care must be taken to prevent sciatic nerve palsy. High level division is a relatively common finding, dividing into its terminal branches in the pelvis and thigh.[2] Neurological and vascular complications following hip arthroplasty are uncommon, and their impact ranges from transient and trivial such as numbness tingling to permanent and devastating, namely, foot drop. The proximity of neural and vascular structures makes any operation in the hip region potentially hazardous. Direct or indirect injuries of sciatica nerve and branches may occur during operative exposure and placement of the implant. Thermal effects of cementing also have hazardous effect on sciatic nerve leading to temporary to permanent damage. Complete awareness of the anatomy of the pelvis and proximal femur is essential before undertaking any procedure. Peripheral nerve injuries may be either at distant sites or within the immediate vicinity of the hip joint. Sciatic nerve injury is the most common nerve and most dangerous injury following total hip arthroplasty.

CASE REPORT

A 60-year-old male came with chief complaints of pain in right hip joint since 6 months. Plain radiograph was taken, suggestive of grade four osteoarthritis of right hip joint. The patient was explained the need for total hip replacement. Routine preoperative investigation was done. Blood profile was within normal limit. Posterior approach was planned for the patient. Patient was kept in lateral position with affected side above. Greater trochanter was by palpating it from lateral condyle of femur. Incision was taken 10 above and 5 cm below the greater trochanter. Soft tissue was dissected in layers. We noticed that sciatic nerve was crossing posteriorly with bifurcation and needed further attention for the same. It was observed that it is type 2 variations which is quite rare and must be documented for future references. We retracted the nerve posteriorly with gentle care, but one of the branches was crossing the surgical site. Another retractor was placed to retract the branch and procedure was continues. Procedure was uneventful and patient had no neurodeficit postoperatively.

DISCUSSION

The sciatic nerve was first described in detail by Ambroise Par'e in the 16th century, and in the 19th century, Cruveilhier

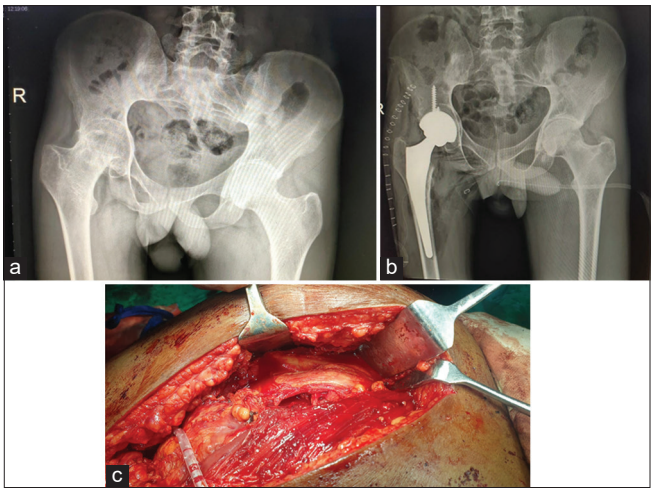

Figure 1: (a) Grade 4 right hip arthritis, (b) Postoperative radiograph of total hip replacement, (c) sciative nerve variation

observed variation in the bifurcation level.14 Variant types include the sciatic nerve passing through the belly of the PM, or the high bifurcation of the sciatic nerve into the tibial nerve and common perineal nerve in the gluteal region, with one of these branches possibly coursing through the PM.[2,3]

Sciatic nerve anatomy and its bifurcation levels are important in clinical and treatment aspects. Under normal circumstances undivided SN courses through greater sciatic foramen below piriformis and divides at the apex of the popliteal fossa topographic variations and relationship of the sciatic nerve and piriformis muscle was studied by Pokorný *et al.*[2] The level of the sciatic nerve division and its relation to the piriformis muscle was also studied by Ugrenovic *et al.*[3] According to both of them, sciatic nerve descends from pelvis through the infrapiriform is foramen in 192 lower limbs (96% cases), while in eight lower limbs (4%) the variable relations between SN and piriformis muscle were detected. Common peroneal nerve traversed through the piriformis and left the pelvis in 5 limbs (2.5%) and Tibial Nerve left the pelvis through the infrapiriform is foramen. In three limbs (1.5%), common peroneal nerve was present above the piriformis and tibial nerve was below the piriformis. Variations in the course of the SN have also been associated with iatrogenic nerve injury during certain procedures, such as total hip arthroplasty, and arthroscopy.[4,5] Authors have given different classifications for the level of division and course of sciatic nerve in relation to piriformis muscle. The degree and prevalence of variation have remained constant in cadaveric and magnetic resonance imaging studies with around 90–93% of cases showing type 1 pattern with anatomic variation in up to 10%. Rare unclassified variations may still be encountered during surgical intervention in this region. Beaton and Anson

classified the relationship of the sciatic nerve to the piriformis and its subdivisions to the muscle.[6] Four main types were observed with Type 5 and 6 were considered hypothetical variations.

Type 1: Undivided nerve below undivided muscle - 90%
Type 2: Division of nerve between and below undivided muscle - 7.1%
Type 3: Division above and below undivided muscle - 2.1%
Type 4: Undivided nerve between heads - 0.8%
Type 5: Division between and above heads.
Type 6: Undivided nerve above undivided muscle.

The prevalence rate of neurologic injury after primary hip arthroplasty is around 0.7–3.5%,[5-8] increasing up to 7.6% after revision hip arthroplasty.[5,6,9,10] Direct causes of sciatic nerve injury during hip arthroplasty include direct external injury, lengthening of the pelvic limbs, thermal injury from bone cement, pressure damage secondary to hematoma, and traction damage due to dislocation of the femoral region. Approximately 40% of the cases the cause of injury remains unknown.[11] The major causes of neurologic injury are stretching, compression, contusion, laceration, thermal injury from bone cement, and vascular compromise occurred during operations. Amongst these causes, stretching is the most common one and is due to either traction or excessive extension of the limb. Secondary risk factors are acetabular hip dysplasia, female gender especially with below-average height and muscle mass, posttraumatic arthritis, minimal invasive procedures, and revision hip arthroplasty; however, neurologic injury can occur in the absence of these risk factors. Therefore, it is better to perform traction operations with caution or to protect the sciatic nerves of high-risk patients in advance to prevent nerve injury. Furthermore, if needed, it is also recommended to prevent bone cement leakage, while understanding the variability of sciatic nerve during posterior approach in total hip replacement. It is also necessary to maintain an optimal level of anticoagulant agents to avoid pressure damage due hematomas. The sciatic nerve branches are most susceptible to injury due to the low mobility of the fibular head of the knee joint and the point projected through the sciatic notch from the pelvis. Damage of the fibular parts is more common than that of the tibial parts; in particular, the outer part of the fibular area is known to be damaged more often. Sciatic nerve injury is the most common peripheral nerve damage following hip arthroplasty.[5-7,12]

CONCLUSION

It is important to be aware of anatomical variation in sciatic nerve during a surgical intervention in the gluteal region especially posterior approach in total hip replacement, so as to reduce the risk of injuring these nerves which are most susceptible to be injured. A detailed anatomical study of such variations will be helpful for evaluating the pain in various test positions. Our case report provides awareness of additional sciatic nerve entrapments that are possible within the gluteal regions. To prevent and minimize neurovascular injuries, one of the complications of posterior approach of hip arthroplasty, it is obligatory to have accurate knowledge of the anatomical structures and to understand clinically anatomical variation. It is very important to be cautious during the posterior approach regarding excessive stretching, damage by the instruments, bone cement leakage, and hematoma formation. Fixation of acetabulum screws should be performed in the posterosuperior quadrant to minimize neurovascular injuries. Finally, movement of acetabulum implants should also be carefully monitored.

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How to cite this article: Agrawal V, Sawant K, Sadar A, Kondewar P, Gupta D, Hifzur SR. Sciatic Nerve Bifurcation and Its Implication in Posterior Approach of Total Hip Replacement: A Rare Case Report. Int J Sci Stud 2022;9(12):14-16.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Case Report

Granular Cell Tumor of Breast: A Rare Case Report

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Abstract

Granular cell tumour of the breast is considered as one of the rare tumours. GCTB, a largely benign tumour, arises from Schwann cells. In rare cases it can exhibit malignancy. It poses a particular problem as its characteristics can mimic breast carcinoma clinically, radiologically and macroscopically. We are reporting a case of a 60-year-old lady who presented with a granular cell tumor in the breast. Patient presented with a 3.0 × 3.0 cm hard immobile mass in the left breast. Mammography revealed an, with ill-defined borders and without any calcification. FNAC was inconclusive and in this patient the mass was considered as benign and excision of lesion was done with some healthy tissue amount of histopathology confirming the diagnosis.

Key words: Breast, Cell, Tumor

INTRODUCTION

The first granular cell tumor was reported by Abrikossoff in 1926 in the tongue. He termed this lesion as myoblastoma and proposed that it originated from striated muscle. His theory was initially supported by the tissue culture studies of three granular cell tumors. Subsequently, his theory was rejected as other authors showed evidence of histiocytic or smooth muscle derivation. Today, the most widely accepted theory is that of a Schwann cell origin, because of the S-100 positivity of the tumor and the similarities of its cells ultrastructural features with those of Schwann cells.[1-5]

CASE REPORT

A 60-year-old female presented to our hospital with the complaint of a mass in her left breast since the past 2 years which was painful and slowly increasing in size. Physical examination revealed a 3 × 3 cm hard immobile mass in upper inner quadrant of the left breast. Examination of the other breast and axilla was normal. No palpable lymph nodes were found.

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

Ultrasonography showed a 3.2 × 2.9 cm diameter mass with diffuse hypodensity along with a small cyst measuring 2 mm in diameter. Mammography revealed an opaque mass with ill-defined borders and without any microcalcifications. FNAC was, however, inconclusive. With these findings, the mass was considered as benign and the lesion was removed with some healthy tissue around it.

The histological examination revealed dilated ducts lined by apocrine cells and filled with eosinophilic secretions. The stroma showed cords and nests of polygonal cells with centrally placed small, round to oval nuclei, and abundant eosinophilic granular cytoplasm. These cells were crowded over the nerve fibers. Mitotic activity was not seen. These granular cells were seen infiltrating the surrounding adipose tissue and were associated with areas of fibrosis. Special stains were done and cytoplasmic granules in the tumor cells were diastase resistant and Perioidic Acid Schiff (PAS) positive. A diagnosis of benign granular cell tumor was made. Tumor cells showed positivity for S-100 and this confirmed our diagnosis [Figures 1 and 2].

DISCUSSION

The cytoplasm shows a granular appearance which may be caused by accumulation of secretory granules, mitochondria, or lysosomes. Mital *et al.* showed evidence of granule origin as infoldings of cell membrane by

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a process similar to myelin formation around nerves and they suggested that subsequent phagocytosis of the infoldings by lysosomes results in the characteristic cytoplasmic granules.

Granular cell tumors can arise throughout the body and these lesions in the breast account for 5–6% of all cases. Granular cell tumors in the breast are usually benign tumors and very few malignant cases have been reported. These tumors commonly occur in women between 30 and 50 years of age ranging from 17 to 74 years with a frequency of approximately 1 in 1000 breast cancers. The tumor arises from the Schwann cells in the intralobular stroma of the breast.

It occurs more frequently in the upper inner quadrant of the breast, in contrast to breast carcinoma, which is found more frequently in the upper outer quadrant. This distribution appears to correspond to the area of innervation of the skin of the breast by the supraclavicular nerve. This tumor usually appears as a solitary unilateral lesion, but rarely it present as multiple lesions in the breast and other parts of the body.

It generally presents as a painless mass in the breast in women but can mimic breast cancer because of its fibrous consistency, fixation to the pectoral fascia, and skin or nipple retraction. On mammography it shows typical stellate mass lacking calcifications with a dense core. It may even present as a round well circumscribed mass resembling fibroadenoma. On ultrasonography granular cell tumors can present as solid, poorly marginated lesions with marked posterior shadowing or as more benign looking well circumscribed solid masses. In our case, the mass was in the inner quadrant but was painful and immobile with no skin retraction. Breast ultrasound revealed a poorly circumscribed hypodense mass with a small cyst measuring 2 mm in diameter. Mammography revealed a poorly circumscribed speculated mass without any microcalcifications. Grossly, the tumor presents as a firm to hard, well circumscribed mass or a poorly defined mass with infiltrative borders. The cut surface is white or gray and may also have a yellow-tan color. Some lesions measuring up to 6 cm have been reported, but the tumors are generally 3 cm or smaller. Fine needle aspiration biopsy is usually inadequate for definitive diagnosis but may be helpful in differentiating the lesion from carcinoma breast. A few cases have been reported describing the cytological features, which are cellular uniformity and cytoplasmic granularity. However, as the granular cell metaplasia can mimic granular cell tumor in cytologic specimens, so excisional biopsy should be undertaken for a definite diagnosis. Microscopically, the lesion comprises compact nests or sheets of cells that contain eosinophilic cytoplasmic granules. These granules are usually prominent and fill the cytoplasm, sometimes showing cytoplasmic vacuolization and clearing. They are diastase resistant and PAS positive. Cell borders are well defined and cells vary in shape from polygonal to spindle shaped. Nuclei are round to slightly oval with an open chromatin pattern and prominent nucleoli. Some cases may show mild nuclear pleomorphism and occasional multinucleated giant cells may also be seen. Small nerve bundles are sometimes seen in the tumor or in close association in the periphery of lesion.

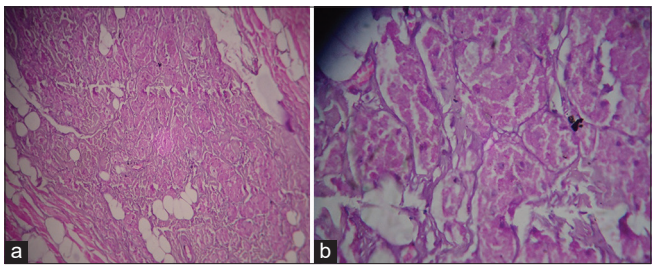

Figure 1: Histopathological section (a and b) showed the cods and nests of polygonal cells with centrally placed small round to oral nuclei and abundant granular eosinophilic cytoplasm. These cells are crowded over the nerve fibers (H&E ×100)

The treatment of granular cell tumor is wide local resection. Local recurrence may sometimes occur after incomplete excision, but sometimes it may be hard to distinguish between recurrence and multifocal asynchronous lesions. Chemotherapy or radiotherapy is only given in malignant counterparts. The differential diagnosis is a challenge and

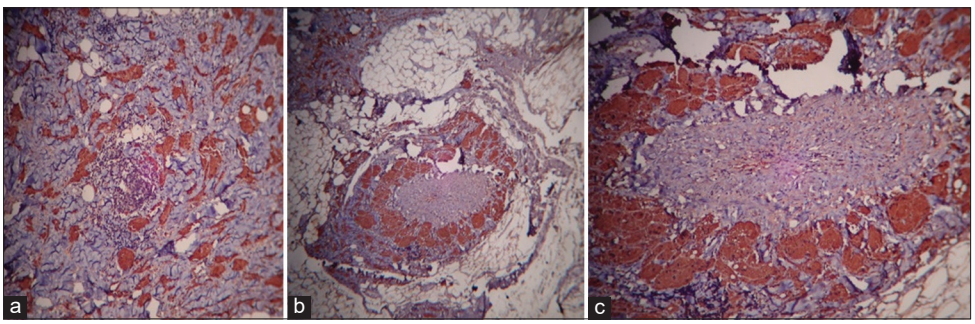

Figure 2: (a-c) Showed positivity for S100 cells (IHC)

the tumor must be differentiated from breast carcinoma, sclerosing adenosis, histiocytic, or metastatic lesions.[6-9]

CONCLUSION

Granular cell tumor of the breast is a rare benign neoplasm. The clinical and mammographic findings may simulate those seen in carcinoma breast. These tumors should be distinguished from carcinomas with oncocytic appearance, histiocytic lesions, and metastatic carcinomas.

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How to cite this article: Gupta M, Kumar N, Bhasker H, Bansal M, Sharma R, Munjal D. Granular Cell Tumor of Breast: A Rare Case Report. Int J Sci Stud 2022;9(12):17-19.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

A Prospective Study of Clinical Profile and Laboratory Diagnosis Which Predicts the Severity of Scrub Typhus in Children

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Abstract

Background: Scrub typhus is an acute febrile illness caused by the obligate intracellular Rickettsial organism, Orientiatsutsugamushi. It is transmitted by the bite of larval forms of trombiculid mites, Leptotrombium mite (Chiggers). Approx one million adults and children are affected worldwide annually. Once an uncommon disease, this potentially fatal zoonosis is re-emerging in many parts of India such as Maharashtra, Karnataka, Tamil Nadu, Pondicherry, and Kerala in the past decade. Here, we tried to find out the predictors of severity of scrub typhus and evaluate clinical profile and laboratory diagnosis and complications which predict the severity of scrub typhus.

Materials and Methods: This Descriptive Observational longitudinal hospital-based study was conducted in the Department of Pediatric Medicine, R G Kar Medical College and Hospital prospectively from Dec 2018-Nov 2019. Children below 12 years of age with scrub typhus were admitted in the Department of Pediatric Medicine, R G Kar Medical College, and Hospital. A total of 60 participants was taken in this study.

Result and Analysis: In non-severe scrub typhus, no children had AKI. In severe scrub typhus, 4(16.7%) children had AKI. Association of AKI versus. scrub typhus group was statistically significant ($P = 0.0112$). In non-severe scrub typhus, 36 (100.0%) children were discharged. In severe scrub typhus, 3 (12.5%) children died and 21 (87.5%) children were discharged. Association of outcome versus. scrub typhus group was statistically significant ($P = 0.0295$).

Conclusion: Symptoms of scrub typhus are quite non-specific. The presence of these factors should alert the physician about the impending life-threatening complications and should warrant intensive care monitoring, treatment or referral to the tertiary care center. Early recognition of the disease is very important as any delay in treatment can lead to severe morbidity and high mortality.

Key words: Clinical profile, Laboratory diagnosis, Predictors, Scrub typhus, Severity

BACKGROUND

Scrub typhus is an acute febrile illness caused by the obligate intracellular Rickettsial organism, Orientiatsutsugamushi. It is transmitted by the bite of larval forms of trombiculid mites, Leptotrombium mite (Chiggers).[1] Approx one million adults and children are affected worldwide annually. Once an uncommon disease, this potentially fatal zoonosis is re-emerging in many parts of India like Maharashtra, Karnataka, Tamil Nadu, Pondicherry, and Kerala in the past decade.[1] Now a days many cases are reported from West Bengal. Pediatric scrub typhus is a very common clinical syndrome encountered in the last few years. The first phase of the illness is parallel to any other undifferentiated fever making early diagnosis complicated. Moreover, serological diagnosis cannot be made before 7 days of onset of fever, further negating the chance of early diagnosis. Scrub typhus is essentially a focal or perivasculitis that can involve any organ system leading to widespread complications. Meningoencephalitis,

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

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septic shock, acute kidney injury, severe thrombocytopenia, myocarditis, acute respiratory distress syndrome, and multi-organ dysfunction syndrome are some of the clinically significant complications seen in pediatric scrub typhus.[2] Most of these complications are life-threatening and have to be picked up early in the course of illness and treated for full recovery.

Orientiatsutsugamushi and Rickettsia species are important causes of non-malarial febrile illness in Southeast Asia preceded only by dengue. Among rickettsioses, scrub typhus is most common followed by Indian tick typhus. The incubation period for symptoms ranges between 6 and 21 days from exposure. Patients may present with sudden fever, chills, headache, backache, profuse sweating, vomiting, and enlarged lymph nodes. A macular or maculopapular rash may appear on the trunk, and later it may extend to the arms and the legs. An eschar at the wound site is the single most useful diagnostic clue. The Indirect Immuno fluorescence Assay test is currently the reference standard for the diagnosis of scrub typhus.[3]

Treatment with doxycycline is associated with a rapid abatement of fever and this effect has even been considered almost diagnostic. Azithromycin is also effective and is easier to administer, given its shorter treatment duration, and less gastrointestinal side effects. It is suitable for use in pregnancy and for children. The symptoms of scrub typhus are usually mild and its clinical course is uneventful. However, some patients experience severe or fatal events. Serious complications include pneumonitis, acute respiratory distress syndrome, acute renal failure, myocarditis, and septic shock. Mortality rates in untreated patients range from 0 to 30%.[4]

The infection often causes vasculitis and multiple-organ failure. Patients with such complications usually have poor prognosis that may end with death, especially those with delayed diagnosis and treatment. Systemic complications commonly reported as causes of death include respiratory involvement (15–36%), cardiovascular involvement (2–34%) renal involvement (9–20%), hepatic involvement (4–31%) central nervous system involvement (4–23%) or multiple-organ involvement (11.9%). Mortality is reported in up to 30% of cases.

Clinical individuality for prognostication of scrub typhus severity and death has been the subject of many studies. These characters may include any combination of the following systems: respiratory system-dyspnea, crepitation, and abnormal chest film; cardiovascular structure-septic shock; hepatobiliary system-serum albumin ≤3 g/dl, bilirubin >1.5 mg/dl, and more than twofold increase in aspartate aminotransferase; and kidney system-serum creatinine >1.4 mg/dl and positive urine albumin.[5] Early detection of these characteristics might be used to assist clinical guidelines for patient management.

Information about common presentations and complications along with timely analysis and intervention are central in limiting the morbidity and mortality. Though there are studies on clinical profile of severe scrub typhus in Indian children, very few looked into predictors of severity in those cases. Most of our understandings about the predictors of severity in scrub typhus are from adult studies, which cannot be extrapolated to children for obvious reasons.[6,7] Former information of factors predicting severity would help in anticipation, timely intervention, or referral in these children.

We tried to find out the predictors of severity of scrub typhus and evaluate clinical profile and laboratory diagnosis and complications which predict the severity of scrub typhus.

MATERIALS AND METHODS

Study Area and Study Population

Department of Pediatric Medicine, R G Kar Medical College, and Hospital, Kolkata. Children below 12 years of age with scrub typhus were admitted in R G Kar Medical College and Hospital, Kolkata from December 2019 to November 2020.

Inclusion Criteria

All children below 12 years of age admitted in R G Kar Medical College and Hospital, Kolkata with acute febrile illness during the study period, with positive scrub typhus IgMserology were included in the study.

Exclusion Criteria

a. Patients diagnosed to have febrile illness due to a underlying specific disease (e.g. Dengue fever, Malaria, Typhoid, UTI, Tuberculosis) and other comorbid conditions like chronic lung disease, chronic hepatitis, and immune-deficient children.
b. Those patients who were unwilling to give their consent for the study.

Method of Data Collection

Data were collected in a preformed proforma from the patient who fulfilled the inclusion criteria after obtaining informed consent from the parents to include their children in the study.

Statistical Analysis

For statistical analysis, data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 24.0. and

GraphPad Prism version 5. A chi-squared test ($\chi 2$ test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a Chi-squared distribution when the null hypothesis is true. Without other qualification, "Chi-squared test" often is used as short for Pearson's chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. $P \leq 0.05$ was considered for statistically significant.

RESULT AND ANALYSIS

We showed in our study 36 (60.0%) children's had non-severe scrub typhus and 24 (40.0%) children's had severe scrub typhus.

Our study showed 3 (5.0%) children died and 57 (95.0%) children were discharged. In non-severe scrub typhus, 17 (47.2%) children were female and 19 (52.9%) children were male. In severe scrub typhus, 11 (45.8%) children were female and 13 (54.2%) children were male. Association of sex versus. scrub typhus group was not statistically significant ($P = 0.9158$). In non-severe scrub typhus, 4 (11.1%) children had >14 days of fever and 32 (88.9%) children had 7–14 days of fever. In severe scrub typhus, 4 (16.7%) children had >14 days of fever and 20(83.3%) children had 7–14 days of fever. Association of duration of fever versus. scrub typhus group was not statistically significant ($P = 0.5351$).

We found in non-severe scrub typhus, 4 (11.1%) children had maculopapular rash. In severe scrub typhus, 5 (20.8%) children had maculopapular rash. Association of maculopapular rash versus. scrub typhus group was not statistically significant ($P = 0.3015$). In non-severe scrub typhus, 8 (22.2%) children had headache. In severe scrub typhus, 6 (25.0%) children had headache. Association of headache versus. scrub typhus group was not statistically significant ($P = 0.8031$). In non-severe scrub typhus, 8 (22.2%) children had tachypnoea. In severe scrub typhus, 2 (8.3%) children had tachypnoea. Association of tachypnoea versus. scrub typhus group was not statistically significant ($P = 0.1573$).

We showed in non-severe scrub typhus, 1 (2.8%) child had breathlessness. In severe scrub typhus, 10 (41.7%) children had breathlessness. Association of breathlessness versus. scrub typhus group was statistically significant ($P = 0.0001$). In non-severe scrub typhus, 12 (33.3%) children had coughed. In severe scrub typhus, 10 (41.7%) children had coughed. Association of cough versus. scrub typhus group was not statistically significant ($P = 0.5116$). In non-severe scrub typhus, 16 (44.4%) children had myalgia. In severe scrub typhus, 14 (58.3%) children had myalgia. Association of myalgia versus. scrub typhus group was not statistically significant ($P = 0.2918$). In non-severe scrub typhus, 6 (16.7%) children had abdominal pain. In severe scrub typhus, 5 (20.8%) children had abdominal pain. Association of abdominal pain versus. scrub typhus group was not statistically significant ($P = 0.6828$). In non-severe scrub typhus, 2 (5.6%) children had altered sensorium. In severe scrub typhus, 12 (50.0%) children had altered sensorium. Association of altered sensorium versus. scrub typhus group was statistically significant ($P < 0.0001$).

Our study showed that in non-severe scrub typhus, 4 (11.1%) children had hepatomegaly. In severe scrub typhus, 5 (20.8%) children had hepatomegaly. Association of hepatomegaly versus. scrub typhus group was not statistically significant ($P = 0.3015$). In non-severe scrub typhus, 4 (11.1%) children had splenomegaly. In severe scrub typhus, 5 (20.8%) children had splenomegaly. Association of splenomegaly versus. scrub typhus group was not statistically significant ($P = 0.3015$). In non-severe scrub typhus, 3 (8.3%) children had hypoalbuminemia. In severe scrub typhus, 15 (62.5%) children had hypoalbuminemia. Association of hypoalbuminemia versus. scrub typhus group was statistically significant ($P < 0.0001$). In non-severe scrub typhus, 8 (22.2%) children had hyponatremia. In severe scrub typhus, 20 (83.3%) children had hyponatremia. Association of hyponatremia versus. scrub typhus group was statistically significant ($P < 0.0001$).

We found in non-severe scrub typhus, 3 (8.3%) children had hyperbilirubinemia. In severe scrub typhus, 11 (45.8%) children had hyperbilirubinemia. Association of hyperbilirubinemia versus. scrub typhus group was statistically significant ($P = 0.00076$). In non-severe scrub typhus, no children had ARDS. In severe scrub typhus, 2 (8.3%) children had ARDS. Association of ARDS versus. scrub typhus group was not statistically significant ($P = 0.0781$). In non-severe scrub typhus, no children had pneumonia. In severe scrub typhus, 5 (20.8%) children had pneumonia. Association of pneumonia versus. scrub typhus group was statistically significant ($P = 0.0042$). In non-severe scrub typhus, no children had shock. In severe scrub typhus, 9 (37.5%) children had shock. Association of shock versus. scrub typhus group was statistically significant ($P < 0.0001$).

Our study showed in non-severe scrub typhus, no children had severe thrombocytopenia. In severe scrub typhus, 3 (12.5%) children had severe thrombocytopenia. Association of severe thrombocytopenia versus. scrub typhus group was statistically significant ($P = 0.0295$). In non-severe scrub typhus, no children had AKI.In severe scrub typhus, 4 (16.7%) children had AKI. Association of AKI versus. scrub typhus group was statistically significant

(P = 0.0112). In non-severe scrub typhus, 36 (100.0%) children were discharged. In severe scrub typhus, 3 (12.5%) children died and 21 (87.5%) children were discharged. Association of outcome versus. scrub typhus group was statistically significant (P = 0.0295) [Table 1].

DISCUSSION

We found that 36 (60.0%) children's had non-severe scrub typhus and 24 (40.0%) children's had severe scrub typhus.

Sankhyan *et al.*[8] found that 15 children (9 boys) tested positive for scrub typhus. Thrombocytopenia, hypoalbuminemia. Roy *et al.*[9] found that the mean age of the children was 5.5 years, 61% were male, 91% had rural habitats and admissions peaked between August and December. Mean duration of fever before the presentation was 10.3 days.

In non-severe scrub typhus, 17 (47.2%) children were female and 19 (52.9%) children were male. In severe scrub typhus, 11 (45.8%) children were female and 13 (54.2%) children were male. Association of sex versus. scrub typhus group was not statistically significant (P = 0.9158).

Narayanasamy *et al.*[10] found that Clinical (symptoms and signs) and laboratory factors were analyzed between severe and non-severe groups. Other factors such as age group, sex of the child, headache, vomiting, abdomen pain, epatomegaly, splenomegaly, hemoglobin level, absolute eosinophil count, and absolute monocyte count showed no significant difference (P > 0.05) between these groups. The mean duration for the fever to touch the baseline and mean duration of hospital stay was 36 h and 6.5 d, respectively, in non-severe scrub typhus cases. The time for fever defervescence was 47 h and mean duration of hospital stay was 7.5 d in severe scrub typhus group. There was no mortality seen during the study period.

We found that 8 (13.3%) children's had >14 days of fever and 52 (86.7%) children's had 7–14 days of fever. 13 (21.7%) children's had eschar. 9 (15.0%) children's had maculopapular rash. 18 (30.0%) children's had generalized lymphadenopathy. 16 (26.7%) children's had edema. 14 (23.3%) children's had headache. 10 (16.7%) children's had tachypnoea. 11 (18.3%) children's were breathlessness. Twenty-two (36.7%) children's had cough. 30 (50.0%) children's had myalgia. Eleven (18.3%) children's had abdominal pain. 14 (23.3%) children's had altered sesorium. Nine (15.0%) children's had hepatomegaly. Nine (15.0%) children's had splenomegaly.

Bal *et al.*[11] found that Eschar was found in 17.9% of cases.

It was found that 20 (33.3%) children's had leucocytosis. Eighteen (30.0%) children's had hypoalbuminemia.

Table 1: Association between Sex, Duration of fever, Maculopapular rash, Edema, Headache, Tachypnoea, Breathlessness, Cough, Myalgia, Abdominal pain, Altered sensorium, Hepatomegaly, Splenomegaly, Hypoalbuminemia, Hyponatremia, Hyperbilirubinemia, Ards, Pneumonia, Shock, Severe thrombocytopenia, Aki and Outcome: group

Variables	Non severe scrub typhus	Severe scrub typhus	Total	Chi-square value	*P*-value
Sex					
Female	17	11	28	0.0112	0.9158
Male	19	13	32		
Duration of fever					
>14 days	4	4	8	0.3846	0.5351
7–14 days	32	20	52		
Maculopapular rash					
Absent	32	19	51	1.0675	0.3015
Present	4	5	9		
Edema					
Absent	23	21	44	4.1051	0.0427
Present	13	3	16		
Headache					
Absent	28	18	46	0.0621	0.8031
Present	8	6	14		
Tachypnoea					
Absent	28	22	50	2.0000	0.1573
Present	8	2	10		
Breathlessness					
Absent	35	14	49	14.5455	<0.0001
Present	1	10	11		
Cough					
Absent	24	14	38	0.4306	0.5116
Present	12	10	22		
Myalgia					
Absent	20	10	30	1.1111	0.2918
Present	16	14	30		
Abdominal pain					
Absent	30	19	49	0.1670	0.6828
Present	6	5	11		
Altered sensorium					
Absent	34	12	46	15.9006	<0.0001
Present	2	12	14		
Hepatomegaly					
Absent	32	19	51	1.0675	0.3015
Present	4	5	9		
Splenomegaly					
Absent	32	19	51	1.0675	0.3015
Present	4	5	9		
Hypoalbuminemia					
Absent	33	9	42	20.1190	<0.0001
Present	3	15	18		
Hyponatremia					
Absent	28	4	32	21.6071	<0.0001
Present	8	20	28		
Hyperbilirubinemia					
Absent	33	13	46	11.3199	0.00076
Present	3	11	14		
Ards					
Absent	36	22	58	3.1034	0.0781
Present	0	2	2		
Pneumonia					
Absent	36	19	55	8.1818	0.0042
Present	0	5	5		

(Contd...)

Table 1: (*Continued*)

Variables	Non severe scrub typhus	Severe scrub typhus	Total	Chi-square value	*P*-value
Shock					
Absent	36	15	51	15.8824	<0.0001
Present	0	9	9		
Severe thrombocytopenia					
Absent	36	21	57	4.7368	0.0295
Present	0	3	3		
AKI					
Absent	36	20	56	6.4286	0.0112
Present	0	4	4		
Outcome					
Death	0	3	3	4.7368	0.0295
Discharged	36	21	57		

Twenty-eight (46.7%) children's had hyponatremia. Fourteen (23.3%) children's had hyperbilirubinemia. Two (3.3%) children's had ARDS. Five (8.3%) children's had pneumonia. Four4 (6.7%) children's had myocarditis. Nine (15.0%) children were shocked. Three (5.0%) children's had severe thrombocytopenia. Four (6.7%) children's had AKI. Two (3.3%) children's had hepatic dysfunction. Two (3.3%) children's had meningoencephalitis. Three (5.0%) children were death and 57 (95.0%) children were discharged.

Bhat *et al.*[12] found that all children presented with fever. Other common symptoms were vomiting (56%), facial swelling (52%), cough (35%), abdominal pain (33%), breathlessness (29%), and decreased urine output (29%). High-grade fever (>101 oF) was recorded in 91% of children. Other common signs were hepatomegaly, splenomegaly, edema, tender lymphadenopathy, and hypotension, observed in 82%, 59%, 39%, 38%, and 36% of cases, respectively.

We found that in non-severe scrub typhus, 10 (27.8%) children's had eschar. In severe scrub typhus, 3 (12.5%) children's had eschar. Association of eschar versus. scrub typhus group was not statistically significant ($P = 0.1593$). Association of maculopapular rash versus. scrub typhus group was not statistically significant ($P = 0.3015$).

Khandelwal *et al.*[13] found that common clinical features were fever in 52 (100%), hepatomegaly in 34 (65.3%), nausea/vomiting in 23 (44.2%), lymphadenopathy in 22 (42.3%), abdominal pain, and splenomegaly each in 21 (40.3%), generalized swelling in 17 (32%) and headache in 12 (23%) patients. Eschar was seen in one patient only.

Lakshmanan *et al.*[14] found that of these 55 were boys and 28 were girls. Prolonged fever (100%), gastrointestinal symptoms (76%) such as vomiting, diarrhea, and abdominal pain, lymphadenopathy (96%), and hepatosplenomegaly (61%) were common signs and symptoms of pediatric scrub typhus. Only six patients had severe illnesses. Out of these 83 patients, eschar was seen in 50 (60%) patients.

Our study found that in non-severe scrub typhus, 8 (22.2%) children had headache. In severe scrub typhus, 6 (25.0%) children's had headache. Association of headache versus. scrub typhus group was not statistically significant ($P = 0.8031$).In non-severe scrub typhus, 8 (22.2%) children's had tachypnoea. In severe scrub typhus, 2 (8.3%) children's had tachypnoea. Association of tachypnoea versus. scrub typhus group was not statistically significant ($P = 0.1573$).

It was found that in non-severe scrub typhus, 1 (2.8%) child was breathlessness. In severe scrub typhus, 10 (41.7%) children were breathlessness. Association of breathlessness versus. scrub typhus group was statistically significant ($P = 0.0001$). Our study found that in non-severe scrub typhus, 12 (33.3%) children's had coughed. In severe scrub typhus, 10 (41.7%) children's had coughed. Association of cough versus. scrub typhus group was not statistically significant ($P = 0.5116$). In non-severe scrub typhus, 16 (44.4%) children's had myalgia. In severe scrub typhus, 14 (58.3%) children's had myalgia. Association of myalgia versus. scrub typhus group was not statistically significant ($P = 0.2918$). It was found that in non-severe scrub typhus, 6 (16.7%) children's had abdominal pain. In severe scrub typhus, 5 (20.8%) children's had abdominal pain. Association of abdominal pain versus. scrub typhus group was not statistically significant ($P = 0.6828$). Our study found that in non-severe scrub typhus, two (5.6%) children's had altered sensorium. In severe scrub typhus, 12(50.0%) children's had altered sensorium. Association of altered sensorium versus. scrub typhus group was statistically significant ($P < 0.0001$). Our study found that in non-severe scrub typhus, 4 (11.1%) children's had hepatomegaly. In severe scrub typhus, 5 (20.8%) children's had hepatomegaly. Association of hepatomegaly versus. scrub typhus group was not statistically significant ($P = 0.3015$). It was found that in non-severe scrub typhus, 4 (11.1%) children's had splenomegaly. In severe scrub typhus, 5 (20.8%) children's had splenomegaly. Association of splenomegaly versus. scrub typhus group was not statistically significant ($P = 0.3015$). It was found that in non-severe scrub typhus, 3 (8.3%) children's had hypoalbuminemia. In severe scrub typhus, 15 (62.5%) children's had hypoalbuminemia. Association of hypoalbuminemia versus. scrub typhus group was statistically significant ($P < 0.0001$).

Khandelwal *et al.*[13] found that among the laboratory parameters raised SGOT was seen in 49 (94.2%), raised SGPT in 41 (78.8%), thrombocytopenia in 46 (88.4%),

leucopenia in 12 (23%) and leukocytosis in 11 (21.1%) patients.

It was found that in non-severe scrub typhus, 8 (22.2%) children's had hyponatremia. In severe scrub typhus, 20 (83.3%) children's had hyponatremia. Association of hyponatremia versus. scrub typhus group was statistically significant ($P < 0.0001$). It was found that in non-severe scrub typhus, 3 (8.3%) children's had hyperbilirubinemia. In severe scrub typhus, 11 (45.8%) children's had hyperbilirubinemia. Association of hyperbilirubinemia versus. scrub typhus group was statistically significant ($P = 0.00076$).

Our study found that association of ARDS versus. scrub typhus group was not statistically significant ($P = 0.0781$).

Zhao *et al*.[15] found that early recognition of the patients at risk of MODS would be helpful in providing timely management and reducing mortality. The patients were classified into MODS present (64 cases, 14.3%) or MODS absent (385 cases, 85.7%). Multivariate logistic regression analyses revealed that the prognostic factors for MODS included skin rash.

In non-severe scrub typhus, 36 (100.0%) children's were discharged. In severe scrub typhus, 3 (12.5%) children were death and 21 (87.5%) children were discharged. Association of outcome versus. scrub typhus group was statistically significant ($P = 0.0295$).

CONCLUSION

We found that duration of fever was higher in severe scrub typhus than non severe scrub typhus disease in children. It was found that the presence of breathlessness was significantly associated with severe scrub typhus than non-severe scrub typhus. The present study showed that altered sensorium was significantly higher with severe scrub typhus than non-severe scrub typhus. We also found that leukocytosis, hypoalbuminemia, hyponatremia, and hyperbilirubinemia were significantly related with severe scrub typhus than non-severe scrub typhus disease in children. It was found that morbidity and mortality were higher with severe scrub typhus disease in children.

Scrub typhus should be considered in the differential diagnosis of acute febrile illness associated with gastrointestinal symptoms, hepatosplenomegaly, and lymphadenopathy including those with organ dysfunctions such as hepatitis, thrombocytopenia, MODS, meningitis, or ARDS. Empirical treatment for scrub typhus may be given in cases with strong clinical suspicion.

Symptoms of scrub typhus are quite non-specific. The presence of these factors should alert the physician about the impending life-threatening complications and should warrant intensive care monitoring, treatment, or referral to tertiary care center. Early recognition of the disease is a very important as any delay in treatment can lead to severe morbidity and high mortality.

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How to cite this article: Ray S, Basu S, Jana D. A Prospective Study of Clinical Profile and Laboratory Diagnosis Which Predicts the Severity of Scrub Typhus in Children. Int J Sci Stud 2022;9(12):20-25.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Comparison of Three Methods of Biofilm Detection by Clinically Significant Coagulase Negative Staphylococci

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Abstract

Introduction: Coagulase negative staphylococci (CoNS) have risen from commensal or laboratory contaminants to pathogens causing variety of infections. Their meager nutritional requirements and ability to withstand various physical and chemical agents have made CoNS a successful pathogen. One of the main virulence factor associated with CoNS infections is biofilm formation. Biofilm helps CoNS adhere to surfaces and escapes the assault by immune mechanisms and antibiotics. The estimation of biofilm will help identify pathogenic CoNS.

Aims: The aim of the study was to determine clinically significant CoNS and to ascertain their virulence using qualitative and quantitative methods of biofilm detection.

Material and Methods: A total of 82 clinically significant isolates were identified for the study. These isolates were segregated into two groups – Isolates with definite clinical significance (Group A – 45 isolates), and isolates with doubtful significance (Group B – 30 isolates). Qualitative methods Congo red agar method and Tube method were employed. Quantitative detection of biofilm was detected by microtiter plate method.

Results: More sensitive and quantitative were microtiter plate method. In Group A, 21 were moderate biofilm producers and 14 were strong biofilm producers. In Group B, eight out of 30 were moderate biofilm producers and six were strong biofilm producers. The comparison of the three methods showed that microtiter plate method was more sensitive in detection and quantitative assessment of biofilm. Statistical significance of difference between Group A and Group B isolates was found to be statistically significant, *P* value being 0.004.

Conclusions: Methods employed are cost-effective and need minimal training of laboratory staff. The detection of biofilm production will help differentiate pathogenic and commensal CoNS. The reporting of biofilm will help the clinician to plan the appropriate line of therapy.

Key words: Biofilm, Coagulase negative staphylococci, CONS, Congo red agar, Microtitre plate method, *Staphylococcus epidermidis*

INTRODUCTION

Coagulase negative staphylococci (CoNS) were considered as commensals and until recently their isolation in clinical samples would merely mean contamination. However, over a period of time, CoNS have established themselves as pathogens. The role of CoNS as nosocomial pathogens has been documented over the past five decades. This increase is mainly due to the increase in use of devices in patient care and increasing population of immunocompromised people. CoNS are successful in establishing themselves as pathogens mainly due to their ability to adhere to surface of medical devices, form biofilms, and their non-fastidious nature. The most common species implicated in human infections are *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Staphylococcus hemolyticus*, *Staphylococcus lugdunensis*, *Staphylococcus hominis*, *Staphylococcus warneri*, *Staphylococcus cohnii*, *Staphylococcus simulans*, *Staphylococcus schleiferi*, *Staphylococcus warneri,* and *Staphylococcus capitis*. CONS are implicated in

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

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variety of conditions which include Bacteremia, native and prosthetic valve endocarditis, urinary tract infection, ophthalmic infections, prosthetic joint infections, catheter-related urinary tract infections, and device associated infection (CSF shunts, indwelling CSF catheters, intrathecal pumps, and ventriculostomy sites). The abundance of CoNS in the skin and mucous membrane of the patient and the deadly combination of multidrug resistant CoNS strain and its transmission by hands of health-care workers make CoNS a successful nosocomial pathogen. The capacity to adhere to polymer surfaces and consequent biofilm production adds to the pathogenicity of CoNS.[1,2,3,4]

Biofilm and CoNS

Biofilms are communities of microorganisms that stick together or to the surfaces by production of extracellular matrix comprising of polysaccharides and proteins.[5] In the initial phase, bacterium attaches to surfaces by the use of non-specific factors such as hydrophobicity and surface charge. Bacterium may also adhere to surfaces through cell wall teichoic acids and proteins, such as autolysins or cell wall associated proteins that interfere with collagen, fibronectin, or other matrix proteins.[6] After this initial phase of adherence comes the stage of actual biofilm formation where the bacteria produce factors helping in cell to cell contact. The most commonly isolated CONS; *S. epidermidis* produces polysacchride intracellular adhesion (PIA). PIA comprises of ß-1, 6-linked glucose aminoglycan substituted with different side groups. Other factors that mediate biofilm are surface associated proteins, accumulation associated proteins (Aap), and biofilm associated proteins (Bap/Bhp). CoNS in hospital environment or in device associated infections differ from the commensal CoNS. Nosocomial CoNS form thick multilayered biofilms on polymers or metals.

The differentiation of CoNS with respect to its biofilm may help in assessing the impact of CoNS in relation to device associated infections. Studies done in the past indicate that clinically significant bloodstream isolates of CoNS produced slime.[7,8,9,10] Among the slime producers, *S. epidermidis* was the most prevalent species.[8,11] Nearly, 40–50% of CoNS isolates from clinical specimens can be slime producers.[11,12,13,14] Bacterial films produced by a standard slime producing strain of CoNS on plastic tissue culture plates varied with the type of fixative.[15] The incidence of biofilm production by *S. saprophyticus* is comparatively less than *S. epidermidis*.[16] The percentage of slime-producing CoNS ranged from 20% in peritoneal fluid to 66% in CSF.

A number of tests are available to detect slime production by staphylococci. The methods include microtiter plate (MTP) method,[17] Tube method (TM),[18] Congo red agar,[2,19] bioluminescent assay, and light or fluorescence or confocal microscopic examination.

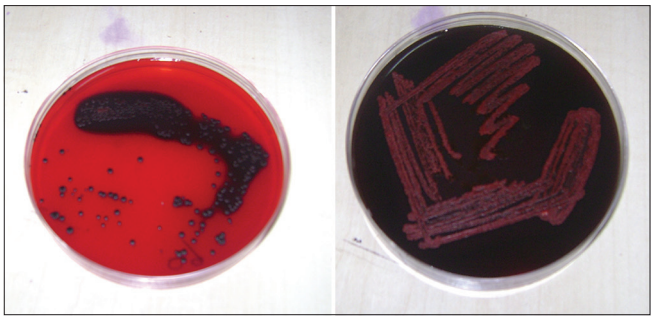

Figure 1: *Staphylococcus epidermidis* biofilm by congo red agar method

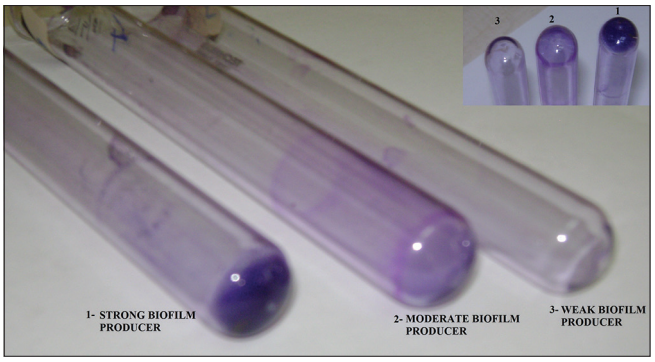

Figure 2: Biofilm procdution by *Staphylococcus epidermidis* using tube method

Figure 3: Biofilm procdution by *Staphylococcus epidermidis* using microtitre plate method

The adherence of CoNS to smooth surfaces has been estimated by measuring the optical densities of stained bacterial films adherent to the floors of plastic MTPs. The optical densities of bacterial films adherent to plastic MTPs act as a quantitative model for the study of the adherence of CoNS to medical devices. This may correlate with pathogenesis of infections in the presence of medical devices. The modified tissue culture plate method was most sensitive (96.2%), specific (94.5%), and accurate (97.3%) in terms of discriminating between biofilm producers and non-producers. In the case of TM, though the strong

biofilm producers could be easily detected, the difficulty in differentiating between moderate and weak biofilm forming isolates affected its performance in terms of sensitivity (77.9%), specificity (96.0%), and accuracy (86.8%). The Congo read agar method showed very little correlation with corresponding methods and the parameters of sensitivity (7.6%), specificity (97.2%), and accuracy (51.3%) were very low.[18] The tissue culture plate or MTP method also has the advantage of being a quantitative model to study the adherence of staphylococci on biomedical devices.[19]

SUBJECTS AND METHODS

The study was conducted to determine the ability of CoNS to form biofilms. This was studied employing two different qualitative methods, namely, Congo red agar method[7] and TM.[18] Quantitative detection of biofilm (adherence) was detected by microtiter plate method.[17]

In this study, 337 isolates of CoNS were isolated from clinical samples.[18] Two hundred and fifty-five samples were ruled out of the study as contaminants. A total of 75 isolates were considered as clinically significant isolates based on clinical and laboratory parameters and were taken up for the study. These isolates were segregated into two groups – Isolates with definite clinical significance (Group A) and isolates with doubtful significance (Group B). Group A comprised of 45 isolates of *S. epidermidis* and Group B comprised of 30 isolates of *S. epidermidis*.

Modified Congo red agar method – The Congo red test is based on the ability of this dye to stain polysaccharides black. Hence, if a strain is able to synthesize capsular polysaccharide and if the Congo red is incorporated in the culture medium, the colony will be black in color (Freeman *et al.* 1989). The media comprised of Trypticase soy broth, 5% sucrose, agar 3%, and Congo red dye 0.4%. The test cultures were inoculated on the Congo red agar plates and incubated aerobically for 24–48 h. Different concentrations of agar (2% and 3%) were tested with varying concentration of Congo red dye (0.2%, 0.4%, and 0.8%) and were tried. About 3% agar with 0.4% of Congo red stain gave consistent results with clear demarcation between biofilm forming and negative strains.[18]

The appearance of black colored colonies was indicative of biofilm formation and isolates producing black colonies were considered as strong biofilm producers. Weak biofilm producers produced dark pink colonies. Non-biofilm producers were seen as red and dry colonies (Figure 1).

TM – Test isolates were inoculated in Trypticase soy broth and incubated overnight at 37°C. After incubation, the tubes were decanted and washed thrice with phosphate buffer saline (pH 7.3). The tubes were air dried and stained with 0.1% crystal violet. After incubation for 10 min, the stain was decanted and washed with phosphate buffer saline. The tubes were dried in inverted position and observed for biofilm formation. Biofilm formation was considered positive when a visible film lined the wall and bottom of the tube. Tubes were examined and the amount of biofilm formation was scored as absent, weak, moderate, or strong. Ring formation at the liquid interface was not indicative of biofilm formation (Figure 2).

Microtiter plate method – Test isolates were inoculated in Trypticase soy broth. The tubes were incubated overnight aerobically at 37°c. The broth culture was diluted 1:10 with freshly prepared Trypticase soy broth. A 96 well microtiter plate with flat bottom was used. First three wells served as media controls without addition of cultures. Two known in house positive and two negative controls were inoculated in each plate. The test organism diluted in Trypticase soy broth was inoculated in triplicate and incubated overnight at 37°C aerobically. After 24 h of incubation on microtiter plate was washed 3 times with phosphate buffer saline to remove the free floating planktonic bacteria, 300 μl of methanol was added to each well and allowed to stand for 15 min. The excess of methanol was discarded and the wells of tissue culture plate were stained using 0.1% safranin stain. After 20 min of staining, the excess stain was discarded and washed with phosphate buffer saline. Finally, 33% glacial acetic acid was added to fix the stain. OD readings were determined using ELISA autoreader at a wavelength of 490 nm. The OD readings were considered as an index of bacteria adhering to surface and forming biofilms (Figure 3).

RESULTS

Three methods of detection of biofilm, namely, the modified Congo red agar method, TM, and microtiter plate method were evaluated. Many authors have suggested brain heart infusion agar with addition of 5% sucrose and 0.8% of Congo red dye. However, this combination of brain heart infusion agar, 5% sucrose, and 0.8% Congo red dye did not work well in our hands. Hence, Trypticase soy broth was tried instead of brain heart infusion agar. Various concentrations of Congo red dye (0.2%, 0.4%, and 0.8%), sucrose (2%, 4%, and 6%) and agar (2%, 3%, and 4%) were tried. A combination of Trypticase soy broth with 5% sucrose, 0.4% Congo red dye, and 3% agar gave satisfactory results. Using this method among Group A isolates, 34 of 45 isolates of *S. epidermidis* were found to be non-biofilm producers. Seven out of 45 isolates were weak biofilm producers, one isolate of *S. epidermidis* was

found to be moderate biofilm producer and four out of 45 isolates of *S. epidermidis* were found to be strong biofilm producers producing jet black crystalline colonies. Among Group B isolates, 22 out of 30 *S. epidermidis* were found to be non-biofilm producers (70%), five out of 30 isolates were categorized as weak biofilm producers, and three out of 30 isolates were strong biofilm producers. TM of assessment of biofilm was evaluated using 0.1% crystal violet stain. In Group A, 25 out of 45 isolates of *S. epidermidis* were found to be non-adherent, three out of 45 isolates of *S. epidermidis* were weak biofilm producers, nine out of 45 isolates of *S. epidermidis* were moderate biofilm producers, and nine out of 45 isolates of *S. epidermidis* were strong biofilm producers. In Group B, 11 out of 30 isolates of *S. epidermidis* were non-adherent, four out of 30 isolates were weak biofilm producers, ten out of 30 isolates of *S. epidermidis* were moderate biofilm producers, and six out of 30 isolates were strong biofilm producers. Both modified Congo red agar method and TM did not provide a quantitative analysis on biofilm production. The results of both these methods were prone to observer bias.

The more sensitive and quantitative method of estimation of biofilm production was by microtiter plate method. Two dyes, namely, 0.1% crystal violet and 0.1% safranin were tried. In our study, 0.1% safranin yielded better results. In Group A, 11 out of 45 isolates of *S. epidermidis* were found to be weak biofilm producers, 21 were moderate biofilm producers, and 14 were strong biofilm producers. In Group B, 17 out of 30 isolates of *S. epidermidis* were weak biofilm producers, eight out of 30 were moderate biofilm producers, and six were strong biofilm producers. The comparison of the three methods showed that microtiter plate method was more sensitive in detecting of biofilm and helps in quantitative assessment on the amount of biofilm formation.

Statistical significance of difference between Group A and Group B isolates of *S. epidermidis* with reference to the degree of biofilm production was assessed using Chi-square test and was found to be statistically significant, *P* value being 0.004.

DISCUSSION

CONS are ubiquitous in nature. Their presence in large numbers on the skin and their minimal nutritional requirements coupled with very potent virulence factors such as biofilm formation provides a survival advantage to this Gram-positive cocci. The increased use of indwelling devices and inadvertent use of antibiotics have helped this commensal become a potential pathogen. In the era of increasing immunocompromised population and emerging and re-emerging infections, CoNS has established itself as a pathogenic bacteria. The dilemma exists in differentiating commensal CoNS from the offending organism. Antibiotic resistance (MR-CoNS) alone cannot be taken into account for differentiating commensal from pathogenic CoNS as many of the commensal CoNS exhibit resistance to cefoxitin. The cost-effective alternative available is assessment of biofilm formation. Biofilm if present would mean that the antibiotics may not be fully effective as bacteria are not exposed to the action of antibiotic. The use of nucleic acid amplification techniques for detection of biofilm associated genes is costly, cumbersome, and need technical expertise which may not be available everywhere. Biofilm production is one of the major characters which help a commensal bacterium to become pathogenic under appropriate situations. Biofilms are communities of microorganisms that stick to each other or to the surfaces by production of extracellular matrix comprising of polysaccharides and proteins. First, the bacterium attaches to surfaces by the use of non-specific factors such as hydrophobicity and surface charge. Bacterium may also adhere to surfaces through cell wall teichoic acids and proteins, such as autolysins or cell wall associated proteins that interfere with collagen, fibronectin, or other matrix proteins. After this initial phase of adherence comes the stage of actual biofilm formation where the bacteria produce factors helping in cell to cell contact. The most commonly isolated CoNS, *S. epidermidis* produces PIA. PIA comprises of ß-1,6-linked glucose aminoglycan substituted with different side groups. Other factors that mediate biofilm are surface associated proteins, Aap,and Bap/Bhp. CoNS in hospital environment or in device associated infections differ from the commensal CoNS. Nosocomial CoNS form thick multilayered biofilms on polymers or metals.

Three methods of detection of biofilm, namely, the modified Congo red agar method, TM, and microtiter plate method were evaluated. Many authors have suggested brain heart infusion agar with addition of 5% sucrose and 0.8% of Congo red dye. However, this combination of brain heart infusion agar, 5% sucrose, and 0.8% Congo red dye did not work well in our hands. An alternative method using Trypticase soy broth was tried instead of brain heart infusion agar was tried. Various concentrations of Congo red dye (0.2%, 0.4%, and 0.8%), sucrose (2%, 4%, and 6%), and agar (2%, 3%, and 4%) were tried. A combination of Trypticase soy broth with 5% sucrose, 0.4% Congo red dye, and 3% agar gave satisfactory results.

The comparison of these three methods of biofilm production leads us to conclude that the biofilm detection by Microtiter plate method is more sensitive and also helps in qualitative assessment of biofilm formation. In our

study, 30.4% of isolates causing infections were strong biofilm producers.

CONCLUSION

The above mentioned methods are cost-effective and need minimal training of laboratory staff and do not require any special instruments. The procedure can be carried out along with the routine bacteriological workup of a laboratory. The detection of biofilm production will be an added tool in the hands of a microbiologist to differentiate pathogenic and commensal CoNS. The reporting of biofilm will help the clinician to plan the appropriate line of therapy. Routine reporting of biofilm will create an atmosphere where the microbiologist and clinician can join hands toward successful antibiotic stewardship.

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How to cite this article: Sheriff R. Comparison of Three Methods of Biofilm Detection by Clinically Significant Coagulase Negative Staphylococci. Int J Sci Stud 2022;9(12):26-30.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Effectiveness of Honey and *Aloe Vera* in the Treatment of Minor Aphthous Ulcer among Young Adults-A Single Blinded Randomized Clinical Trial

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Abstract

Background: Recurrent aphthous stomatitis (RAS) with a prevalence of 5–25% is one of the most prevalent oral mucosal diseases found worldwide. Herbal remedies have been advocated as an alternative method of therapy such as honey and *Aloe vera*. Therefore, the purpose of this analysis is to compare the effects of topical *A. vera* and honey on minor aphthous stomatitis ulcers.

Materials and Methods: This research consisted of 60 clinically diagnosed people with minor aphthous stomatitis diagnosed clinically.

Results: The reduction in the size of ulcer was little more in Group B (*A. vera*) as compared to Group A (honey) at visit 2 (0–3 day). However, the difference was statistically not significant at 1st Visit, 3rd and 7th Visit ($P > 0.05$).

Discussion: It has been detected that the main antibacterial activity in honey is due to enzymatically produced hydrogen peroxide in the honey. In the present study, pain level and burning sensations were assessed by VAS scores, which showed improvement in the honey group.

Conclusion: The present study revealed that both the remedies were effective in the treatment of aphthous ulcer. Although in this study, we found honey to be more effective than *A. vera* in the reduction of pain and burning sensation, further studies with larger sample size in a controlled environment need to be done to prove the same.

Key words: *Aloe vera*, Apthous ulcer, Burning sensation, Honey, Pain

INTRODUCTION

Recurrent aphthous stomatitis (RAS) etiology is very diverse and includes systemic, genetic, local, and immune factors, as well as food and chemical sensitivities, bacterial and viral agents.[1] Other etiological factors have also been suggested, such as stress, physical or chemical trauma.[2] For the treatment of RAU, antimicrobials, topical analgesics, immunosuppressive agents, anti-inflammatory agents, and laser therapy have all been used.[3] Herbal remedies have been advocated as an alternative method of therapy because of the potential adverse effects of steroid medication and the risk for the development of secondary oral candidiasis from long-term steroid use. Several herbal products for the promotion of wound healing have been investigated.[4] *Aloe vera* is a tropical plant grown in North Africa and most areas of Asia with succulent leaves which have been used for thousands of years as herbal medicine.[5] The healing property of *A. vera* has been highlighted by large number of studies. According to literature, the enhanced healing of *A. vera* is by increasing the flow of blood, which further results in increase in oxygenation.[6]

Honey is nectar extracted and collected by honey bees from several plants. In wound care, honey has major benefits, especially for the treatment of chronic and contaminated wounds.[7] Very few studies have been performed to show the effects of *A. vera* and honey on RAS. The purpose

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

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of this analysis is thus to compare the effects of topical *A. vera* and honey on minor aphthous stomatitis ulcers. This research consisted of 60 clinically diagnosed people with minor aphthous stomatitis diagnosed clinically. The entire sample was randomly divided into two groups with 30 patients each.

MATERIALS AND METHODS

From November 2018 to November 2019, this study was performed in the Public Health Dentistry Department. This research consisted of 60 clinically diagnosed people with minor aphthous stomatitis diagnosed clinically, who gave informed consent. Consent was also obtained from the Institutional Ethical Committee. The entire sample was randomly divided into two groups with 30 patients each. The subjects were provided with the honey and *A. vera* in similar colored containers. To measure the effectiveness of honey and *A. vera* gel in Group A and Group B respectively, patients were advised to spread a thin layer of *A. vera* and honey using sterile cotton applicator 4 times daily (after meals and at bedtime) for 7 days as a sole remedy without using any other medication. After both medications were applied, all patients were advised to avoid solid and liquid diets for 30 min. On the 3 day, the patients were recalled for follow-up and were again prescribed the medicine for 4 days following the aforementioned guidelines. Patients were recalled for further evaluation on the 7th day.

Inclusion Criteria

- The study involved patients who had a positive history of having similar oral mucosal ulcers for 3–4 months and ulcers for <48 h.
- Clinically diagnosed patients with chronic aphthous stomatitis measuring ≤5 mm in size in the oral cavity and who gave written consent for participation.
- Only single ulcers were considered for the study.

Exclusion Criteria

- The study excluded patients with a history of associated systemic disease.
- Cases of chronic aphthous stomatitis (major), lesions of herpetic form, numerous RAS lesions, and smoking.
- In addition, no consideration was given to patients with a history of hypersensitivity to honey or *A. vera*.

Clinical Parameters

The following clinical parameters have been recorded and evaluated.

a. Size of ulcers (in mm)-after starting treatment, ulcer size was recorded on every 3 day and 7th day/till the ulcer heals completely using a calibrated dental probe with millimeter marking.
b. Pain-Visual Analog Scale (0–10) was used to determine the intensity of pain.
c. Burning sensation-Visual analog scale (0–10) was also used to determine the intensity of burning sensation.

Statistical Analysis

The data were entered on the Microsoft Excel spreadsheet and imported for statistical analysis into the Statistical Package for Social Sciences (SPSS) version 22. Frequency distribution tables were created, and the chi square test was used to determine variable's association. Mean and standard deviations were measured for ulcer size, VAS scores for pain and burning sensation, and significant differences were observed by applying the Independent t-test. Statistical significance was set at $P < 0.05$.

RESULTS

Table-1 is showing the age group distribution of Group A (Honey) and Group B (*Aloe vera*).

Table 2 is showing that in Group A (Honey), out of 60 patients 24 (40%) patients were Male and 36 (60%) patients were Female. In group B, 28 (46.7%) patients were male and 32 (53.3 %) patients were female. There was no significant difference in gender of patients in between Group A (Honey) and in Group B (*A. vera*) ($P > 0.05$).

- Table 3 is revealing that the most common site in Group A (Honey) was Lateral border of tongue that is in 40% (24 out of 60), followed by 30% in both of Buccal Mucosa (18 out of 60) and Labial Mucosa (18 out of 60).
- In group B, the Labial Mucosa was the most common site-40% (24 out of 60), followed by Lateral border of tongue that is in 33.3% (20 out of 60) and 26.7 % (16 out of 60) in Buccal Mucosa.
- There was no significant difference in site of ulcer in between Group A (Honey) and Group B (*A. vera*) ($P > 0.05$).

Table 4 shows that the size of the ulcer ranges from 1 to 4 mm in diameter in the entire sample. The mean and standard deviation were compared for the size of ulcer. The mean size of ulcer in patients receiving honey at the time of visit 1(i.e., 0th day) was 3.70 ± 0.47 mm; whereas, at visit 3 (i.e., 7th day), the ulcer had disappeared completely.

The mean size of ulcer receiving *A. vera* at the time of visit 1 was 3.63 ± 0.49 mm; whereas, at visit 3, the ulcer had disappeared completely. The reduction in the size of ulcer was little more in Group B (*A. vera*) as compared to Group A (honey) at visit 2 (0–3 day). However, the difference was statistically not significant at Ist Visit, 3rd and 7th Visit ($P > 0.05$).

Table 5 reveals the mean VAS score for Pain in Group A (Honey) at the time of visit 1 was 6.10 ± 0.84, reduced to 0 at visit 7th day visit. The mean VAS score for Pain in Group B (*A. vera*) at the time of visit 1 was 6.25 ± 1.00, and reduced to 0 at visit 7th day visit. The change in VAS scores for pain at visit 2 (0–3 day) in Group A, that is, patients receiving Honey group was little bit more as compared to Group B (*A. vera*), and the difference was statistically significant at 3rd day Visit ($P < 0.05$), and the difference was not significant at 1st and 7th day Visit ($P > 0.05$).

Table 6 reveals the mean VAS score for burning sensation in Group A (Honey) at the time of visit 1 was 7.70 ± 0.79 and reduced to 0 at 7th visit day. The mean VAS score for burning sensation in Group B (*A. vera*) at the time of visit 1 was 7.87 ± 0.76, and reduced to 0 at visit 7th day visit. The change in VAS scores for burning sensation at visit 2 (0–3 day) in Group A, that is, patients receiving Honey was more as compared to Group B(*A. vera*), and the difference was statistically significant at 3rd Visit ($P < 0.05$), difference was not significant at 1st and 7th Visit ($P>0.05$).

DISCUSSION

The most common ulcerative disease of the oral mucosa is RAS. Its diagnosis and management constitute common problems in dental practice. In the present study, herbal medicine like honey and *A. vera* has been examined as an alternative topical therapy for minor RAS.

In folk medicine, herbal products have been used for many years. Van Ketel in 1892 first recognized the antibacterial property of honey. When diluted at least 9 times, honey has adequate antibacterial potency to stop bacterial development due to its acidic pH, hygroscopic properties, and hydrogen peroxide.

Glucose+H2O+O2→Gluconic acid+H2O2.

It has been detected that the main antibacterial activity in honey is due to enzymatically produced hydrogen peroxide in the honey. It also induces the release of cytokines, tumor necrosis factors alfa, interleukin 1 (IL 1) and IL 6 by monocytes in cell culture, which triggers the immune response to infection.[8]

In the present study, pain level and burning sensations were assessed by VAS scores, which showed improvement in the honey group. These findings were in contrast with the studies conducted by Yelmaz *et al.*[7] and Pandharipande *et al.* where the researchers found that Curcumin group showed statistically significant result as compared to honey.[9] However, Haddad *et al.* conducted a study which was in agreement to our study which concluded that honey was safe and effective in reducing minor aphthous ulcer pain,

Table 1: Age group distribution of Group A (Honey) and Group B (*Aloe vera*)

Age (in years)	Group A (Honey)		Group B (*Aloe vera*)	
	Number	Percentage (%)	Number	Percentage (%)
<20	10	16.7	6	10.0
20–29	31	51.6	32	53.3
≥30	19	31.7	22	36.7
Total	60	100.0	60	100.0

X^2=3.273, *P*-value=0.195 (not significant)

Table 2: Gender distribution of Group A (Honey) and Group B (*Aloe vera*)

Gender	Group A (Honey)		Group B (*Aloe vera*)	
	Number	Percentage (%)	Number	Percentage (%)
Male	24	40.0	28	46.7
Female	36	60.0	32	53.3
Total	60	100.0	60	100.0

X^2=0.857, *P*-value=0.836 (not significant)

Table 3: Site of ulcer in Group A (Honey) and Group B (*Aloe vera*)

Site	Group A (Honey)		Group B (*Aloe vera*)	
	Number	Percentage	Number	Percentage
Buccal Mucosa	18	30.0	16	26.7
Labial Mucosa	18	30.0	24	40.0
Lateral border of tongue	24	40.0	20	33.3
Total	60	100.0	60	100.0

X^2=0.669, *P*-value=0.716 (not significant)

Table 4: Size of ulcer in Group A (Honey) and Group B (*Aloe vera*) at different visit.

Size	Group A (Honey)	Group B (*Aloe vera*)	t-value	*P*-value
	Mean±SD	Mean±SD		
1st Visit	3.70±0.47	3.63±0.49	0.770	0.443
3rd Visit	1.50±0.50	1.30±0.65	1.891	0.061
7th Visit	0.0±0.0	0±0	0	0

SD: Standard deviation

Table 5: VAS score for pain in Group A (Honey) and Group B (*Aloe vera*) at different visit

Visit	VAS score for pain		t-value	*P*-value
	Group A (Honey) Mean±SD	Group B (*Aloe vera*) Mean±SD		
1st day Visit	6.10±0.84	6.25±1.00	0.890	0.376
3rd day Visit	1.40±0.68	1.73±0.76	2.558	0.012*
7th day Visit	0±0	0±0	0	0

*statistically significant, SD: Standard deviation

Table 6: VAS score for burning sensation in Group A (Honey) and Group B (*Aloe vera*) at different visit

Visit	VAS score for burning sensation		t-value	*P*-value
	Group A (Honey)	Group B (*Aloe vera*)		
	Mean±SD	Mean±SD		
1st day Visit	7.70±0.79	7.87±0.76	1.156	0.250
3rd day Visit	1.80±0.76	2.08±0.50	2.429	0.017*
7th day Visit	0±0	0±0	0	0

*statistically significant, SD: Standard deviation

size and erythema.[10] The effect of honey on the healing of oral ulcers conducted by Mohamed *et al.* was also in accordance to our study. In this research, the investigators concluded that the ulcerations disappeared entirely after 3 days of honey dressing therapy.[11]

Different mechanisms have been proposed to elucidate the wound-healing effects of *A. vera*, including keeping the wound moist, increasing epithelial cell migration, rapid maturation of collagen, enhancing collagen cross-linking, and increasing blood supply. Glucomannan and gibberellin, two constituents of *A. vera*, interact with growth factor receptor on fibroblasts, stimulating their activity and proliferation, to increase collagen synthesis. The anti-inflammatory effects of aloe are related to its inhibition of the cyclooxygenase pathway of arachidonic acid and reduction of prostaglandin E2. The anti-inflammatory compound, C-glycosyl chromone, was isolated from *A. vera* extracts, as well as the peptidase bradykinase which breaks down bradykinin that induces pain.[2]

A research to explain the safety and efficacy of acemannan, a polysaccharide isolated from *A. vera*, in the treatment of oral aphthous ulceration, was performed by Bhalang *et al.* The investigators concluded that acemannan's efficacy was superior to that of control in reducing ulcer size and pain which was in contrast to our study.[4]

In terms of pain and burning sensations, *A. vera* gel had a better response as concluded by Giroh *et al.*, which was in contrary to our study.[12] However, our study was in agreement with a study conducted by Babaee *et al.* which concluded that the healing times for pain were significantly lower in the *A. vera* treated group.[5]

In the present study, honey and *A. vera* were compared for the treatment of minor aphthous ulcer. *A. vera* was more efficient in the reduction of ulcer size; however, the results were not statistically significant. In the reduction of pain and burning sensations, honey scored better as compared to *A. vera*, and the results were statistically significant.

CONCLUSION

The present study revealed that both the remedies were effective in the treatment of aphthous ulcer. These herbal remedies, therefore, can be recommended for use in place of conventional treatment modality in the management of RAS as they are cost-effective, easily available and possibly no adverse effects. Although in this study, we found honey to be more effective than *A. vera* in the reduction of pain and burning sensation, further studies with larger sample size in a controlled environment need to be done to prove the same.

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How to cite this article: Mir H, Shivalingesh KK, Ashraf W, Srivastava D, Saleem A. Effectiveness of Honey and *Aloe Vera* in the Treatment of Minor Aphthous Ulcer among Young Adults-A Single Blinded Randomized Clinical Trial. Int J Sci Stud 2022;9(12):31-34.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Clinical Profile of Patients with Uveitis – A Hospital-based Study

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Abstract

Background: Uveitis is a worldwide prevalent disease that mainly affects young people. It is one of the leading causes of visual impairment and blindness. The underlying etiology of uveitis shows a wide regional variation. An understanding of the clinical and microbial profile of uveitis helps us in improved management of this sight-threatening condition.

Material and Methods: Our study is a prospective, observational, and hospital-based study of 70 patients suffering from uveitis, conducted in the Eye Department of R. D. Gardi Medical College, Ujjain, India. All patients underwent comprehensive ocular examination as well as laboratory investigation.

Results: In Our study, 70 patients with uveitis were enrolled. About 45 (64.3%) were male patients while 25 (35.7%) were females. Anterior uveitis was found in 39 patients (55.7%). About 21 patients (30%) had posterior uveitis and 8 patients (11.4%) had intermediate uveitis. Acute anterior uveitis was found in 30 patients (76.9%) whereas 6 patients (15.4%) had chronic uveitis and only 3 patients (7.7%) had recurrent uveitis. The majority of patients 32 (82%) had non-granulomatous uveitis and 7 patients (18%) had granulomatous uveitis. On examination, 53 eyes (46.14%) had visual acuity between 3/60 and 6/60. About 36 eyes (25.71%) had visual acuity between 6/36 and 6/24. Only 7 eyes (5%) had visual acuity <3/60, it shows that uveitis causes visual impairment as well as blindness.

Conclusion: Anterior uveitis was the most common type of uv eitis found in our study. Timely detection and appropriate management are recommended to prevent prolonged ocular morbidity and blindness.

Key words: Blindness, Choroid, Ciliary body, Inflammation, Uveitis

INTRODUCTION

The uveal tissue which comprises of iris, ciliary body, and choroid is a very vascular tissue which is predisposed to inflammation. Inflammation of uveal tract is called uveitis and prevalence of uveitis varies world over from region to region. This uveitis can be anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis.

Uveitis affects both males as well as females only the ratio may vary. The prevalence of uveitis varies in different regions of the world. Uveitis is the fifth most common cause of visual loss in the developed world accounting for nearly 10–15% cases of total blindness.[1]

The etiology of uveitis ranges from non-infectious cause to infectious causes. Tuberculosis, syphilis, arthritis, toxoplasmosis, sarcoidosis, and autoimmune disease are some of the leading causes of uveitis. Systemic diseases play an important role in etiology of uveitis. Uveitis is a disease if not detected and treated properly will result in blindness. World over it has been found that uveitis contributed to 0.7% of worldwide blindness.[2]

In this study, we aim to understand the epidemiology, the predisposing factors, clinical profile, and the outcome of uveitis patients presenting to our hospital, which is a tertiary care hospital located in the state of Madhya Pradesh in Central India.

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

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MATERIALS AND METHODS

Our study is a prospective, observational, and hospital-based study conducted in the Department of Ophthalmology, R. D. Gardi Medical College, Ujjain, Madhya Pradesh, India, over a period of 1.5 years. Prior approval for the study was obtained from the Institutional Ethics Committee. Seventy patients found to be suffering from uveitis were included in the study.

A written informed consent was obtained from each patient. The preliminary data of patients such as name, age, sex, and occupation were recorded first. Occupation was specially noted as uveitis cases are directly linked to occupation of patients. A detailed history was taken, with regard to the chief complaint, past history, and any other disease.

All the patients underwent a detailed and comprehensive ocular examination. Ophthalmic examination included a record of the unaided visual acuity as well as the best corrected visual acuity. Slit lamp examination was done specially cornea to look for corneal edema, corneal opacities, Keratic precipitates. KP's if found were recorded as to whether they were fine KP's, mutton fat, and old or fresh KP's. The anterior chamber was specially examined for presence of aqueous cells, flare, hypopyon, or hyphema. Iris was examined for color, pattern, synechiae, iris atrophy, rubeosis iridis, and iris bombe. IOP was noted, fundus examination was done. After detailed examination of patients, we use Standardization of Uveitis Nomenclature (SUN) for knowing the type of uveitis.

Laboratory investigations such as CBC, ESR, blood sugar, urine routine microscopy, RA factor, VDRL, ELISA, TORCH, and X-ray were done.

Patients were properly diagnosed according to the type of uveitis and proper treatment was initiated in all patients depending on underlying etiology. All patients were regularly follow-up at 1 week and 4 week interval.

Exclusion Criteria

- Patients with central corneal opacity where examination of uveal tissue is not possible will be excluded from the study.
- Pregnant females will be excluded from the study.
- Patients with phthisis bulbi and atrophic bulbi will be excluded from the study.
- Patients who are on treatment with cytotoxic drugs or immune suppressant's will be excluded from the study.

RESULTS

Our study was a hospital-based study, in which, 70 patients suffering from uveitis were included in the study. We found that uveitis was more predominantly seen in male patient 45 (64.3%) as compared to 25 (35.7%) female patients [Table 1]. About 42 patients (60%) belong to age group of 20–40 years which suggests that uveitis is a disease affecting young individuals predominantly. In our study, 23 (32.9%) patients were laborers, 22 (31.4%) patients were field workers, and 42 (60%) patients belong to low socioeconomic group.

In our study, 39 patients (55.7%) had anterior uveitis, 21 patients (30%) had posterior uveitis, and 8 patients (11.4%) had intermediate uveitis. Only 2 patients (2.9%) had panuveitis [Table 2]. Out of 39 patients with anterior uveitis, 30 patient (76.9%) had acute anterior uveitis whereas 6 (15.4%) patients had chronic and only 3 (7.7%) had recurrent uveitis [Figure 1]. We also found that 32 (82%) patients had non-granulomatous uveitis and 7 (18%) had granulomatous uveitis. We found that 29 eyes (20.71%) showed fine KPs while large mutton fat KPs were seen in 7 eyes (5%). Old KPs were seen in 3 eyes (2.14%). In our study, 15 eyes (10.7%) had aqueous cells

Table 1: Sex distribution of patients in study group (*n*=70 patients)

Sex	Number of patients	Percentage
Male	45	64.3
Female	25	35.7
Total	70	100

Table 2: Type of uveitis in patients in our study group (*n*=70 patients)

Diagnosis	Number of patients	Percentage
Anterior	39	55.7
Intermediate	8	11.4
Posterior	21	30
Panuveitis	2	2.9
Total	70	100

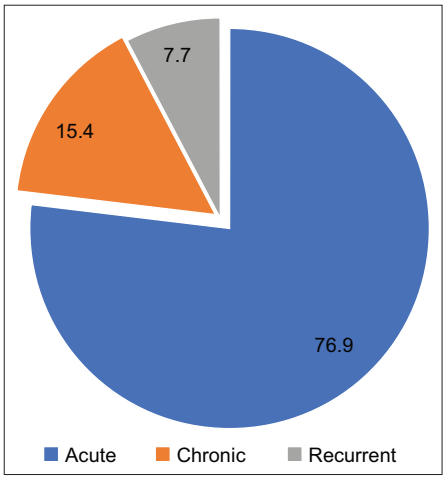

Figure 1: Distribution of Anterior Uveitis in study group(n = 39)

between 1 and 5, 11 eyes (7.85%) had cells between 6 and 15. About 6 eyes (4.28%) had aqueous cells between 26 and 50 and only three eyes had cells over 50. Faint flare was present in 5 eyes (3.5%) whereas moderate flare was present in 19 eyes (13.57%) where as intense flare was present in 11 eyes (7.85%). About 7 eyes (5%) showed presence of thick broad based synechiae whereas 15 eyes (10.7%) showed thin synechiae. On fundus examination, 5 eyes (3.57%) showed patches of active choroiditis, 11 eyes (7.85%) showed patches of active chorioretinitis, and 3 eyes (2.14%) showed evidence of snow banking. Vitritis was present in five eyes. On examination, 53 eyes (46.14%) had visual acuity between 3/60 and 6/60. About 36 eyes (25.71%) had visual acuity between 6/36 and 6/24. Only 7 eyes (5%) had visual acuity <3/60, it shows that uveitis causes visual impairment as well as blindness ($P = 0.016$).

We found that 41 patients (58.6%) were suffering idiopathic uveitis, 5 patients (7.1%) showed autoimmune disorder as underlying etiology. Bacterial and viral infections were seen in 8 (11.4%) and 4 (5.7%) patients, respectively [Table 3]. Thirty-nine patients suffering from anterior uveitis were managed with topical steroids and cycloplegic, whereas all 21 patients suffering from posterior uveitis required systemic steroids as well as topical steroids for the management [Table 4]. In our study, out of 70 patients, 5 (7.14%) patients had cystoid macular edema, 7 (10%) patients had glaucoma while phthisis bulbi and retinal detachment were seen in one patient, respectively [Figure 2].

DISCUSSION

Uveal tract is composed of iris, ciliary body, and choroid and is highly predisposed to inflammation on account of its vascularity. The prevalence of uveitis varies worldwide and requires numerous investigations to reach the etiological diagnosis.

In our study, we found that uveitis is a disease affecting young individuals predominantly, 42 patients (60%) belong to age group of 20–40 years. Similarly Filho *et al.* in their study found that 7% patients were up to 16 years of age, 28.5% were between 17 and 40 years of age while 63.5% were over 40 years of age and suggested that uveitis is more common in adults between 17 and 60 years of age.[3]

We found that uveitis was more predominantly seen in male patient 45 (64.3%) as compared to 25 (35.7%) female patients. This result of our study proves the fact that there is a significant male predisposition for uveitis. This result is comparable to Ayanru *et al.* in which they found that male to female ratio was 2:1. Furthermore, Venkatesh *et al.* in their study of 161 patients found 114 patients to be male as compared to 47 females suffering from uveitis. This clearly suggests about male preponderance for uveitis.[4] Uveitis can occur in any individual irrespective of the type of occupation.

In our study, 39 patients (55.7%) had anterior uveitis, 21 patients (30%) had posterior uveitis, and 8 patients (11.4%) had intermediate uveitis. Only 2 patients (2.9%) had panuveitis according to the SUN classification. Similarly Ebrahim *et al.* in their study show anterior uveitis (49.6%) as the most common form of uveitis followed by posterior uveitis (15.5%). They also quoted in their study that idiopathic uveitis was the most common form of anterior uveitis.[5] Furtjermore, Singh *et al.* studied 1233 patients and found anterior uveitis as the most common type of uveitis.[6]

Uveitis is the most complicated disease which has got a very varied etiology and in many cases it is impossible to

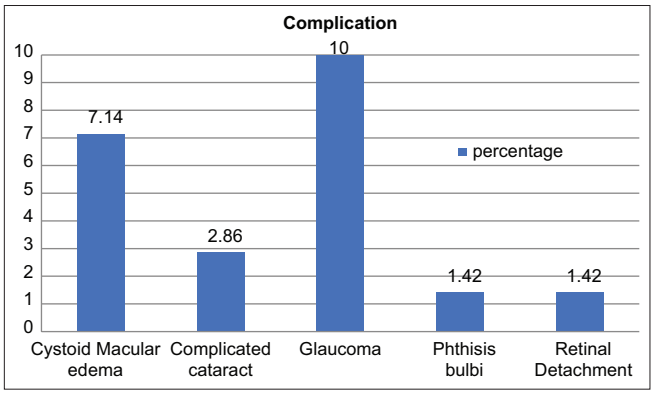

Figure 2: Distribution Of complication associated with uveitis in study group (n = 70)

Table 3: Etiology of uveitis in patients in study group (*n*=70 patients)

Etiology	Number of patients	Percentage
Idiopathic	41	58.6
Autoimmune disorder	5	7.1
Bacterial infection	8	11.4
Viral infection	4	5.7
Fungal infection	0	0
Post-surgical uveitis	4	5.7
Toxoplasma	6	8.6
Post-traumatic	2	2.9
Total	70	100

Table 4: Management done of patients in study group

Management done	Ant.	Inter.	Post.	Pan.	Total	Percent
Topical steroids with cycloplegics	37	0	0	0	37	52.8
Steroid injection (periocular/intraocular)	2	5	0	0	7	10
Topical steroids with systemic steroids	0	3	21	2	26	37.2
Total	39	8	21	2	70	100

find an etiology associated with development of uveitis. These etiological agents may be infective or non-infective in nature. Anesi and Foster in their study of anterior uveitis quoted that a large number cases are idiopathic and many cases are attributed to herpes simplex virus or trauma to eye.[7] Furthermore, Khairallah *et al.* in their study found that frequency of idiopathic uveitis was 37.9%. The result of above mentioned study correlates with our study where we found out of 39 patients of anterior uveitis 28 (71.79%) were idiopathic, 5 out of 8 patients (62.5%) patients of intermediate uveitis were idiopathic and 8 (38.09%) out of 21 patients with posterior uveitis had toxoplasmosis as underlying etiology.[2]

In our study, anterior uveitis was seen in 39 patients out of 70 patients and most of these patients showed evidence of keratin precipitates, aqueous cells, and flare. About 29 (20.71%) showed fine KPs while large mutton fat KPs were seen in 7 eyes (5%). Old KPs were seen in 3 eyes (2.14%). This shows that fine KPs were more common in patients with anterior uveitis. About 15 eyes (10.7%) had aqueous cells between 1 and 5. About 11 eyes (7.85%) had cells between 6 and 15 (4.28%), 6 eyes (4.28%) had aqueous cells between 26 and 50, and only 3 eyes (2.14%) had cells over 50. Ninety-three eyes did not have any aqueous cells. Seven eyes showed presence of thick broad based synechiae whereas 15 eyes (10.7%) showed presence of thin synechiae. On fundus examination, 5 eyes (3.57%) showed patches of active choroiditis, 11 eyes (7.85%) showed patches of active chorioretinitis, and 3 eyes (2.14%) showed evidence of snow banking. Vitritis was present in five eyes. On examination, 53 eyes (46.14%) had visual acuity between 3/60 and 6/60. About 36 eyes (25.71%) had visual acuity between 6/36 and 6/24. Only 7 eyes (5%) had visual acuity <3/60, it shows that uveitis causes visual impairment as well as blindness ($P = 0.016$). These results of our study collaborate with the results of Hogan *et al.* (1959).[8]

Thirty-nine patients suffering from anterior uveitis were managed with topical steroids and cycloplegic, whereas all 21 patients suffering from posterior uveitis required systemic steroids as well as topical steroids for the management [Table 4]. In our study, out of 70 patients, 5 (7.14%) patients had cystoid macular edema, 7 (10%) patients had glaucoma while phthisis bulbi and retinal detachment were seen in one patient, respectively. This result of our study suggests that steroids play a very strong role in the management of uveitis and this result of our study commensurate with the study of Bartlett and Jaanus.[9] We recommend that steroids should be used properly in the management of uveitis but special precaution taken regarding rise of intraocular pressure.

CONCLUSION

Our study was a hospital-based study, in which, 70 patients suffering from uveitis were included in the study. We found that uveitis was more predominantly seen in male patient 45 (64.3%). About 42 patients (60%) belong to age group of 20–40 years. In our study, 42 (60%) patients belong to low socioeconomic group. In our study, 39 patients (55.7%) had anterior uveitis, 21 patients (30%) had posterior uveitis, and 8 patients (11.4%) had intermediate uveitis. Only 2 patients (2.9%) had panuveitis. We found that 41 patients (58.6%) were suffering idiopathic uveitis, 39 patients suffering from anterior uveitis were managed with topical steroids and cycloplegic, whereas all 21 patients suffering from posterior uveitis required systemic steroids as well as topical steroids for the management.

Our study recommends that patients with uveitis should undergo comprehensive ocular and systemic investigations to find the underlying etiology. All the patients must be managed according to the type of uveitis, they are suffering from and a watch should be kept on all the possible likely complications which will help a lot in preventing blindness from uveitis.

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How to cite this article: Mehta M, Mehta S, Gupta A. Clinical Profile of Patients with Uveitis – A Hospital-based Study. Int J Sci Stud 2022;9(12):35-38.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Is 1-Point Fixation at Zygomatic Buttress Adequate in Non-Comminuted Zygomatic Complex Fracture? A Prospective Comparative Study

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Abstract

zygomatic complex fractures generally require open reduction internal fixation through several approaches. The aim of this study was to compare 1-point fixation at zygomatic buttress area with 2-point fixation at frontozygomatic (FZ) and zygomatic buttress areas in non-comminuted zygomatic complex fractures. Ten patients (Group 1) were treated with 2-point fixation and other 10 patients (Group 2) were treated with 1-point fixation. Both the groups were postoperatively assessed for unfavorable scars, palpability of plates, bony movement in the FZ area, and satisfaction with surgical outcomes. Postoperatively, all patients had satisfactory approximation of fractured segments when evaluated radiographically at 1 week and 6 weeks interval in both the groups. All patients from Group 1 had complaint of palpability of plates at FZ region and four patients from Group 1 were unsatisfied with the scar. One-point fixation in the zygomatic buttress area can avoid unsightly scars, palpability of plate, and high satisfactory surgical outcomes in non-comminuted zygomatic fractures.

Key words: Zygomatic complex fractures, 1-point fixation, Zygomatic buttress, Tripod fracture

INTRODUCTION

Zygomaticomaxillary tripod fracture is relatively common and generally requires open reduction-internal fixation through several approaches. Conventionally, the fixation of zygomaticomaxillary complex (ZMC) fractures is done at 3 points – the zygomatic buttress, infraorbital rim, and the frontozygomatic (FZ) suture area. A number of surgeons have used 2 of the 3 points at zygomatic buttress and FZ suture area for fixation of the ZMC fractures and have reported satisfactory results. In this fixation method, there is a need for extraoral lateral eyebrow incision and that may leave unsightly scar, palpability of plates, and risk of penetration into anterior cranial fossa and swelling resulting from severed muscles and soft tissues as they are thin in FZ area. When plates are removed in case of infection, repeated lateral eyebrow incision may give more chances to leave external scar.

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

However, 1-point fixation in ZM buttress region gives sufficient stability and can avoid external unsightly scars or palpability of plates or screws and give high satisfactory surgical outcome. In addition, when plates or screws are removed through intraoral vestibular approach and leave no external scars.[1-4]

MATERIALS AND METHODS

The study was approved by the Institutional Ethical Board and the consent was obtained from all the patients included in the study. Retrospective data of 10 patients with ZMC fractures treated by 2-point fixation between 2015 and 2017 were assigned as Group 1. Prospective patients with ZMC fractures from November 2017 to May 2019 (18 months) treated with 1-point fixation were assigned as Group 2 [Figure 1]. All cases with blowout fracture of the orbital floor, extraocular muscle entrapment or herniation of periorbital fat, and comminuted fracture were excluded from this study.

All patients were operated under general anesthesia to expose ZM buttress through intraoral approach and reduction was done by intraoral elevation. Reduction was

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Figure 1: Group-1: Patient treated with 2-point fixation at frontozygomatic suture and zygomatic buttress regions. 1. a – Pre-operative; 1. b – Intraoperative; 1. c – Post-operative

Figure 2: Group-2: Patient treated with 1-point fixation at zygomatic buttress region. 2. a – Pre-operative; 2. b – Intraoperative; 2. c – Post-operative

considered satisfactory when the gap at the fractured site/s was not more than 1 mm, malar projection was symmetrical when viewed from birds view and worms view, and the occlusion was stable. Fixation was achieved using suitable 2 mm (4 holed) titanium L-shaped plate and monocortical screws (2/6 mm) and then intraoral wounds were sutured [Figure 2].

RESULTS

All the patients included in the study underwent post-operative clinical, radiographic, and photographic evaluation at 1 week and 6 weeks interval.

All 20 patients had satisfactory approximation of fractured segments when evaluated radiographically at 1 week and 6 weeks interval. Five patients required post-operative IMF from Group 1 while none from Group 2. Five patients including two female patients were unsatisfied with the acceptability of scar at lateral eyebrow region at the end of 1 week. At the end of 6 weeks, four patients were unsatisfied with the scar. One patient from each group had the asymmetry of malar projection persisted for 6 weeks and the esthetics was considered unsatisfactory. All patients from Group 1 had the plates at the FZ suture palpable. In Group 1, enophthalmos was persistent in one patient till the end of 6 weeks with no other orbital complication.

One patient had wound dehiscence at the lateral eyebrow incision site at 1 week and secondary wound closure occurred by the end of 6 weeks.

DISCUSSION

The ZMC is an essential component of the facial configuration. Because of its location, it is subjected to trauma more often than any other element of the face except the nose. Although some injuries will involve an isolated orbital rim or antral wall fracture, most injuries will include the zygomatic bone and thus the term "zygomaticomaxillary." The consequences of such injuries may involve ocular function, orbital shape, facial esthetics, and mandibular mobility.[5]

ZMC fractures requiring open reduction and internal fixation (ORIF) are often treated through several approaches. Although different treatment modalities have been advocated for the management of ZMC fractures, at present, ORIF with non-compression plates is considered the standard of care. Few randomized prospective clinical studies have compared the stability of zygoma after 3-, 2-, and 1-point fixation with miniplates.

Fractured zygomatic segment has six possible directions of motion: Translation across x, y, and z axis; rotation about x, y, and z axis. A miniplate applied across the FZ suture will resist translatory movement and also rotation along an axis perpendicular to the plane of miniplate because of the width of the plate. At the same time, it will offer little resistance to rotation along the linear axis of the plate.[6,7] However, 1-point fixation in ZM buttress region gives sufficient stability and can avoid external unsightly scars or palpability of plates or screws, short surgical period and gives high satisfactory surgical outcome.[1,4,8-10]

Mean vertical change improved from 1.28° to 0.58° ($P < 0.001$), and the mean horizontal change improved from 1.71° to 0.92° ($P < 0.001$). Post-operative vertical movement of the zygoma was not significantly affected by communition of the inferior orbital wall, zygomaticofrontal process displacement, or comminution of the ZMB area and zygomatic arch ($P > 0.05$ for each). However, comminution of the ZMB area had an adverse effect on horizontal movement of the zygoma ($P = 0.03$).[4] Displacement at the fractured site of <2 mm at the end of 1 week and 6 weeks was considered satisfactory fixation.[11] One-point fixation at the ZMC gives 3-point alignment and sufficient rigidity when the fractures are not comminuted.[2,3,12-14] None of the patients complained of bony movement and pain in the FZ area with no fixation in the FZ area.[1] In our study, we found satisfactory fixation in all the patients.

Kim *et al.* in their study of 30 patients reported that 16 patients (53%) were unsatisfied with the scar at the lateral brow incision site. Unsightly scars are a serious problem because maxillofacial fractures occur mostly in young adults.[1,4]

In our study, the patients and the surgeon's perception of the scar at the end of 1 week and 6 weeks was evaluated. We had 4 patients (40%) who were unsatisfied with the scar at the FZ suture region at the end of 6 weeks in Group I. In the same patients, the surgeon found the scar to be satisfactory in nine patients and unsatisfactory in one patient. In Group II, no patients had complaints about visibility of scar.

In our study, we evaluated the malar projection both clinically and on photographic evaluation. Displacement of zygoma <2 mm in either anteroposterior or lateral direction was considered satisfactory. We had malar asymmetry in 1 patient (10%) in Group I treated with 2-point fixation and 1 patient (10%) in Group II treated with 1-point fixation.

In our study, palpability of the plates was evaluated clinically, we had 10 patients (100%) with palpability of plates at the FZ region in Group I and no patient (0%) had palpability of plates at the FZ region in Group II as closed reduction was carried out.

However, because the ZM buttress plays a key role in withstanding contraction of the masseter muscle and supporting zygoma, rigid fixation at the ZMB is important in the treatment of tripod fractures.

The advent of miniplate osteosynthesis revolutionized the treatment of ZMC fractures. Rigid internal fixation is the modality with the most reliable results. However, the surgical approaches to the fracture sites, the optimal time schedule for operation, and the number of sites for miniplate osteosynthesis are still a focus of debate. Stability and accuracy of the reduction are also debated with regard to the number of plates applied to the facial buttresses.

CONCLUSION

No definitive conclusions have been made evaluating the efficacy of 1-point fixation for the management of ZMC fractures. Hence, this study was designed to evaluate the efficacy of 1-point fixation for ZMC fractures and the results were compared with 2-point fixation in terms of stability of fixation, esthetic, orbital, and functional parameters, along with the evaluation of post-operative complications.

Surgeons should utilize 1-point fixation at ZM buttress in all cases of non-comminuted ZMC fractures to achieve equivalent results without an additional fixation site with its

associated complications, additional cost of hardware, and prolonged operative time. This technique allows sufficient stability, avoids external scar, and palpability of plates at FZ suture area and less invasive. The use of single miniplate in the management of isolated ZMC fractures is, therefore, quite justified as the advantages far outweigh the disadvantages. However, this fixation is not feasible in patients with (1) comminuted zygomatic fractures; (2) incomplete or unsatisfactory reduction through a buccogingival incision; and (3) fractures combined with orbital complications.

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How to cite this article: Tadas K, Halli R. Is 1-Point Fixation at Zygomatic Buttress Adequate in Non-Comminuted Zygomatic Complex Fracture? A Prospective Comparative Study. Int J Sci Stud 2022;9(12):39-42.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

A Study on Clinical and Pathological Aspects of Salivary Gland Swellings

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Abstract

Introduction: Salivary gland swellings can be broadly classified into inflammatory, non- inflammatory, and neoplastic swellings. Most of primary epithelial tumors occur in parotid glands. About 7–11% in the submandibular glands are malignant. Less than 1% occurs in the sublingual glands. About 9–23% occur in the minor glands. About 15–30% of tumors of parotid gland are malignant. About 40% in the submandibular gland are malignant. About 50% in the minor salivary gland are malignant. About 70–90% of sublingual glands are malignant. Appropriate treatment management should be planned earlier, local excision for benign neoplasm, or radical surgery for malignancy. With non-neoplastic lesions, metastasis and lymph proliferative disorders, conservative management, chemotherapy, or radiotherapy might be respectively preferable.

Methodology: In this study, an attempt has been made to present various conditions of the salivary gland swellings admitted in surgical units in tertiary centers Osmania General Hospital and surgical oncology unit MNJ Cancer Hospital, Hyderabad, from December 2018 to November 2020. All the cases are analyzed and compared to the data available in literature.

Results: The incidence of salivary gland swellings is highest in the 3rd and 4th decade of life. In this series, 17 patients were male (34%) and 33 (66%) patients were female, with male-to-female ratio of 1:1.9. The most common salivary swellings were seen in parotid gland with 32 cases (64%). Out of 50 cases, 18 cases (36%) were due to non-inflammatory and non-neoplastic swellings. Out of which, 14 cases (77.8%) were due to submandibular sialolithiasis and 3 cases (16.7%) were due to ranula of the sublingual glands and 1 (5.6%) case of sublingual retention cyst. Thirty-two cases (64%) were due to salivary gland tumors. Out of 32 tumors, pleomorphic adenoma is seen in 27 cases (84.4%), Warthin's tumor is seen in 4 cases (12.5%), and one case of adenoid cystic carcinoma (3.1%). Incidence of tumors was highest in the parotid. Incidence of benign tumors is 31 (96.8%) and malignant tumors are 1 (3.1%). Patients presented with a history of swellings varying from 4 months to 5 years. Swelling is the most common symptom. Pain was the second most common symptoms. Pain was noticed in 52% of the cases and tenderness was noticed in 56% of the cases. History and physical examination complement fine-needle aspiration cytology (FNAC) and help in diagnosis. FNAC is the reliable and sensitive tool for diagnosing salivary gland tumors. There was an overall diagnostic accuracy of 100%. Surgery is the treatment in all the cases of salivary swelling. Out of 32 cases of parotid tumor, superficial parotidectomy was done in 28 cases (87.5%) and total parotidectomy for 4 cases (12.5%). For all the submandibular gland lesions, sialadenectomy was done. Sublingual gland excision was carried out for three cases of ranula and one retention cyst excision. Wound infection was the major complication with 5 cases (62.5%) and three cases of facial nerve paralysis (37.5%) were observed. The results were compared with previously published studies, with respect to objectives.

Conclusion: With proper diagnosis and appropriate treatment Salivary gland swelling can be cured with almost 100%. Successful management of the salivary gland neoplasm depends on accurate clinical assessment and diagnosis, with appropriate use of fine-needle aspiration and computed tomography or magnetic resonance imaging. Since the most malignant tumors are asymptomatic and long-standing benign tumors can undergo malignant change, community awareness and early referral are necessary, as prognosis is good if treated early.

Key words: Salivary gland tumors, Pleomorphic adenoma, Fine-needle aspiration cytology, Parotid, Submandibular gland, Sublingual glands, Ranula, Sialoadenectomy, Facial nerve paralysis

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

INTRODUCTION

Salivary gland swellings can be broadly classified into inflammatory, non-inflammatory, and neoplastic swellings such as benign tumors or malignant tumors and connective tissue diseases such as hemangioma, lymphangioma, and neurofibroma, and other autoimmune diseases

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such as Sjogren's syndrome and Mikulicz disease.[1] Accurate pathological diagnosis is necessary for proper management of neoplastic disorders. Most of primary epithelial tumors occur in parotid glands. About 7–11% in the submandibular glands are malignant. Less than 1% occurs in the sublingual glands. About 9–23% occur in the minor glands. About 15–30% of tumors of parotid gland are malignant. About 40% in the submandibular gland are malignant. About 50% in the minor salivary gland are malignant. About 70–90% of sublingual glands are malignant.[2-4] These salivary gland tumors usually occur in adults with a female predominance. Warthin's tumor (WT) is more common in males.[5,6] Fine-needle aspiration cytology (FNAC) of salivary gland tumors is helpful to both the patient and the clinician. Its immediate results, accuracy, lack of complications, and economy are favorable. Appropriate treatment management can be planned earlier, local excision for benign neoplasm, or radical surgery for malignancy. With non-neoplastic lesions, metastasis and lymph proliferative disorders, conservative management, chemotherapy, or radiotherapy might be respectively preferable.[7] In this study, an attempt has been made to present various conditions of the salivary gland swellings admitted in tertiary centers Osmania General Hospital and MNJ Cancer Hospital, Hyderabad,

Table 1: Incidence of salivary gland swellings at Osmania General Hospital and MNJ Cancer Hospital, Hyderabad

Year	Total no. of surgical admissions	Total no. of salivary gland swellings	Percentage
December 2018–November 2020	12,361	50	0.4%

Table 2: Age incidence of salivary gland swellings

Age	Frequency	Percent
Below 20	6	12
21–30	4	8
31–40	15	30
41–50	9	18
51–60	6	12
61–70	8	16
71–80	2	4

Table 3: Correlation of age with HPE

Age in years	Number (%)	Histopathologic examination result				Total	*P* value
		Pleomorphic adenoma of parotid	Warthin's tumor of parotid	Adenocarcinoma parotid	Retention cyst		
Below 20	Count	4	0	0	1	5	0.052
	% within age in years	80.0%	0.0%	0.0%	20.0%	100.0%	
	% within histopathologic examination result	14.8%	0.0%	0.0%	100.0%	15.2%	
21–30	Count	1	0	0	0	1	
	% within AGE IN YEARS	100.0%	0.0%	0.0%	0.0%	100.0%	
	% within histopathologic examination result	3.7%	0.0%	0.0%	0.0%	3.0%	
31–40	Count	8	1	0	0	9	
	% within AGE IN YEARS	88.9%	11.1%	0.0%	0.0%	100.0%	
	% within histopathologic examination result	29.6%	25.0%	0.0%	0.0%	27.3%	
41–50	Count	6	0	0	0	6	
	% within AGE IN YEARS	100.0%	0.0%	0.0%	0.0%	100.0%	
	% within histopathologic examination result	22.2%	0.0%	0.0%	0.0%	18.2%	
51–60	Count	2	2	0	0	4	
	% within age in years	50.0%	50.0%	0.0%	0.0%	100.0%	
	% within histopathologic examination result	7.4%	50.0%	0.0%	0.0%	12.1%	
61–70	Count	5	1	0	0	6	
	% within age in years	83.3%	16.7%	0.0%	0.0%	100.0%	
	% within histopathologic examination result	18.5%	25.0%	0.0%	0.0%	18.2%	
71–80	Count	1	0	1	0	2	
	% within age in years	50.0%	0.0%	50.0%	0.0%	100.0%	
	% within histopathologic examination result	3.7%	0.0%	100.0%	0.0%	6.1%	
Total	Count	27	4	1	1	33	
	% within age in years	81.8%	12.1%	3.0%	3.0%	100.0%	
	% within histopathologic examination result	100.0%	100.0%	100.0%	100.0%	100.0%	

from December 2018 to November 2020. All the cases are analyzed and compared to the data available in literature.

Aims and Objectives of the Study

The aims and objectives of the study were as follows:

1) To study the age and sex distribution among cases of salivary gland swellings.
2) To study the mode of clinical presentation of various salivary gland swellings.
3) To study the accuracy of FNAC in the diagnosis of salivary gland swellings
4) To study the methods of current surgical treatment of salivary glands swellings.

METHODOLOGY

This prospective study of consecutive cases of salivary gland swellings is based on 50 cases admitted in various surgical units in Osmania General Hospital and MNJ Cancer Hospital, Hyderabad, from December 2018 to November 2020. Fifty cases of salivary gland swelling are studied and data are presented here, which were analyzed and conclusion drawn, presented in tabular form with explanatory notes below each table. The statistics has been compared with different standard studies conducted on same subject by various authors around world.

Table 4: Sex incidence

Sex	No. of patients	Percentage
Male	17	34
Female	33	66

Inclusion Criteria

- All patients admitted to surgical and surgical oncology wards of Osmania General Hospital and MNJ Cancer Hospital, Hyderabad, with salivary gland swellings due to obstructions of the salivary duct and neoplasia.
- Patients who are willing for investigation and treatment were included in the study.

Exclusion Criteria

- All salivary gland swellings arising as a result of congenital conditions.
- Salivary gland swellings arising as a result of inflammation (e.g., mumps and parotitis). Salivary swellings associated with systemic diseases (Sjogren's syndrome).

All patients admitted were evaluated by documenting the history, through clinical examination, routine laboratory investigations, and specific investigations such as FNAC and X-rays of mandible were done for all patients in the study group. After evaluation of the swellings by clinical examination and by specific investigations, a surgical plan was formulated. The final decision was taken peroperatively by the surgeon. The required specimen was sent for histopathological examinations. Appropriate antibiotics and analgesics are administered postoperatively for all cases. Drainage tube was removed when the drain was <20 ml and sutures were removed on the 5th day. The adjuvant treatment was decided depending on the final HPE report. Different modalities of treatment adopted in this study are as follows: (1) Surgery alone and (2) surgery and post-operative radiotherapy. The follow-up period

Table 5: Correlation of sex with HPE reports

Sex	Number (%)	Histopathologic examination result				Total	*P* value
		Pleomorphic adenoma of parotid	Warthin's tumor of Parotid	Adeno carcinoma parotid	Retention cyst		
Male	Count	8	1	1	1	11	
	% within sex	72.7%	9.1%	9.1%	9.1%	100.0%	
	% within histopathologic examination result	29.6%	25.0%	100.0%	100.0%	33.3%	
Female	Count	19	3	0	0	22	0.232
	% within sex	86.4%	13.6%	0.0%	0.0%	100.0%	
	% within histopathologic examination result	70.4%	75.0%	0.0%	0.0%	66.7%	
Total	Count	27	4	1	1	33	
	% Within Sex	81.8%	12.1%	3.0%	3.0%	100.0%	
	% within histopathologic examination result	100.0%	100.0%	100.0%	100.0%	100.0%	

of these patients ranged from 1 month to 10 months. All patients were asked for follow-up after 15 days of surgery then every month to detect morbidity and recurrence. Long-term follow-up is necessary to study the actual prognosis of the patients and tumor recurrence and to know the ideal mode of treatment for each condition which was not possible in this study. Statistical analysis was done with SPSS software.

Table 6: Mode of clinical presentation

Mode	No. of cases	Percentage
Swelling	50	100.0
Pain	26	52.0
Fever	3	6.0
Increased salivation	1	2.0
Tenderness	28	56.0
Fixity of swelling	7	14.0
Ear lobe elevation	24	48.0
Deep lobe involvement	5	10.0
Facial nerve paralysis	3	6

Table 7: Site for various salivary gland swellings

No. of cases	Parotid	Submandibular	Sublingual
50	32	14	4
%	64	28	8

RESULTS

A total number of admission to the department of general surgery and surgical oncology were 12,361, 50 cases of salivary gland swellings were admitted during November 2018–August 2020. This constitutes 0.4% of total admissions as shown in Table 1.

In our study, age of the patients varied from 18 years to 80 years, average age of the patient was 40 years. The case of lowest age group, that is, 18 years was of non-inflammatory swelling and the case of highest age, that is, 80 years was of tumor swelling as shown in Table 2.

On descriptive statistical analysis, of age in year with HPE reports, *P* value was found to be = 0.052, which was > 0.050 and hence *P* value was not significant. It indicates not significant between age group and HP reports in our study. Graph 1 shows the age incidence with hpe and table-3 shows the correlation of age with hpe.

In our study of salivary gland swelling due to various causes, out of 50 cases, 17 (34%) cases were of male and 33 (66%) cases of female. as shown in Table 4. On descriptive statistical analysis, of sex distribution with HPE reports,

Table 8: Correlation of site with HPE reports

Gland involvement	Number (%)	Histopathologic examination result				Total	*P* value
		Pleomorphic adenoma of parotid	Warthin's tumor of parotid	Adenocarcinoma parotid	Retention cyst		
Parotid	Count	21	4	1	0	26	
	% within gland involvement	80.8%	15.4%	3.8%	0.0%	100.0%	
	% within histopathologic examination result	77.8%	100.0%	100.0%	0.0%	78.8%	
Submandibular duct	Count	6	0	0	0	6	
	% within gland involvement	100.0%	0.0%	0.0%	0.0%	100.0%	
	% within histopathologic examination result	22.2%	0.0%	0.0%	0.0%	18.2%	<0.001
Sublingual gland	Count	0	0	0	1	1	
	% within gland involvement	0.0%	0.0%	0.0%	100.0%	100.0%	
	% within histopathologic examination result	0.0%	0.0%	0.0%	100.0%	3.0%	
Total	Count	27	4	1	1	33	
	% within gland involvement	81.8%	12.1%	3.0%	3.0%	100.0%	
	% within histopathologic examination result	100.0%	100.0%	100.0%	100.0%	100.0%	

Table 9: Various causes of salivary gland swellings

Lesions	No. of cases	Percentage
Non-inflammatory, non-neoplastic	18	36.0
Neoplastic	32	64.0
Total	50	100.0

Table 10: Incidence of non-inflammatory, non-neoplastic swellings

Lesions	No. of cases	Percentage
Sialolithiasis	14	77.8
Ranula	3	16.7
Retention cyst	1	5.6

Table 11: site involvement in non-inflammatory, non-neoplastic swellings

No. of cases	Parotid		Submandibular		Sublingual	
	R	L	R	L	R	L
18	-	-	6	8	4	-

Table 12: Incidence of benign and malignant salivary gland tumors

Lesions	No. of cases	Percentage
Benign	31	96.88%
Malignant	1	3.1%

Table 13: Incidence of various salivary glands tumors

Lesion	No. of cases	Percentage
Pleomorphic adenoma	27	84
Warthin tumor	4	14
Adenoid cystic carcinoma	1	2
Total	32	100

Table 14: Correlation of FNAC and histopathology

Lesion	No. of cases	FNAC (%)	Biopsy (%)
Pleomorphic adenoma	27	100	100
Warthin tumor	4	100	100
Adenoid cystic Ca.	1	100	100

Table 15: Surgical procedures adopted for various salivary gland swellings

Procedures	No. of cases	Percentage
Excision of submandibular gland	15	30%
Superficial parotidectomy	26	52%
Total parotidectomy	5	10%
Excision ranula	3	6%
Retention cyst	1	2%
Total	50	100

Table 16: Post-operative complications

Nature of complications	No. of patients	Percentage
Facial nerve paralysis	3	37.5
Wound infection	5	62.5

Table 17: Occupation

Occupation	Frequency	Percent
Agri	5	10.0
Coolie	3	6.0
EMPL	1	2.0
Farmer	7	14.0
H.W	23	46.0
STU	6	12.0
Vendor	5	10.0

Table 18: Incidence per year of salivary gland tumors in different series

Series	No. of tumors	Period of study	No. of cases per year
Potdar *et al.*,[8]1969	188	10	18
Gupta *et al.*,[9] 1975	113	21	05
Khazanchi *et al.*,[10] 1988	88	6	15
Fennetal,[11] 1982	57	15	04
Renehan *et al.*,[12] 1996	1194	45	27
Present study	32	0.9	28

Table 19: Incidence of sialolithiasis in various studies

Series	No. of cases	parotid	Submandibular	Sublingual
Antognini *et al.*,[13] 1971	396	8.3	91.4	0.3
Pizzirani *et al.*,[14] 1985	102	7.8	92.2	-
Lustmann *et al.*,[15] 1990	245	4.5	94.3	0.4
Present study	14	-	100	-

Table 20: Frequency of benign and malignant salivary tumors in different series

Series	No. of tumors	Benign	Malignant
Foote *et al.*,[16] 1954	730	68.30%	31.70%
Skolnik *et al.*,[17] 1977	435	59340%	30.60%
Khazanchi *et al.*,[10] 1988	88	63.60%	36.40%
Renehan *et al.*,[12] 1996	1194	80.00%	0.00%
Present study	32	96.8%	3.1%

Table 21: Location of various tumors in different series

Series	Parotid	Submandibular	Sublingual
Budhraja *et al.*,[18] 1974	82.10%	12.40%	5.5%
Sharkey *et al.*,[19] 1977	80.50%	6.00%	9.0%
Everson *et al.*,[20] 1985	72.90%	10.70%	16.4%
Renehan *et al.*,[12] 1996	91.00%	4.0%	5%
Present study	100%	-	-

Table 22: Incidence of superficial and deep lobe involvement of parotid gland tumors in different series

Series	Total no. of cases	Superficial	Deep
H. Leverstein *et al.*, 1997[21]	245	192 (78.3%)	54 (22%)
H. Laccourreve *et al.*,[22] 1994	229	118 (51.5%)	111 (48.4%)
Present series	32	27 (88.46%)	5 (11.53%)

Table 23: Average age incidence of salivary gland tumors in different series

Series	Average age in years	
	Benign	Malignant
Potdar *et al.*,[8] 1969	40	49
Budhraj *et al.*,[18]1947	41	41
Skolnik *et al.*,[17]1977	45	56
Khazanchi *et al.*,[10] 1988	44	50
Renehan *et al.*[12] 1996	55	59
Present study	47	80

Table 24: FNAC comparison with pathologic diagnosis in different series

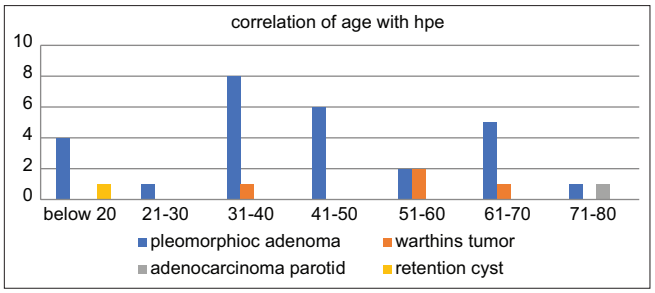
Series	Benign	Malignant
Frable and Frable, 1982[23]	91%	92%
Spiro *et al.*, 1974[24]	98%	93%
Present study	100%	100%

P value was found to be = 0.232 (>0.05) so not significant as represented in Table 5. Graph 2 shows the correlation of sex with hpe reports.

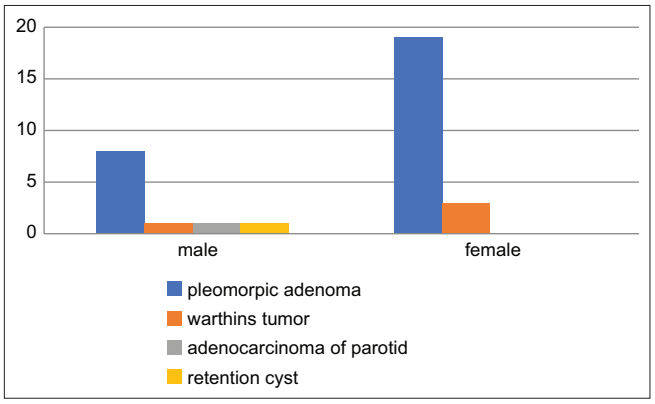
In our study, all cases presented with symptoms of swelling (100%), 52% (26) presented with pain. About 56% (28) presented with tenderness. Five cases were with deep lobe involvement (10%), 24 cases of ear lobe elevation (48%). Facial nerve paralysis occurred in 3 cases (6%) as shown in Table 6. Graph 3 below shows the various mode of clinical presentation.

In our study, 64% (32 cases) were found in the parotid gland, 28% of cases (14) in submandibular gland, and 8% of cases (4) in the sublingual gland as shown in Table 7 and Graph 4.

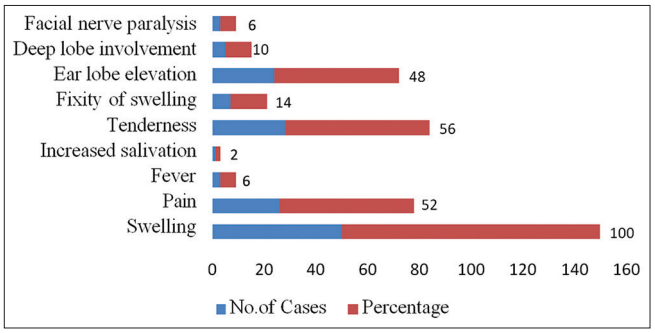
On the descriptive statistical analysis of gland involvement with HP reports, *P* value was found to be = to 0.000 (<0.01) highly significant. Therefore, correlation of gland involvement with HP reports was highly significant shown in Graph 5 and Table 8.



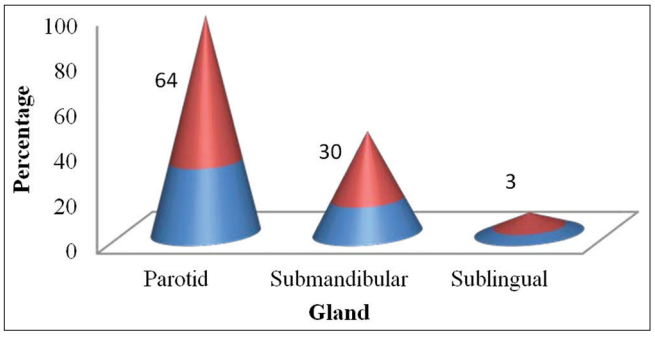
Graph 1: Age incidence with HPE



Graph 2: Correlation of sex with HPE reports

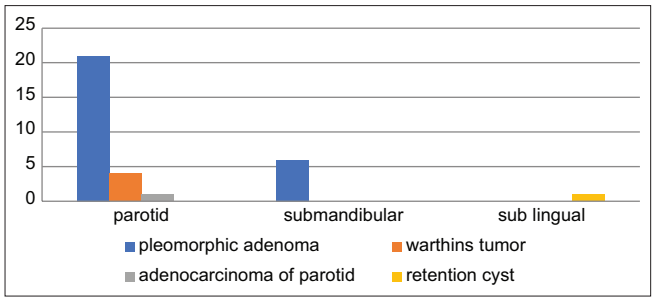


Graph 3: Mode of clinical presentation

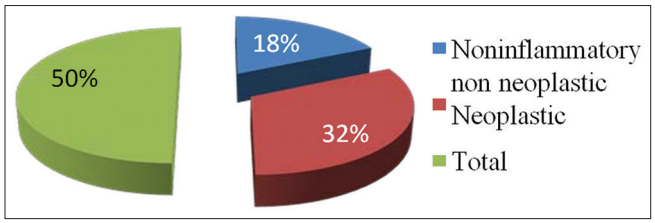


Graph 4: Sites of various salivary swellings

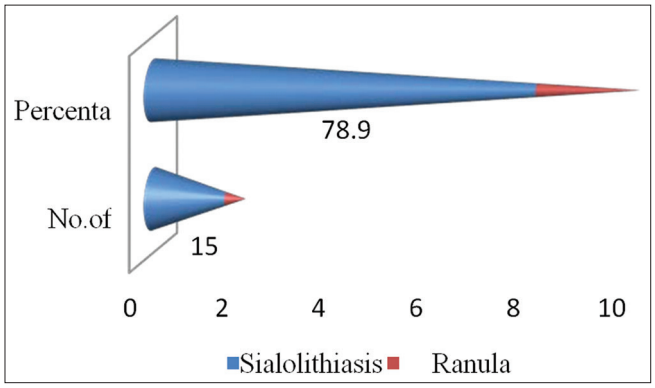
In our study, out of 50 cases, neoplastic lesions of 64.0% (32 cases) and non-inflammatory, non-neoplastic lesions of 36% (18 cases) were seen as shown in Table 9 and Graph 6.



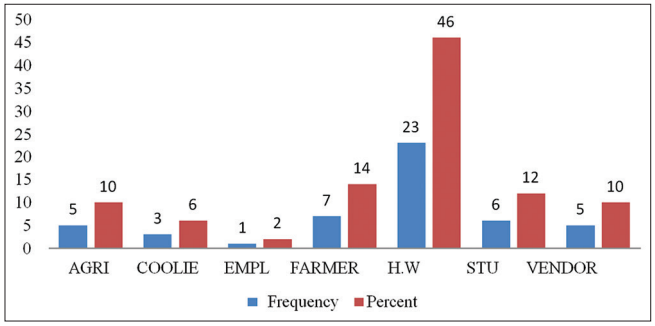
Graph 5: Correlation of site with HPE reports



Graph 6: Causes of salivary swellings



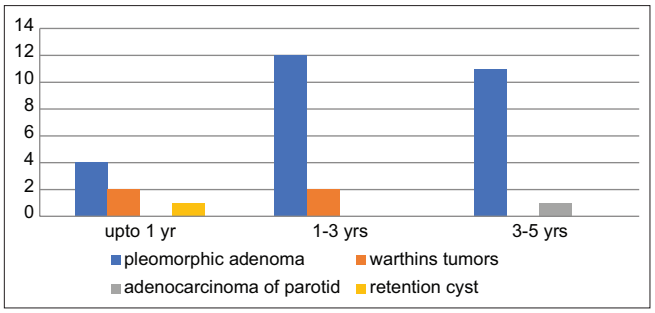
Graph 7: Incidence of non-inflammatory, non-neoplastic swelling



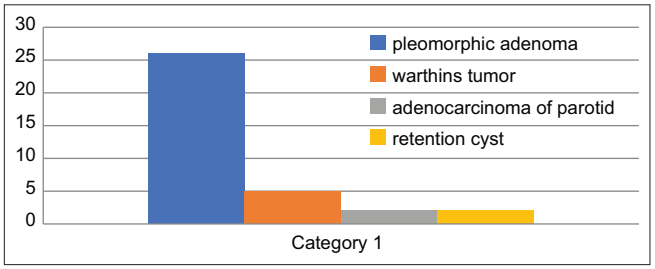
Graph 8: Occupation

In our study, out of 19 cases, 14 (78.9%) were sialolithiasis and 3 cases (21.1%) of sublingual ranula and one retention cyst as shown in Table 10 and Graph 7.

In our study, six cases of sialolithiasis were in the right submandibular gland, eight cases in the left submandibular gland, and four cases of ranula were seen in the right sublingual gland only as shown in Table 11.



Graph 9: Correlation of the duration of swelling in years with HPE reports



Graph 10: Correlation of clinical diagnosis with HPE reports

In our study, out of 32 salivary tumors, 93.75% (30) were benign and 6.25% (2) were malignant malignant as shown in Table 12.

In our study, out of 25 salivary gland tumors, pleomorphic adenoma was 84% (27), 14% (4) of Warthin tumor, and 1 case (2%) of adenoid cystic carcinoma as shown in Table 13.

In our study, the accuracy of FNAC was 100% in case of benign salivary gland tumors, for pleomorphic adenoma, Warthin tumor, and adenoid cystic Ca as shown in Table 14.

In our study, surgery was the treatment for all cases of tumors. Superficial parotidectomy was done in all the 26 cases of parotid tumor (52%) without deep lobe involvement and total parotidectomy was done in 5 cases (10%) with deep lobe involvement. In all the cases of submandibular gland lesions, excision of submandibular gland was done. Excision of the sublingual gland was done in three cases of ranula and one retention cyst excision as shown in Table 15.

Post-operative complications are my study of 50 cases which were low. Three cases of facial nerve paralysis occurred after parotid tumor surgery and wound infection was noticed in five cases. On correlation of occupation with HP reports P value = 0.458 (>0.05) and hence not significant as shown in Table 16.

On the bases of occupation, housewife was more commonly affected (46%) followed by farmers (14%). Least common were employees 2%.

On descriptive analysis of duration of swelling with HPE reports P value = 0.161 (>0.05) therefore not significant. On distributive analysis, 1–3 years swellings were common followed by 3–5 years. Up to 1 year was less common as shown in Graph 9.

On descriptive analysis of clinical diagnosis with HPE reports P value = 0.000 (<0.01) therefore highly significant. as shown in Graph 10 Therefore, there is a strong association between clinical diagnosis and HP reports.

DISCUSSION

Comparison of Our Present Series of 50 Cases with Various Series of Other Authors

In our series, mean incidence is 28 cases per year. This incidence correlates with most of studies by other authors as shown in Table 18.

In our study, incidence percentage of sialolithiasis, that is, 14 cases was found in submandibular gland which correlates with most of the authors in the above table series.

In accordance with the observation in other series, the benign tumors predominate in our study as shown in Table 20.

In our study, all the salivary gland tumors were observed in parotid gland. Comparative study was in accordance to Renehan *et al.* Tumors of sublingual glands are extremely rare and no cases were recorded with submandibular gland, because of small number of cases and short study period as shown in Table 21.

In our study, out of 32 parotid tumors, 27 (88.46%) were seen in superficial lobe of parotid and 5 (11.53%) in deep lobe which is in accordance with the Leverstein *et al.* series as shown in Table 22.

In our series of salivary gland tumors out of 32 cases, 31 cases were benign with mean age 45 and one case was malignant of 80 years age. The results observed in our study are consistent with other studies shown in the Table 23. In our study of 50 cases of salivary gland swelling, shows that, surgery is the treatment of choice in all cases of salivary gland swellings. FNAC plays an important role in the diagnosis of salivary gland tumors and accuracy rate was 100% in our series. In our study, there were no recurrence and nil mortality. Benign swelling of the salivary gland found in lower decade of life, whereas, malignant swelling was found in the 8th decade of life, which correlates with many authors in other series.

In our study of 50 cases, FNAC was in accordance with the other author's series shown in above Table 24.

CONCLUSION

Following the study of 50 cases of salivary gland swellings, the following conclusions can be made.

- Diagnosis of the salivary gland tumors must be considered in any patient presenting with salivary gland swelling
- Salivary gland swelling occur more commonly in the 3rd and 4th decades of life and seen most common in females
- Neoplastic salivary gland swellings were more common than non-inflammatory swellings.
- Sialolithiasis is the predominant non-inflammatory swelling.
- Sialolithiasis occurs more commonly in the submandibular salivary glands.
- Salivary gland tumors occur more commonly in the parotid gland, most often benign, pleomorphic adenoma constitute majority of all neoplasm
- History and physical examination complement FNAC and help in diagnosis. FNAC has good accuracy in diagnosing salivary gland swellings.
- Surgery is the main modality of treatment in salivary gland sialolithiasis. Most commonly done surgery is excision of submandibular salivary gland. Most commonly done surgery is superficial parotidectomy.
- Since the most malignant tumors are asymptomatic and long-standing benign tumors can undergo malignant change, community awareness and early referral are necessary, as prognosis is good if treated early.

SUMMARY

- The clinical material in this study includes the details of 50 cases of salivary gland swellings admitted in surgical units, surgical oncology of Osmania General Hospital and MNJ Cancer Hospital, Hyderabad, from December 2018 to November 2020.
- The incidence of salivary gland swellings is highest in the 3rd and 4th decade of life.

  Benign tumors were more common in 20–50 years and malignancy was seen in one patient of age 80 years.
- In this series, 17 patients were male (34%) and 33 (66%) patients were female, with male-to-female ratio of 1:1.9
- The most common salivary swellings were seen in parotid gland with 32 cases (64%)
- In this series, 18 cases (36 %) of salivary swellings were due to non-inflammatory and non-neoplastic swellings and 32 cases (64%) was due to neoplastic swellings.
- Incidence of non-inflammatory, non-neoplastic swellings was most often seen in submandibular salivary glands.

About 80% (14) were seen affecting the submandibular gland and 20% (4) were seen affecting the sublingual glands.

- Incidence of tumors was highest in the parotid. Incidence of benign tumors is 31 (96.8%) and malignant tumors are 1 (3.1%). Pleomorphic adenoma is the most common benign tumor and adenoid cystic carcinoma was the only malignant tumor.
- Patients presented with a history of swellings varying from 4 months to 5 years. Swelling is the most common symptom. Pain was the second most common symptoms. Pain was noticed in 52% of the cases and tenderness was noticed in 56% of the cases.
- Patient with malignant tumor had other symptoms in addition to the swelling, like pain, facial asymmetry due to facial nerve paresis.
- Final diagnosis was arrived at by physical examination and FNAC. FNAC is the reliable and sensitive tool for diagnosing salivary gland tumors. There was an overall diagnostic accuracy of 100%
- Surgery is the treatment in all the cases of salivary swelling. Out of 32 cases of parotid tumor, superficial parotidectomy was done in 28 cases (87.5%) and total parotidectomy for 4 cases (12.5%). For all the submandibular gland lesions, sialadenectomy was done. Sublingual gland excision was carried out for three cases of ranula and one retention cyst excision.
- Wound infection was the major complication with 5 cases (62.5%) and three cases of facial nerve paralysis (37.5%) were observed.
- Out of 50 cases, 18 cases (36%) were due to non-inflammatory and non-neoplastic swellings. Out of which, 14 cases (77.8%) were due to submandibular sialolithiasis and 3 cases (16.7%) were due to ranula of the sublingual glands and 1 (5.6%) case of sublingual retention cyst. Thirty-two cases (64%) were due to salivary gland tumors. Out of 32 tumors, pleomorphic adenoma is seen in 27 cases (84.4%), Warthin's tumor is seen in 4 cases (12.5%), and one case of adenoid cystic carcinoma (3.1%).
- With proper diagnosis and appropriate treatment, salivary gland swelling can be cured with almost 100%.
- Successful management of the salivary gland neoplasm depends on accurate clinical assessment and diagnosis, with appropriate use of fine-needle aspiration and computed tomography or magnetic resonance imaging. Moreover, knowledge of the particular behavior of each tumor type guides the development of an appropriate treatment plan for each individual patient.
- There was no mortality in our study of 50 cases after follow-up for 1 months–10 months. However, follow-up period was inadequate as salivary gland tumors are known for their late recurrence. The adequacy of treatment cannot be commented because of short period of follow-up.
- The study group in this series is small, as compared to large series in Western literature.

Hence, statistical data in this series may not represent the actual data quoted in Western literature.

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How to cite this article: Shalini T, Rajesh S, Anusha P. A Study on Clinical and Pathological Aspects of Salivary Gland Swellings. Int J Sci Stud 2022;9(12):43-51.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

A Prospective Observational Study of Clinical Profile of Patients with Cervical Myelopathy

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Abstract

Introduction: Cervical myelopathy (CM) is a commonly occurring ailment especially in advanced age. It carries vague clinical presentation and no definable natural history. 80% of people above 55 years of age have radiographic degenerative changes in the cervical spine. Asians are at increased risk. This observational study was undertaken to evaluate the clinical profile of patients of CM.

Materials and Methods: Forty consenting patients with features suggestive of CM were studied over 2 years. A detailed clinical examination especially neurological and investigations were carried out in each patient.

Results: In the present prospective observational study, 29 were male and 11 were female. Compressive etiology was found in 33 (82.5%) and non-compressive in 7 (17.5%) cases. Cervical spondylotic myelopathy 14 (35%) followed by trauma 7 (17.5%) were the commonest causes. Weakness (distal > proximal) of upper limbs was seen in 32.5%, lower limbs in 22.5%. 42.5% of patients complained of paresthesia of upper and or lower limbs. 30% of patients had urinary incontinence, 27.5% had positive Lhermitte's sign, 20% stiff gait, and 17.5% of patients had hand wasting. Impaired proprioception was seen in 15% of patients and hypoesthesia of hands in 12.5%.

Conclusion: Cervical spondylosis and trauma are two common causes of compressive myelopathy. Weakness and tingling and numbness were the most common symptoms. Lower cervical spinal cord bore the brunt of insult in both compressive and non-compressive cases.

Key words: Cervical, Compressive, Myelopathy, Non-compressive

INTRODUCTION

Acute or chronic neck pain has a prevalence of 10–20% in the adult population and may be a manifestation of cervical myelopathy (CM) secondary to compression or due to various inflammatory, degenerative and demyelinating disorders of spinal cord. The syndrome of degenerative cervical spondylotic myelopathy (CSM) was first described by Lord Brain. According to Lord Brain, 80% of people above 55 years of age have radiographic degenerative changes in the cervical spine which may or may not be symptomatic.[1] The incidence and prevalence of myelopathy due to degeneration of the spine are estimated at a minimum of 41 and 605 per million in North America, respectively. Incidence of CSM-related hospitalizations has been estimated at 4.04/100,000 person-years.[2] Asians are at increased risk (1.9–4.3% of individuals older than 30 years) due to their increased prevalence of ossification of the posterior longitudinal ligament.[3]

Compressive myelopathy may be caused by acute trauma, spinal cord tumors, degeneration of discs, osteophyte formation, granulomatous diseases, formation of syrinx, or congenital anomalies of vertebral spine and spinal cord. Degenerative CM (DCM) includes several disorders causing spinal cord impairment, including CM, degenerative disc disease, ossification of the posterior longitudinal ligament, and ligamentum flavum.[4] Non-compressive myelopathy (NCM) may be infectious, post-infectious, post-vaccinal, autoimmune, demyelinating, neoplastic, nutritional, paraneoplastic, and post-radiation in etiology. Other patient-specific factors, including

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www.ijss-sn.com

Month of Submission: 01 - 2022
Month of Peer Review: 01 - 2022
Month of Acceptance: 02 - 2022
Month of Publishing: 03 - 2022

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smoking, participation in contact sports, and regular heavy load carrying on the head, may precipitate or aggravate the risk of development of myelopathy.

CM carries vague clinical presentation and no definable natural history. The patient may present with radicular pain, paresthesia, and muscle atrophy with or without long tract signs, spastic paraparesis, posterior column deficit, bladder and bowel symptoms or brain stem signs. The presentation and the course of illness may also be affected by comorbidities such as rheumatoid arthritis (RA) and movement disorders like Parkinson's disease or malignancy. The course of myelopathy may be short as in cases of trauma, secondary malignant deposits, post-infectious or post-vaccinal myelopathy, or long with period of non-progressive disability as due to DCM, autoimmune and demyelinating conditions. Myelopathy due to compressive etiologies is usually amenable to definitive treatment.

In view of protean symptomatology and signs of this rather common ailment, this study was conducted in a tertiary care teaching hospital in western India to evaluate the clinical profile of patients of CM.

Aim

This study aims to study the clinical profile of patients with CM.

MATERIALS AND METHODS

Forty consenting patients with features suggestive of CM were studied over 2 years. The patients were taken from tertiary care, multispecialty, teaching hospital in western Maharashtra. A detailed medical history was recorded and comprised of age, sex, occupation, socio-economic status, extramarital or premarital exposure, recent vaccination, and interval between onset of the first symptom and the time of presentation. History of trauma to head and neck, viral exanthem, diminished sensation of pain and hot and cold in the upper extremities, shooting pain in the arms, sensation of numbness and tingling, pain in the neck, sensation of coldness or weight in the upper limbs, weakness in the upper and lower extremities, wasting of upper and lower extremities, and impairment of sphincter control was obtained. A detailed systemic clinical examination especially neurological, was conducted in each patient. Cases were subjected to radiographic examination of the cervical spine. CSF study was carried out to establish the etiology where indicated.

OBSERVATIONS AND RESULTS

In the present prospective observational study, 29 were male and 11 were female; majority of the patients were male (29) and were in the age group 30–59 years (72.5%). The youngest patient was an 11-year-old with cervical trauma. The oldest patient was a 71-year-old-lady with atlantoaxial dislocation (AAD) secondary to RA. 23 patients were security personnel, 10 manual laborers, four students, and three were office workers. Three students and one office worker were female.

Etiology

Compressive etiology was found in 82.5%; non-compressive cause was seen in 17.5% cases. The commonest cause for compressive myelopathy was CSM (14 patients, 35%) followed by cervical fracture-dislocation (7 patients, 17.5%). Four (10%) patients had syringomyelia (SM), 3 (7.5%) intraspinal tumors (7.5%), and two (5%) each had tuberculosis of spine and atlantoaxial dislocation (AAD). One patient of AAD was a diagnosed case of RA for previous 20 years (Pie Diagram).

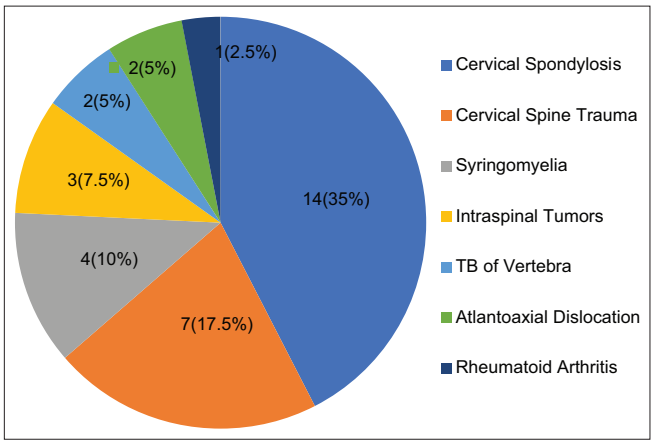
NCM was seen in only seven of 40 (17.5%) patients. Three patients had multiple sclerosis (relapsing-remitting), 2 post-viral myelitis, and 2 patients had AIDS with the AIDS dementia complex.

History of trauma to head and neck was forthcoming in all seven patients who had fracture/dislocation of the cervical spine. Trauma was also an important factor in cases of AAD and RA. The two patients of HIV/AIDS provided history of premarital sexual exposure. Two cases due to post-infective myelopathy gave history of viral exanthems preceding myelopathy. A history of relapsing and remitting neurological deficit was present in the three patients with demyelinating myelopathy.

Onset and course of illness ten cases had acute onset, seven <4 weeks, 20 patients had 1 to 7 weeks, and 3 patients had >6 months.

Symptoms [Table 1]

Tingling and numbness in the upper limb was observed as a symptom in 17 patients (42.5%). This was a common



Pie Diagram: Causes of Compressive Cervical Myelopathy

presenting complaint in patients with CSM (11 of the 14 patients). All three patients with multiple sclerosis had this complaint along with tingling and numbness in the lower limbs. One patient with SM and one each with post-infectious myelopathy and HIV had this complaint.

Weakness in the upper limbs was noticed in 13 patients (32.5%) which developed over a period of 2–6 months. Of these, four patients with SM presented with weakness of the small muscles. In three of these patients, weakness was present in only one hand and subsequently involved the muscles of forearm. Out of three patients with intraspinal tumors, two (1 ependymoma, 1 astrocytoma) had weakness in both the forearms. Two patients with tuberculosis of vertebra and five with cervical spondylosis had upper limb weakness. Weakness in the lower limbs was observed in 9 patients (22.5%). This was a presenting feature in the three patients with multiple sclerosis, four patients with cervical spondylosis and two patients with HIV/AIDS. Weakness involving both upper and lower limbs was seen in 18 patients (45%); 10 cases of cervical spondylosis, five cases of cervical spine trauma, two patients of AAD, and one patient of RA.

Impairment of sphincter control twelve patients had urinary incontinence (7 with spinal trauma, 2 with spinal tumors who developed incontinence later in the course of the disease). Two of the three patients with multiple sclerosis and one with HIV also had bladder involvement.

Pain in neck shooting pain in the neck on bending the neck forwards was observed as a symptom in 11 patients (7 with cervical spondylosis, 2 each with spinal tuberculosis, and multiple sclerosis). Dull aching pain in the nape vexing on movement of neck was seen in nine patients and was commonly at level of cervical C6/C7. Seven patients of these patients had cervical spondylosis and two had tuberculosis of the vertebra. Diminished sensation of hot and cold was a symptom in five patients (3 SM, 2 intramedullary tumors. The two patients of AIDS dementia complex gave history of generalized tonic-clonic seizures.

Stiffness of gait was noticed in eight patients. Out of these, five patients had cervical spondylosis, two intraspinal tumors and one patient had SM.

Wasting of the muscles of forearm and hand was seen in seven patients. These included four patients with SM (weakness and wasting of the small muscles of the hand), one with intraspinal tumor (wasting of the forearm muscles), and two patients with cervical spondylosis who also noticed a difference in the bulk of muscles on the two sides.

Clinical Examination [Table 2]

Optic nerve involvement was seen in two cases of multiple sclerosis and fifth cranial nerve involvement leading to diminished sensation of hot and cold over the lower half of face was seen in a case of syringobulbia.

Motor system muscle bulk was reduced in 13 patients in the upper limb. Of these, four patients with SM had gross wasting of the small muscles of the hand. The two patients with intraspinal tumors had reduced bulk of muscles in one forearm. Two patients with tuberculosis of the vertebra & five patients with cervical spondylosis had reduced bulk in the upper limbs. Hypotonia was a more common finding in the upper limbs compared to hypertonia.

Power was reduced in the upper extremity more than it was in the lower extremity. The distal group of muscles in the upper limb was affected more than the proximal group. In 14 patients, the reduced power, being Grade IV/V in the proximal group of muscles and Grade Ill/V in the distal group in the upper limb. Weakness was more pronounced in the lower limbs in patients with cervical fracture and AAD and in the patient with RA. Deep tendon jerks were

Table 1: Frequency of symptoms in cases of cervical myelopathy

Symptom	DCM	Trauma	SM	Tumor	TBS	AAD	MS	Misc.	Total
Weak- ness									
UL	5		4	2	2				13
LL	4						3	HIV-2	09
UL+LL	10	5				2		RA-1	18
Wasting UL	2		4	1					7
Stiff Gait	5		1	2					8
Incontinence		7		2			2	HIV-1	12
Paresthesia UL	11		1				3	HIV-1	17
								PIM-1	
Pain Nape	7				2				9

DCM: Degenerative cervical myelopathy, SM: Syringomyelia, TBS: Tuberculosis of spine, AAD: Atlanto-axial dislocation, MS: Multiple sclerosis, PIM: Post-infectious myelitis

Table 2: Neurological findings in cases of cervical myelopathy

Sign	DCM	Trauma	SM	Tumor	TBS	AAD	MS	Misc	Total
Wasting	5		4	2	2				13
Hypotonia UL	5		4	2	2				13
Hyper-tonia									
UL	5						1		6
LL	7					2			9
Weak-ness									
UL	7		3	2			2		14
LL		7				2		RA-1	10
Hypoasthesia			4	1					5
Priopioception	6				1	1			8
Lhermitte Sign	7				2		2		11

DCM: Degenerative cervical myelopathy, SM: Syringomyelia, TBS: Tuberculosis of spine, AAD: Atlanto-axial dislocation, MS: Multiple sclerosis, PIM: Post-infectious myelitis

exaggerated in all limbs in 8 patients in the upper limbs in 7 patients and in lower limbs in 8 patients. Spastic gait was observed in 14 patients.

Sensory system pain and temperature sensation were impaired in the four patients with SM. Of these, in two patients, the pain and temperature loss was over the C4 - C7 dermatome, in one patient, the involvement was over the C3 - C7 dermatome, and the fourth patient with syringobulbia had V cranial nerve involvement as well. Similarly, pain & temperature loss was seen in one patient with intramedullary tumor. Vibration and joint position sense was impaired in 6 patients of cervical spondylosis, and one each of spinal TB and AAD.

DISCUSSION

Age and Sex

The maximum number of cases (72.5%) were in the age group of 30–50 years. Similar results were found in a study by Faysal *et al.* wherein the mean age of CM was 35 ± 13.9 years (range 13–65 years).[5] This age group correlates well with the increasing incidence of CSM. CSM is the most common cause for spinal cord dysfunction in the more mature segment of the population.[6] CSM is responsible for hospitalization at the rate of 4.04 per 100,000 person-years. The incidence of cervical spondylosis increases with aging before 50 years of age. The incidence decreases with aging after age 50 years, especially in the elderly after 60 years.[5,7] On the contrary, younger age group is more often victim of traumatic spinal cord injury., In the study of 804 SCI patients by Güzelküçük *et al.*, the mean age at the time of injury was 32.58 ± 14.71 years (range: 4–79 years), and the largest age group was 16–30 years (n = 117, 48.3%), followed by 31–45 years (n = 70, 28.9%).[8]

There was overall male preponderance in our study (62% vs. 38%) if the composite diagnosis of CM was considered. Similar results were found in other studies as well.[5,9] CSM was more common among females. Spinal Trauma were seen more often among males. Traumatic spinal injuries are more common among males possibly due to being involved in vehicular accidents, falls, and sports.[8,10]

Occupation

CSM was seen more frequently in laborers who carried heavy loads on their heads and usually affected them at a younger age group. The two patients with HIV and CM were sailors who contracted the disease due to sexual promiscuity. There are contradictory findings in the literature regarding association of head-load carrying with development of cervical spondylosis. Some studies found positive association between the two, while others have reported a negative association.[10,11]

Compressive versus NCM 82.5% percent of the cases in the present study were due to a compressive etiology; of this CSM and cervical trauma constituted a large portion. SM, intraspinal tumors and tuberculosis of vertebra, in that order constituted the other causes of compressive myelopathy. Demyelination, post-infective & myelopathy due to AIDS constituted the non-compressive causes (17.5%). Compressive myelopathy has been found to be more common cause of myelopathy in other studies as well.[5,12] Tuberculosis, followed by CSM, tumors, and CV anomalies was found to be most common cause of compressive paraplegia by Chaurasia *et al.* in their series of 204 cases of non-traumatic myelopathy.[13]

Symptoms

Weakness in the upper limbs was noticed in 13 patients (32.5%) of compressive myelopathy, including all four patients with SM. Weakness in the lower limbs was noticed in 22.5% of patients. As found in our study, upper limb numbness, hand clumsiness, and distal weakness is a common sign of CM and CM without symptoms in the upper extremities is rare.[14]

Cervical pain was seen in nine patients (22.5%), predominantly in those with cervical spondylosis. Of these, four patients with lateral osteophytes had radicular pain. Neck pain is a very common symptom with an annual prevalence rate of 10-20%. Therefore, it is important to recognize the 'red-flag' symptoms requiring further evaluation. Focal weakness, Lhermitte's sign, neck pain associated with headache, visual disturbance, fever, or unexplained weight loss requires further evaluation.[15,16]

Tingling and numbness were seen in a large proportion of patients (42.5%), especially in the upper limbs in patients with CSM. This large percentage of patients with tingling and numbness represents subset of patients with predominantly central cord syndrome with severe motor and sensory disturbances, with greater expression in the upper extremities.[17] Lhermitte's sign was seen in 11 cases (27.5%). There is a large variation in the incidence of this symptom as reported in literature; various studies have reported its frequency from 9-41% in multiple sclerosis.[18,19] Lhermitte's sign was seen in high percentage of patients in the current study, probably because most of the patients with CSM had a central cord syndrome. Lhermitte's sign is not pathognomonic of multiple sclerosis; it can be seen in spinal cord compression from any cause, conditions including but limited to cervical spondylosis, trauma, SM, and Arnold-Chiari Malformation. It can also be seen in radiation myelopathy, Vitamin B12 Deficiency, cisplatin toxicity, SLE, and post-dural puncture headache.[20]

Wasting of the muscles was prominently observed as a symptom by three patients with SM, and one patient with

intraspinal tumor. Wasting of small muscles of hand can be seen in mid-cervical cord compression from any cause such as cervical spondylosis, SM, and RA.[21,22] Impairment of sphincter control was a prominent feature of patients with multiple sclerosis, fracture-dislocation, and HIV myelopathy. 22.72% had bladder sphincter disturbance in the study by Faysal *et al.*[5] Bladder or bowel dysfunction is an indicator of advanced disease and poor prognosis.[23]

Signs

Cranial nerve involvement was seen in three patients. Two patients of multiple sclerosis had optic nerve involvement. One patient with syringobulbia had loss of pain and temperature sensation over the lower part of the face. Spinal nucleus of the trigeminal nerve and cranial nerves XI and XII may be involved in upper cervical cord compression. Murahashi *et al.* in their study of 24 cases of CM at C1-C2 level, found a case of dysphagia due to glossopharyngeal nerve, vagal, and hypoglossal nerve dysfunction.[24]

Muscle wasting was recorded in 13 patients (32.5%) and was seen commonly in an asymmetrical distribution in the upper limb. This is to be expected considering the involvement of cervical spine. The weakness in the upper extremities was more pronounced in the distal group of muscles. We, in our study, did not find the "amyotrophic type of myopathic hand" wherein there is wasting of intrinsic and extrinsic muscles of hand but not accompanied by sensory loss or spastic quadriparesis.[25]

Thirteen out of 40 patients (32.5%) had sensory disturbance in our study. Pain and temperature sensation was impaired in four patients of SM and one patient of intramedullary tumors. Eight patients (20%) had impaired position and vibration sense. Out of these eight patients, six had cervical spondylosis and two were due to demyelinating illness. Similar findings were also reported by Yoshiyama *et al.*, who found "pseudo-neuropathic sensory loss including impaired pin-prick and vibration sense in 10 out of 61 patients.[26] On the contrary, higher frequency of sensory disturbance (60–70%) has been reported in other studies.[5,27] Prolonged central motor conduction time measured in Abductor halluces could be useful test for detection of CM in those without sensory disturbance of hands.[28]

SUMMARY

CM as a manifestation of spinal cord compression could be due to varied etiology. It could be due to compressive or non-compressive causes. It can present with radicular pains, paresthesia, and muscle atrophy with long tract signs, spastic paraparesis, posterior column deficit, bladder and bowel symptoms, or brain stem signs. Forty cases with features suggestive of CM were studied over 2 years. Most of the patients in the present study were in the age group of 30–59 years. Compressive myelopathy was the cause in 82.5% of these 40 patients. Of these, cervical spondylosis was the most important cause followed by cervical trauma. SM and intraspinal tumors came a close third and fourth as the cause, respectively. Multiple sclerosis, post-infective causes and HIV formed the non-compressive group.

CONCLUSION

CM is an important clinical entity because most of the patients belong to the most productive period of life. Cervical spondylosis and trauma are two common reasons for compressive myelopathy. Weakness and tingling and numbness are the most common symptoms. Lower cervical spinal cord bore the brunt of insult in both compressive and non-compressive cases. Compressive myelopathy is the ones where a definitive treatment can be offered.

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How to cite this article: Tyagi A, Handa AK, Shrivastava AK, Khare AB. A Prospective Observational Study of Clinical Profile of Patients with Cervical Myelopathy. Int J Sci Stud 2022;9(12):52-57.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

A Clinical Pharmacological Study on the Molecular Pharmacodynamic Mechanisms of Organoids and its Pharmacotherapeutic Significance in Biobanking: An Observational Descriptive Analytical Research

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Abstract

Background: Organoids are three-dimensional cell structures, grown *in vitro* from the stem cells. The organoids are formed of cells which differentiate, undergo spatially restricted lineage commitment, and acquire the specific tissue patterning to develop into several endoderm, mesoderm, and ectoderm-derived tissues. These organoids mostly tend to resemble the *in vivo* original organs, with the preservation of their genetic, phenotypic, and behavioral traits.

Objectives: The objective of this clinical pharmacological study was to perform an observational descriptive analytical research on the molecular pharmacodynamic mechanisms of organoids and its pharmacotherapeutic significance in biobanking.

Methods: The present study was an observational, descriptive analytical clinical research study of retrieved study literature derived from a thorough current investigative research database, research study literature, medical evidences, and review literature search, record and review from various available offline and online medical literature databases on organoids, for an evidence-based analysis of the molecular pharmacodynamic mechanisms of the organoids and their pharmacotherapeutic significance in biobanking, which was concluded on the basis of the extensive observational and evidence-based descriptive analytical derivations from the research on organoids.

Results: This evidence-based clinical pharmacological study comprehensively elaborated on the molecular pharmacodynamic mechanisms of the organoids and their clinical pharmacotherapeutic significance in biobanking.

Conclusion: With appropriate cellular composition, proper engraftment and vascularization into the host and adequately manifested functional activity, the efficacy and safety of organoid-based therapies can be properly instituted in different global institutes, hospitals, and medical health-care centers.

Key words: Biobanking, Clinical pharmacology, Evidence-based medicine, Molecular pharmacodynamics, Organoids, Pharmacology

Access this article online

www.ijss-sn.com

Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

INTRODUCTION

Organoids are three-dimensional (3D) cell structures, grown *in vitro* from the stem cells. These stem cells are mainly isolated from the biopsies or from the pluripotent stem cells (PSCs) that are extensively similar to the endogenous organs, in both their structural development and functional performance.

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The organoids are formed of cells which differentiate, undergo spatially restricted lineage commitment, and acquire the specific tissue patterning to develop into several endoderm, mesoderm, and ectoderm-derived tissues. These organoids mostly tend to resemble the *in vivo* original organs, with the preservation of their genetic, phenotypic, and behavioral traits. Organoids, which are derived from the adult stem cells (ASCs), can be developed directly from the diseased epithelium and matched normal tissues, and these organoids can also be genetically manipulated by CRISPR-Cas9 technology. These are not only complex structures but also possess unique capabilities of modeling human organ development and disease, showing wide similarities with the human organ system.[1-4]

Objectives

The objective of this clinical pharmacological study was to perform an observational descriptive analytical research on the molecular pharmacodynamic mechanisms of organoids and its pharmacotherapeutic significance in biobanking.

METHODS

Study Type

The present study was an observational, descriptive analytical clinical pharmacological study with evidence-based molecular pharmacodynamics research.

Study Period

The study period was 7 months, from February 2020 to March 2020 and May 2021 to January 2022.

Place of Study

This research study was done in the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Rational Pharmacotherapeutics, Pharmacovigilance, Evidence Based Medicine, Clinical Research, Clinical Medicine, Molecular Medicine, Rama Medical College Hospital and Research Centre, Rama University; Mamata Medical College and Hospitals; Departments of Stem Cell Therapy and Regenerative Medicine, GIOSTAR Institute of Regenerative Medicine Institutes, Hospitals, and Laboratories; and Fortis Hospitals.

Study Procedure

In this qualitative clinical research study, a multivariate analysis of the retrieved study literature derived from a thorough current investigative research database, research study literature, medical evidences, and review literature search, record and review from various available offline medical literature databases on organoids was performed, such as, any or all types of original research studies, systematic reviews, meta-analyses, case reports, case series, narrative reviews, study series, parallel studies and similar kind of studies or reviews, which were either qualitative, or quantitative, or both qualitative as well as quantitative, within institutes, hospitals, laboratories, medical health-care centers, medical libraries and archives, as well as, various available online medical literature databases, like, any or all types of original research studies, systematic reviews, meta-analyses, case reports, case series, narrative reviews, study series, parallel studies and similar kind of studies or reviews, which were either qualitative, or quantitative, or both qualitative as well as quantitative, on organoids, including published medical articles and archival literature, obtained from various global electronic medical search engines and databases such as Google Scholar, EMBASE, MEDLINE, Cochrane Library, PubMed, review of proceedings from selected scientific meetings, medical conferences, medical congress, medical summits, clinical trial registries, bibliographies of retrieved citations and reference lists, and expert recommendations, were also searched, to record and review, with thorough observational descriptive analysis of the molecular pharmacodynamic mechanisms of organoids and their pharmacotherapeutic significance in biobanking. A multi-variate evidence-based medical research study was conducted, with comparative analysis of the global heterogenous multi-disciplinary experimental and analytical study literature on the molecular pharmacodynamic mechanisms of organoids and their clinical pharmacotherapeutic significance in biobanking, by recording, reviewing, analyzing, and comprehensively analyzing the molecular pharmacodynamic mechanisms of organoids, from the deduced research study findings. This study was concluded on the basis of the extensive observational and evidence-based descriptive analytical derivations from the research on organoids.

RESULTS AND DISCUSSION

This thorough qualitative observational and evidence-based descriptive analytical clinical pharmacological study on organoids, elaborated on the following molecular pharmacodynamic mechanisms of organoids and their clinical pharmacotherapeutic significance in biobanking, with the following certain selective analytical elaborations:

Organoids can be derived from: (i) PSCs, such as embryonic stem cells and induced PSCs (iPSCs), or (ii) ASCs. iPSCs-derived organoids included development from optic cup, intestine, stomach, liver, lung, thyroid, and kidney. Each germ layer (endoderm, mesoderm, and ectoderm) is represented among this set of organs. iPSCs are expanded and subsequently differentiated through a multi-step protocol, that moves toward a fully differentiated structure. Specific cocktails of growth factors are required for each step. The differentiation process usually takes about 2–3 months, which depends on the specific type of organ.

The structure of iPSCs-derived organoids is complex and may contain mesenchymal, as well as epithelial and endothelial components.

Another Air-Liquid Interface (ALI) method was introduced allowing for the preservation of both epithelium and matched *in vitro* stromal microenvironment. The ALI method employs a Boyden chamber-like structure where primary tissue is seeded in extracellular matrix (ECM) gel in an inner Transwell dish which is exposed to air to enhance oxygenation. Culture medium is added to the outer dish and can diffuse through the permeable Transwell into the inner dish. ALI method has been applied in PSCs derived organoid culture. The continuous patterning and dynamic morphogenesis of hepatic, biliary and pancreatic structures, invaginating from ALI culture of anterior and posterior gut spheroids differentiated from human PSC. Adapted ALI culture of human cerebral organoids and neocortical organoid derived from PSCs were also developed.

Complementary to PSCs-derived organoids recapitulate development *in vitro*, ASCs-derived organoids model adult tissue repair, and can be established only from regenerative tissue compartments. There are different culture methods for ASCs-derived organoids. In the WENR method, epithelial organoids are derived from tumor biopsies directly in Matrigel with cocktail growth factors, with long-term expansion but no tumor micro environment. In the air-liquid interphase (ALI) method, tumor biopsies are cultured in ALI in the entire tumor microenvironment as a cell suspension of all cell types, including immune cells and other non-epithelial cell types, but with limited expansion. ASCs-derived organoids were successfully developed from Lgr5-positive intestinal stem cells in culture conditions modeling the stem cell *niche* of intestine. By providing the Wnt agonist R-spondin (RSPO), epidermal growth factor (EGF), and the bone morphogenetic protein inhibitor Noggin, and embedding the cells in an ECM-providing basement membrane extract (WENR method, Wnt3a+EGF+Noggin+RSPO1), Lgr5-positive stem cells are able to self-organize, proliferate and form differentiated crypt-villus like organoids. Since then, by modifying cocktails of growth factors and cell isolation procedures, cultures of patient-derived organoids have been successfully established for various human tissues by biopsy or resection, including the esophagus, stomach, colon, liver, pancreas, salivary gland, fallopian tube, ovary, prostate, breast, airway, taste buds, endometrium, kidney, bladder, thyroid, biliary tract, oral mucosa, and glioblastoma. A counterintuitive phenomenon is found that normal epithelium organoids often outgrow tumor organoids, which, in some instances, can be prevented using cancer-specific selection methods. For example, tumor organoids from colorectal cancer (CRC) can be selectively expanded on withdrawal of Wnt3a and RSPO1. Nearly all CRCs harbor activating mutations in the Wnt pathway or fusion of RSPO1 genes, allowing for the expansion of cancer cells without Wnts and RSPO, while normal epithelial cells arrest. Another approach to culture tumor cells selectively is to stabilize wild-type P53 by adding the MDM2 inhibitor Nutlin-3. Tumor cells are not affected by Nutlin-3 due to a loss of TP53, while normal cells in culture present cell cycle arrest and death, allowing for the selection of tumor cells. In general, patient derived organoids (PDOs) using WENR method can be derived from any epithelium of normal tissues as well as malignant or otherwise diseased tissues within approximately 7 days after embedding the cells into ECM matrix. PDOs can be expanded long term and cryopreserved while remaining genetically stable, making organoids an ideal tool for disease modeling. In addition, this type of organoid culture allows the direct parallel expansion of diseased cells and matched normal cells from individual patients, which allows for the generation of living tumor organoid biobank and facilitates its potential application in personalized therapy. However, nearly all PDOs types represent only the epithelial parts of organs, and there is an absence of stroma, nerves, and vasculature. Adopting ALI method, researchers can generate ASCs-derived organoids from various murine tissues including small intestine, colon, stomach, and pancreas, and then extending to culture clinical tumor samples, accurately recapitulating stem cell populations and their multi-lineage differentiation. The ALI model preserves tumor microenvironment with tumor parenchyma and stroma, including functional tumor infiltrating lymphocytes (TILs), providing a promising model for immunotherapy research for patients with cancer.

The organoids are proved amenable to all standard laboratory techniques, as well as to genetic modification. Organoids can be fast expanded, cryopreserved and applied to high-throughput analyses. Organoids are a promising research model bridging the gap between cell lines and patient-derived xenografts. Organoids have medium cost and heterogeneity. Organoids match normal control, have stable genetic and phenotypic features and cause genetic modification. Organoid cultures cannot mimic interactions with vasculature and stroma.

The dynamic organs undergo renewal by the process of constant growth and differentiation, with the continual growing tissue maintenance and cell differentiation by the stem cells. Organoids, which are derived from the ASCs or PSCs, can be grown with similarities with the original organs. The organoids have already been utilized in the medical and surgical clinics, an example including its clinical utilization in the treatment of inflammatory bowel disease in personalized medicine. The current organoid technology and the organoids have found their wide-spread applications

in basic and medical research, involving the modeling of human development and diseases, for example, genetic, infectious and malignant diseases, drug development, development of new treatments, personalized treatment and regenerative medicine, including biobanking of patient derived organoids for many cancers and cystic fibrosis, and also have shown potentials, yet beyond.

Although the organoids have extensive use in basic research, their translational biomedical application mostly involves drug testing and initial cell replacement strategies.

The regulatory frameworks and general guidelines required for organoids and their clinical applications, for example, drug testing using organoids in Europe, include "Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches" by the European Medicines Agency, the regulatory requirements for cell and gene-based therapies, and good manufacturing practices (GMP) of a pharmaceutical drug, for the clinical use of organoids.

In regenerative medicine, organoids have huge potential applications, provided the following limitations are overcome:

(i) Clonal variation, developmental stage, pluri-/multi-potency, and chromosomal stability of stem cells;
(ii) Reproducibility, accuracy, and scalability of the methodologies proposed;
(iii) Meaningful functional assessment of resulting organoids; and
(iv) Preclinical validation.

Organoid technology can be employed for novel approaches in several surgical operative procedures, like the replacement of severely damaged organs, such as the pancreas, in patients with type 1 diabetes. The human pancreas organoids is a cell-based medicinal product, produced pharmaceutically, with present GMP compliant guidelines. The regenerative process by the human pancreas organoids is an intricate mechanism. The presently practiced methods of replacement and regeneration of certain organs, like pancreas, are obviously prolonged, complex, expensive, and lack reproducibility. Therefore, improvements in the overall bioprocess design, serum-free culture media, and the starting materials, while in compliance with the quality and global regulatory guidelines, and other specifications, would result in an improvisation in the critical quality attributes of the entire process of replacement and regeneration of organs, including the organoid technology, itself. The feasibility of human pancreas organoid generation from the human pancreas has been refined by GMP-compliant regulations in the in-process controls and media formulations, through replacing RSPO1 conditioned medium, with recombinant RSPO1 protein, thus developing a cryopreserved human pancreas organoid, for further use in allogeneic therapies for type 1 diabetes.

Human-iPSC-derived retinal organoids have been developed, according to GMP standards, for the generation of transplantable photoreceptor cells for future clinical applications. Liver buds have also been developed, in accordance with GMP standards, for transplantation processes. Cell production, which occurs under fully defined, xeno-free conditions, and which is beneficial for therapeutic applications among patients suffering from different diseases, have improved reproducibility, without causing any xeno-mediated disease or immune rejection.

Organoids is an ideal *in vitro* tool for the identification of novel stem cell markers. Organoid culture allows for the generation of specific cell types that were previously impossible in 2D cultures. For disease modeling, organoids can be genetically engineered to model genetic and malignant diseases by using CRISPR-Cas9. Normal organoids can be transplanted to wounds for tissue repair. Tumor-derived organoids can be used for basic research by genetic modification and modeling rare cancer. For translational research, tumor derived organoids can be used for biobanking, genetic repair, and drug screening studies, both for personalized medicine and drug development, as well as immunotherapy research. Human and murine organoids have been orthotopically transplanted into mice to model disease or to show tumorigenic potential.

Because of their characteristics, organoids have enormous potential for drug development and precision medicine, which aims to increase cost effectiveness and risk-benefit ratios of therapies by more precisely targeting therapies to individual patients. Biobank research on patient-derived organoids has already led to successful personalized treatment of cystic fibrosis. To facilitate such research, organoids are cultivated from patient-derived stem cells and stored in tissue repositories called "biobanks." Biobanks facilitate multidisciplinary research aimed at a variety of purposes such as drug screening, drug development and disease modeling, as well as enabling large-scale data sharing. Organoids are applied for translational research, and the living organoid biobanks are a tool for personalized treatment and drug development. Organoids can be efficiently established from patient-derived normal and tumor tissue samples, which can be cryopreserved and stored in living organoid biobanks. PDOs resemble the tumor epithelium they were derived from both phenotypically and genetically. Combined molecular and therapeutic profiling of PDOs may help predict treatment response and contribute to personalized cancer treatment and drug development. Among the organoid biobanks, a colon cancer derived biobank of 22 lines, is of significant mention, where all the samples had

performed RNA sequencing and whole genome sequencing analysis. The molecular characteristics of PDOs cover all five consensus molecular subtypes of CRC. The mutations in the organoids were largely concordant with the original tumors, which was validated in a set of organoids established of colorectal metastases. High-throughput screening of a panel of 83 compounds found that there are differences in drug sensitivity among the organoid lines that in some cases correlated with specific mutation. For example, RNF43-mutant organoids were sensitive to WNT secretion inhibitors, and KRAS-mutant organoids were resistant to the epidermal growth factor receptor (EGFR) inhibitors, including cetuximab and afatinib. Later, in a biobank of 35 organoid lines from CRC, the organoid models reproduce most of the genetic and transcriptomic characteristics of the donors, but determined less complex molecular subtypes for the absence of stroma. Drug screening with therapeutic compounds representing the standard of care for CRC, combined with molecular profiles, helped identify a signature outperforming RAS/RAF mutation which has predictive value for sensitivity to the EGFR inhibitor cetuximab. Drug response in organoids and clinical response was also observed to prove that the *in vitro* organoid response correlates with the *in vivo* response. A clinical study of PDOs derived from metastatic gastroesophageal and CRC showed a strong correlation (100% sensitivity, 93% specificity, 88% positive predictive value, and 100% negative predictive value) between the *in vitro* organoid response to a set of targeted therapies and chemotherapies and the response of the tumor in patients. Another study adopted organoids for colon cancer chemoprediction showing that PDOs test predicted more than 80% of patients' response treated with irinotecan-based therapies. Together, these studies indicate the potential of tumor-derived organoids to predict patients' responses. Recently, two studies showed the applications of PDOs derived from rectal cancer to predicting patient responses to neoadjuvant chemoradiation therapy. A rectal cancer derived biobank (n=80) was generated and PDOs' sensitivity to 5-FU, irinotecan, or radiation were tested. They incorporated a correlation between *in vitro* responses in organoids and the histopathologically determined tumor regression scores after surgical resection to define prognostic cut-offs. Using these parameters, the *in vitro* responses could predict clinical responses with an impressive area under the curve of 0.88 and an accuracy of 84%. In the other study, 65 PDO lines from rectal cancer were established to test responses to neoadjuvant chemoradiation therapy, including the standard FOLFOX chemotherapy and radiation. The PDO responses significantly reflected the patients' progression-free survival.

For pancreatic cancer, a much larger PDAC biobank (n=114) was generated and exposed a subset of these organoid lines to the standard-of-care chemotherapies. Their sensitivities paralleled clinical responses in patients. Besides, gene expression signatures of chemosensitivity based on organoids were developed to help predict responses to chemotherapy in both the adjuvant and advanced disease settings. By high throughput drug screening, they nominated alternative treatment strategies for chemo refractory PDO. Another study also used PDOs (n=30) to identify novel therapeutics to target pancreatic tumor cells in a biobank covering different histological subtypes, including PDACs, acinar cell carcinoma, cholangiocarcinoma, adenosquamous-PDACs, intraductal papillary mucinous neoplasm-derived PDACs and papilla of Vater adenocarcinomas. PDOs were exposed to 76 therapeutic agents currently not exploited in the clinic. The Protein Arginine Methyltransferase 5 inhibitor, EZP015556, was shown to target methyl thioadenosine phosphorylase (MTAP)-negative tumors, but also appeared to constitute an effective therapy for a subset of MTAP-positive tumors, indicating the importance of personalized approaches for cancer treatment. A liver tumor biobank (n=13) containing hepatocellular carcinoma and cholangiocarcinoma, as well as the rarer lymphoepithelioma-like cholangiocarcinoma was also developed. In drug screening experiments with 29 compounds, the extracellular regulated protein kinases inhibitor SCH772984 was found to effectively inhibit the growth of tumor organoids, which was validated *in vivo* using xeno transplanted organoid lines in mice, highlighting SCH772984 as a possible therapeutic agent. Biliary tract carcinomas-derived organoids biobank was also established, covering intrahepatic cholangiocarcinoma, gallbladder cancer, and neuroendocrine carcinoma of the ampulla of Vater. Gene expression profiling of the organoids indicated that SOX2, KLK6 and CPB2 could be potential prognostic biomarkers. Drug screening using a compound library of 339 drugs showed that the antifungal drugs, amorolfine and fenticonazole, significantly suppressed the growth of biliary tract carcinomas organoids with little toxicity to normal biliary epithelial cells. An organoid biobank of high-grade serous ovarian cancer (HGSC) (n=33) was established. Up to 50% of all patients with HGSC have DNA repair defects, typically mutation of BRCA1 or BRCA2. These patients were thought to benefit from treatment with poly (ADP-ribose) polymerase (PARP) inhibitors.[1-4]

CONCLUSIONS

The present study well-elaborated and analyzed the distinctive molecular pharmacodynamic mechanisms of organoids and their pharmacological functioning. This study also described, in details, the significance of organoids in biobanking. To conclude, with appropriate cellular composition, proper engraftment and vascularization into the host and adequately manifested functional activity, the efficacy and safety of organoid-based

therapies can be properly instituted in different global institutes, hospitals, and medical health-care centers. The forthcoming human leukocyte antigen-homozygous iPSC initiatives would hugely improvise the clinical applications of organoid technologies. This would also accelerate the development of patient compatible regenerative therapeutic approaches, through large-scale production of organoids and organoids biobanking. The blending of organoid technology with 3D bioprinting and vascularization approaches might produce macrostructures with the desired cellular composition, thus, complementing successful transplantation. A proper co-ordination of all these strategies of clinical biotechnology would delineate the most successful clinical pharmacotherapeutic utilization of organoids and organoid technologies.

ACKNOWLEDGMENTS

My sincere acknowledgments to the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Rational Pharmacotherapeutics, Pharmacovigilance, Evidence Based Medicine, Clinical Research, Clinical Medicine, Molecular Medicine, Rama Medical College Hospital and Research Centre, Rama University; Mamata Medical College and Hospitals; Departments of Stem Cell Therapy and Regenerative Medicine, GIOSTAR Institute of Regenerative Medicine Institutes, Hospitals, and Laboratories; and Fortis Hospitals, for the completion of this research project.

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How to cite this article: Hazra M. A Clinical Pharmacological Study on the Molecular Pharmacodynamic Mechanisms of Organoids and its Pharmacotherapeutic Significance in Biobanking: An Observational Descriptive Analytical Research. Int J Sci Stud 2022;9(12):58-63.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Evaluation of the Results of Type I Endoscopic Tympanoplasty with Underlay Composite Cartilage Graft

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Abstract

Background: The diagnosis of chronic otitis media implies a permanent abnormality of the pars tensa or pars flaccida, most likely a result of earlier acute otitis media, negative middle ear pressure, or otitis media with effusion.

Objectives: The aim was to compare the pre- and post-operative hearing status and to evaluate the hearing improvement at 3 and 6 months and to study the outcome of graft uptake at 3 s.

Materials and Methods: A total of 34 patients with pars tensa tympanic membrane perforation without any ossicular abnormality were studied during the study period of 2 years using analysis of graft uptake after tympanoplasty surgery with underlay composite cartilage graft and post-operative pure tone audiometry and air-bone gap (ABG).

Results: Most of the patients in our study were from the age group of 25–34 years (44.1%) with female: male ratio of 2.4:1. Majority (97.1%) were found to have a successful graft uptake at 3 months after tympanoplasty and a failure rate of 2.9%. The degree of hearing loss reduced gradually from 36.90 ± 6.92 dB to 25.49 ± 8.69 dB at 6 months postoperatively.

Conclusion: Composite cartilage graft tympanoplasty is an effective procedure for closure of tympanic membrane perforations, especially in large perforations.

Key words: Cartilage, Graft, Perforation, Tympanoplasty, Underlay

INTRODUCTION

Chronic mucosal diseases of middle ear cleft or chronic suppurative otitis media has been traditionally defined as a chronic inflammation of the middle ear and mastoid usually associated with perforation of the tympanic membrane and otorrhoea.[1]

Tympanoplasty is now an established surgery for tympanic membrane perforation. The principal aims of tympanoplasty are to create an intact tympanic membrane and to restore functional hearing.[2] Since the introduction of tympanoplasty, a wide variety of graft material has been used for the closure of perforation: Skin, fascia lata, temporalis fascia, vein, perichondrium, and duramater.[3]

The ideal grafting material used for tympanic membrane closure should meet certain criteria namely, low rejection rate, sufficient quantity, good tensile strength, conductive properties similar to that of tympanic membrane and easy availability. Membranous grafts like temporalis fascia and perichondrium meet these criteria and result in closure of tympanic membrane perforation in 95% of ears with normal ventilation. However, in situations such as recurrent perforation, total perforation, and chronic mucosal dysfunction or severe atelectatic tympanic membrane, fascia and perichondrium may undergo atrophy and results in graft reperforation.[4,5] In these cases, many surgeons have

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

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used cartilage as a grafting material because of its increased stability and resistant to negative middle ear pressure.[3]

There have been many adaptations to cartilage tympanoplasty techniques,[6] most of which are composite cartilage perichondrium (CCP) graft.[7] CCP grafting can be divided into palisade techniques and one piece graft techniques. One piece graft techniques appear to have considerably higher acoustic and mechanical property.[8] Tragal cartilage perichondrium serves to be an ideal graft material for tympanic membrane as tragal cartilage being composed of collagen type II which is physiologically similar to the nature of tympanic membrane.[9]

The study was conducted to evaluate the outcome of composite cartilage graft in pars tensa perforations as an underlay technique in endoscopic type I tympanoplasty.

MATERIALS AND METHODS

This was a prospective study conducted in 34 patients of 13–45 years of age regardless of sex with a perforation in pars tensa of tympanic membrane attended the outpatient department under the Department of Otorhinolaryngology, Regional Institute of Medical Sciences, Imphal, Manipur, India, from September 2017 to August 2019. Patients unwilling to give informed written consent, marginal perforation, evidence of cholesteatoma, obvious ossicular deformity, sensorineural hearing loss, and patients with complications of COM were excluded from the study. Informed written consent was obtained from all the participants.

Study variables such as age, sex, area of residence, pre-operative pure tone audiogram, and air-bone gap (ABG) were used. Outcome variables were assessed by status of graft uptake, post-operative pure tone audiometry (PTA), and ABG at 3 and 6 months.

All the patients underwent routine ENT evaluation in addition to general medical examination, ear findings were noted with emphasis on size, site and margin of perforation, state of drum, remnants, status of middle ear mucosa, presence or absence of ear discharge and tuning fork tests, and PTA including ABG.

After pre-operative evaluation, patients underwent endoscopic Type I tympanoplasty with underlay composite cartilage graft under general anesthesia. Tragal cartilage with perichondrium was harvested by giving an incision on the posterior face of tragus. The incision was closed with 4–0 non-absorbable suture. After the removal of perichondrium from one side, the perichondrium cartilage composite graft was cut into strip. The margin of the perforation was freshened using a sickle knife or an angled pick. Using a drum knife, a curvilinear incision was made about 5 mm lateral to the annulus. The incision ideally extended between the 12-O' clock, 3-O' clock, and 6-O' clock positions in the left ear and 12-O' clock, 9-O' clock, and 6-O' clock positions in the right ear. The tympanomeatal flap was slowly elevated away from the bone of the external canal and bony annulus.

Continuity of the ossicles was checked by round window reflex test and direct palpation. Provided the remaining anatomy of the middle ear is intact, few gel foam placed into the mesotympanum area and subsequently the perichondrium cartilage composite graft was placed using the underlay technique, with the cartilage toward the tympanic cavity and perichondrium toward the external auditory canal. The annulus was placed back into position posteriorly and the vascular strip carefully moved into its anatomic place. Gelfoam was placed over the drum remnant graft, the external canal was filled with antibiotic ointment impregnated cotton gauze. Mastoid bandage was placed to provide light pressure and protection.

After the surgery, the patients were called for follow-up at 21 days for inner pack removal and to check the neotympanum. Then, at 3 months, the patients were called for follow-up to check graft uptake by 0° endoscopy and hearing improvement by PTA. Again at 6 months, patients were called to check hearing improvement and the condition of the graft.

Data collected and entered into IBM SPSS Statistics 21 for Windows (IBM Corp. 1995, 2012). Descriptive statistics such as frequency, percentages, mean, and standard deviation were used for data presentation. Paired *t*-test was used to compare between two means and $P < 0.05$ was taken as statistically significant. Further, an ethical approval was obtained from the Institutional Research Review Board of RIMS.

RESULTS

A total of 34 patients who attended the ENT department in our hospital during the study period were taken.

Out of 34 patients, the mean age of the patients was 31.35 ± 17.64 years with a minimum of 15 years and maximum of 44 years. Majority of the patients were in the age group of 25–34 years [Table 1]. Gender distribution showed a female preponderance with a female: male ratio of 2.4:1 [Table 2]. More than half (64.7%) of the patients were from rural area while the remaining 35.3% were from urban area [Table 3].

Majority (97.1%) were found to have a successful graft uptake at 3 months after tympanoplasty and a failure of rate 2.9% [Table 4]. The degree of hearing loss reduced gradually from pre-operative PTA threshold 36.90 ± 6.92 dB to 28.33 ± 6.58 dB and 25.49 ± 8.69 dB at 3 and 6 months, respectively [Table 5] and was found to be statistically significant ($P < 0.05$).

There was a significant difference in the ABG at 3 and 6 months post-operative period as compared to pre-operative ABG [Table 6] and this difference was found to be statistically significant ($P < 0.05$).

DISCUSSION

Patients undergoing composite cartilage tympanoplasty in 15–45 years age group were included according to inclusion and exclusion criteria of the study. A total of 34 patients who attended ENT department in our hospital during the study period were taken.

In our study, graft uptake was seen in 33 (97.1%) patients and failure in 1 (2.9%) patient. This finding was found to be consistent to the study conducted by Tyagi BS *et al.*[10] where out of 55 cases, graft uptake was found in 52 (96.36%) and failure in 3 (3.64%) cases. In the study conducted by Chhapola *et al.*[9] at 6 month after surgery, out of 61 patients, graft uptake was seen in 60 (98.36%) and failure in 1 (1.63%).

The pre-operative average hearing threshold was 36.90 ± 6.92 dB and post-operative average hearing threshold at 3 and 6 months is obtained as 28.33 ± 6.58 dB and 25.49 ± 8.69 dB, respectively. This finding was found to be similar with the study conducted by Cicek MM *et al.*[11] where average hearing threshold at pre-operative and post-operative was obtained as 34.3 ± 13.31 and 26.2 ± 14 dB, respectively.

Mean pre-operative ABG was 16.37 ± 2.17 dB and mean post-operative ABG at 3 and 6 months is 7.44 ± 2.89 dB and 5.9 ± 3.02 dB, respectively. This finding was found to be consistent to the study conducted by Albirmawy OA.[12] where the mean pre-operative ABG was 26.62 ± 1.73 dB and the mean post-operative ABG was 10.95 ± 2.12 dB. Thus, in their study, mean ABG was decreased by 14.67 ± 2.10 dB.

Temporalis fascia has been regarded as the ideal graft material for tympanoplasty. However, various studies have shown that it often does not seem to withstand the negative middle ear pressure in the post-operative period. The ideal grafting material for tympanic membrane closure should have certain properties, namely, low rejection rate, good tensile strength, conductive properties similar to that of tympanic membrane, and easy availability.[4,5]

It has also been revealed that cartilage graft has long-term survival and also remains alive with its rigidity and resist against retraction even in Eustachian tube dysfunction. The incorporated cartilage would give it the necessary stiffness and mechanical stability to avoid retraction. Furthermore, it

Table 1: Age distribution of the patients (*n*=34)

Age group (years)	No. of patients	Percentage
15–24	7	20.6
25–34	15	44.1
35–45	12	35.3
Total	34	100.0

Table 2: Gender distribution of the patients (*n*=34)

Gender	No. of patients	Percentage
Male	10	29.4
Female	24	70.6
Total	34	100.0

Table 3: Area of residence (*n*=34)

Area of residence	No. of patients	Percentage
Urban	12	35.3
Rural	22	64.7
Total	34	100.0

Table 4: Graft status of the patients studied at 3 months (*n*=34)

Status of graft	No. of patients	Percentage
Uptake	33	97.1
Failed	1	2.9
Total	34	100.0

Table 5: Pre-operative and post-operative PTA

PTA threshold	No. of patients	dB HL* Mean±SD
Pre-operative	34	36.90±6.92
Post-operative at 3 months	34	28.33±6.58
Post-operative at 6 months	34	25.49±8.69

*dB HL: Hearing loss in decibels

Table 6: Pre-operative and post-operative air-bone gap

Air-bone gap	No. of patients	dB HL* Mean±SD
Pre-operative	34	16.37±2.17
Post-operative at 3 months	34	7.44±2.89
Post-operative at 6 months	34	5.9±3.02

has a low metabolic rate and good acceptance in the middle ear. Because of the stiff nature of the cartilage, it could reduce the vibratory properties of neotympanum. However, adequate thinning of the cartilage seems to overcome this problem.[13] The advantages of composite cartilage grafts are as follows: It can be obtained easily with cosmetically acceptable incision, has its own blood supply, easy to shape, low metabolic rate, no extra cost, and low extrusion rate.[9]

In our study, we found a satisfactory results in terms of graft uptake and hearing improvement with the use of a composite cartilage graft as an underlay Type I tympanoplasty.

The present study had some limitations. All the patients were from same examination center, so selection bias could not be excluded. Sample size was small and some of the patients did not come for follow-up. Studies involving a large population are required to obtain more conclusive results.

CONCLUSION

In the present study, graft uptake was observed in majority of the patients with failure rate of 2.9%. Significant hearing improvement was observed in the follow-up at 3 months and further at 6 months. Hence, it can be concluded that the success of tympanic membrane closure at tympanoplasty using composite cartilage graft is satisfactory in terms of graft uptake and hearing improvement. Perichondrium is a tough graft material showing good revascularization. The incorporation of cartilage in perichondrium as a composite would counteract negative middle ear pressure. This is of paramount importance in poor Eustachian tube function and in ear with a large perforation. Moreover, cartilage perichondrium is easy to harvest and readily available at the site of surgery.

ETHICAL APPROVAL

Ethical approval obtained from the research ethics board committee.

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How to cite this article: Khumanthem G, Singh NJ, Babu M, Yumlembam S, Devi SP, Singh TS. Evaluation of the Results of Type I Endoscopic Tympanoplasty with Underlay Composite Cartilage Graft. Int J Sci Stud 2022;9(12):64-67.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Association of the Left Ventricular Function Before and After Percutaneous Balloon Mitral Valvotomy in Patients with Rheumatic Mitral Stenosis

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Abstract

Aims: This study aims to identify subclinical left ventricle (LV) dysfunction by 2D strain echo before percutaneous balloon mitral valvuloplasty (PBMV) in patients with rheumatic mitral stenosis (MS). Our study also analyze the post-operative evaluation of overall LV systolic function (by conventional and 2D strain echo) and serial follow-up and evaluation of the LV systolic function over a period of 6 months.

Materials and Methods: A cross-sectional, observational study was attending Cardiology Outpatient Department, NRS Hospital. One hundred patients aged between 18 and 45 years who were fulfill inclusion criteria. Pre-PBMV echocardiographic data were taken (both 2D and strain echo) and recorded. After completion of successful PBMV as denoted by mitral valve area >1.5 cm^2 and reduction of pressure gradient across mitral valve >50% with no significant mitral regurgitation, follow-up echocardiographic evaluation was done after 24 h of procedure, at 1 month and 6 months.

Results: In pre-operative, the mean ejection fraction (EF) (mean ± S.D.) of patients was 58.9000 ± 5.6147. In after 24 h, the mean EF (mean ± S.D.) of patients was 59.3600 ± 5.3664. In after 1 month, the mean EF (mean ± S.D.) of patients was 57.3200 ± 6.1314. In after 6 months, the mean EF (mean ± S.D.) of patients was 55.8200 ± 6.4470. Distribution of mean EF versus group was statistically significant ($P = 0.0001$). We found that in pre-operative, the mean mitral annular plane systolic excursion (MAPSE) (mean ± S.D.) of patients was 11.2840 ± 1.0907. In after 24 h, the mean MAPSE (mean ± S.D.) of patients was 11.9470 ± 1.3094. In after 1 month, the mean MAPSE (mean ± S.D.) of patients was 13.2420 ± 1.4659. In after 6 months, the mean MAPSE (mean ± S.D.) of patients was 14.7560 ± 1.5787. Distribution of mean MAPSE versus group was statistically significant ($P < 0.0001$).

Conclusion: Patients with MS and preserved EF% had a lower 2D longitudinal LV systolic S and Sr compared to the control group. 2D longitudinal LV systolic S and Sr imaging appears to be useful in the detection of subclinical LV systolic dysfunction in patients with MS and preserved EF%.

Key words: Echocardiography and left ventricular, Mitral stenosis, Percutaneous balloon mitral valvotomy, Rheumatic mitral stenosis

INTRODUCTION

Measuring left ventricular (LV) function has a critical importance in diagnosis and treatment of patients with cardiac diseases. This is particularly more important in patients with valvular heart disease (VHD). Rheumatic heart disease (RHD) remains one of the most important causes of VHD in India. In RHD, mitral valve involves commonly either alone or in combination with other valve. RHD is the result of autoimmune response triggered by Group A beta-hemolytic streptococcal pharyngitis leading to immune inflammatory injury of the cardiac valves. Mitral valve stenosis (MS) remains the most common manifestation of chronic rheumatic valvulitis. MS affects the LV functions at various levels due to inflammatory and hemodynamic factors. In general, gross LV systolic function in isolated MS is well preserved.[1] The LV chamber typically is normal or small. However, coexisting mitral regurgitation (MR), aortic valve disease, ischemic heart disease, systemic

Access this article online

www.ijss-sn.com

Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

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Table 1: Distribution of mean LV EDD, EF, and MAPSE group

Variables	Number	Mean	SD	Minimum	Maximum	Median	*P*-value
LV EDD							
Pre-operative	100	43.6280	4.5521	34.9000	52.3000	43.7000	<0.0001
After 24 h	100	44.0400	4.3186	34.9000	51.9000	44.6000	
After 1 month	100	45.0800	3.8851	35.5000	51.9000	46.0000	
After 6 months	100	46.2920	3.8046	37.0000	53.4000	46.1500	
EF							
Pre-operative	100	58.9000	5.6147	50.0000	69.0000	59.5000	0.0001
After 24 h	100	59.3600	5.3664	51.0000	69.0000	60.0000	
After 1 month	100	57.3200	6.1314	46.0000	69.0000	57.0000	
After 6 months	100	55.8200	6.4470	44.0000	69.0000	54.5000	
MAPSE							
Pre-operative	100	11.2840	1.0907	9.4000	14.0000	11.3000	<0.0001
After 24 h	100	11.9470	1.3094	9.5000	15.0000	12.0000	
After 1 month	100	13.2420	1.4659	10.5000	18.0000	13.1000	
After 6 months	100	14.7560	1.5787	11.0000	18.0000	14.9500	

LV EDD: Left ventricle end-diastolic dysfunction, EF: Ejection fraction, MAPSEL: Mitral annular plane systolic excursion

hypertension, and cardiomyopathy, all may be responsible for the elevation of the LV end-diastolic pressure.[2] The LV dysfunction has been described in pure mitral stenosis (MS), which may be a due to change in interaction between the right and LVs, myocardial fibrosis, or a chronic decrease in preload. In patients with rheumatic MS, there is alteration in the LV compliance, diastolic dysfunction, abnormal interaction with the right ventricle, pulmonary hypertension, thickening of subvalvular apparatus, and chronic myocardial inflammation and all these factors lead to subclinical LV dysfunction. In a few patients with MS, ultrastructural, pathological alterations might occur in the muscle cells of the LV. In proportion with these alterations, contractile functions of the LV also decrease. In the assessment of the LV systolic function, a number of imaging techniques – such as echocardiography, magnetic resonance imaging, scintigraphy, and computed tomography scan have been used. In echocardiography, traditionally, ejection fraction (EF), tissue Doppler imaging (TDI), strain echo, and strain rate imaging were extensively used for the assessment of the LV function (a).[2] Subclinical systolic dysfunction has been shown through TDI in patients with MS.[3] In TDI velocity analysis used for the evaluation of regional myocardial functions, some problems, such as continuing elongation of myocardium-like structures and transmission of active and passive deformation in adjacent segments, have been encountered.

Although there is a downward trend in the prevalence of rheumatic fever and rheumatic MS in developed countries, it stands out as a huge public health problem in the developing countries. It particularly affects young people aged between 5 and 15 years. Although in India, rheumatic fever can occur even in 3 years of age. Major determinants of this persistent high burden of RHD are low socioeconomic status, overcrowding, lack of proper surveillance, and lack of effective implementation of primary and secondary preventive strategies. Acute rheumatic fever (ARF) leads to pancarditis (inflammation of the all three layers of heart). Pericarditis and myocarditis generally resolve, but endocarditis along with valvulitis became chronic. In chronic rheumatic valvulitis, there are chronic inflammation and scarring thickening of the subvalvular apparatus along with calcification. In patients with ARF, valvular regurgitations are common, whereas stenosis is the rule for chronic rheumatic valvulitis. The most common form of chronic rheumatic valvulitis is MS. Concomitant aortic valve or tricuspid valve involvement may present. Pulmonary valve involvement is rare in rheumatic fever. MS is a slowly progressive disease with long latency period. The LV function generally well preserved in the initial period unless there is concomitant regurgitation. Traditional echocardiographic parameters failed to show any abnormality in gross LV systolic function. Even with normal EF (indicating preserved global LV function), there can be impairment in long-axis function (measured by tissue Doppler echocardiography).[4] Altered LV long-axis movement has been shown to be a sensitive indicator of early myocardial dysfunction. Atrial fibrillation has shown to cause impairment of the LV function. Pulsed-wave Doppler tissue velocities have been proven to be a good tool for the assessment of long-axis ventricular shortening and lengthening. In the echocardiographical assessment of the LV function, the EF, TDI, Doppler strain, and 2D strain have been widely used. EF is the most widely used index of contractile function, but has high interobserver variability.[5] TDI and Doppler strain are characterized by limitations of angle dependence, limited spatial resolution, and deformation analysis in one dimension. 2D strain is a novel technique which evaluates LV systolic functions more objectively and quantitatively, and does not have the limitations seen in EF, TDI, and Doppler strain; thus, it has become more commonly used in recent years. Strain echocardiography is particularly important to assess

subclinical LV systolic dysfunction.[6] In the diagnosis of the LV dysfunction due to MS, some studies have shown EF, TDI, and Doppler strain to be useful, however, there is a paucity of data.

1. To identify subclinical LV dysfunction by 2D strain echo before percutaneous balloon mitral valvuloplasty (PBMV) in patients with rheumatic MS
2. Post-operative evaluation of overall LV systolic function (by conventional and 2D strain echo)
3. Serial follow-up and evaluation of the LV systolic function over a period of 6 months.

MATERIALS AND METHODS

Study Population

Patients aged between 18 years and 45 years with severe rheumatic MS who were attended Cardiology Outpatient Department, NRS Hospital, and eligible for PBMV were included in this study. Written informed consent was taken from patient or their relatives in their own language before enrollment in the study.

Study Period

The study period was from July 2019 to December 2020 (18 academic months).

Inclusion Criteria

Severity of MS was determined by:

1. Mitral valve area <1.5 cm^2 calculated by planimetric method in parasternal short axis view of conventional 2D echocardiography
2. Mean pressure gradient across mitral valve >10 mm of Hg
3. Peak pulmonary systolic pressure >50 mm of Hg – Pulmonary artery pressure (PAP) was measured from the apical 4-chamber view and was derived from the tricuspid regurgitant jet velocity using the simplified Bernoulli equation assuming a right atrial pressure of 10 mmHg.

Selection of patient for PBMV eligibility was done by Wilkins score.[7]

Exclusion Criteria

Patients with severe MS who have any one of the following criteria were excluded from the study.

1. Hypertension or diabetes mellitus
2. Patient with atrial fibrillation
3. Significant other VHD (i.e., coexisting MR or aortic valve disease)
4. Coronary artery disease (significant in coronary angiography)
5. Presence of the left atrial thrombus, clot, or spontaneous echo contrast.

Statistical Analysis

For statistical analysis, data were entered into a Microsoft Excel spreadsheet and then analyzed by SPSS 24.0. and GraphPad Prism version 5. A Chi-squared test (χ^2 test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a Chi-squared distribution when the null hypothesis is true. Without other qualification, "Chi-squared test" often is used as short for Pearson's Chi-squared test. Unpaired proportions were compared by Chi-square test or Fisher's exact test, as appropriate. $P \leq 0.05$ was considered for statistically significant.

RESULTS AND DISCUSSION

We found that the mean age (mean ± S.D.) of patients was 35.2400 ± 9.3885 years. Fifty-eight (58.0%) patients had female and 42 (42.0%) patients had male. The mean body mass index (mean ± S.D.) of patients was 23.8360 ± 2.3035 kg/m^2.

Bilen *et al.*[7] found that the study population consisted of 103 patients (age 40.9 ± 8.3 years, 75.7% female). There were no significant differences between MS patients and control subjects regarding age and gender. There were no significant differences in the LV-EF and LV systolic/diastolic dimensions between the groups. Systolic PAP increased significantly from Group 1 through to Group 4.

Rajesh *et al.*[8] found that there were 43 patients (25 in sinus rhythm) in the study group and 20 subjects in the control group. Majority were female with no significant gender difference in either group (79.1% vs. 75%, $P = 0.718$). Heart rates were also similar ($P = 0.084$). Intraclass coefficient was analyzed for assessing inter- and intra-observer variability. For intra-observer variability, intraclass coefficients were mitral annular systolic velocity (MASV) – 0.95, myocardial performance index (MPI) – 0.86, E0 – 0.91, and mitral annular plane systolic excursion (MAPSE) – 0.97. For interobserver variability, intraclass coefficients were MASV – 0.92, MPI – 0.84, E0 – 0.89, and MAPSE – 0.96. All the parameters had intraclass coefficient more than 0.7 (acceptable range 0.7–1). Maximum intra- and inter-observer variabilities were for MPI.

We found that in pre-operative, the mean LV end-diastolic dysfunction (EDD) (mean ± S.D.) of patients was 43.6280 ± 4.5521. In after 24 h, the mean LV EDD (mean ± S.D.) of patients was 44.0400 ± 4.3186. In after 1 month, the mean LV EDD (mean ± S.D.) of patients was 45.0800 ± 3.8851. In after 6 months, the mean LV EDD (mean ± S.D.) of patients was 46.2920 ± 3.8046. Distribution of mean LV EDD versus group was statistically significant ($P < 0.0001$) [Table 1].

We found that in pre-operative, the mean LVESD (mean ± S.D.) of patients was 27.8200 ± 4.4725. In after 24 h, the mean LVESD (mean ± S.D.) of patients was 28.0880 ± 4.3234. In after 1 month, the mean LVESD (mean ± S.D.) of patients was 28.4480 ± 4.1846. In after 6 months, the mean LVESD (mean ± S.D.) of patients was 28.8060 ± 4.2468. Distribution of mean LVESD versus group was not statistically significant ($P = 0.3960$).

In pre-operative, the mean EF (mean ± S.D.) of patients was 58.9000 ± 5.6147. In after 24 h, the mean EF (mean ± S.D.) of patients was 59.3600 ± 5.3664. In after 1 month, the mean EF (mean ± S.D.) of patients was 57.3200 ± 6.1314. In after 6 months, the mean EF (mean ± S.D.) of patients was 55.8200 ± 6.4470. Distribution of mean EF versus group was statistically significant ($P = 0.0001$).

In patients with MS, varying degrees of deterioration in the LV function have been reported. The data on the prevalence of longitudinal LV dysfunction in rheumatic MS are not enough. Rajesh *et al*.[8] showed that lower MAPSE, MASV, and E0, with higher MPI in MS patients, compared to controls. Rajesh *et al*.[8] showed that 77% of the study group had evidence of LV longitudinal dysfunction. The higher prevalence of longitudinal LV dysfunction in our group may be due to the fact that they have taken only patients with severe MS. Other factors that may have contributed to this are the delay to medical care from onset of symptoms, as well as earlier onset of valvular disease in Indian population.

The study by Ozdemir *et al*.[4] showed that MS affects long-axis left ventricular performance. The myocardial velocities of the LV indicating left ventricular function were found to be significantly lower in patients with pure MS. Ozer *et al*.[3] examined LV long-axis function of patients with pure MS. There was no significant difference in global systolic function, but tissue Doppler systolic velocities were significantly lower in patients with MS than in controls. Our study showed lower indices of the LV function (MPI) in AF subset, though EF difference was non-significant between the groups. In patients with MS and AF, the causative mechanisms of the LV dysfunction are not well known.

We found that in pre-operative, the mean fractional shortening (mean ± S.D.) of patients was 30.0000 ± 3.2660. In after 24 h, the mean fractional shortening (mean ± S.D.) of patients was 29.6400 ± 2.7980. In after 1 month, the mean fractional shortening (mean ± S.D.) of patients was 29.3000 ± 2.8302. In after 6 months, the mean fractional shortening (mean ± S.D.) of patients was 28.6600 ± 4.1420. Distribution of mean fractional shortening versus group was statistically significant ($P = 0.0314$).

We found that in pre-operative, the mean LV Tei Index (mean ± S.D.) of patients was 0.3442 ± 0.0351. In after 24 h, the mean LV Tei Index (mean ± S.D.) of patients was 0.3512 ± 0.0336. In after 1 month, the mean LV Tei Index (mean ± S.D.) of patients was 0.3546 ± 0.0327. In after 6 months, the mean LV Tei Index (mean ± S.D.) of patients was 0.3294 ± 0.0320. Distribution of mean LV Tei Index versus group was statistically significant ($P < 0.0001$).

We found that in pre-operative, the mean MAPSE (mean ± S.D.) of patients was 11.2840 ± 1.0907. In after 24 h, the mean MAPSE (mean ± S.D.) of patients was 11.9470 ± 1.3094. In after 1 month, the mean MAPSE (mean ± S.D.) of patients was 13.2420 ± 1.4659. In after 6 months, the mean MAPSE (mean ± S.D.) of patients was 14.7560 ± 1.5787. Distribution of mean MAPSE versus group was statistically significant ($P < 0.0001$).

Rajesh *et al*.[8] showed that EF and MAPSE did not show significant change with BMV. MASV and E0 showed improvement immediate post-BMV, while MPI showed a decrease only at 3-month follow-up. The immediate improvement of the LV long-axis parameters may be due to mechanical effect of BMV, while the improvement of MPI (indicating global LV function) took longer time. Another possible explanation for lack of MPI change immediate post-BMV could be due to the fact that MPI, though averaged for 5 cycles in AF patients, could produce significant intraobserver variability. In a study by Lee *et al*.,[9] most patients with impaired LV EF showed improvement after mitral valvuloplasty. A study by Nurcan *et al*.[10] which included 76 consecutive patients, who underwent BMV for isolated rheumatic MS, showed improvement in MASV and E0 post-BMV. The LV global function by MPI did not improve significantly 48 h and 3 months after BMV. This is in contrast to the results of our study, which showed a decrease in MPI at 3 months following BMV. Thus, serial evaluation of changes in mitral annular velocities by Doppler tissue imaging aids clinical assessment of immediate improvement in the LV function after BMV.

Subclinical LV dysfunction related to MS has been evaluated through several different methods. Dogan *et al*.[11] used Doppler strain, and Ozdemir *et al*.[12] used 2D strain imaging (for the 1st time) in the assessment of subclinical LV dysfunction in patients with MS. In almost all of these studies, mild and moderate MS patients were included in the studies, while the number of severe MS patients was either very small or excluded.

Rajesh *et al*.[8] found that magnitude of change in MPI post-BMV had inverse correlation to baseline MPI. The improvement of global LV function after BMV is thus

inversely correlated to baseline global LV function. Hence, it may be assumed that the performance of early BMV, before significant worsening of global LV function may yield better long-term outcomes and needs to be assessed by future studies with larger sample size.

We found that in pre-operative, the mean GLS (mean ± S.D.) of patients was −16.4240 ± 1.6995. In after 24 h, the mean GLS (mean ± S.D.) of patients was −17.4860 ± 1.6318. In after 1 month, the mean GLS (mean ± S.D.) of patients was −17.9720 ± 1.7786. In after 6 months, the mean GLS (mean ± S.D.) of patients was −19.3640 ± 1.3759. Distribution of mean GLS versus group was statistically significant ($P < 0.0001$).

CONCLUSION

There was a significant reduction in the LV function parameters in severe rheumatic MS. Impaired LV long-axis function was present in 77% of the study group. Immediately after BMV, there was an improvement in the LV long-axis function. There was a gradual improvement in global LV function post-BMV.

Patients with MS and preserved EF% had a lower 2D longitudinal LV systolic S and Sr compared to the control group. 2D longitudinal LV systolic S and Sr imaging appears to be useful in the detection of subclinical LV systolic dysfunction in patients with MS and preserved EF%.

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How to cite this article: Chakraborty S, Jana D. Association of Left Ventricular Function Before and After Percutaneous Balloon Mitral Valvotomy in Patients with Rheumatic Mitral Stenosis. Int J Sci Stud 2022;9(12):68-72.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Latest Trends of Substance Abuse among Teenagers: An Original Research Study at a Tertiary Health Care Centre in Northern India

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Abstract

Introduction and Purpose: The current situation of drug abuse and dependence in the adolescent age group is becoming a global hazard and also in India. Many studies have revealed various risk factors which are usually responsible for drug abuse in children of substance abusers, peer pressure, especially depressed and suicidal teens and sometimes peer pressure. Hence in this study, we tried to estimate the extent, pattern, and trends of drug abuse among adolescents at a tertiary health care in Northern India.

Materials and Methods: This study was a survey-based study conducted after approval of the ethical committee at Shri Guru Ram Rai Institute of Medical and Health Sciences and Attached Hospital in Dehra Dun, Uttarakhand in the department of psychiatry in Indoor Patient Department as well as in De-addiction center and it was conducted under the guidance of Department of Forensic Medicine and Toxicology.

Results: In our study out of 50 cases 47 (94%) individuals were male. Most frequently abused substance by adolescents was Tobacco (36%) followed by Cannabis-derived substances such as Charas, Ganja (22%). In this study, the most common age group for substance abuse was 16–18 years (40%) and about 62% of the subjects initiated before 15 years of age.

Conclusion: The authors suggest that the availability of such substances should be totally prohibited by stringent laws. Furthermore, counseling centers and call centers for teenagers who wish to confess and give up such substance abuse. If such steps are taken then the future of India will be in safe and secure hands.

Key words: Adolescents, Cannabis, Drug addiction, Opioids, Peer pressure, Substance abuse

INTRODUCTION

Substance abuse as identified is a process of misuse of the various substances and drugs in various ways. Currently, the substance abusers are using a substance that is easily available such as pain killer ointments, thinners, cough syrups, and glue. Consumption of diverse substances has been in existence in India for many centuries since antiquity. Indian religious text (Vedas), mention Somras and considered Cannabis as sacred plants and referred to it as "sources of happiness," "joy giver" and "liberator."[1] It is said that Indian farmers gave it to their oxen to provide them strength to plough the fields. Many Sadhus or ascetics still use this drug to experience hallucination and a sense of timelessness and bhang drinking is well established social custom in many parts of East and North India.[1] The current situation of drug abuse and dependence in adolescent age group is becoming a global hazard and is also reaching at an alarming position in India. This increase is partially attributed to the aging baby boomer population who has had more exposure to drugs, alcohol and tobacco from a younger age, which is reported to be a risk factor for use and abuse of these substances in later years.[2,3] Many researchers in other countries have tried exhaustive

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

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research regarding this problem. Recently, such researches have also been initiated in our developing country, but very few researchers in North India have addressed this health hazard. Substance abuse needs to be addressed instantly because of shifting trends in the prevalence of substance use and the rising magnitude of the problem. Recently India has seen a drastic rise in adolescents who abuse drugs who are future of this country. Many studies have revealed various risk factors which are usually responsible responsible for drug abuse in children of substance abusers, peer pressure, adolescents who are victims of physical, sexual, or psychological abuse, adolescents with mental health problems, especially depressed and suicidal teens and sometimes peer pressure. Hence in this study, we tried to estimate the extent, pattern, and trends of drug abuse among adolescents at a tertiary health care in Northern India

MATERIALS AND METHODS

The project was found to confirm the institutional ethics committee regulations and was approved. This study was a survey-based study conducted at Shri Guru Ram Rai Institute of Medical and Health Sciences and Attached Hospital, a tertiary Health care center in Dehra Dun, Uttarakhand (Northern India) in the department of psychiatry in Indoor Patient Department as well as in De-addiction center and it was conducted under the guidance of Department of Forensic Medicine and Toxicology. The subjected population consists of 50 people both male and female of the age group between 13 and 19 years. Individual with only one substance abuse was included in the study. Individuals with multiple substance abuses were excluded from the study. A semi-structured proforma/questionnaire (annexure) was used to record age group, education, religion, gender, and locality of their subjects of the study.

Clinical and Substance Use Profile

This included the types of predominantly used substance, duration of dependence (onset marked from the year in which the patient first used the drug), treatments, and the other substances used. This profile also included list of different drugs used, frequency of drug abuse, and the form in which substance was taken.

OBSERVATION AND RESULT

In our study out of 50 cases, 47 (94%) individuals were male. Education clearly seems to play a very important role in modeling our lives as our study found out that 39 (78%) individuals were uneducated. Our studies also depicted the fact very well. According to our study, the most common abused substance by adolescents was Tobacco (36%) followed by Cannabis-derived substances such as Charas, Ganja (22%). Alcohol as substance abuse was found in 12% of individuals [Table 1].

The aim of the study was to identify the cause behind the high incidence of drug abuse among teenagers. Males (96%) were observed to be the significant part of the study group. We observed two major factors played a key role in it Peer pressure (36%) and Study problems (28%) [Figure 1]. 86% of individuals were from nuclear families.

Our studies prominently depicted the fact that females were less involved in drug abuse as compared to men (96%). Education also clearly was an important role in modeling of our lives. Our studies also depicted the same fact very well as we clearly observe that educated teenagers were only 22% and remaining 78% were uneducated. Our studies also indicated that the individuals from higher-income group were majority (64%). In our study, the most common age group for substance abuse was 16–18 years (40%) followed by the age group 13–15 years (32%). The most abused substance in the age group 16–18 years was Tobacco (20%). Ten out of 11 individuals with cannabis as substance abuse were below 18 years of age. Alcohol as a substance of abuse was seen exclusively above 16 years of age with the majority of cases above 18 years (4 out of 6 individuals) [Table 2].

Table 1: Distribution of subjects according to substance abuse

List of drugs	No. patients using this drug (*n*=50)	Percentage
Tobacco	18	36%
Cannabis Derived Substances	11	22%
Alcohol	06	12%
Smack (Heroine)	05	10%
Cocaine	02	04%
Opioids and its derivatives	01	02%
Volatile substances	04	08%
Vicks/Cough Syrup	03	06%
Total	50	100%

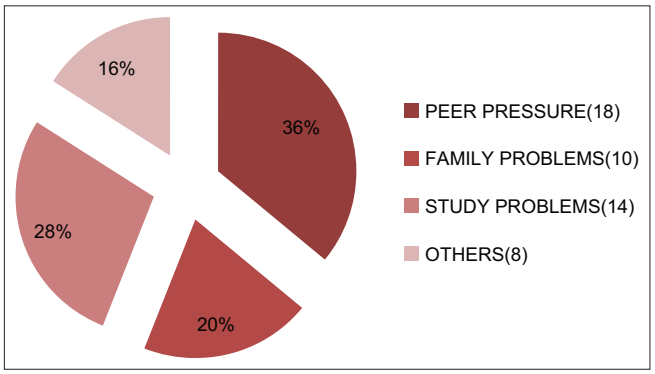

Figure 1: Reasons for starting using drugs

In our study, the individuals were almost equally distributed in between urban (48%) and rural localities (52%). In our study, we found that out of 25 individuals who were using Opiods, Alcohol and Cannabis Derived Substances 21 individuals were from urban Back ground, where as substances such as tobacco and volatile substance were more common in Rural Background [Figure 2].

In the current study, it was found that the individuals initiated substance abuse at quite young age. About 62% of the subjects initiated before 15 years of age with about majority from 13 to 15 years of age group (46%). The youngest age to initiate the substance was found out to be as young as 8 years [Table 3].

DISCUSSION

The latest trends and various studies show that in recent years abuse of substances have increased many folds in teenagers and young adults. Many studies have been aimed towards young adults and college students but very scarce studies have been done for teenagers only. In this study, we tried to analyze various spectrum of drugs used and its relation with the various socio-demographic factors.

In this study, we analyzed 50 cases which were involved in only single substance abuse. The study like many other studies[4,6-8] revealed that the males were the most affected individuals but these findings were against the study conducted by Kushwaha *et al.*[5] and Ahmad *et al.*[14] The subjects with tobacco abuse were majority (36%) which were in consonance with study done by Ahmed *et al.*[6] at Department of Community Medicine, Jawaharlal Nehru medical college and Dhawan *et al.*[9] at National Drug Dependence Treatment Centre, All India Institute of Medical Sciences. Tobacco can be used as chewable (Gutkha, Khaini, Zarda) and can also be smoked(cigarettes and Cigars). The high prevalence of tobacco can be due to its easy availability at every street corner at very low prices, even as low as Rs. 1 which can be easily procured by lower socio-economic status individuals. Cigarettes and Cigars are usually considered as a status symbol by urban teenagers. It is also considered as a way of rebelling and showing independence. Another alarming result was consumption of cannabis derived substances (such as charas, ganja, hasish, marijuana) by teenagers with 22% of the total cases. It is also known as *"weed"* in youngster's urban slang nowadays. Recent trends show that the use of cannabis is in increasing trend. According to a study the youngsters now days prefer Cannabis-derived substances over alcohol and tobacco.[10] There are estimated 31 million users of Cannabis in India according to WHO. The individuals from the age group of 10–17 years are around 2.8 lakhs.[11] These statistics indicate the growing menace in the form of cannabis abuse all over India. Our state is also suffering from the same peril. The increasing trend in our state can be due to easy and illegal availability of cannabis as growing of cannabis for only industrial purpose has been legalized in our state.[12] The urban population as compared to rural population in our study was more involved in cannabis-derived substance abuse as its trend is increasing in the urban class and is popularly known as *"smoking up"* and rave parties. Another important finding in tour study was the use of opium and its derivatives with about 8 cases who were mostly 18 or 19 years of age (10%). It might indicate that procurement of opium and its derivatives is easier for the older age group rather than the younger age group as no individual was from 13 to 15 years. Underage drinking is now a global problem and our state is also has not escaped from the same. Although only 12% of the total of the study population was involved

Table 2: Distribution of subjects according to age group

List of drugs	13–15 years	16–18 years	Above 18 years	Total
Tobacco	05 10%	10 20%	03 06%	18 (36%)
Cannabis Derived Substances	06 12%	04 08%	01 02%	11 (22%)
Opioids and its derivatives)	00 00%	03 06%	05 10%	08 (16%)
Alcohol	00 00%	02 04%	04 08%	06 (12%)
Volatile substances	03 06%	01 02%	00 00%	04 (8%)
Vicks/Cough Syrup	02 04%	01 02%	00 00%	03 (06%)
Total	16 32%	20 40%	14 28%	50 (100%)

Table 3: Distribution of subjects according to age of initiation of abuse

Age group	No. of Subjects (Percentage)
Before 12 years	08 16%
13–15 years	23 46%
16–18 years	12 24%
Above 18 years	07 14%
Total	50 100%

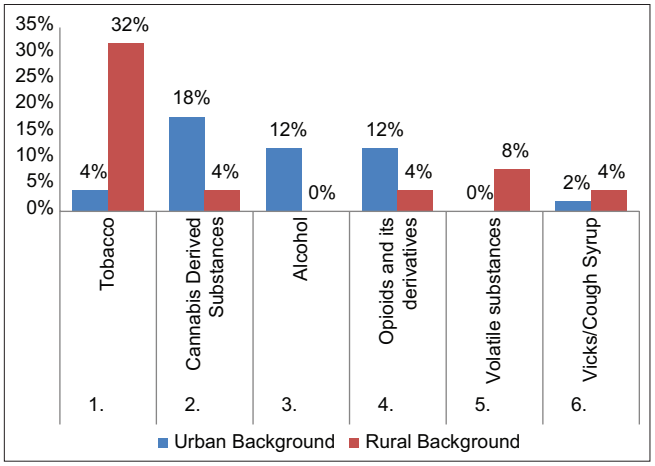

Figure 2: Distribution of subjects according to rural/urban background

in alcohol abuse these statistics indicate the problem of underage drinking in our state. The age group which was more involved in alcohol abuse was above 15 years which was similar to study done by Mahanta.[13] Other abused substances (8%) were volatile substances such as thinner, whitener, glue-sniffing which were almost exclusively seen in the age group of 13–15 years (3 of 4 cases) and exclusively in rural background. It indicates that lower socio-economic status and younger age is most vulnerable as younger subjects from rural background does not have easy accesses of money therefore, they are forced to have suck easy and cheap options such as thinner and glue. Majority of subjects involved started the abuse due to peer pressure which was similar to study done by Ahmed *et al.*[6] but were against the study conducted by Saluja *et al.*[4] and where curiosity was the major reason.

Another finding in our study was that alcohol, opium, cannabis, and their derivatives were almost strictly were seen in urban subjects. This can be due to the easy availability and better socio-economic status of the urban background. The substance of abuse like tobacco and volatile substances were seen in rural population. Most individuals of the study group initiate substance abuse in between 13 and 15 years. It can be attributed to the reason of onset of puberty and also the current young generation often wants to try new experiences, especially ones that they think are thrilling or daring or rebellious.

CONCLUSION

Substance abuse in young age has come to notice in recent times and is of a major concern. Teenage phase of life is a very important period as it lays the road map for the rest of the life which might be blemished by substance abuse. Hence to solve this problem one needs to acknowledge the problem and prepare a proper policy for its eradication. Drug addiction, however, can be treated with treatment medications and psychological treatment, prevention is a major goal in adolescents with programs such as providing normative education and capability enhancement.[15] It is the duty of every common citizen and not only the duty of the state government to take a step forward. The authors suggest that the availability of such substances should be totally prohibited by stringent laws. Furthermore, counseling centers and call centers for teenagers who wish to confess and give up such substance abuse. If such steps are taken then the future of India will be in safe and secure hands.

ACKNOWLEDGMENT

Many thanks should be given to the staff at the Psychiatry Ward of the Hospital, for their help and cooperation.

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How to cite this article: Alam S, Mangare VK, Varshney LK, Barwa J. Latest Trends of Substance Abuse among Teenagers: An Original Research Study at a Tertiary Health Care Centre in Northern India. Int J Sci Stud 2022;9(12):73-76.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Correlation between Maternal Serum Vascular Endothelial Growth Factor Levels and Fetal Outcome in Females with Recurrent Abortions

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Abstract

Objective: The objective of the study was to analyze the relationship between the maternal serum vascular endothelial growth factor (VEGF) levels and the fetal outcome.

Materials and Methods: It is a comparative study to find the correlation between maternal serum VEGF levels and fetal outcome was evaluated in North Indian women comprising 60 pregnant females with a history of recurrent abortion (study group) and 60 normal pregnant females. The serum VEGF levels of all the females were measured and the correlation of serum VEGF levels and fetal outcome in the form of birth weight, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score, term/preterm, and intrauterine growth restriction was conducted.

Results: The mean maternal serum VEGF levels in the study group – adverse outcome, study group – normal outcome, and control group – the normal outcome are 486 pg/ml, 546 pg/ml, and 1524 pg/ml, respectively, and there is a positive correlation between serum VEGF and fetal outcome.

Conclusion: The study concluded that there is a positive correlation between the maternal serum VEGF levels and a fetal outcome such as the birth weight, APGAR score, and growth.

Key words: APGAR score, Birth weight, Recurrent abortion, Vascular endothelial growth factor

INTRODUCTION

Vascular endothelial growth factor (VEGF) family consists of VEGF-A, placenta growth factor, VEGF-B, VEGF-C and VEGF-D, VEGF-E, VEGF-F, and their receptors: VEGF-1/Flt/1, VEGFR-2/KDR, and VEGFR-3/FLT-4. All these members have a common VEGF homology and play an essential role in fetal angiogenic development. VEGF is a soluble angiogenic factor produced by epithelial and stromal cells in the upper layers of the endometrium, whereas its receptors are expressed in the endothelial cells, which can stimulate different endothelial functions. It is a strong mitogen for the endothelial cells derived from arteries, veins, and lymphatics but it lacks consistent and effective activity for other cells. The VEGF expression has been noticed in other tissues such as macrophages, keratinocytes, platelets, and renal mesangial cells.[1-5]

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

The physiological changes in uterine circulation during early pregnancy are regulated by various hormones such as progesterone and human chorionic gonadotropin (hCG) secreted by syntiotrophoblastic cells. They play an important role in the implantation process during pregnancy, such as cell growth and differentiation besides the maintenance of the corpus luteum. hCG hormones acting on the luteinizing hormone/hCG receptors produce many characteristic changes in the trophoblast cell phenotype and uterine vascularization that is required for the embryonic recruitment of the primate

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maternal circulation. hCG can stimulate the expression of VEGF. The VEGF expression increases significantly in syntiotrophoblasts and decidua during pregnancy. It exhibits positive functional regulation by estrogen and progesterone in a steroid receptor-dependent manner. Thus, the formation, maintenance of the vascularization, and receptors of endometrium depend on angiogenesis and are promoted by the expression of VEGF and angiogenic factors such as angiopoietins. The progesterone and hCG appear to be regulating the expression of ovarian VEGF and also enhance vascularization and stabilization of corpus luteum in pregnant women.[6-10]

There is an increase in the VEGF level during pregnancy could be due to trophoblastic villi which are generally hypoxic during the advancement interaction at early pregnancy; upkeep of sufficient blood dissemination was needed during placental development, and blood and oxygen supply is needed in the fetal development process. Various studies have shown that the VEGF and the expression of its receptor in placental tissue were identified during the whole pregnancy time frame and the intensity expanded with advancing pregnancy.[11-13] In this study, we explored the correlation between the maternal serum VEGF levels and a fetal outcome such as birth weight, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score, and growth/intrauterine growth restriction (IUGR).

MATERIALS AND METHODS

It is a comparative study conducted in the Department of Anatomy, and the subjects for the study were obtained from the Department of Obstetrics and Gynecology, Lady Hardinge Medical College. There were 120 pregnant females who were divided into a study and control group with equal distribution of 60 females each. The inclusion criteria for the study group subjects were as follows: (a) Pregnant females within the age of 20–35 years, (b) suffered three or more spontaneous abortions, (c) a single partner, and (d) no anatomical, physiological, hormonal, chromosomal, infective, or autoimmune causes for recurrent abortions identified previously. The control group females were (a) from same age group, (b) at least given birth to one live newborn, and (c) never suffered pregnancy loss previously. Further subjects suffering from diseases/disorders related to thyroid, autoimmunity, bleeding, endocrine, uterine, and congenital were excluded from the study. Written informed consent was received from all included females. A detailed general physical examination, relevant investigations, and ultrasound of the pelvis were carried out. The maternal serum VEGF levels were measured through the enzyme-linked immunoassay technique.

Statistical Analysis

The concentration of maternal serum VEGF levels was evaluated using the Student's *t*-test. $P < 0.01$ was considered statistically significant. The paired test was used to compare the relation between the maternal serum VEGF levels and fetal outcome factors such as APGAR score and birth weight.

RESULTS

The mean value of serum VEGF in the study group with adverse outcome, mean value of serum VEGF in the study group with normal outcome and mean value of serum VEGF in the control group with normal outcome was 450 pg/ml, 560 pg/ml and 1524 pg/ml respectively as shown in Table 1. The adverse outcome seen in the study group were pre-term delivery with low birth weight (5%), pre-term with normal birth weight (8.3%) and term delivery with intra-uterine growth retardation (8.3%). The correlation of VEGF with birth weight of the newborn was significant ($r = 0.282$, $P = 0.001$) as shown in Figure 1. The correlation of VEGF with APGAR score was very highly significant ($r = 0.285$, $P = 0.028$) as shown in Figure 2.

DISCUSSION

The VEGF has been written to be responsible for the adequate perfusion, oxygenation, nutrition, growth of the fetus, and placenta. It has also been mentioned to be a factor for mediating the maternal cardiovascular adaptation to pregnancy. The significant pregnancy-related hemodynamic changes incorporate expanded heart yield, increased blood volume, and diminished systemic vascular obstruction and blood pressure. These progressions add to the ideal development and advancement of the fetus and assist in protecting the mother from delivery complications. The decrease of serum VEGF levels may be related to inhibited fetal growth and development. In our study, we tried to determine the correlation between maternal serum VEGF levels and fetal outcomes such as birth weight, APGAR score, and growth. The mean maternal serum VEGF levels were higher in normal pregnancy and term pregnancy with normal weight/normal baby in comparison to the pre-term delivery with IUGR and underweight babies. There was a positive correlation between maternal serum VEGF and both birth weight and APGAR score.[14-16]

There had been few studies conducted in the past on establishing the correlation we tried to establish in the present study. Here is a brief from the studies:

Birth Weight

In 1999, Wheeler *et al.* reported that serum VEGF concentrations were positively correlated with birth weight

Table 1: Serum VEGF levels and fetal outcome

Pregnancy and fetal outcome	Study group *n*=60 (%)	Control group *n*=60	Mean S. VEGF Conc. pg/ml
Pre-term delivery+LBW	3 (5)	-	485.38
Pre-term+NBW	5 (8.3)	-	546
Term delivery+IUGR	5 (8.3)	-	320
Term delivery with normal baby	47 (78)	-	560
Term delivery+normal birth weight	-	60	1524

VEGF: Vascular endothelial growth factor, LBW: Low birth weight, Mean value of serum VEGF in the study group with adverse outcome=486 pg/ml, mean value of serum VEGF in the study group with normal outcome=546 pg/ml, mean value of serum VEGF in the control group with normal outcome=1524 pg/ml

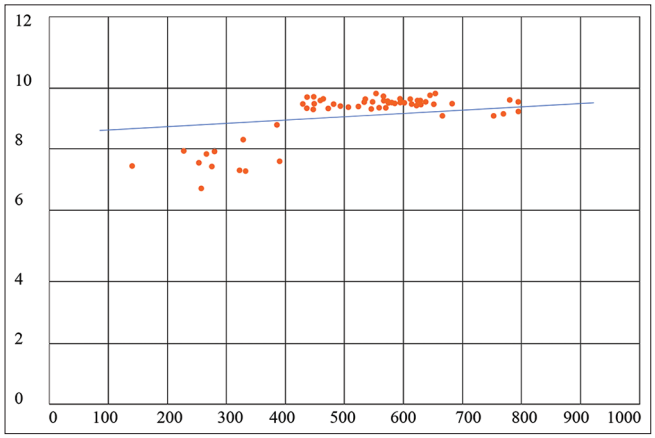

Figure 1: Scatter diagram showing positive correlation between serum vascular endothelial growth factor and Appearance, Pulse, Grimace, Activity, and Respiration score in recurrent abortion patients

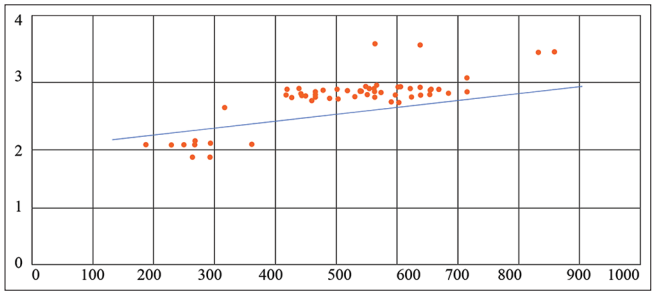

Figure 2: Scatter diagram showing positive correlation between serum vascular endothelial growth factor and birth weight in recurrent abortion patients

(r = 0.10, *P* = 0.02), VEGF could be a factor for mediating the maternal cardiovascular adaptation to pregnancy. The maternal plasma VEGF levels were positively (*P* < 0.05) correlated with birth weight.[17] In 2019, Tang *et al.* showed a positive correlation between the serum VEGF level and neonatal weight (r = 0.435, *P* < 0.001).[18]

APGAR Score

In 2019, Tang *et al.* found a positive correlation between the serum VEGF level and Apgar score (r = 0.357, *P* < 0.001).[18]

IUGR

In 2014, Darling AM found that the women who gave birth to SGA infants had notably lower median levels of VEGF-A (9.43 pg/ml (interquartile range [IQR] 7.81, 85.38) vs. 51.08 pg/ml (IQR 7.81, 363.54)) women who gave birth to AGA infants.[19] However, the studies conducted by Ariadne Malamitsi-Puchner *et al.* in 2005 and Kulkarni *et al.* in 2010 who showed that mothers giving birth to IUGR infants, the maternal serum VEGF levels were not found to correlate with the infant's centile/birth outcome.[20,21] Further, D. Borras *et al.*, in 2014, found that maternal plasma f-VEGF was significantly higher in IUGR compared with controls (p = 0.01 and 0.001, respectively).[22]

The studies conducted in the past have shown results similar to our study with a positive correlation between birth weight and APGAR score but different results and observations as well when it comes to the relation between maternal serum VEGF levels and IUGR as some reporting positive relation and others no relation. The difference could be partially explained due to the difference in the use of total and free VEGF levels but there is a need to further investigate it with a large study.

Strengths

There is a paucity of research and literature pertaining to the subject published in the current article.

Limitations

The study sample size is small. It should be further tested with a bigger sample size for confirmation.

CONCLUSION

Based on our study, there is a positive correlation between maternal serum VEGF levels and fetal outcomes such as term delivery, birth weight, and APGAR score but it needs to be confirmed with a larger study.

ETHICAL STANDARD COMPLIANCE

Consent from Participants

Written informed consent was taken from all the participants.

Ethical Clearance

Ethical clearance was obtained from the Institution Ethical Committee.

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How to cite this article: Jeph RB, Agarwal S, Jeph V, Tuli A, Mehta V. Correlation between Maternal Serum Vascular Endothelial Growth Factor Levels and Fetal Outcome in Females with Recurrent Abortions. Int J Sci Stud 2022;9(12):77-80.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Comparison of Posterior versus Anterior Approach for Spinal Accessory to Suprascapular Nerve Transfer in Patients of Brachial Plexus Injury

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Abstract

Objective: The aim of the study was to compare posterior approach versus anterior approach for suprascapular to spinal accessory nerve transfer in patients with brachial plexus injury.

Methods: The study includes patients with brachial plexus injuries operated for spinal accessory to suprascapular nerve transfer. The patients were divided into two groups A and B. Patients in Group A were operated through anterior approach and patients in Group B were operated through posterior approach. The study was conducted on a total of 16 patients; eight patients in each group.

Results: We have studied 16 male patients in age group 22–40 years. All patients were operated within 1year of injury. In Group A, we obtained M1 strength in three patients and M2 strength in five patients. In Group B, we obtained M1 strength in two patients, M2 strength in three patients, M3 strength in two patients, and M4 strength in one patient.

Conclusion: Posterior approach for transfer of spinal accessory to suprascapular nerve transfer is a good option in patients with late presentation, double injuries and scapular fractures.

Key words: Brachial plexus injury, Spinal accessory nerve, Suprascapular nerve, Anterior approach, Posterior approach

INTRODUCTION

Brachial plexus injuries (BPIs) are severely traumatizing and disabling injuries for the patients.

BPIs occur because of trauma (open or closed), pediatric BPI post-delivery, compression, tumor, inflammation, infection, toxins, and other etiology.

Clinical examination and proper history taking remain the key steps in evaluation of patient, establishing site of injury, estimating degree of injury, and determining surgical treatment and prognosis.

Imaging studies such as magnetic resonance imaging and computerized tomography, investigations such as electromyography, nerve conduction studies help in diagnosing, and localizing the lesion.

- Neurotization, nerve repair, nerve grafts, nerve transfers, and free functioning muscle transfers are possible options for brachial plexus reconstruction. Different levels of injuries have different reconstructive strategies.
- Shoulder stabilization and recovery of abduction are considered one of the priority objectives in brachial plexus surgeries.
- The spinal accessory nerve (SAN) to suprascapular nerve (SSN) transfer is a widely used procedure for shoulder stabilization. This can be done through anterior and posterior approaches.

Usually, the transfer was done through the same approach as for brachial plexus through anterior approach.

The occurrence of injury of SSN at scapular notch, nerve lesions not identified microscopically, and lesion identified at SSN prevents realization of anterior approach, hence, posterior approach was started.[1-5]

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www.ijss-sn.com

Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

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PATIENTS AND METHODS

Study Design and Patients

- This is a retrospective study carried out in Department of Burns and Plastic Surgery, Civil Hospital Ahmedabad.
- The study was carried out in 16 patients with BPI after road traffic accident.
- The patients were randomly divided into two groups – Group A was operated by anterior approach and Group B was operated by posterior approach.
- The period of study included patients operated from 2014 to 2021.
- The results were decided on the basis of approach of surgery, degree of shoulder abduction, shoulder stabilization, and scar characteristics.

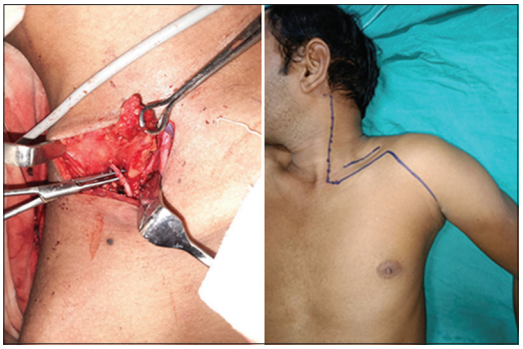
Inclusion and Exclusion Criteria

Patients were investigated by image MRI, electromyography, and nerve conduction study. Sixteen male patients between the age of 22–40 years were included in the study.

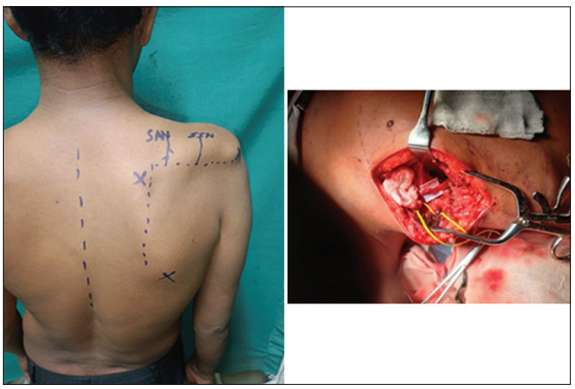
Mainly, patients with upper trunk (C5 and C6) injuries, pan brachial (C5-T1) injuries, irreparable from the roots through grafts, and time period more than 2.5 months from injury were included in the study.

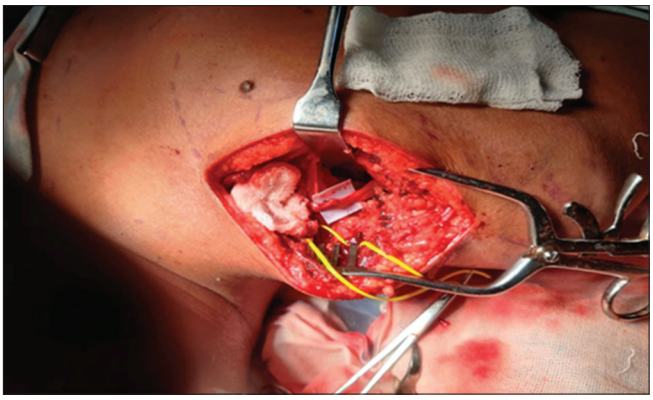
Surgical Photos

Anterior approach



Posterior approach





Evaluation

All patients were followed up and evaluated at regular intervals. Physiotherapy and nerve stimulation were started after 21 days in all patients.

Patients were evaluated on the basis on shoulder abduction; the degree of range of motion; and the power of muscles.

For shoulder abduction strength, we used:

- M0, no evidence of contractility;
- M1, muscle contractions, but no active movement;
- M2, abduction less than 60°;
- M3, abduction more than 60° (for 10 s);
- M4, abduction to 60° against the resistance applied to elbow; and
- M5, abduction to 60° against resistance applied to forearm.

RESULTS

We have studied 16 male patients in age group 22–40 years. All patients were operated within 1 year of injury. Following is the table of results seen:

The quantitative variables were expressed as mean and standard deviation. Mann–Whitney test for comparison between groups was used, assuming a significance level of 0.05.

GROUP A:

PATIENT LIST	AGE	INTERVAL BETWEEN INJURY AND SURGERY	SHOULDER ABDUCTION	TIME PERIOD AT WHICH RESULT NOTED
PATIENT 1	28	5 MONTHS	M1	2 YEARS
PATIENT 2	30	5 MONTHS	M2	2 YEARS
PATIENT 3	35	6 MONTHS	M1	4 YEARS
PATIENT 4	22	5 MONTHS	M2	2 YEARS
PATIENT 5	25	9 MONTHS	M2	1.5 YEARS
PATIENT 6	30	4 MONTHS	M2	1.5 YEARS
PATIENT 7	38	5 MONTHS	M2	2.5 YEARS
PATIENT 8	22	6 MONTHS	M1	1 YEAR

Group B:

PATIENT LIST	AGE	INTERVAL BETWEEN INJURY AND SURGERY	SHOULDER ABDUCTION	TIME PERIOD AT WHICH RESULT NOTED
PATIENT 1	30	3 MONTHS	M1	7 YEARS
PATIENT 2	36	3 MONTHS	M4	6 YEARS
PATIENT 3	25	2.5 MONTHS	M3	3 YEARS
PATIENT 4	24	3 MONTHS	M5	4 YEARS
PATIENT 5	35	2.5 MONTHS	M2	6 YEARS
PATIENT 6	20	6 MONTHS	M2	3 YEARS
PATIENT 7	26	2 MONTHS	M2	2 YEARS
PATIENT 8	30	3 MONTHS	M1	6 MONTHS

The critical value for U at $P < 0.05$ is 13. Therefore, the result is not significant.

In Group A, we obtained M1 strength in three patients and M2 strength in five patients.

In Group B, we obtained M1 strength in two patients, M2 strength in three patients, M3 strength in two patients, and M4 strength in one patient.

Based on Mann–Whitney U test, there is no statistical significance between time interval of surgery and strength of shoulder abduction obtained.

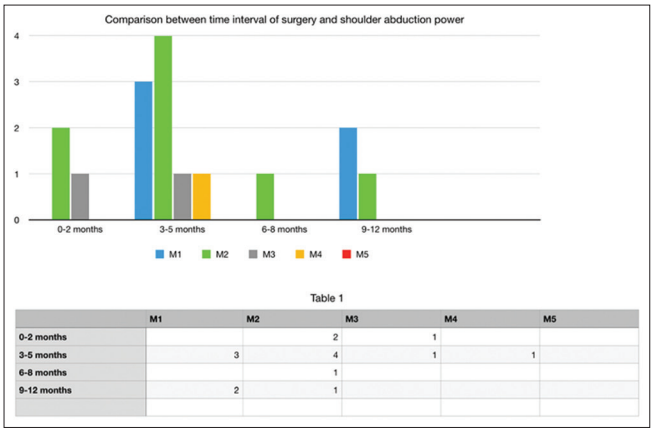


Table 1

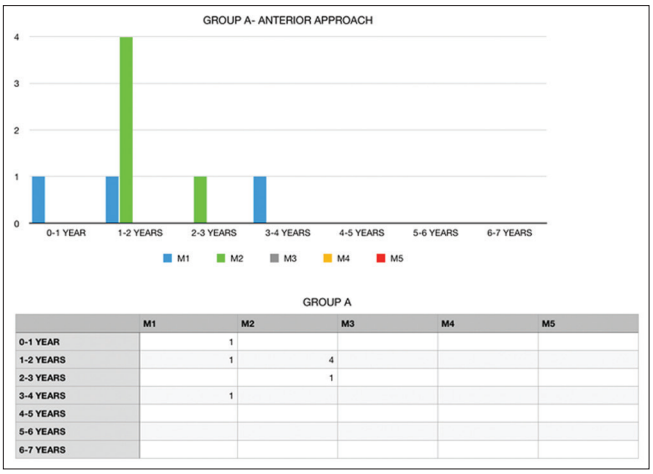
	M1	M2	M3	M4	M5
0-2 months		2	1		
3-5 months	3	4	1	1	
6-8 months		1			
9-12 months	2	1			

Based on the comparison between a total group patients and time interval of surgery, the majority of the patients gained strength M2 irrespective of time after surgery.

It can be observed from the table that in patients operated after 6 months, patient operated by posterior approach have gained strength M2 compared to M1 in anterior approach.

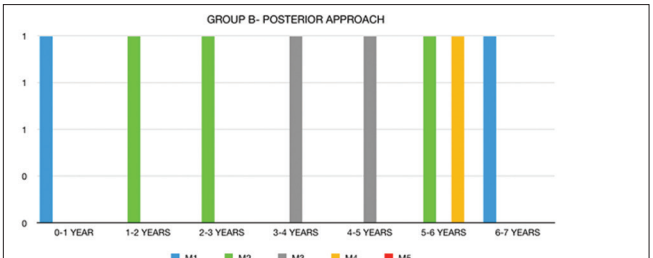
As it can be observed from the two graphs, patients operated by anterior approach are recovering.

At 6 years of follow-up, patients operated by posterior approach showed up to M4 power.



GROUP A

	M1	M2	M3	M4	M5
0-1 YEAR	1				
1-2 YEARS	1	4			
2-3 YEARS		1			
3-4 YEARS	1				
4-5 YEARS					
5-6 YEARS					
6-7 YEARS					



GROUP B

	M1	M2	M3	M4	M5
0-1 YEAR	1				
1-2 YEARS		1			
2-3 YEARS		1			
3-4 YEARS			1		
4-5 YEARS			1		
5-6 YEARS		1		1	
6-7 YEARS	1				

As nerve regeneration is a slow process and requires continuous nerve stimulation, exercises, and physiotherapy along with a lot of motivation by the patient himself, those patients in Group A showing up to M2 power in within 2 years may show good recovery at 5–6 year follow-up.

DISCUSSION

The direct transfer of SAN to SSN is required for shoulder abduction and stabilization in most patients.

Comparison of advantages and disadvantages

	Group A	Group B
Approach	Familiar approach	Less familiar approach
Surgical time	Shorter	Longer
In case of double injury	Exploration not possible	Exploration possible
Need to change position intra op	Not required	Required
Coaptation to muscle	Farther	Closer
Cosmesis	Better as multiple procedures can be done via same incision	Different incisions required for different procedures

Nerve transfer was adopted as primary surgery, then patient was put on regular physiotherapy and nerve stimulation after 21 days of surgery. Depending on type of results obtained, patient was planned for secondary procedure.

- Some conditions favored transfer of SAN to SSN through posterior approach: (a) Greater proximity to the muscle to be reinnervated; (b) leaving free nerve in an area where it could have been 1 s stretch injuries or direct injury; (c) exclusion of the articular branch reinnervation and preventing waste of axons; (d) preservation of former trapezius muscle without affecting the esthetics and can be used as a second treatment option in the failure of reinnervation of deltoid (the insertion of the trapezius transfer to the humerus).[6-10]

CONCLUSION

The posterior reinnervation of the SSN is presented as a good option to improve functional outcome in patients with traumatic BPI in patients with late presentation, double injuries, and scapular fractures

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How to cite this article: Suri MP, Ganapathy N, Sachde JP, Rana HA, Mistry K, Nakka AK, *et al*. Comparison of Posterior versus Anterior Approach for Spinal Accessory to Suprascapular Nerve Transfer in Patients of Brachial Plexus Injury. Int J Sci Stud 2022;9(12):81-84.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Relationship of C-reactive Protein to Alvarado Score and Computed Tomography Scan in Diagnosing Acute Appendicitis

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Abstract

Introduction: Acute appendicitis (AA) is a common gastrointestinal disease affecting 5.7–57/100 individuals each year with the highest incidence in children and adolescents. The variation of incidence is due to variations in ethnicity, sex, age, obesity, and season of the year.

Aim: The aim of ours study was to correlate C-reactive protein (CRP) to Alvarado score (AS) and computed tomography (CT) scan in diagnosing AA.

Material and Method: This prospective and observational study was conducted in the Department of General Surgery, Indian Centre for Advancement of Research and Education (ICARE) Institute of Medical Science and Research. Kolkata. This study was conducted for a period of 2 years, September 2019–August 2021. All patients above the age of 18 years were included in this study with high clinical suspicion of an acute attack of appendicitis and patient with whole abdominal contrast-enhanced CT as a part of protocol at ICARE Institute of Medical Science and Research, Kolkata.

Results: About 49 (64.5%) patients had AA in CT scan finding and 12 (15.8%) patients had chronic appendicitis in CT scan finding. According to the histopathological examination finding, 64 (84.2%) patients had AA and 12 (15.8%) patients had chronic appendicitis.

Conclusion: The positive correlation was found between CRP with AS which was statistically significant. AS and CRP levels in combination provide us to confirm or rule out AA safely.

Key words: Alvarado Score, Computed tomography scan, Acute appendicitis, and C-reactive protein.

INTRODUCTION

Acute appendicitis (AA) is a common gastrointestinal disease affecting 5.7–57/100 individuals each year with the highest incidence in children and adolescents. The variation of incidence is due to variations in ethnicity, sex, age, obesity, and season of the year.[1]

AA is the most common cause of acute surgical abdomen, with an estimated lifelong risk of 8.6% in men and 6.7% in women.[2] It is often regarded as a disease of the young population with a peak incidence in the 2nd and 3rd decades of life.[2,3] Appendectomy is generally accepted as a first-line treatment for non-complicated AA. Reports have shown that pre-operative radiographic evaluation has helped to decrease negative appendectomy rates from 20% to as low as 5%.[4] Computed tomography (CT) has been frequently used as an imaging modality in the evaluation of AA and has improved the diagnostic ability leading to a significant reduction in the number of negative appendectomies.[5] With a reported sensitivity of up to 96.5% and specificity of about 98%, CT plays a major role in the clinical decision-making process in AA and is considered as a first-line imaging modality in the diagnostic work-up for suspected AA.

C-reactive protein (CRP) is an abnormal serum glycoprotein produced by the liver during the acute inflammation.

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

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Because it disappears rapidly when the inflammation subsides its detection signifies the presence of a current inflammatory process.

The function of CRP is related to its role in the innate immune system. Similar to immunoglobulin G (IgG), it activates complement, binds to Fc receptors, and acts as an opsonin for various pathogens. Interaction of CRP with Fe receptors leads to the generation of proinflammatory cytokines that enhance inflammatory response. Unlike IgG, which specifically recognizes distinct antigenic epitopes, CRP recognizes altered self and foreign molecules based on pattern recognition. Thus, CRP is thought to act as a surveillance molecule for altered self and certain pathogens. This recognition provides an early defense and leads to a proinflammatory signal and activation of the humoral and adaptive immune system. CRP binds to molecular groups found on a wide variety of bacteria and act as an opsonin.

CRP may also be important in the recognition of necrotic tissues. CRP binds to apoptotic cells, protects the cells from assembly of the terminal complement components, and sustains an anti-inflammatory innate immune response.

Aim

The aim of the study was to correlate CRP to Alvarado Score (AS) and CT scan in diagnosing AA.

Objective

1. The objective of the study is to assess, on admission, whether CRP levels are a good predictor for AA.

MATERIAL AND METHOD

Study Design

This was a prospective and observational study.

Study Site

This study was conducted in the Department of General Surgery, Indian Centre for Advancement of Research and Education (ICARE) Institute of Medical Science and Research, Kolkata.

Sample Size

N (sample size)= zα2p (1−p)/e2 where p is proportion and e is precision

Here, $\alpha = 5\%$, hence, $z\alpha = 1.96$, p (incidence of AA) = 4.7% e = 5%. Using these values in the above formula, n is coming as 109. Hence, minimum 69 patients were included in the study 100. On adding 10% to make up for dropouts during the study, the sample size comes as 76.

Study Period

This study was conducted for a period of 2 years, September 2019–August 2021.

Study Population

The source of data for study was 69 patients, admitting during period of 24 months commencing from September 2019, in the Department of General Surgery, at Calcutta Medical Research Institute and Tata Motors Hospital. Adding 10% to make up for dropouts during the study, the sample size comes as 76.

Inclusion Criteria

The following criteria were included in the study:

1. All patients above the age of 18 years
2. High clinical suspicion of an acute attack of appendicitis
3. Patient with whole abdominal contrast-enhanced CT (CECT) as part of protocol at ICARE Institute of Medical Science and Research, Kolkata.

Exclusion Criteria

The following criteria were excluded from the study:

1. Immunocompromised patients.
2. Patients on steroids or immunosuppressants
3. Patients with other infective or inflammatory conditions in the body
4. Pregnant patients.
5. Patients with renal compromise.

Statistical Analysis

For statistical analysis, data were entered into a Microsoft Excel spreadsheet and then analyzed by SPSS 24.0 and GraphPad Prism version 5. A Chi-squared test ($\chi 2$ test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a Chi-squared distribution when the null hypothesis is true. Without other qualification, "Chi-squared test" often is used as short for Pearson's Chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. $P \leq 0.05$ was considered for statistically significant.

RESULT AND DISCUSSION

This prospective and observational study was conducted in the Department of General Surgery, Calcutta Medical Research Institute, Kolkata and Tata Motors Hospital, Jamshedpur, Jharkhand. This study was conducted for a period of 2 years, September 2019–August 2021. The source of data for study was 69 patients, admitting during period of 24 months commencing from September 2019, in the Department of General Surgery, at Calcutta Medical Research Institute and Tata Motors Hospital. Adding 10% to make up for dropouts during the study, the sample size comes as 76.

All patients above the age of 18 years were included in this study with high clinical suspicion of an acute attack of appendicitis and patient with whole abdominal CECT as a part of protocol at ICARE Institute of Medical Science and Research, Kolkata.

In our study, the most of the patients had AA (49 [64.5%]) and only 12 (15.8%) patients had chronic appendicitis in CT scan finding.

Our study showed that the most of the patients had acute (Superficial) appendicitis in histopathological examination (HPE) (37 [48.7%]). Rest 1 (1.3%) patient had AA in HPE, 17 (22.4%) patients had acute (Phlegmonous and non-perforated) appendicitis in HPE, 8 (10.5%) patients had acute (Phlegmonous and perforated) appendicitis in HPE, 1 (1.3%) patient had acute (Phlegmonous and Perforated) appendicitis in HPE, and 12 (15.8%) patients had chronic appendicitis in HPE.

We found that 64 (84.2%) patients had AA in HPE final and 12 (15.8%) patients had chronic appendicitis in HPE final.

Tanrıkulu *et al.*[6] (2016) found that 278 patients were included in this study. Patients were separated into two main groups as the surgery group (n = 184) and non-operative group (n = 94). Inflammatory parameters were not predictive for histopathologic results, although higher CRP and PCT levels were significant in perforated and necrotizing appendicitis. Multifactorial regression analyzes showed that AS was not of significant predictive value in the non-operative group. There was no superiority of AS and/or US in the diagnosis of AA.

It was found that the mean AS (mean ± S.D.) of patients was 6.9737 ± 1.9458. The mean CRP (mean ± S.D.) of patients was 21.7724 ± 9.5334. The mean total lymphocyte count (mean ± S.D.) of patients was 14240.1316 ± 4750.8176.

We found that in AA, 16 (25.0%) patients were 21–30 years old, 21 (32.8%) patients were 31–40 years old, 6 (9.4%) patients were 41–50 years old, 4 (20.3%) patients were 51–60 years old, and 8 (12.5%) patients were 61–70 years old. In chronic appendicitis, 3 (25.0%) patients were 21–30 years old, 3 (25.0%) patients were 31–40 years old, 2 (16.7%) patients were 41–50 years old, and 4 (33.3%) patients were 51–60 years old. It was not statistically significant (P = 0.5626).

Our study showed that in AA, 19 (29.7%) patients were female and 45 (70.3%) patients were male. In chronic appendicitis, 4 (33.3%) patients were female and 8 (66.7%) patients were male. This was not statistically significant (P = 0.8008).

Pipal *et al.*[7] (2016) found that in HPE confirmed appendicitis in 90 patients with 10 negative appendicectomies.

In our study, the most of the AA patients had febrile fever (60 [93.8%]) compared to chronic appendicitis patients (3 [25.0%]). In AA, 4 (6.3%) patients had afebrile fever and 60 (93.8%) patients had febrile fever. In chronic appendicitis, 9 (75.0%) patients had afebrile fever and 3 (25.0%) patients had febrile fever. Association of fever versus HPE final was statistically significant (P < 0.0001).

It was found that the higher number of AA patients (58 [90.6%]) had nausea and vomiting compared to chronic appendicitis patients (9 [75.0%]) which was not statistically significant (P = 0.1242).

We found that in AA, 26 (40.6%) patients had tachycardia. In chronic appendicitis, 7 (58.3%) patients had tachycardia. This was not statistically significant (P = 0.2560).

We also found that 30 (46.9%) AA patients had tachypnea where in chronic appendicitis group, no patients had tachypnea which was statistically significant (P = 0.0023).

Tanrıkulu *et al.*[6] (2016) showed that 278 patients were included in this study. Patients were separated into two main groups as the surgery group (n = 184) and non-operative group (n = 94). In the surgery group, clinical predictive factors for histopathologic results such as AS ≥7, AA signs on US, neutrophilia, and leukocytosis were significant. Neutrophilia and leukocytosis had the highest accuracy rate among these factors.

Wang *et al.*[7] (2012) found that participants were divided into two groups: Leukocytosis (LK group) and non-leukocytosis (non-LK group). In the first phase of the analysis, there were statistically significant differences in white blood cell count (13.5 K vs. 10.9 K per μL), neutrophilia (81.5% vs. 73.5%), and hospital stay (4.9 vs. 3.5 days) between the two groups.

In our study, neutrophilic leukocytosis was significantly higher in AA patients (48 [75.0%]) compared to chronic appendicitis patients (1 [8.3%]) and it was statistically significant (P < 0.0001).

Pipal *et al.*[8] (2016) showed that AS in combination with ultrasonography is a valuable tool for diagnosing AA in spite of sophisticated investigations like CT, thus reducing the cost of the treatment and preventing negative appendicectomy rate.

Vaghela *et al.*[9] (2017) found that the correlation between appendiceal diameter and AS was 78.7% (P = 0.01 <0.05).

Presence of appendiceal diameter above 6.5 mm on CT, periappendiceal inflammation, fluid, and appendicoliths should prompt the diagnosis of AA. Since patients with AA may not always show the typical signs and symptoms, CT is a helpful imaging modality for patients with relatively low AS and leukocytosis, when physical examination is confusing.

Wang *et al.*[7] (2012) found that CT scan is necessary for patients with relatively low AS when leukocytosis is noted.

Al-Faouri *et al.*[10] (2016) showed that the diagnostic performance of CT scan was superior to that of AS with sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of 94.2 versus 85.4%, 90 versus 65%, 9.42 versus 2.44, and 0.065 versus 0.224, respectively ($P < 0.05$). The overall diagnostic accuracy of CT scan was 92.6% compared to 77.5% for AS. The AS was far from good and CT scan is more accurate in diagnosis of AA in their patient population.

Our study showed that in AA, all patients (64 [100.0%]) had AA as per CT scan finding. In chronic appendicitis, all patients (12 [100.0%]) had chronic appendicitis as per CT scan finding. It was statistically significant ($P < 0.0001$).

We found that in AA, 1 (1.6%) patient had AA in HPE, 17 (26.6%) patients had acute (Phlegmonous and non-perforated) appendicitis in HPE, 8 (12.5%) patients had acute (Phlegmonous and perforated) appendicitis in HPE, 1 (1.6%) patient had acute (Phlegmonous and Perforated) appendicitis in HPE, and 37 (57.8%) patients had acute (Superficial) appendicitis in HPE. In chronic appendicitis, 12 (100.0%) patients had chronic appendicitis in HPE. Association of HPE versus HPE final was statistically significant ($P < 0.0001$).

In our study, the mean age (mean ± s.d.) of chronic appendicitis patients was higher (42.1667 ± 13.6437 years) than the AA patients (41.4688 ± 13.5892) which was not statistically significant ($P = 0.8708$).

Talabi *et al.*[11] (2021) evaluated the diagnostic value of AS, white blood cell count, and serum CRP in children with AA. The sensitivity and specificity of AS, CRP estimation, and total white blood cell count in diagnosing AA were 86.4% and 63.2%, 98.8% and 36.8%, and 51.9% and 89.5%, respectively. AS has the highest area under ROC curve analysis 0.824, 95% CI of 0.724 to 0.924 compared with CRP, 0.769. 95% CI of = 0.647 to 0.891 and WBC count, 0.765, 95% CI of 0.643 to 0.887. Both CRP and WBC count showed higher discriminatory values between complicated and uncomplicated appendicitis, $P < 0.001$.

Thirumallai *et al.*[12] (2014) showed that patients were categorized into three groups retrospectively based on the AS. Group I: Score 7–10 ($n = 155$), Group II: Score 4–6 ($n = 71$), and Group III: Score <3 ($n = 10$). Overall, 169 of 234 (72.2%) had histopathological confirmation of AA. The predicted accuracy of AS was 84.5% in Group I, 50.7% in Group II, and 25% in Group III. The PPV of high CRP and NPV of normal CRP for Group I was 88% and 36.4%, in Group II, 63% and 72%, in Group III, 33% and 86%, respectively. The AS and CRP taken together improve the predictive value of diagnosing AA.

Farahbakhsh *et al.*[13] (2020) showed that the sensitivity, specificity, positive predictive value, negative predictive

Table 1: Association between CT Scan Finding and Neutrophilic Leukocytosis: HPE Final

		HPE Final				
		Acute Appendicitis	Chronic Appendicitis	Total	Chi-square value	*P*-value
CT Scan Finding	Acute Appendicitis	64	0	64	76.0000	<0.0001
	Row %	100.0	0.0	100.0		
	Col %	100.0	0.0	84.2		
	Chronic Appendicitis	0	12	12		
	Row %	0.0	100.0	100.0		
	Col %	0.0	100.0	15.8		
	TOTAL	64	12	76		
	Row %	84.2	15.8	100.0		
	Col %	100.0	100.0	100.0		
Neutrophilic Leukocytosis	Absent	16	11	27	19.6080	<0.0001
	Row %	59.3	40.7	100.0		
	Col %	25.0	91.7	35.5		
	Present	48	1	49		
	Row %	98.0	2.0	100.0		
	Col %	75.0	8.3	64.5		
	TOTAL	64	12	76		
	Row %	84.2	15.8	100.0		
	Col %	100.0	100.0	100.0		

value, and accuracy were 77%, 19%, 78%, 17, and 64% in Anderson, 95%, 7%, 75%, 30%, and 77% in Alvarado, and 92%, 7%, 79%, 20%, and 75% in Alvarado + CRP scoring systems, respectively. Anderson scoring system had lower diagnostic accuracy than the Alvarado system.

Alhames *et al.*[14] (2021) showed that AS categories were retrospectively calculated as low (0–4 points), intermediate (5–6 points), or high (7–10 points). The cutoff levels were >0.5 mg/dl for CRP. According to the AS, 108 (32.6%) were at low risk, 76 at (23.0%) intermediate risk, and 147 (44.4%) at high risk of AA. The AUCs of ROC were 0.76 (0.70–0.81) for AS and 0.79 (95% CI 0.75–0.84) for CRP-AS being the difference statistically significant (P = 0.003). The CRP for diagnosis AA in low-risk AS group had negative predictive value of 95.8% (95%CI 87.3–98.9) and likelihood ratio negative of 0.4 (95%CI 0.2–1.0). CRP-AS has shown to increase the diagnostic accuracy of AS for AA.

Zouari *et al.*[15] (2016) conducted a study where patients were categorized into three groups based on the AS: Group I: Score 7–10, Group II: Score 5–6, and Group III: Score 0–4. The difference between predictive values of AS alone and AS with CRP was not statically significant. The PPV increased from 74.29% (AS and CRP) to 93.75% (AS and US) in Group I (P = 0.001) and the NPV increased from 64.86 and 79.69% (AS and CRP) to 82.6 and 88.2% (AS and US) in Group II (P = 0.01) and Group III (P = 0.001), respectively.

It was found that the mean AS (mean ± s.d.) of AA patients was higher (7.6094 ± 1.3641 (than the chronic appendicitis patients (3.5833 ± 0.5149) and this was statistically significant (P < 0.0001) [Table 1].

CONCLUSION

The positive correlation was found between CRP with AS which was statistically significant.

We concluded that using AS and CRP levels in combination provide us to confirm or rule out AA safely.

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How to cite this article: Kanjilal N, Jana D. Relationship of C-reactive Protein to Alvarado Score and Computed Tomography Scan in Diagnosing Acute Appendicitis. Int J Sci Stud 2022;9(12):85-89.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Anesthetic and Peri-operative Challenges of COVID-19 Associated Rhino-Orbito-Cerebral Mucormycosis

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Abstract

Purpose: The pupose of the study was to appraise the anesthetic management, peri-operative course, complications, and outcome of patients undergoing surgery for COVID-19 associated mucormycosis (CAM).

Methods: It was an observational retrospective study conducted at a tertiary care teaching public hospital. Detailed perioperative data were collected from all the patients who underwent surgical debridement of CAM.

Results: A total of 41 patients were operated for CAM during the study period of 4 months, comprising 31 (75.6%) males and 10 (24.4%) females. Mean age was 56.07 ± 11.980SD years. About 19.5% patients were reverse transcription polymerase chain reaction (RT-PCR) positive at the time of the procedure. General anesthesia (GA) was administered 85.4% and monitored anesthesia care (MAC) in 14.6% patients. Central vein access was secured in 16 (41.5%) and arterial cannulation in 17 (41.5%) patients. Intraoperative events were observed in 30 (73.17%) patients. They were difficult airway in 17 (41.5%), bronchospasm in 10 (24.4%), desaturation in 5 (12.2%), electrocardiogram (ECG) changes and arrhythmia in 20 (48.8%) and hypotension in 8 (19.5%) patients. Occurrence of intraoperative complications was highly observed in patients of age >60 years, multiple comorbidities, hyperglycemia (blood sugar >140), moderate to severe COVID, CORAD >10, high inflammatory markers (Ferritin. D-dimer), RT-PCR positive status, pre-operative acidosis, hypokalemia, and extensive disease.

Conclusion: CAM are emergency procedures providing insufficient time for pre-operative optimization. Anesthesia technique of choice is GA and MAC in select cases. Thorough preparedness for difficult airway management, invasive monitoring, vasopressors, ionotropic, venodilators, and antiarrhythmic drugs is vital. Common intraoperative challenges were unstable hemodynamics, ECG changes (arrhythmia, ischemia etc.), and respiratory complications in COVID lung. High vigilance for prompt management of complications in susceptible patients is crucial to reduce morbidity and mortality.

Key words: Anesthesia, Complications, COVID-19 associated mucormycosis, COVID-19, Mucormycosis

INTRODUCTION

The second wave of COVID-19 pandemic in India was accompanied by a surge in mucormycosis, an opportunistic fungal infection. It has been declared as a notifiable disease in 11 states under the Epidemic Diseases Act 1897. COVID-19 associated mucormycosis (CAM) is a progressive and invasive rhino-orbito-cerebral disease. The triad of high index of suspicion for early diagnosis, antifungal therapy, and urgent surgical debridement is the cornerstone of optimum management. Even after waning of second wave of COVID, CAM continues to be reported and these patients require prolonged course of treatment and repeated surgical debridement under anesthesia.[1-4]

Patients undergoing surgery for CAM present multiple challenges for anesthetic and perioperative management. Being an emergency surgical procedure there

Access this article online

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

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is usually inadequate time for sufficient investigations and optimization of the patient preoperatively. These patients pose high risk for perioperative challenges and complications due to variety of causes. Managing the interplay of all these challenges to decrease morbidity and mortality in CAM crucial and insights based on experiences is required. Hence, we conducted a retrospective observational study with primary objective to appraise the anesthetic management and perioperative course of all the CAM patients undergoing anesthesia. The demographic parameters, co-morbidities, intraoperative, and post-operative complications, factors associated with it and outcome of the patient were also studied. The derivatives of the study will aid in anticipation of a variety of challenges and complications, prepare for them and manage them promptly and possibly will help to prepare an evidence based standard perioperative management protocol in these patients.

METHODOLOGY

It was an observational retrospective study conducted at a tertiary care teaching public institute which was converted to a dedicated COVID hospital and tertiary referral center for mucormycosis. Institute's ethics committee approval (ECARP/2021/114) was obtained. Study period comprised of 4 months, from February 15, 2021, to June 15, 2021. Waiver of consent was obtained owing to the observational nature of the study and retrospective data collection. All the patients who underwent surgical debridement of CAM under anesthesia during the study period were included in the study.

Following data were collected from the medical records: demographics (age, sex), associated co-morbidities, detailed airway assessment and Mallampati classification, biochemical parameters and available investigations, electrocardiogram (ECG), available radiological findings from X-Ray chest, and computed tomography (CT) scan of thorax high-resolution CT (HRCT). COVID-19 reverse-transcriptase-polymerase chain reaction (RT-PCR) status on the day of surgery and history, severity of COVID-19 (mild, moderate, and severe) and treatment details including medications and oxygen, ventilator therapy was recorded. American society of Anaesthesiologist Physical Status (ASA-PS) classification, anesthesia techniques and details of anesthesia management, surgical procedure and duration of surgery were recorded. Vital parameters: Heart rate (HR), systolic and diastolic blood pressure, oxygen saturation (SpO_2), ECG was noted. Intraoperative investigations such as arterial blood gases (ABG), serum electrolytes (sodium, Na^+, and potassium, K^+), and blood sugar (BS) were recorded. Perioperative complications, details of interventions and complication management were noted.

Outcome of the patient in the immediate post-operative period and at the end of 1 week was noted and categorized either as discharge, still undergoing treatment or death and the cause of mortality was recorded.

Statistical Analysis

Qualitative data were represented in form of frequency and percentage. Quantitative data were represented in form of Mean ± Standard Deviation (SD), median and interquartile range. Appropriate statistical software, including but not restricted to MS Excel, and PSPP version 1.0.1, was used for statistical analysis. Graphical representation was done in MS Excel package included in Microsoft Office 365. An alpha value (*P*-value) of <0.05 was used as the cutoff for statistical significance.

RESULTS

A total of 41 patients were operated for CAM during the study period of 4 months, comprising of 31 (75.6%) males and 10 (24.4%) females. Mean age was (56.07 ± 11.980 SD) years. Demographic and investigational parameters across study population are shown in Table 1. Comorbidities were present in 38 (92.7%) patients as depicted in Figure 1, and 25 (60.97%) had multiple comorbidities. All patients had history of COVID within the previous 6 weeks of presentation and eight (19.51%) were positive at the time of the procedure. Figure 2 mentions the details of COVID infection and treatment received.

According to the ASA PS classification, 15 (36.5%) patients were ASA 2 and 23 (56%) were ASA 3, 4 whereas two patients (4.8%) were designated ASA1

Table 1: Distribution of demographic and investigational parameters across study population

Parameters	Mean	Std. Deviation	Std. Error	95% Confidence Interval of the Difference	
Age	56.07	11.980	1.871	52.29	59.85
CT score	14.39	5.152	0.805	12.76	16.02
HB	10.50	1.537	0.240	10.01	10.98
TLC	9.97	3.586	0.560	8.84	11.11
PLT	202.756	67.0846	10.4768	181.582	223.931
PH	7.32	0.041	0.006	7.31	7.33
FBS	220.76	72.334	11.297	197.92	243.59
Creat	2.050	1.1595	0.1811	1.684	2.416
NA	137.122	4.7392	0.7401	135.626	138.618
K	2.91	0.585	0.091	2.73	3.10
CRP	38.34	27.264	4.256	29.74	46.95
LDH	436.83	142.388	22.237	391.89	481.77
Ferritin	610.85	170.899	26.690	556.90	664.79
Surgery duration	125	39.0013	6.0910	112.690	137.310

CT: Computed tomography, PLT: Platelet, FBS: Fetal bovine serum, CRP: C-reactive protein, LDH: Lactate dehydrogenase

status. General anesthesia (GA) was the most common anesthesia technique used, in 35 (85.4%) patients and 6 (14.6%) patients underwent Monitored Anesthesia Care (MAC). MAC converted to GA in four patients due to surgical requirements. GA was administered using standard balanced anesthesia technique. Induction was done using propofol in (80.9%), etomidate (14.6%), and thiopentone sodium (2.43%). Prepared difficult airway cart was ensured for all cases and fiber optic bronchoscope was kept ready for indicated cases. Anesthesia was maintained with atracurium, sevoflurane, and dexmedetomidine. Volume control and pressure control volume guaranteed (PCV-VG) mode of ventilation with application of positive end expiratory pressure was used in all patient.

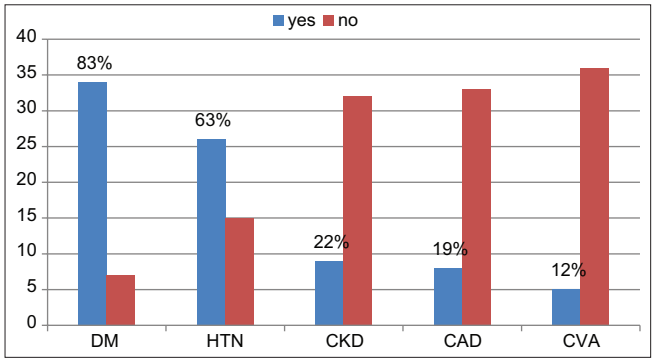

Figure 1: Comorbidities. DM - Diabetes Mellitus, HTN - Hypertension, CKD - Chronic Kidney Disease, CAD - Coronary Artery Disease, CVA - Cerebrovascular accident

Central venous cannulation (CVC) and arterial cannulation were required in 16 (39.02 %) and17 (41.46%) patients, respectively. Peri-operative course was eventful in 30 (73.17%) patients. Difficult airway was encountered in 18 (43.9%) patients among whom ten had difficult mask ventilation, 13 had difficult laryngoscopy and intubation, and five patients had both. Tracheostomy was done in one patient. Peri-operative events are described in Figure 3. Immediate postoperative intensive care unit (ICU) care was needed in 10 (24.39%) patients for continued hemodynamic and ventilatory support. Five patients (12.2%) came for recurrent surgeries.

We analyzed the risk factors associated with occurrence of perioperative events. The significant factors were presence of more than one comorbidity ($P = 0.023$), moderate to severe COVID 19 ($P = 0.006$), and HRCT score >10 ($P = 0.006$). There was no mortality in the immediate post-operative period. At the end of 1 week from the day of surgery four (9.8%) patients were discharged, 33 (80.5%) were still continuing treatment, and four (9.8%) died due to multiorgan failure in invasive mucormycosis [Figure 4].

DISCUSSION

A total of 41 patients were operated for CAM, showing male preponderance in the age group of 50–60 years. All the patients had been reported RT-PCR positive within the previous 6 weeks and 19.5% patients were positive at the time of surgery. Most of the patients (92.7%) had

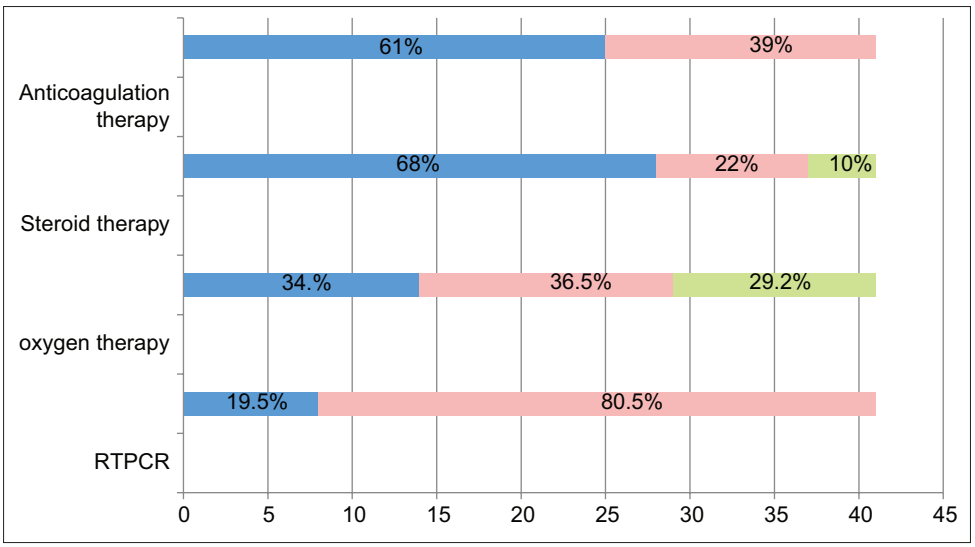

Figure 2: COVID related history
Anticoagulation therapy: yes no
Steroid therapy: Methylprednisolone Dexamethasone None
Oxygen therapy: Non Invasive Ventilation Non rebreathing Mask Nasal Prongs
RTPCR: Positive Negative

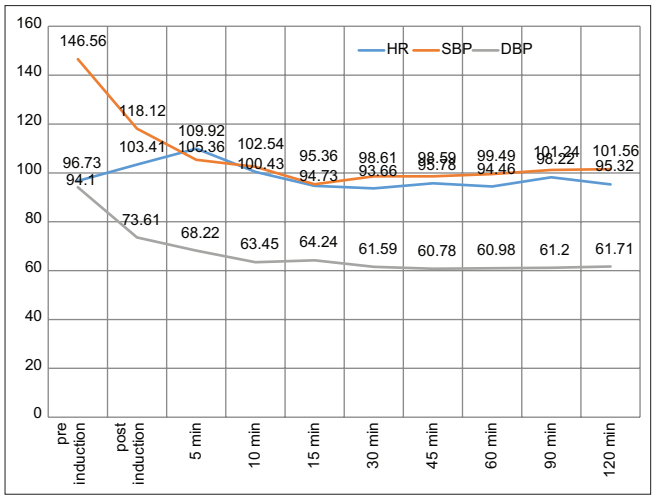

Figure 3: Trends of hemodynamic variables. HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

uncontrolled comorbidities. Although some comorbidities were pre-existing, many were diagnosed at the time of evaluation for CAM. Use of steroids (Methyl prednisolone or dexamethasone), tocilizumab, oxygen, and raised ferritin were found in most of the patients. Home treated and patients transferred from periphery had not received anticoagulation during COVID. Although we did not study causation of CAM; immunosuppression, hyper-ferritinemia and hyperglycemia in COVID with microthrombi may form favorable conditions for thriving mucor as suggested by Song *et al*, Rawson *et al.*, and Elinay *et al.*

Invasive mucormycosis has high morbidity and mortality and urgent radical debridement is necessary along with amphotericin therapy. Hence, once diagnosis was made time elapse for preoperative optimization of patients and multi-disciplinary intervention was not advisable and patients were posted as emergency. Most of the patients had uncontrolled hypertension, hyperglycemia, acidosis, and hypokalemia. We observed that the risk stratification by ASA-PS status alone underestimated the perioperative risk as many other factors like active COVID infection and its pulmonary and hematological sequalae, invasive mucormycosis pathology, airway changes, and acute conditions such as hyperglycemia, fever, resting tachycardia, changes in blood gas status, influenced the risk. Hyperglycemia (median BS 215 mg/dl) was the universal finding both preoperative as well as intraoperative period and it was difficult to achieve normoglycemia in spite of insulin infusion. Studies have mentioned that hyperglycemia in COVID is due to pancreatic islet is or stress hyperglycemia and is difficult to optimize. Amphotericin B therapy associated adverse effects such as nephrotoxicity, renal insufficiency, hypokalemia, hypermagnesemia, and metabolic academia were observed in most patients. Therefore, perioperative blood sugar, blood gases and electrolytes monitoring are advised at regular intervals along with titrated insulin therapy and correction of arterial blood pH and dyselectrolytemia.

GA with endotracheal intubation and controlled ventilation with throat packing was the anesthesia technique of choice in 85.4% patients whereas MAC was rendered to14.6% patients for superficial, small redo debridement and confirmed readiness to convert to GA. MAC was converted to GA in four patients as the disease spread was deeper. Balanced anesthesia with titrated anesthetic doses was used for all patients. Standard monitoring including SpO_2, NIBP, ECG, urine output for all cases and neuro-muscular transmission, gas analysis and airway pressures were additionally monitored for cases under GA.

Difficult airway was found in 18 (43.90%) patients. Challenges during mask ventilation and laryngoscopy were encountered due to facial swelling, extensive invasive mucormycosis involving face, maxilla and teeth, limited mouth opening, obesity, short neck, and restricted neck movements. Four patients had tobacco related oral submucous fibrosis. Video laryngoscope and McCoy blade were used as indicated. Cormack Lehane grade 3 in five and grade 4 in two patients were observed and Bougie guided intubation was needed in seven patients. As nasal intubation is contraindicated in mucormycosis, oral fibre optic intubation, retrograde guide wire guided intubation and tracheostomy was needed in one patient each. Extensive rhino-orbito-cerebral mucormycosis and diabetes mellitus have increased incidence of difficult airway. Hence, preparedness for difficult airway scenario is must and if available a video laryngoscope may be used.

An ultrasonography guided CVC and arterial cannulation was done in 16 (39.02%) and 17 (41.46%) patients respectively for various indications. They were CKD, acute kidney injury (AKI), severe hypovolemia, uncontrolled hypertension, labile hemodynamic status, need for vasopressors, ionotropic and bicarbonate therapy, serial ABG sampling, electrolytes monitoring and unavailability of peripheral intravenous access. Difficulty was faced in establishment of peripheral intravenous access in most patients due to prolonged hospital stay and Amphotericin B induced thrombophlebitis.

Several studies have cited respiratory complications in COVID due to reactive airway, increased secretions and active inflammatory process in acute stage and restrictive or obstructive lung disease, pulmonary fibrosis, decreased pulmonary compliance as post-COVID-19 illness pulmonary sequalae. Higher mean airway pressures were observed in most patients (28-38 cm H_2O). These patients were initially ventilated on volume control mode but due

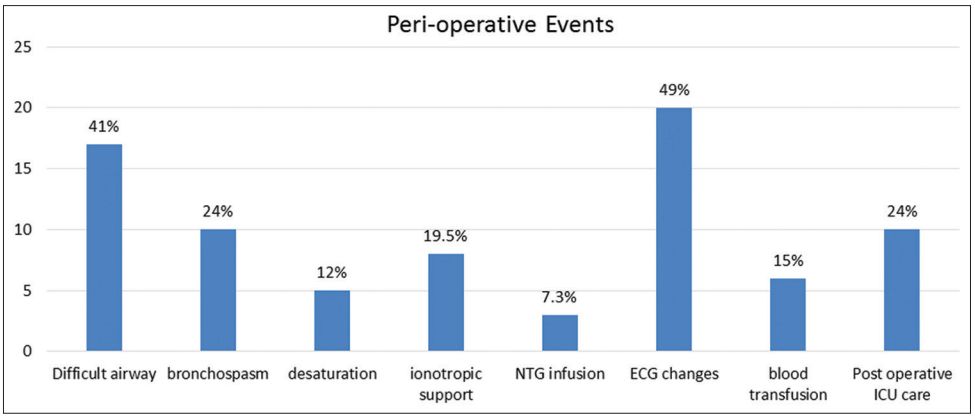

Figure 4: Perioperative Events

to persistently raised airway pressures were changed to PCV-VG mode to maintain a tidal volume of 6 ml/kg. Few patients were observed to have persistently raised $EtCO_2$ (>35 mm Hg) and decreased tolerance for apnea during laryngoscopy, intubation and endotracheal suction despite supplemental apneic oxygenation. Bronchospasm was seen 21.95% of the study population and desaturation (SpO_2 90%) was seen in 12%. Perioperative steroids, bronchodilator nebulization, and supplemental apneic oxygenation were used in these patients. Anticipating respiratory complications in COVID lung, use of steroid supplementation, bronchodilator nebulization, supplemental apneic oxygenation and monitoring airway pressures and use of appropriate mode for optimum ventilation for better outcome is recommended. Immediate post-operative ICU care was needed in 10 (24.39%) patients for continued hemodynamic and ventilatory support. Dedicated ICU/HDU for perioperative care of CAM is necessary in the current scenario.

Preoperatively most patients presented with hypertension and tachycardia which persisted in spite of anxiolysis and hydration. Intraoperative labile hemodynamic parameters were observed with hypotension and tachycardia commonly in patients with uncontrolled HT and intra-operative vasopressor support was required in eight (19.5%) patients and was continued in two patients in the post-operative period. Cardiac complications in form of ECG changes were seen in 20 (48.8%) patients. They were ST-T changes seen in three patients, cardiac arrhythmias in 12 patients in form of ventricular premature complexes, atrial premature complexes and atrial fibrillation and hypokalemia induced ECG changes in five patients. Anti-arrhythmic drugs such as lidocaine, amiodarone, diltiazem, and beta-blockers (metoprolol) for rate control were used for respective arrhythmias. Possible causes of perioperative labile hemodynamic parameters, hypotension, and arrhythmias could be pre-existing cardiac diseases, COVID induced myocardial dysfunction, post-COVID and steroid induced adrenal suppression, multiorgan dysfunction due to sepsis, and amphotericin which have been reported. 2-D Echocardiography could be available only in few patients due to emergency. Blood loss during the surgery was within the acceptable limit ranging from 250 ml to 400ml. Blood transfusion was required in six patients due to pre-existing severe anemia. Furthermore, intraoperative hyperglycemia, acidosis, and hypokalemia were observed in most of the patients and titrated infusions of insulin, bicarbonate and potassium were used when indicated. Hence, it is essential to maintain adequate mean arterial pressure, cardiac output and normovolemia guided by invasive monitoring and timely measurement and correction of BS, blood gas, pH, and electrolyte abnormalities and for better perioperative outcome and prevent postoperative complications.

Occurrence of perioperative events and complications were clinically highly observed in patients of age >60 years, multiple comorbidities, hyperglycemia (BS >140), severe COVID, CORAD >10, high inflammatory markers (Ferritin, C-reactive protein), RT-PCR positive status, preoperative acidosis, hypokalemia and extensive, invasive rhino-orbito-cerebral, and mucormycosis. Although, statistical significance was proved in patients with the presence of more than one co-morbidity, severe COVID 19, and HRCT score >10. All these factors can be used to predict perioperative outcome in CAM and can be used to devise a scoring system in addition to ASA for perioperative risk stratification and predicting occurrence of perioperative events and complications. If complications can be predicted using above factors and score, better preparedness and prompt management will help to reduce perioperative morbidity and mortality. As the current study has limitations due to observational, retrospective and single center study, further randomized controlled studies would help to validate these factors.

Few unique cases presented with multiple challenges deserve mention. Acute febrile illness and highly raised

total leukocyte counts and inflammatory markers at the time of surgery, multiorgan dysfunction with sepsis presented with severe hemodynamic instability. Multiple uncontrolled comorbidities, extensive disease involving orbit, maxilla, and face with severely restricted mouth opening was present in one of the patients and required tracheostomy. A patient with extensive cerebral mucormycosis uncontrolled seizures required extensive surgery and prolonged ICU stay. Pulmonary thromboembolism and intractable atrial fibrillation were observed and required intensive prolonged management for the same. Two patients were renal transplant recipients and one of them was in graft rejection phase with oliguria, deranged renal function tests, dyselectrolytemia and anemia required hemodialysis preoperatively. One patient who had severe COVID pneumonia (CT score 22/25), obstructive sleep apnea, and obesity (body mass index 35 kg/m^2) required post-operative mechanical ventilation and further prolonged CPAP support. Five out of 41 patients (12.2%) came for recurrent surgeries and each time presented with additional challenges. Teamwork among various specialties to manage this prolonged and recurrent disease is essential to reduce overall morbidity and mortality. There was no mortality in the immediate postoperative period. At the end of one week from the day of surgery four patients (9.8%) died due to multiorgan failure in extensive, invasive mucormycosis. Reported mortality in mucormycosis and CAM varies between 50% and 80% in various studies.

We conclude that CAM present as emergency procedures providing insufficient time for preoperative optimization for uncontrolled hypertension, hyperglycemia, acidosis, hypokalemia, AKI, etc. Anesthesia technique of choice is standard balanced GA or MAC in few select cases. Common intraoperative challenges were difficult airway, unstable hemodynamic status, ECG changes (arrhythmia, ischemia etc.), respiratory complications in COVID lung and metabolic and electrolyte derangements. Invasive monitoring, central venous and arterial cannulation, vasopressors, veno-dilators, anti-arrhythmic and post-operative ICU care may be required and should be promptly available. Patients with presence multiple co-morbidity, severe COVID 19, and HRCT score>10 are at higher risk for perioperative complications. All these factors can be used to predict perioperative outcome and can be used as a scoring system in addition to ASA for perioperative risk stratification. Further large randomized controlled studies would help to validate these factors.

Thus, from the experiences of this study we may recommend high watchful expectancy and preparedness for anticipated and unanticipated adverse events. Comprehensive preparedness for difficult airway management, invasive monitoring, unstable hemodynamic, ischemia, arrhythmia, and metabolic derangements is vital. High vigilance for respiratory complications in COVID lung and use of apneic oxygenation, steroids, bronchodilator nebulization, monitoring airway pressures and use of appropriate mode for optimum ventilation may help for better outcome. Risk estimation to predict perioperative complications and outcome should be inclusive of ASA-PS, COVID severity and lung involvement, degree of invasion by mucormycosis, multiorgan involvement and acute biochemical and metabolic derangements. Peri-operative dedicated ICU care should be ensured. Anticipation, meticulous preparation and vigilant monitoring for prompt detection and management of complications in susceptible patients is crucial to reduce perioperative morbidity and mortality.[5-10]

CONCLUSION

CAM are emergency procedures providing insufficient time for pre-operative optimization. Anesthesia technique of choice is GA and MAC in select cases. Thorough preparedness for difficult airway management, invasive monitoring, vasopressors, ionotropic, venodilators, and antiarrhythmic drugs is vital. Common intraoperative challenges were unstable hemodynamics, ECG changes (arrhythmia, ischemia etc.), and respiratory complications in COVID lung. High vigilance for prompt management of complications in susceptible patients is crucial to reduce morbidity and mortality.

ACKNOWLEDGMENT

We would like to acknowledge all the members of Department of Anaesthesia, Medicine, ENT and all allied surgical and medical branches for working as a team to manage this epidemic and pandemic.

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How to cite this article: Harde M, Devaraj N, Zile V, Dighe P. Anesthetic and Peri-operative Challenges of COVID-19 Associated Rhino-Orbito-Cerebral Mucormycosis. Int J Sci Stud 2022;9(12):90-96.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Propeller Flaps for the Coverage of Lower 1/3 Leg Defect

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Abstract

Background: Local propeller flaps preserve the main vascular arteries of the lower extremity and muscle function, avoiding the need for a microsurgical anastomosis and the benefit of providing a coverage. Our goal in this study was to demonstrate the versatility, safety, and complications of the propeller flaps for lower 1/3 leg defect.

Methods: We present a series of 11 patients from August 2019 to December 2021 whom we used local propeller flaps to restore small-to-medium soft-tissue defects of the lower limb in the Department of Burns and Plastic Surgery, Civil Hospital, Ahmedabad. Flap was based on single perforator of peroneal artery and posterior tibial artery rotated to 90–180°. Defect size was from 4 cm × 3 cm to 7 cm × 5 cm.

Results: Two patient developed partial flap necrosis, which was managed with skin grafting. Two patients developed venous congestion, which subsided spontaneously without complications. Three patients develop venous congestion which led to complete flap loss. Rest of the flaps survived well with good aesthetic results.

Conclusion: The perforator-based propeller flap for distal leg and ankle defects is a good option. This flap design is safe and reliable in achieving goals of reconstruction. The technique is convenient, less time consuming, and with minimal donor site morbidity. It provides esthetically good result.

Key words: Propeller flap, Lower 1/3 leg defect, Minimal donor morbidity and Aesthetically good results

INTRODUCTION

Soft-tissue reconstruction of the lower 1/3 of leg is difficult and challenging. Due to limited mobility and availability of overlying skin, even a small defect in the distal leg may require a microsurgical reconstruction.

The field of reconstructive surgery has taken a significant leap forward with the introduction of perforator flaps. This has been made possible with the development of knowledge in vascular anatomy and cutaneous circulation.

Advantage of perforator flaps is that they are safe, reliable, and with minimal donor site morbidity. A propeller flap has additional advantage of wider mobilization and rotation so as to increase reach of local flap and their versatility.

The propeller flap was first described in 1991 by Hyakusoku *et al.*, as a fasciocutaneous flap rotated 90° to cover defects resulted from release of post-burn contracture in cubital and axillary area.

In this study, the experience with perforator-based propeller flap based on posterior tibial and peroneal artery is reported. The flap was rotated from 90 to 180° to cover the defect over the lower 1/3/leg defect.[1-6]

MATERIALS AND METHODS

From August 2019 to December 2021, 11 patients were treated with perforator-based propeller flap for distal leg defect. All were male. Mean age was 44 years.

One patient had diabetes mellitus and no history of other comorbid conditions. One patient presented with medial malleolar soft-tissue defect, one patient with lateral

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www.ijss-sn.com

Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

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malleolar defect, and five patients presented with defect over anterior aspect of the lower tibia.

Size of defects ranged from 4 × 3 to 7 × 5 cm. The flaps were based on posterior tibial artery in two patient and peroneal artery in nine patients.

All flaps were islanded on a single perforator. The perforator-based propeller flap used in our series is a "skeletonized perforator flap."

Flap Design

- Concept of propeller flap corresponds to two blades of propeller of unequal length and perforator forming the pivot point. When two blades rotated, the long blade fills the defect
- The distance between proximal tip of the flap and the perforator should be equal to the distance between the perforator and the distal limit of the defect with 1 cm added to prevent tension in the flap [Figures 1-4].

For Coverage of Defect Therapy over Lateral Malleolus

For coverage of defect over lateral malleolus is title of Figure 2.

For Coverage of Defect Therapy over Media Malleolus

For coverage of defect over medial malleolus is title of Figure 3.

For Coverage of Defect over Anterior Lower Tibia

For coverage of defect over anterior lower tibia is title of Figure 4.

RESULTS

- Eleven patients with defect over the lower 1/3 leg defect region were operated from August 2019 to December 2021.
- Two patients developed partial flap necrosis with marginal wound dehiscence which was managed with skin grafting
- Two patients developed transient venous congestion, which subsided spontaneously without complications
- Three patients developed venous congestion which led to complete flap loss possibly due to high velocity trauma
- Other patients provided stable coverage of the defect with good contour and skin cover.

DISCUSSION

- There are many possible reconstructive options for this region such as local flaps, distant flap, and free flap. Local flap includes random pattern flaps, fasciocutaneous flaps, reverse sural fasciocutaneous flap, and muscle flap
- Distant includes cross leg flap and free flaps. Random pattern flaps have high incidence of failure. Free flaps have significant donor site morbidity and long operating time
- The concept of perforator flaps has progressed with improvement in understanding of flap perfusion based on different studies of Taylor on angiosomes of the body
- A propeller perforator flap is more advantageous in gaining tension-free reach to the defect due to wider mobilization and rotation options

Patient	Age/sex	Location of defect	Size (in cm)	Perforator	Follow-up (months)	Complications	Mode of injury
1	25/Male	Anterior lower tibia	4×3	Peroneal	3 months	None	Moderate velocity trauma
2	50/Male	Anterior lower tibia	5×5	Peroneal	3 months	Marginal wound dehiscence	High velocity trauma
3	60/male	Lower anterior tibia	3×3	Peroneal	3 months	None	Moderate velocity trauma
4	68/Male	Medial malleolus	3×3	Posterior tibial artery	3 months	Transient Venous congestion	Low velocity trauma
5	30/Male	Lower anterior tibia	5×5	Peroneal	3 months	None	Moderate velocity trauma
6	57/Male	Lateral malleolus	3×4	Peroneal	1.5 months	None	Low velocity trauma
7	50/male	Anterior lower tibia	5×5	Peroneal	1.5 months	Transient venous congestion	Moderate velocity trauma
8	50/Male	Anterior lower tibia	3×3	Peroneal	-	Venous congestion	High velocity trauma
9	30/Male	Anterior o-medial lower tibia	4×3	Peroneal	-	Marginal wound dehiscence	High velocity trauma
10	38/Male	Anterior o-medial lower tibia	5×5	Peroneal	-	Venous congestion	High velocity trauma
11	30/Male	Medial malleolus	3×3	Posterior tibial artery	-	-	High velocity trauma

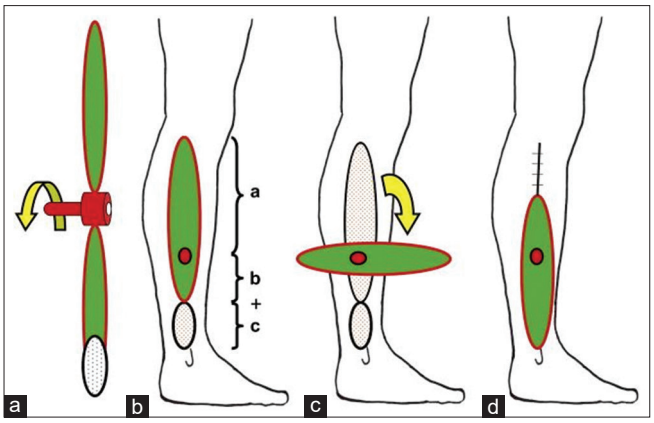

Figure 1: Flap design

Figure 2: (a) Intra-operative, (b) Pre-operative, (c) Intra-operative, (d) Post-operative, (e) Follow-up.

- In all our patients, we used a flap design rotated up to 180 degrees to cover ankle defects based on "propeller ankle defec With 180° rotations, the distant reach of the flap is possible and reliable. This flap design increases the reach of local perforator flaps, thus increasing their versatility. This flap is found to be suitable in small-to-moderate size defects (4 × 3 cm–7 os flap is found to be suitable in small-to-

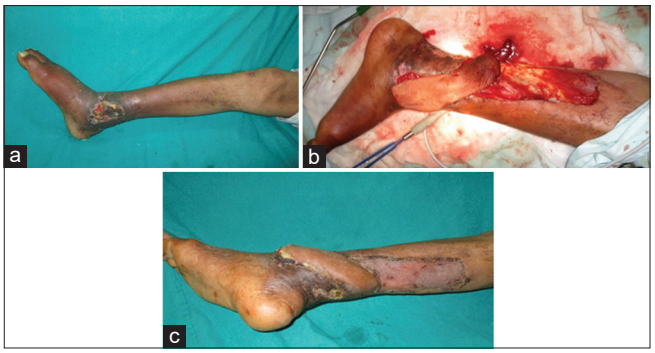

Figure 3: (a) Post-operative, (b) Pre-operative, (c) Intra-operative.

Figure 4: (a) Post-operative, (b) Pre-operative, (c) Marginal wound dehiscence follow by split thickness skin graft

- Three flaps underwent total flap necrosis most probably due to the high velocity trauma besides other factors
- In diabetic mellitus and atherosclerosis, peroneal artery-based perforator flap is comparatively safe because it is the last artery to be affected in the lower limb.[7-13]

CONCLUSION

The perforator-based propeller is a simple and versatile technique and is less time consuming with no donor site morbidity. It is ideal for reconstruction of small-to-medium size defects of the lower 1/3 leg defect with good cosmetic, excellent color, and thickness match

Disadvantages of these propellers flap have a limited role in large defects and variable location of the perforators.

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How to cite this article: Rana HA, Mistry KR, Suri MP, Sachde JP, Ganapathy N, Krishna A, Kachhchhadiya N. Propeller Flaps for the Coverage of Lower 1/3 Leg Defect. Int J Sci Stud 2022;9(12):97-100.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Various Modalities of Reconstruction of Nasal Defects

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Abstract

The nose represents the most important site for the esthetic face. The smallest loss of substance will create aesthetic and psychosocial concerns for patients; therefore, surgeons who perform nasal reconstruction should be strictly confident with the normal as well as abnormal surgical anatomy to execute perfectly the procedure for patient's condition. To achieve, the original shape is the end target of any reconstruction in terms of appropriate of three-dimensional geometry, proper establishment of symmetry, and good color and texture match to the adjacent structures that are paramount features. At present, we have multiple surgical options to re-establish normal or near normal function and anatomy; nevertheless, the management of nasal defects can be often challenging. The present goal is to highlight some of the more common techniques used to reconstruct cutaneous, cartilage or composite defects of the nose with a specific focus on decision-making based on the esthetic subunit and defect size. Our aim is to share common problems and offer practical suggestions that we have found helpful in their clinical experience.

Key words: Forehead flap, Local flap, Nasal defect, Nasal reconstruction, Naso labial flap, Subunit

INTRODUCTION

Nasal defects can be post-surgery, burns, and trauma. In this article, we aim on reconstruction of all nasal defect except post-onco surgical defect. This criteria can be effectively applied to traumatic issue, in the cases of burns and trauma.[1] Initial management should be focused on removing any possible wound contamination before surgery. The nose and the periocular region own a key position in the aesthetic face; its distinct anatomy combined with the functional, social, and esthetic concerns makes reconstruction challenging.[2] We may come across patients with unrealistic expectations. In all cases, esthetics face is the main concern. Post-animal bite, road traffic accident, and post-burn defect cases remain main pool of patients with the nasal defect; one will come across in India.[3] Nasal defects can involve the skin, cartilage, bone, or the internal mucosal lining up to various degrees, and even the smallest loss of substance will create esthetic and psychosocial concerns for patients.[4] Therefore, surgeons who perform nasal reconstruction should be strictly confident with the pertinent surgical anatomy to tailor the procedure to the patient's needs.[5]

The first technical description of nasal reconstruction was made by Indian physicians thousands of years ago. Since then, many refinements have been made to these primitive procedures, and many novel techniques have been reported. Burget and Menick have further improved nasal reconstruction techniques by establishing the esthetic subunit principle.[6] Loco regional flaps and skin grafts still play a significant role in the reconstruction of soft tissue and cutaneous defects; microsurgery can offer alternative options, especially for total or subtotal nasal reconstruction.[7]

The present goal is to highlight some of the more common techniques used to reconstruct cutaneous defects of the nose with a specific focus on decision-making based on esthetic subunit and defect size.[8]

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

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Evaluation of Defect

Nasal tissue can be divided into cover (skin, subcutaneous tissue, and muscle), support (cartilage and bones), and internal lining (vestibular skin and nasal mucosa).[9] The key for a successful nasal reconstruction is a careful evaluation of the defect and local tissue status. The most critical aspects to investigate are the size, depth, and location of the defect.[10]

Small defects of <1.5 cm can be closed primarily or reconstructed with a flap (local tissue) or full thickness skin graft (FTSG). Medium defects of 1.5–2.5 cm can be reconstructed with a flap (regional or local tissue) or FTSG. When the defects are large, that is, >2.5 cm, a flap (regional tissue) or FTSG should be exploited.[11] However, inconsistent recommendations for a general ranking are found in the literature, and disagreements exist about whether the cutoff for a primary closure should be 1 cm instead of 1.5 cm or whether a regional flap is mandatory for a medium-sized defect.[12]

Variation 0.5 cm should be applied to any difference in size and skin mobility among patients; a pinch test has to be completed preoperatively, especially when performing a primary closure or a local flap.[13] Healing by secondary intention not to be allowed considering the esthetic importance of face in that case, it is likely to be unacceptable. It requires weeks of careful wound care and, often, social segregation; surgical site infection.[14] The literature is inconclusive about this matter. Indeed, the small scars that result from second intention healing located in natural concavities (i.e., alar grooves) are often less evident than the bulkiness of flaps and grafts; anyway, secondary healing is much more unpredictable than primary healing, and a subsequent alar elevation would be an esthetic disaster.[15]

Microvascular free flaps are the gold standard in head-and-neck reconstruction and they have proven to be highly reliable and effective in total and subtotal nasal reconstruction. These patients should be counseled about their increased risk for complications.[16]

Nose-union of Subunits

The nose is one of the esthetic units of the face and is subdivided into its nine esthetic subunits.[17] They are identified by distinctive convex or concave surfaces, more specifically, from above downward as dorsum and paired sidewalls, nasal tip and paired alae, columella, and paired soft-tissue facets. Cutaneous nasal defect reconstruction should be considered in light of nasal esthetic subunit principles. If most of the surface area (>50%) of a convex subunit (tip or ala) is excised, reconstructing the whole subunit is usually preferable: The safe part of the subunit should be excised and the whole subunit should be reconstructed [Figure 1].[18]

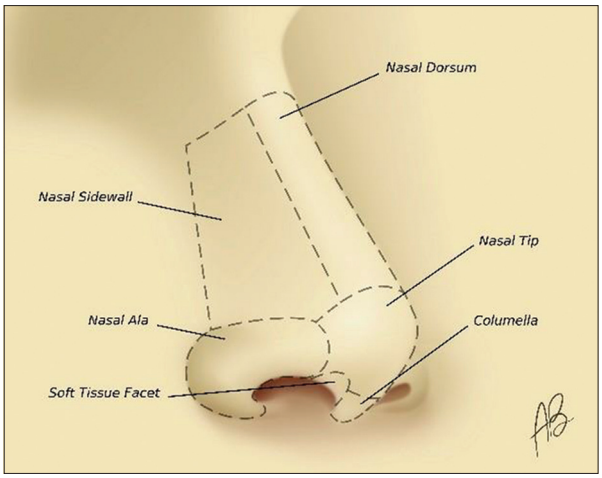

Figure 1: Esthetic subunits of the nose

The subunits differ in skin quality and shape and the latter is determined by the size and contour of the underlying structural framework. The nasal tip, nasal ala, and cranial dorsum (radix) have the thickest skin with more pilosebaceous units.[19] Conversely, the skin of the mid-lower dorsum and the upper nasal sidewall is usually the thinnest.[20] Reconstructive surgeons should be conscious of these difference because the recruitment of skin with a thickness that differs from that of the recipient area may lead to suboptimal results; moreover, a thick and non-elastic skin interferes with flap transposition by increasing wound tension and developing conspicuous standing cutaneous deformities.[21]

MATERIALS AND METHODS

All the patients signed an informed consent form and a photo release form. Peri-operative antibiotics such as amoxicillin with clavulanic acid were administered in all nasal reconstruction cases. We inject bupivacaine and with epinephrine in flap donor area with the aim of preventing bleeding during surgery. When facing a nasal cutaneous defect, we never choose healing by secondary intention because the outcomes are unpredictable in terms of cosmetic results. Local flap reconstruction is generally chosen over skin grafts, although the latter can be beneficial in following patients: (1) Patients who reject any staged procedure and/or multiple flap harvest, (2) patients with superficial defects, and (3) patients with significant medical comorbidities; anyway, a higher necrosis rate should be taken into account if compared to local flap surgery, and a suboptimal result should be expected in terms of contour and color match.

Defects and reconstructive strategies	
Esthetic Subunit	**Technique**
Dorsum and Sidewalls Cm	
<1.5	Primary closure
	Transposition flap (sidewall)
	Glabella flap
1.5–2.5	Glabellar flap (cranial defect) Bi lobed flap
	Dorsal nasal flap
>2.5	Para medial Forehead Flap
	Dorsal Nasal Flap
	Cheek advancement Flap
Tip, cm	
<0.5	Primary Closure
<1.5	Bi lobed Flap
	V-Y Island Pedicle Advancement Flap
1.5–2.5	Dorsal Nasal Flap
	Para medial Forehead Flap
>2.5	Para medial Forehead Flap
Ala	Nasolabial Flap
	Nasolabial Interpolated Flap
	Paramedial Forehead Flap

Management of Defects

Following table shows that different modalities were categorized as per size of defect so as to standardized it.

Skin Grafting

Grafting is be giving suboptimal result. Full-thickness skin grafts are suitable for reconstruction most superficial defects; however, the color-blending could be often disappointing, especially in sun-damaged reddish skin, where the FTSG will appear as a pale patch. When facing a large multi-subunit defect, the surgeon should be encouraged to adopt the well-recognized concept of reconstructing the nose in esthetic subunits. Using the subunit, principle is often ideal [Figure 2].

Figure 2: (a) Pre-operative, (b) Intra-operative, (c) Post-operative

An FTSG was planned and harvested from the retroauricular area (The 2-month post-operative picture shows an acceptable result in terms of color and contour match).

Considerations in choosing a donor site include the size, thickness and grade of sun exposure of the donor and recipient site skin, and the resultant cosmetic deformity/easy concealment of the donor site. Preferred donor sites include pre-auricular, post-auricular, and supraclavicular, and inner arm area; this site is more concealable than the supraclavicular area. FTSG exploited for tip reconstruction should be thinned minimally due to the characteristics of caudal nose skin.

Dorsal Nasal Flap

This flap can be used for large-sized defects of >2.5 cm located on the caudal dorsum–tip of the nose. However, in those cases, a paramedian forehead flap should be preferred to obtain a more acceptable esthetic outcome [Figure 3].

If a direct closure is planned, a careful and extensive undermining should be always accomplished to avoid any standing cutaneous deformity (SCD) and wound closure tension. In the caudal dorsum, a transverse fusiform excision should be reserved for the elderly to obtain a pleasing tip rotation (balancing nasal tip ptosis); if otherwise exploited, such direct closure could cause a tip distortion. If a thickness mismatch is present (i.e., glabellar skin moved to the inner canthus), thinning of the flap is mandatory to obtain a pleasing result.

The dorsum and sidewalls are treated together because these two esthetic subunits are similar in terms of skin characteristics and reconstructive options. The dorsal and sidewall skin is usually mobile and less sebaceous. Local tissue can be easily mobilized to reconstruct small-to-medium-sized defects; instead, flaps from adjacent areas are exploited for large defects.

Small defects of <1.5 cm could be closed primarily due to the slight redundancy of cutaneous tissues. In the dorsum, the decision of whether to orient direct closure in the transverse or craniocaudal dimension should be made according to the shape and size of the defect.

Medium defects of 1.5–2.5 cm are not suitable for a primary closure. A local flap reconstruction is mandatory. In the cephalic dorsum (and sidewalls), a glabellar flap can mobilize a conspicuous amount of skin and cover a defect extending to the canthus. The flap can be harvested as a V-Y advancement flap or a more typical glabellar rotation flap.

Bilobed Flap [Figure 4]

Small defects of <1.5 cm could be treated with a bi-lobed flap. A bi-lobed flap (a double transposition flap with a

Figure 3: Dorsal nasal flap, pre-operative markings. A "V" shape was designed in an upside-down fashion over the glabella; then, a curvilinear line was drawn on the nasal–cheek junction till reaching the defect site. Pre-operative, (b) Intra-operative, (c) Post-operative

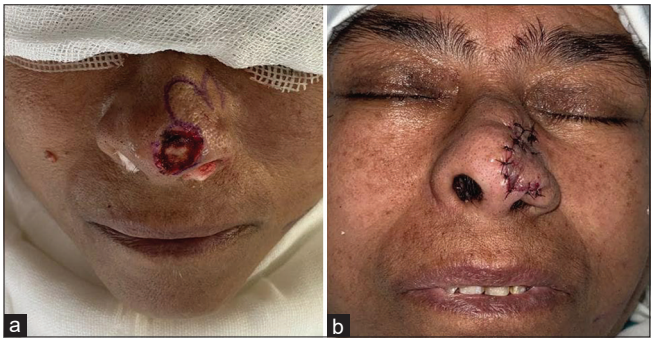

Figure 4: (a and b) Bilobed flap. Preoperative picture. A laterally based bilobed flap was planned to repair the skin defect (1.4 cm). The surface area and the width of the first lobe should be the same as the defect. The second lobe was designed in a triangular shape; the width was slightly less and the height was approximately 1.5 times greater than the first lobe

single base) with its geometrical features recruits elastic skin from contiguous subunits and minimizes the wound closure tension and standing cutaneous deformities The bi-lobed flap can be based laterally or medially. The first lobe (curvilinear) is designed immediately adjacent to the defect. The surface area and the width of the first lobe should be the same as the defect. The second lobe should have a surface area smaller than that of the defect and should be designed in a triangular shape; the width should be slightly less and the height should be approximately 1.5 times greater than the first lobe. The straight axes passing through the center of each lobe and defect are placed at about 45° from each other. The dissection is carried out below the muscular plane and above the perichondrium/periosteum. As for any other transposition flap, the donor site of the second lobe is closed first. Then, the first lobe is transferred to reconstruct the nasal defect. Finally, the second lobe is trimmed and stitched in the donor defect of the first lobe and the SCD is excised.

Forehead Flap [Figure 5]

The forehead flap is based on the supra trochlear vessels that pierce the orbital bone at about 2 cm lateral to the midline. It is commonly used for total resurfacing of the tip, nasal dorsum, and sidewalls or ala. The procedure can

Figure 5: Pre-operative, (b) Post-operative, (c) Follow-up

also be used for reconstruction of multiple subunits. It is a staged operation; two-stage reconstruction is more commonly performed, but it also can be performed in three stages to reduce complications and enhance the esthetic outcomes. A paramedian forehead flap (PFF) will usually give a more natural result because the entire esthetic unit can be restored and the scars can be concealed in natural boundaries.

Large defects of >2.5 cm are commonly reconstructed with a PFF.

Nasolabial Flap [Figure 6]

A nasolabial transposition flap is a viable option for alar reconstruction; anyway, this single-stage option results in a deformation of the alar facial sulcus (if left intact after tumor removal) and loss of symmetry that has to be restored with subsequent poor cosmetic result. An interpolated melolabial flap does not retain such downsides and it is a recommended option if the alar facial sulcus. This two-stage procedure leaves the alar facial sulcus untouched without the need for subsequent reconstruction The main drawback of this flap is a cosmetic deformity that lasts 3 weeks; a second procedure is necessary to divide the flap pedicle and inset the flap. Defects also affecting the alar facial sulcus and/or alar groove often require a third stage during which these natural boundaries are accurately recreated.

Post-operative Care and Complications

- Peri-operative antibiotics
- Head elevated
- Proper wound dressing is mandatory to avoid bleeding and infection
- In case, a hematoma is noticed, it should be promptly

Figure 6: Nasolabial folded flap. (a) Preoperative picture. A 22-year-old patient defect of the nasal ala. A nasolabial folded flap was planned to repair the full-thickness defect in two stages. (b) A nasolabial flap was folded to reconstruct the lining and external coverage after being thinned. Stage I: Immediate post-operative picture. A povidone iodine impregnated gauze was positioned. The donor site was sutured primarily. (d) The 3-month post-operative (Stage II) picture shows an optimal result; the nasal ala regained a good contour and alar facial sulcus was restored. Pre-operative, (b) Intra-operative, (c) Post-operative, (d) Post-operative

treated to avoid any compromise
- Trap-door deformity
- Lymphedema.

RESULTS

Out of the 20 patients, 14 were men and six were women, with ages ranging from 5 years to 60 years. Road traffic accidents accounted for six cases; post-human bite defects account for one cases; seven cases were due to post-animal bite, one case was due to Kite string injury, one case was congenital defect, one case was post-burn nasal defect, and 3 cases were post-surgical defect.

Full thickness defect was in 18 patients. In two patients, there was only cover defect. Defect of dorsum of the nose was there for two patients. Defect of the ala alone was there for two patients. Defect of ala and dorsum was presented for eight patients. Both the alae with tip present were found defective for one patients. Dorsum with ala, tip, and columella was present for five patient. Defect of tip alone presents for two patients.

All the post-traumatic and post-excision cases underwent secondary reconstruction. All the post-excision defects were reconstructed primarily. Reconstruction with PFF was performed in 10 patients. Dorsal nasal flap was done for one patients. Four cases underwent reconstruction with nasolabial flap. Two defects were resurfaced with FTSG and the graft take was 100% in all cases. One patient reconstruction with bilobed flap for nasal defect. One patient reconstructed with free radial forearm flap. One patient underwent only SSG because of poor general condition later prosthesis was applied to him.

Two patients had associated eye injury. Two patients had associated upper lip injury. Two patients had pre-operative nostril stenosis which was cleared postoperatively. Five patients required only one operative stage. Thirteen patients had two stages of surgery. Two patients had three stages of surgery.

All the pedicled flaps survived completely. In our study, none of the patients underwent reconstruction for support. Midline forehead flap based on the supra-trochlear vessels was used in the majority of patients with dorsal and tip nasal defects which is comparable to other studies. The maximum size of the defect was 43 × 39 mm and the minimum was 12 × 8 mm.

None of our patients had any significant complications. The results were evaluated as follows: Regarding the color, small-to-moderate nasal defects were reconstructed quite well with the midline forehead flap. The forehead flap had the same color and a superb texture match with the facial skin.

In our study, at 3–6 month follow-up, the contour of the reconstructive nose was found to be satisfactory and retained the good shape of the nose and projection of the tip. There was no need for reconstruction of the support. All the pedicled flaps survived completely. The two nasolabial flaps needed thinning as a second stage surgery.

CONCLUSIONS

Nasal reconstruction is deeply founded on the nasal subunit principle and the physician must bear in mind the various tissue quality among the subunits when outlining a reconstructive strategy. Primary targets of nasal reconstruction were satisfactory cosmetic and functional result. PFF is very versatile flap which can be used for almost type of nasal subunit defect. Forehead flap with inner lining by FTG, STG, and cheek flap can be used. Nasolabial and cheek flap can be used for only alar defect undoubtedly. Reconstructive surgeons should treat each patient as a distinct individual with a peculiar defect and the procedure should be customized according to the clinical conditions and the demands and wishes of our patients.

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How to cite this article: Sachde JP, Kachhadiya N, Rana H, Suri MP, Mistry K, Ganpathy N, Nakka A. Various Modalities of Reconstruction of Nasal Defects. Int J Sci Stud 2022;9(12):101-106.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Assessment of Anxiety among Pediatric Patients of Age 5–12 Years, Toward Dentist with and without Personal Protective Equipments

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Abstract

Introduction: The widespread transmission of COVID-19 pandemic has increased the need for Personal Protective Equipment (PPE) in dental and all health care settings. Treating child patients with the use of PPEs increase the efforts of dentists to manage the child and to make the parents convinced about the treatment modalities.

Aim: The aim of this study was to evaluate the anxiety in pediatric patients toward dentist with and without wearing PPE s using Buchanan's facial image scale.

Materials and Methods: Forty children (22 males and 18 females) were included in this study. They were examined by a dentist in normal attire in the first appointment, and dentist wearing PPEs in the next appointment, respectively. Anxiety rate was assessed using Buchanan's facial image scale in both appointments.

Results: Anxiety rate was found to be increased in the second appointment by mean score of 1.20. There was no statistically significant association between gender and anxiety of children toward a dentist wearing PPEs.

Conclusion: Efforts to practice with child friendly PPE s should be encouraged and success should be evaluated.

Key words: Anxiety, COVID-19, Pediatric patients, Personal protective equipments

INTRODUCTION

Dental fear and anxiety are a significant issue that affects pediatric patients and creates challenges in oral health management.[1] The importance of a person's outlook was highlighted by psychologists to develop a positive interpersonal relationship. There is still a continuing debate regarding dentists' attire and the choice of a white coat, suit, scrubs, or personal protective equipments (PPE) influence patient's view of dentist.[2] Several studies were published regarding child's preference toward dentist attire. However, all the studies give an overall view on child's preference level toward white coat, scrubs, formal attire, or a child friendly attire. It is important to understand the reasons behind their preference for particular attire and it should be on their own views and to their level of understanding.

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Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

The widespread transmission of COVID-19 pandemic has increased the need for PPE in dental and all health care settings. To maximize the quality of patient care, the protection of patients and dental staff PPE is part of standard precautions for infection prevention and control. The term PPE is used to describe all protective equipment that a dentist or dental nurse may use in the surgery such as gloves, gowns, shoe covers, head covers, masks, respirators, eye protection, face shields, and goggles.[3] With regard to pediatric dentistry, the PPE affects the voice tone, makes it more difficult for children to understand what a dentist is communicating, does not allow children to read facial expressions which are important for building their trust with a dentist, adds to white coat syndrome, and overall hinders interaction with the patient.[1] Although some

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techniques to manage the anxiety level are still possible and still performed, the additional safety measures may effectively worsen the relationship between pediatric patients and dental surgeons. Treating child patients with the use of PPE increase the efforts of dentists to manage the child and to make the parents convince about the treatment modalities.[4] It is usually more common that the child patient gets frightened and shows hesitation to treatment in a normal clinical atmosphere during this pandemic period. Efforts to practice with child friendly PPE's should be encouraged and success should be evaluated. The present study is a cross-sectional study to evaluate the anxiety in pediatric patients toward dentist with and without PPE s using Buchanan's facial image scale.

MATERIALS AND METHODS

The study was a cross-sectional study conducted among 40 children[5] (22 males and 18 females) presenting to the outpatient Department of Pediatric Dentistry, Government Dental College, Kottayam aged between 5 and 12 years. Parent's consent and child's assent were taken before the study. Two appointments were scheduled to clinically examine the patients. Clinical examination was carried out using mouth mirror and No 23 explorer. Child participants were examined by a dentist without wearing PPEs in the first appointment and the same children were examined in the next appointment by a dentist wearing PPEs. The child was instructed to choose an image from the Buchanan's facial image scale [Figure 1] in both the appointments based on their emotion during clinical examination. Scoring was done to evaluate the anxiety level, based on the image chosen by the patient. Child with no anxiety had a score of 1, low anxiety had a score of 2, moderate anxiety had a score of 3, high anxiety had a score of 4, and very high anxiety had a score of 5 [Table 1].

Inclusion Criteria

The following criteria were included in the study:

- Adults and children who were able to understand and communicate in English or Malayalam language.
- Children who were between 5 and 12 years of age
- Children with physical status level ASA I and II.

Exclusion Criteria

The following criteria were excluded from the study:

- Children who were cognitively disabled and unable to complete the survey independently.
- Children of ASA III and above.
- Children who were not accompanied by their parents.

Statistical analysis was done using SPSS software version 16. Inferential statistics were done using paired and unpaired *t*-test.

RESULTS

Demographic data included 40 study subjects who underwent clinical examination by a dentist before and after wearing PPEs, in which 22 were male and 18 were female. Anxiety rate was evaluated with the help of images chosen by the child participant from the Buchanan's facial image scale and scoring was done accordingly.

The mean anxiety rate among the total participants was found to be 2.53, when they were examined by a dentist without wearing any PPE in the first appointment. The mean anxiety rate was found to be increased to 3.73, when the same children were examined by a dentist wearing PPEs in the next appointment. This clearly shows an increase of mean score of anxiety rate by 1.20 in children, when they had been examined by a dentist with PPE s [Table 2].

Paired *t*-test was carried out and there was a statistically significant difference in the anxiety rate in children during clinical examination by a dentist before and after wearing PPE s [Table 3].

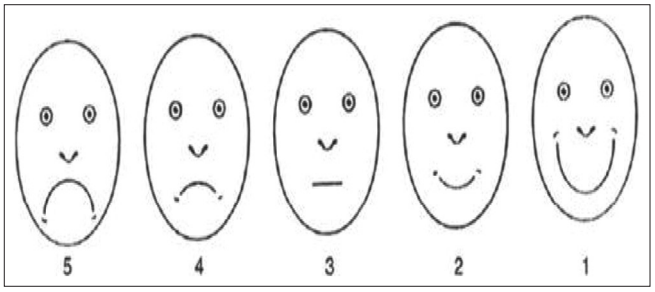

Figure 1: Buchanan's facial image scale

Table 1: Anxiety scores

Anxiety level	Scores
No anxiety	1
Low anxiety	2
Moderate anxiety	3
High anxiety	4
Very high anxiety	5

Table 2: Mean anxiety score before and after PPE

Anxiety scale	Mean	*n*	S.D
Anxiety scale before PPE	2.53	40	0.905
Anxiety scale after PPE	3.73	40	1.086

PPE: Personal protective equipment

Among the total of 40 study participants, 18 participants were female which formed 45% of study sample and 22 participants were male which formed 55% of study sample [Table 4].

Change in anxiety in both the genders was found and mean change in anxiety among males was found to be 1.09 and mean change in anxiety among females was 1.33 [Table 5].

Table 6 indicates the significance of change in anxiety in both the genders. Independent *t*-test was carried out and Levene's test for equality of variances was considered and it was found that there was no significant association of change in anxiety in children of both genders during oral examination by a dentist before and after wearing PPEs.

DISCUSSION

Verbal communication and eye contact are key factors involved in managing patients, especially in case of pediatric patients in dental clinics. During the spread of COVID-19 pandemic, it became a necessary protocol to work under PPEs. Apart from the safer side of this practice during the pandemic, child's perspective toward the dentist was challenging. Majority of the children were found to be anxious and fearful while seeing a dentist wearing PPEs than a dentist in formal attire.

The present study focused on the anxiety assessment in a child toward a dentist with and without PPEs. Anxiety rate was assessed by Buchanan's facial image scale. The child's anxiety level was found to be increased, when they had been examined by a dentist wearing PPEs. This showed that there was a statistically significant association between anxiety of children and personal protective wear of the dentist. This result was in agreement with a study conducted by Ravikumar *et al.* (2016).[6] According to the author, children preferred their pediatric dentist to wear white coat and colored scrubs, but they were highly anxious on seeing their dentist with protective wear. The present study's results were in contrast to a study conducted by Tong *et al.* (2014).[7] Majority of the child patients participated in this study chose PPE kit as better attire for the dentist.

When gender was considered in assessing anxiety, it was found that there is no significant association between gender and anxiety of children toward dentist wearing PPEs. This result was in agreement with a study conducted by Singh *et al.* (2020).[8] This study stated that females had a similar level of dental anxiety as compared to males. The results of the present study were in contrast to a study by Vlad *et al.* (2020),[9] which pointed out that dental anxiety was found to be higher in female children than males, but anxiety toward PPEs was not considered in any of these studies.

CONCLUSION

In the present scenario of COVID-19 pandemic, role of PPEs had become inevitable. However, the child's perspective toward protective wear was always challenging to a pediatric dentist. Anxiety rate of child patients was found to be increased, when the child was examined by a dentist wearing PPEs and there was no significant association between gender of the child and their anxiety toward a dentist with protective wear. To tackle the anxiety, protective wear can be made colored or cartoon printed and can be made a child friendly one.

LIMITATIONS OF THE STUDY

The study was done in a small sample of children, which could have influenced the outcome.

Table 3: Paired differences in anxiety scale before and after PPE

	Paired Differences		df	Sig. (2-tailed)
	Mean	SD		
Anxiety scale before PPE – Anxiety scale after PPE	−1.200	0.608	39	0.000

PPE: Personal protective equipment

Table 4: Gender distribution of study population

Valid	Frequency	Percent
F	18	45.0
M	22	55.0
Total	40	100.0

Table 5: Mean score of change in anxiety among males and females

Gender	*N*	Mean	SD
Change in anxiety			
Male	22	1.09	0.610
Female	18	1.33	0.594

Table 6: Significance of change in anxiety in both the genders

Independent sample *t*-test					
Change in anxiety	F	Sig.	*t*	df	*P*-value
Equal variances assumed	0.799	0.377	−1.265	38	0.214
Equal variances not assumed			−1.268	36.810	0.213

ACKNOWLEDGMENT

We would like to thank all the patients who participated in the study and Dr. Arun Rao, Public Health Dentist, Kottayam, India for helping us with the statistical analysis.

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How to cite this article: Rehna S, Joseph J, Kumar TVA, Syriac G, Sithara A, Sarbas V. Assessment of Anxiety among Pediatric Patients of Age 5–12 Years, Toward Dentist with and without Personal Protective Equipments. Int J Sci Stud 2022;9(12):107-110.

Source of Support: Nil, **Conflicts of Interest:** None declared.

Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

A Descriptive Clinical Oncological Analytical Research Study on the Molecular Pharmacology of Belagenpumatucel-L and Pharmaco-Oncoimmunotherapeutic Vaccines through Evidence-Based Medicine

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Abstract

Introduction: Belagenpumatucel-L, an allogeneic tumor cell vaccine, associated with the oncoimmunotherapeutic target, and transforming growth factor-β2 (TGF-β), is under clinical trial. Oncotherapeutic vaccines are used either as a substitute therapy in the treatment of chemoresistant or chemorefractory, and radioresistant or radiorefractory malignancies; or are used as a combination oncotherapy, along with chemotherapy, radiotherapy, pharmaco-immunotherapeutic targeted therapy, and surgical therapy. These modalities of onco-immunotherapy always increase the efficacy of comprehensive oncotherapy, while reducing the occurrence of frequent adverse effects caused by these oncotherapeutic regimens, otherwise. The monotherapeutic potential of pharmaco-immunotherapeutic anti-cancer vaccines is still in the investigative stages.

Objectives: This study was a descriptive clinical oncological analytical qualitative research study on belagenpumatucel-L and Pharmaco-Oncoimmunotherapeutic Vaccines.

Results: In this study, the efficacious molecular pharmacological mechanisms and potential pharmacotherapeutic significance of belagenpumatucel-L and pharmaco-oncoimmunotherapeutic vaccines were analytically explored, and comprehensively elaborated, along with an emphasis on TGF-β and telomerase, as pharmacotherapeutic targets for oncotherapeutic vaccines, through an evidence-based medicine research approach.

Conclusions: In this study, the significance of belagenpumatucel-L and pharmaco-oncoimmunotherapeutic vaccines, along with TGF-β and telomerase, as pharmacotherapeutic targets for oncotherapeutic vaccines were comprehensively elaborated.

Key words: Belagenpumatucel-L, Clinical oncology, Clinical research, Descriptive analytical research, Evidence-based medicine, Molecular pharmacology, Pharmaco-onco-immuno-therapeutic vaccines, Telomerase associated vaccines, TGF-β associated vaccines

Access this article online

www.ijss-sn.com

Month of Submission : 01-2022
Month of Peer Review : 01-2022
Month of Acceptance : 02-2022
Month of Publishing : 03-2022

INTRODUCTION

Transforming growth factor-β2 (TGF-β) is an unique molecular pharmacological target of oncoimmunotherapeutic vaccines. The uniqueness of TGF-β is associated with the display of its paradoxical activity, as it inhibits cellular transformation and prevents cancer progression in the

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early stages of tumorigenesis, but in the later stages, it promotes tumor progression through facilitating epithelial to mesenchymal transition, stimulating angiogenesis, and inducing immunosuppression. Due to this sort of a correlated balanced synchronization of step-wise chronologically contrasting tumor promoting and tumor suppressive ability, TGF-β and its pharmacodynamic pathway have represented potential opportunities for drug development; and several therapies, including oncovaccines, targeting TGF-β pathway. Blockade of only TGF-β_1 and β_2 is sufficient to enhance the efficacy of oncovaccines, which is further increased by PD-1 checkpoint blockade immunotherapy. TGF-β enables tumor evasion of immune surveillance through various mechanisms most of which converge on the impairment of tumor cell killing by immune effector cells. Along with inhibiting proliferation and differentiation of normal bronchial epithelial cells, TGF-β mediates conversion of CD4 and CD25-T cells to T regulatory (Tregs). Serum TGF-β levels are elevated in patients with lung cancer compared to normal individuals. Elevated plasma levels of TGF-β confer a poorer prognosis for patients with lung cancer.[1-7]

Objective

The objective of this descriptive clinical oncological analytical research study was to analytically explore the molecular pharmacology of belagenpumatucel-L and pharmaco-oncoimmunotherapeutic vaccines through an evidence-based medicine research approach.

METHODS

Ethical Approval

At first, the Institutional Ethics Committee clearance and approval were taken. The study was conducted in accordance with the ethical principles of Declaration of Helsinki and good clinical practices contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6 and ICH-E17), and in compliance with the global regulatory requirements. Informed consent was obtained from the patient participants. This study involved no risk to any patient.

Study Design

The study design was a molecular pharmacological and clinical oncological multivariate, multicenter, retrospective, qualitative, descriptive, and analytical research study.

Study Population

The study population was global patients, suffering from various stages of malignancies or borderline malignancies. The study population database was a global heterogeneous multi-disciplinary experimentations and study literature on pharmaco-onco-immuno-therapeutic vaccines and belagenpumatucel-L.

Study Period

The study period was 1.5 years, from January 1999 to February 1999; January 2002 to June 2002; June 2015; April 2016 to June 2016; May 2017; and June 2021 to March 2022.

Place of Study

This research study and the compilation of the study literature was conducted in the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Rational Pharmacotherapeutics, Pharmacoepidemiology, Pharmacovigilance, Pharmacogenomics, Evidence-based Medicine, Clinical Pathology, Pathology, Molecular Diagnostics, Clinical Oncology, Clinical Medicine, Respiratory Medicine, Clinical Research, Zoology, and Molecular Medicine, Dr. B. R. Ambedkar Medical College and Hospitals, J. J. M. Medical College and Hospitals, Karnataka, India; Presidency College, West Bengal, India; Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Dr. Moumita Hazra's Academic Centre, Dr. Moumita Hazra's Educational Centre, Hazra Nursing Home, Hazra Polyclinic And Diagnostic Centre, Dr. Moumita Hazra's World Enterprises, West Bengal, India, World; Gouri Devi Institute of Medical Sciences and Hospital, West Bengal, India; Mamata Medical College and Hospitals, Telangana, India; Rama Medical College Hospital and Research Centre, Rama University, Uttar Pradesh, India; Hi-Tech College of Nursing, Odisha, India; and Mahuya Diagnostic Centre and Doctors' Chamber, West Bengal, India.

Study Procedure

This study, a molecular pharmacological and clinical oncological multivariate, qualitative, descriptive, and analytical research study of the retrieved literature, derived through a thorough literature analysis from various available literature databases, was performed, to record, review, thoroughly analyze and delineate the molecular pharmacological basis of oncoimmunotherapeutic vaccines from a wide-ranged study literature containing molecular pharmacological researches, reviews, case presentations, and varied databases about the pharmaco-oncoimmunotherapeutic rationale of the clinical use of vaccines in the treatment of cancer patients, with a specific emphasis on telomerase and TGF-β, as molecular pharmacological targets of oncoimmunotherapeutic vaccines. After that, a multivariate evidence-based medical research study of comparative qualitative analysis of the global heterogeneous multidisciplinary experimentations and study literature on oncoimmunotherapeutic vaccines, as well as on telomerase and TGF-β, as molecular pharmacological targets of pharmaco-oncoimmuno-therapeutic vaccines, affecting global malignant and

borderline malignant patients, was conducted. This study was performed, by recording and the subsequent qualitative analyzes of oncoimmunotherapeutic vaccines, TGF-β, telomerase, and belagenpumatucel-L retrieved from the study literature database, along with selective elucidations and elaborations of the deduced study results, to derive an explicit and comprehensive interpretation of the intricate molecular pharmacological mechanisms of belagenpumatucel-L and oncoimmunotherapeutic vaccines, based on this evidence-based medicine research.

RESULTS AND DISCUSSION

This thorough qualitative analytical research study of the retrieved literature recorded from different types of medical experimentations and medical databases about oncoimmunotherapeutic vaccines, TGF-β and telomerase as molecular pharmacological targets of oncoimmunotherapeutic vaccines, and belagenpumatucel-L elaborated the following molecular pharmacological findings:

Since time immemorial, vaccines have been used to adapt the immune system to recognize pathogens, and prevent and treat diseases, such as cancer. Therapeutic cancer vaccines are attractive systemic immunotherapies that activate and expand antigen specific CD8 type and CD4 type T-cells to enhance anti-tumor immunity. Oncotherapeutic vaccines are used either as a substitute therapy in the treatment of chemoresistant or chemorefractory, and radioresistant or radiorefractory malignancies; or are used as a combination oncotherapy, along with chemotherapy, radiotherapy, pharmacoimmunotherapeutic targeted therapy, and surgical therapy. These modalities of oncoimmunotherapy always increase the efficacy of comprehensive oncotherapy, while reducing the occurrence of frequent adverse effects caused by these oncotherapeutic regimens, otherwise. The monotherapeutic potential of pharmaco-immunotherapeutic anti-cancer vaccines is still in the investigative stages. The basic cancer vaccines used include cell-based vaccines including whole cell vaccines, genetically modified tumor cell vaccine and dendritic cell vaccine, anti-idiotype antibody-based vaccine, protein- or peptide-based vaccines, heat shock protein-based vaccine, viral, bacterial or yeast vectors-based vaccines, mRNA or DNA nucleic acid-based vaccines, vaccines based on tumor associated antigens such as overexpressed proteins, differentiation antigens, cancer-testis antigens and oncofoetal antigens, and tumor specific antigens including oncogenic viral antigens, antigen presenting cells (APC) or molecular neoantigens-based vaccines with specific CD8 type T-cells and, CD4 type T-cells, and nanoparticles (NP) vectors-based vaccines. Tecemotide, a peptide vaccine targeting MUC-1 and melanoma-associated antigen-A3, a protein-based vaccine, is under clinical trials. Current bioengineering techniques make use of hydrogels, modified polymers, emulsions, liposomes, virosomes, nanodiscs, cell membranes, self-assembled proteins, virus-like particles, and nucleic acids to deliver and develop biomaterial-based vaccines, used also for personalized oncotherapy. The development of anticancer immunotherapy includes the appropriate monotherapy or combination therapy with cellular vaccines, tumor-associated antigens (TAAs), neoantigens, and chimeric antigen receptor T-cells (CAR-T).

In an evidence-based medical research study, the activities of telomerase and TGF-β on the oncovaccines have been thoroughly analyzed. While analyzing the vaccine-based strategies with TGF-β as oncotherapeutic vaccine targets, it was observed that two types of vaccines combined with TGF-β antisense have been developed, namely, belagenpumatucel-L, and gemogenovatucel-T. Belagenpumatucel-L, a non-viral gene-based allogeneic tumor cell vaccine targeting TGF-β_2, with acceptable safety profile and increased survival rate, is the first vaccine accessing the phase III trial, in non-small cell lung cancer patients. Combinational therapies with radiotherapy, chemotherapy, or immunotherapy are also in investigative phases. The previous clinical studies have shown that the treatment in combination with granulocyte macrophage colony-stimulating factor (GM-CSF) and TGF-β_2 ASO promotes the immune response and further suppresses tumor growth. They constructed a TAG plasmid coexpressing GM-CSF and TGF-β_2 ASO, and the plasmid was incorporated into an autologous whole-cell vaccine. There were selective immune responses to the autologous TAG vaccine with >10-fold increase in IFN-γ expression over baseline. Gemogenovatucel-T is a combination of GM-CSF expression with a novel bifunctional short hairpin RNAi targeting furin convertase, involved in TGF-β_1 and β_2 precursor. In the Phase I trial, there were no adverse events, and the vaccine increased the immune response as reported in a previous study. A Phase II study was also conducted to evaluate its combination with nivolumab, a PD-1 inhibitor, in metastatic NSCLC. A Phase II with favorable 1-year survival in metastatic Ewing's sarcoma supports the justification of further testing and moving to the Phase III trial. In an ongoing Phase II trial, the maintenance of gemogenovatucel-T is investigated in women with high-risk stage ovarian cancer (IIIb-IV) following surgery and primary chemotherapy. There was high rate of induction in T-cell activation and improvement in median relapse-free survival. Considering the broad expression and roles of TGF-β_1 and TGF-β_2 in malignancy, further exploration of gemogenovatucel-T vaccine is required. This evidence-based medical research has also shown that telomerase activation is a major cell immortalization mechanism and is implicated as an essential step in carcinogenesis. Through telomerase activation, cancer

cells acquire the ability of unlimited proliferation. Telomerase activity is also linked to epithelial-to-mesenchymal transition and cancer stemness, providing cancer cells with metastatic potential. Telomerase is expressed in most tumor types across all stages of development and is thus an attractive target for therapeutic vaccination. The tumor types with increased telomerase expression combined with an immune permissive tumor microenvironment increase the therapeutic potential of telomerase targeting oncological vaccines.

Several new cancer vaccine platforms and antigen targets are under development. In an effort to amplify tumor-specific T-cell responses, a heterologous prime-boost antigen delivery strategy is increasingly used for virus-based vaccines. Viruses have also been engineered to express targeted antigens and immunomodulatory molecules simultaneously, to favorably modify the TME. Nanoparticle systems have shown promise as delivery vectors for cancer vaccines in preclinical research. T-win is another platform targeting both tumor cells and the TME, using peptide-based vaccines that engage and activate T-cells to target immunoregulatory molecules expressed on immunosuppressive and malignant cells. With the availability of next-generation sequencing (NGS), algorithms for neoantigen selection are emerging, and several bioinformatic platforms are available to select therapeutically relevant neoantigen targets for developing personalized therapies. Chemorefractory ovarian cancer has limited therapeutic options. Hence, new types of the treatment including neoantigen-specific immunotherapy need to be investigated. Neoantigens represent promising targets for personalized cancer immunotherapy. The clinical and immunological effects of a neoantigen peptide-loaded DC-based immunotherapy have been studied in a patient with recurrent and chemoresistant ovarian cancer. The reactivity against one human leukocyte antigens (HLA)-A2402-restricted neoantigen peptide derived from a mutated PPM1 F protein was detected in lymphocytes from peripheral blood by IFN-γ ELISPOT assay. Furthermore, the neoantigen (PPM1 F mutant)-specific TCRs were detected in the tumor-infiltrating T lymphocytes, post-vaccination. The results showed that vaccination with intranodal injection of neoantigen peptide-loaded DCs may have clinical and immunological impacts on cancer treatment. Neoantigens represent the long elusive immunogens for cancer vaccination. Clinical trials in melanoma and glioblastoma have demonstrated the feasibility, immunogenicity, and signals of efficacy of the personalized immunotherapy approach. Vaccines have been used to train the immune system to recognize pathogens, and prevent and treat diseases, such as cancer, for decades. Molecular-assisted precision oncology gained tremendous ground with high-throughput NGS and supported by robust bioinformatics. The quest for genomics based cancer medicine set the foundations for improved patient stratification, while unveiling a wide array of neoantigens for immunotherapy. Upfront pre-clinical and clinical studies have successfully used tumor-specific peptides in vaccines with minimal off-target effects. Alterations in protein glycosylation at the cell surface not only have functional impact on cancer progression and dissemination but also originate unique molecular fingerprints for targeted therapeutics. Immunotherapy using monoclonal antibodies and cancer vaccines is substitute strategies for colorectal cancer treatment, acting with the influence on its genetic and epigenetic alterations. When cancer immunotherapy is combined with chemotherapy, surgery, and radiotherapy, the colorectal cancer treatment would become excessively efficient, especially using bi-specific antibodies and dendritic cells mRNA vaccines. T-ALL-iPSC-based therapeutic cancer vaccine can elicit a specific anti-tumor effect on T-ALL. Glycolipids activating iNKT cells, such as α-galactosylceramide, can enhance the immune response against codelivered cancer antigens and have been applied in the design of self-adjuvanting anti-tumor vaccines. Alphavirus vectors have been engineered for the high-level gene expression relying originally on replication deficient recombinant particles, more recently designed for plasmid DNA-based administration. As alphavirus-based DNA vectors encode the alphavirus RNA replicon genes, enhanced transgene expression in comparison to conventional DNA plasmids is achieved. Immunization studies with alphavirus-based DNA plasmids have elicited specific antibody production and have generated tumor regression and protection against challenges with infectious agents and tumor cells in various animal models. A minimalist nanovaccine by formulating tumor antigen-encoding mRNA with a lipid-like material named C1 could efficiently deliver mRNA into dendritic cells with simultaneous Toll-like receptor 4 stimulation and induced T-cell activation. C1 mRNA nanovaccine exhibited significant antitumor efficacy on several tumor mouse models. The versatility and nanoscale size have helped NP improve the efficacy of conventional cancer immunotherapy and opened up exciting approaches to combat cancer. Sustained and controlled drug delivery, enhanced cross presentation by immune cells, coencapsulation of adjuvants, inhibition of immune checkpoints, and intrinsic adjuvant like properties have aided NPs to improve the therapeutic efficacy of cancer vaccines. Furthermore, NPs have been efficient modulators of TME. NPs facilitate better penetration of the chemotherapeutic drug by dissolution of the inhibitory meshwork formed by tumor associated cells, blood vessels, soluble mediators, and extra cellular matrix in TME. NPs have shown to achieve this by suppression, modulation, or reprogramming of the immune cells and other mediators localized in TME. Viral NPs are also used to generate cancer vaccines. Studies have been done to develop *in situ* cancer vaccines by enhancing

the immunomodulatory effects for immunogenic cell death (ICD) and tumor microenvironment-triggered *in situ* cancer vaccines inducing dual ICD for elevated antitumor and antimetastatic therapy. Nanovaccines are used as delivery platforms for antigens and adjuvants, which activate APCs and enhance anticancer immune responses. In a study, the therapeutic efficacy of a combinatorial treatment comprising the immunoadjuvant nanocomplex PSPEI-PIC, a DC vaccine, and PD-L1 blockade has also been studied. A study was conducted to analyze a combination of immunoadjuvant nanocomplexes and dendritic cell vaccines in the presence of immune checkpoint blockade for effective cancer immunotherapy. Nanovaccines outnumber the conventional vaccines by virtue of plasticity in physiochemical properties and ease of administration. The efficacy of nano-based vaccines may be attributed to the improved antigen stability, minimum immunotoxicity, sustained release, enhanced immunogenicity, and the flexibility of physical features of NP. Based on these, the nano-based vaccines have potential to evoke both cellular and humoral immune responses. Targeted and highly specific immunological pathways required for solid and long lasting immunity may be achieved with specially engineered nano-vaccines. Bacteria biohybrid oral vaccines for colorectal cancer treatment reduce tumor growth and increase immune infiltration. The development of anticancer immunotherapy is characterized by several approaches, the most recognized of which include cellular vaccines, TAAs, neoantigens, and CAR-T. Antigenic essence technology has also been studied as an effective means for the production of new antigen compositions for anticancer vaccination. This technology is developed *through* proteomics, cell culture technology, and immunological assays. The benefits of this technology over other approaches include the ability to control composition, optimize immunogenicity and similarity to target cells, and evade major histocompatibility complex restriction. Plasma-activated medium (PAM) potentiates the immunogenicity of tumor cell lysates for dendritic cell-based cancer vaccines. A unique atmospheric pressure plasma jet was used to prepare a PAM which induced ICD in tumor cells. This procedure increased the efficacy of tumor lysates in enhancing the immunogenicity of DCs according to their increased maturation, production of IL-12, and the capacity to induce cytotoxic CD8 T-cells able to kill tumor cells. An innovative strategy has been generated termed "biomaterial-mediated combined cell vaccines for immunotherapy," which combines tumor cell and DC vaccines with a cyclodextrin-polyethylene glycol hydrogel and a cytosine-phosphate-guanine nanoadjuvant. The nanoadjuvant promotes antigen presentation and amplifies immune-eliciting potency by codelivery of antigens and adjuvants. Combining cancer vaccines with multiple checkpoint blockade antibodies, novel multifunctional molecules, adoptive cell therapy, and immune system agonists have been used as anti-cancer combination therapies. While these combinations build on the foundation of successful immune checkpoint blockade antibodies, it is increasingly apparent that successful immunotherapy will also require a cancer vaccine backbone to engage the immune system, thereby ensuring that additional immune-oncology agents will engage a tumor-specific immune response. Human cDC1 exclusively expresses the C-type-lectin-like receptor, CLEC9A (DNGR-1) that plays an important role in cross-presentation, the process by which effective CD8 type T-cell responses are generated. CLEC9A antibodies deliver antigen specifically to cDC1 for the induction of humoral, CD4 type, and CD8 type T-cell responses and are therefore promising candidates to develop as vaccines for infectious diseases and cancer. The development of human CLEC9A antibodies now facilitates their application as vaccines for cancer immunotherapy. Tumor types possessing mechanisms of increased telomerase expression combined with an immune permissive tumor microenvironment are expected to increase the therapeutic potential of telomerase targeting cancer vaccines. Rational treatment combinations, such as checkpoint inhibitors, are likely necessary to bring out the true clinical potential of therapeutic cancer vaccines.

Belagenpumatucel-L, an allogeneic tumor cell vaccine, associated with the oncoimmunotherapeutic target, TGF-β, is under clinical trial. Belagenpumatucel-L is an allogeneic tumor cell vaccine, which consists of four irradiated NSCLC cell lines that have been modified with transforming growth factor-β2 (TGF-β2) antisense gene plasmid. TGF-β inhibits T-cell, B-cell, and dendritic cell activation, induces immunosuppressive Treg cells, and inhibits immune effector cell activation. In a Phase II study of patients with low-volume disease, belagenpumatucel-L was well tolerated, induced antibody-mediated response to vaccine HLA, and demonstrated a dose-dependent improvement in survival and response. A Phase III trial compared the efficacy of belagenpumatucel-L with placebo as a maintenance therapy in patients with stages IIIA (T3, N2 only), IIIB, and IV NSCLC without progression after up to six cycles of first-line platinum-based chemotherapy, which had to be completed 4–17 weeks before randomization. In a clinical trial, belagenpumatucel-L was administered as 2.5 × 107 cells/injection intradermally, every month for 18 months, followed by additional two quarterly injections. In a pre-planned subgroup analysis, among patients who received prior radiation therapy and enrolled within 12 weeks, belagenpumatucel-L resulted in significantly improved median overall survival.[1-7]

CONCLUSION

This study was a descriptive clinical oncological analytical qualitative research study, in which the efficacious

molecular pharmacological mechanisms and potential pharmacotherapeutic significance of belagenpumatucel-L and pharmaco-oncoimmunotherapeutic vaccines were analytically explored, and comprehensively elaborated, along with an emphasis on TGF-β and telomerase as pharmacotherapeutic targets for oncotherapeutic vaccines, through an evidence-based medicine research approach. This research study aptly explained that the anticancer vaccines are appropriately effective systemic immunotherapies that systematically enhance the life-long anti-neoplastic prophylactic immunity and produce a very long-lived anti-malignant therapeutic triumph.

ACKNOWLEDGMENTS

My sincere acknowledgements to Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Rational Pharmacotherapeutics, Pharmacoepidemiology, Pharmacovigilance, Pharmacogenomics, Evidence-Based Medicine, Clinical Pathology, Pathology, Molecular Diagnostics, Clinical Oncology, Clinical Medicine, Respiratory Medicine, Clinical Research, Zoology, and Molecular Medicine, Dr. B. R. Ambedkar Medical College and Hospitals, J. J. M. Medical College and Hospitals, Karnataka, India; Presidency College, West Bengal, India; Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Dr. Moumita Hazra's Academic Centre, Dr. Moumita Hazra's Educational Centre, Hazra Nursing Home, Hazra Polyclinic And Diagnostic Centre, Dr. Moumita Hazra's World Enterprises, West Bengal, India, World; Gouri Devi Institute of Medical Sciences and Hospital, West Bengal, India; Mamata Medical College and Hospitals, Telangana, India; Rama Medical College Hospital and Research Centre, Rama University, Uttar Pradesh, India; Hi-Tech College of Nursing, Odisha, India; and Mahuya Diagnostic Centre and Doctors' Chamber, West Bengal, India; for the successful completion of this research project.

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How to cite this article: Hazra M. A Descriptive Clinical Oncological Analytical Research Study on the Molecular Pharmacology of Belagenpumatucel-L and Pharmaco-oncoimmunotherapeutic Vaccines through Evidence-based Medicine. Int J Sci Stud 2022;9(12):111-116.

Source of Support: Nil, **Conflicts of Interest:** None declared.