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

Original Article

Effects of Intramuscular Dexmedetomidine Versus Clonidine on the Duration of Subarachnoid Block and Analgesia for Lower Limb Orthopedic Surgeries

Snehalatha Bhashyam[1], G Prasanna Kumar[2], T Prem Sagar[3], S Gayathri[4]

[1]Assistant Professor, [2]Associate Professor, [3]Professor, [4]Post Graduate, Department of Anesthesiology and Critical Care, Rangaraya Medical College, Kakinada, Andhra Pradesh, India

Abstract

Background: Alpha-2adrenergic agonists, when used simultaneously as systemic adjuvants to local anesthetics show synergistic action and improve the quality of spinal anesthesia and prolong the post-operative analgesia. We aimed to study the effects of intramuscular dexmedetomidine versus clonidine on the duration of bupivacaine sub-arachnoid block, post-operative analgesia, and sedation in patients undergoing lower limb orthopedic surgeries.

Materials and Methods: The study design was a prospective, randomized, and double-blind study. Eighty adult consented patients of ASA I or II, scheduled for orthopedic lower limb surgeries under spinal block were randomized to two groups of 40 patients per group. Group D received IM dexmedetomidine 1 μgkg^{-1}, Group C received IM clonidine 2 μgkg^{-1}, and 30 min before the bupivacaine subarachnoid block. The time of onset of sensory and motor block, the time required for complete sensory and motor recovery, time of the first request of rescue analgesia, and sedation levels were compared between the groups. Collected data were analyzed using the student "*t*" test, Chi-square test/Fisher exact test, and $P < 0.05$ was considered statistically significant.

Results: The mean onset time of sensory and motor block was reduced, the mean time required for complete sensory recovery was increased and the time of the first request of rescue analgesia was prolonged in the dexmedetomidine group compared to clonidine group with a significant $P < 0.05$. Ramsay sedation score was higher in the dexmedetomidine group compared to clonidine group ($P = 0.003$)

Conclusion: Premedication with a single dose of intramuscular dexmedetomidine before bupivacaine spinal anesthesia acts as an effective adjuvant and potentiates the quality of block and prolongs post-operative analgesia more than intramuscular clonidine.

Key words: Clonidine, Dexmedetomidine, Intramuscular, Post-operative analgesia, Premedication

INTRODUCTION

Orthopedic lower limb surgeries are lengthy procedures associated with significant post-operative pain. Although sub-arachnoid block is the most commonly used regional anesthetic technique, it has the disadvantage of a short duration of anesthesia and post-operative analgesia. When compared to general anesthesia, it is associated with less blood loss, surgical stress, useful in difficult airway cases, decreased incidence of thromboembolic events along with a decreased length of stay, cost, aids in early ambulation, and lowers 30-day mortality.[1] Various techniques and adjuvants were tried intrathecally and systemically along with local anesthetics to improve the quality of block, prolong the postoperative analgesia, and to eliminate the anxiety related to surgery during regional anesthesia.[2-3] Alpha-2 adrenergic agonists clonidine and dexmedetomidine have both sedative and analgesic properties[4,5] and potentiate the effect of local anesthetics when used as adjuvants in regional anesthesia. They prolong the duration of sensory and motor block and also post-operative analgesia.[6-8]

Access this article online

www.ijss-sn.com

Month of Submission : 06-2020
Month of Peer Review : 06-2020
Month of Acceptance : 07-2020
Month of Publishing : 07-2020

Corresponding Author: Dr. Snehalatha Bhashyam, 8-11-18/1, Indian Red Cross Society, Red Cross Street, Gandhinagar, Kakinada - 533004, Andhra Pradesh, India.

Clonidine and dexmedetomidine can be administered by intramuscular, oral, intranasal, intravenous, intrathecal, and epidural routes.[9-11] They act by a central and a peripheral mechanism which enables them to give these drugs through different routes with the same effect. Dexmedetomidine a selective α-2-adrenoreceptor agonist is more effective than clonidine as analgesic and sedative with an α_2/α_1 selectivity ratio which is 8–10 times greater than that of clonidine.[12] However, the dose of clonidine 1.5–2 times higher than dexmedetomidine.[13,14]

There are very few studies comparing the effects of intramuscular clonidine and dexmedetomidine on the quality of the sub-arachnoid block. Hence, our objective is to evaluate and compare the effect of intramuscular dexmedetomidine versus clonidine on the onset and duration of sensory and motor block, time for request of the first analgesic, sedation level, and adverse effects if any after sub-arachnoid block in te lower limb orthopedic surgeries.

MATERIALS AND METHODS

After approval of study protocol by the Institutional Ethics Committee, we conducted this prospective randomized double-blind study on 80 consented adult ASA Grades I and II patients of either sex, aged 20–60 years, weighing 50–70 kg, height measuring 150–170 cm, and posted for elective lower limb orthopedic surgeries under spinal anesthesia in the Orthopedic operation theater, Government General Hospital affiliated to Rangaraya Medical College, Kakinada.

Exclusion Criteria

1. Unwilling by Patient,
2. Patients allergic to the amide group of local anesthetics
3. Patients with a history of cardiac disease, diabetes mellitus, hypertension, chronic obstructive respiratory disease, hepatic, renal, neurologic disease, and psychological disease.
4. Patients on Alpha-2 agonists, beta-blockers, alcohol, and drug abuse
5. Patients with bleeding diathesis, pre-existing neurological, spinal deformities, infection at the site of the block (contraindications for the sub-arachnoid block)
6. Pregnancy
7. Emergency surgeries

Written informed consent was obtained from all the 80 patients after completing a thorough pre-anesthetic checkup with all necessary/relevant investigations and every patient was explained about visual analog scale (VAS) 0–10 for pain scoring and was kept on nil by mouth for 8 h before surgery.

Patients subjected to the study were randomized into two groups of 40 subjects each by computer-generated random numbers using sealed envelopes. The premedicant study drugs were premixed by an anesthetist who is unaware of the study. The study drugs were administered intramuscularly to all the patients as a single dose 30 min before giving sub-arachnoid block.

- Group D: n = 40 received intramuscular dexmedetomidine 1 $\mu g/kg^{-1}$ diluted up to 2 ml with normal saline as a single dose.
- Group C: n = 40 received intramuscular clonidine 2 $\mu g/kg^{-1}$ diluted up to 2 ml with normal saline as a single dose.

Standard monitors were attached and vitals such as heart rate (HR), non-invasive blood pressure (NIBP), electrocardiography (ECG), Pulse oximetry (SpO_2), and respiratory rate (RR) were recorded baseline, before injection and post-injection. An 18-G venous cannula was secured and Ringer's lactate solution was infused at the rate of 10 ml/kg before spinal anesthesia. After 30 min, under strict aseptic conditions, the subarachnoid block was performed at L_3–L_4 interspace using a 25 Gauge Quincke–Babcock's needle. After the free flow of CSF, 0.5% hyperbaric bupivacaine 3 ml (15 mg) was injected intrathecally. The time of injection was noted as 0 (time). The observer anesthesiologist who records data was blinded to group allocation. Oxygen was supplied at a rate of 6 L/min using a face mask. The onset and duration of sensory and motor block were tested using the pinprick method. The motor blockage was graded using modified Bromage scale[15] (Grade 0: No paralysis, Grade 1: Unable to raise the extended leg, Grade 2: Unable to flex the knee, and Grade 3: Unable to flex ankle). Sensory and motor block were tested every minute during the first 10 min, every 15 min intraoperative and postoperatively. The time of onset and duration of sensory and motor block were recorded. The time of injection was noted as time 0. The time taken to attain the highest dermatomal level was noted.

The time of recovery of sensory block was considered as two-dermatome regression from the highest sensory level. The time of recovery of motor block was the time to return to Grade 1 on the modified Bromage scale.

VAS

VAS[16] was used to test post-operative pain (Scale 0: No pain and 10: Worst possible pain) at 4, 6, 12, and 24 h. The duration of analgesia was considered as the time since the administration of the sub-arachnoid block until the first request of rescue analgesia. Injection diclofenac sodium 75-mg intramuscular is given for patients with a VAS score of three or more.

Sedation Score

Sedation score was assessed using Ramsay's Sedation Scale[15] (RSS) (Score 1: Anxious or agitated, Score 2: Co-operative and tranquil, Score 3: Drowsy but responsive to command, Score 4: Asleep but responsive to glabellar tap, Score 5: Asleep with sluggish response to tactile stimulation, and Score 6: Asleep and no response). The sedation score was recorded every 10 min after administration of the drug and then 10 min after giving sub-arachnoid block and thereafter postoperatively.

Vital parameters such as non-invasive blood pressure, heart rate, respiratory rate, and SpO_2 were noted baseline, after premedication, 3 min after sub-arachnoid block, every 5 min for the first 15 min, and, after that, every 15 min up to 1 h, after that every 30 min till the end of surgery. The duration of surgery was noted. A drop in MAP from 20% of the baseline is defined as hypotension and managed with intravenous fluid bolus and mephentermine 3 mg increments. Heart rate <50 beats/min is defined as bradycardia and managed with intravenous Atropine 0.5 mg. Respiratory rate <12 breaths/min is defined as respiratory depression and managed with oxygen supplementation. Side effects if any such as hypotension, bradycardia, nausea, and vomiting, respiratory depression, and shivering noted.

The sample size was calculated based on the pilot study observations conducted with a sample of 20 patients, ten patients in each group. To get a difference of >20% increase in the mean time for request of the first analgesic in between the groups with an α-error of 0.05 and power of 85%, we needed a sample size of 37 patients in each group (using power analysis and sample size software.com). Hence, 40 patients were enrolled in each group to account for dropouts. The patients involved in the pilot study were excluded from the original study.

Statistical Analysis

The collected data were finally analyzed using Microsoft Excel and GraphPad.com software. Data were disclosed as mean, standard deviation, ratio or percentage (%) or absolute numbers, and compared using student's *t*-test, Fisher's exact test, and Chi-square test to detect the significance of study parameters between the two groups. $P < 0.05$ was considered statistically significant.

RESULTS

All the 80 patients completed the study successfully under spinal anesthesia. The demographic data of the patients in terms of age, sex, weight, height, ASA I/II, and mean duration of surgery were comparable without any statistically significant difference between the groups [Table 1].

Premedication with intramuscular dexmedetomidine before sub-arachnoid block with bupivacaine resulted in earlier onset of sensory (3.58 ± 1.16 min) and motor block (4.56 ± 1.32 min) in Group D when compared to clonidine (Group C) which has a mean onset time of 4.51 ± 1.32 min and 5.46 ± 1.04 min for sensory and motor block, respectively, with a statistically significant difference between the groups ($P = 0.001$) [Table 2, Figure 1].

The mean time required for complete sensory recovery was 218.31 ± 24.82 min in Group D which was higher than Group C (199.05 ± 26.84 min), which was statistically significant ($P = 0.001$), [Table 2, Figure 2].

The mean time for complete motor recovery was similar in both groups. It was 223.42 ± 16.58 min in Group D and 216.31 ± 18.06 min in Group C, respectively, with no statistically significant difference among the groups ($P = 0.070$) [Table 2, Figure 2].

The mean time of the first request of analgesia was increased in Group D (339.04 ± 22.73 min) as compared to Group C (228.38 ± 26.20 min) with a statistically

Table 1: Demographic data of the patients

Parameters	Mean±Standard Deviation (*n*=40)		*P* value
	Group D	Group C	
Age in years	38.81±10.16	40.02±9.92	0.591
Weight in kg	55.43±5.8	56.20±5.49	0.539
Height in cm	159.65±6.92	159.83±6.70	0.906
Gender (%): Male/ Female	32/08	35/5	0.545*
ASA I/II	30/10	32/8	0.789*
Duration of surgery(Min)	106.35 ± 25.01	104.72± 26.21	0.776

Data expressed as mean (SD) or ratio or absolute numbers, Student *t*-test, *Chi-square test/Fisher exact test

Table 2: Comparison of outcome parameters

Parameters	Mean±Standard Deviation (*n*=40)		*P* value
	Group D	Group C	
Onset of Sensory blockade (Min)	3.58±1.16	4.51±1.32	0.001*
Onset of motor block (Min)	4.56±1.32	5.46±1.04	0.001*
Time of sensory recovery (Min)	218.31±24.82	199.05±26.84	0.001*
Time of motor recovery (Min)	223.42±16.58	216.31±18.06	0.070
Time of first request of analgesic(Min)	339.04±22.73	228.38±26.20	0.001*

Data expressed as mean (SD) or ratio or absolute numbers, Student *t*-test, **P*<0.05 Statistically significant

significant difference between the groups (P = 0.001), [Table 2, Figure 3].

Regarding the distribution of vital data, lower heart rates were observed in Group D than that of Group C but without any statistically significant difference except 5 min after the sub-arachnoid block where there was a significantly lower mean heart rate (P = 0.024) in Group D. The mean heart rates (HR) were maintained hemodynamically stable above 70/min in both the groups [Figure 4].

There was no significant difference in MAP in both the groups after pre-medication and the MAP was maintained hemodynamically stable above 75 mm of Hg throughout the perioperative period among the groups [Figure 5].

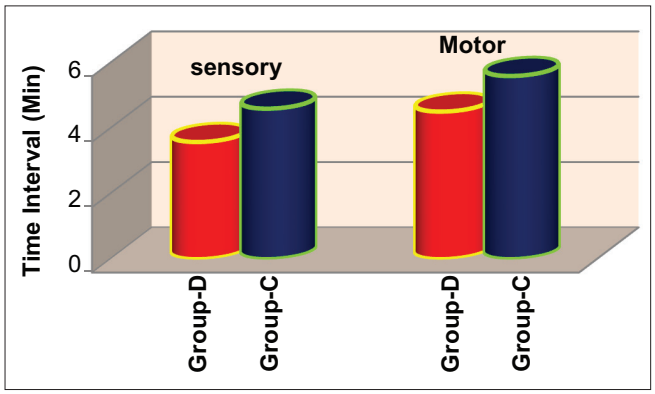

Figure 1: Onset of sensory and motor block

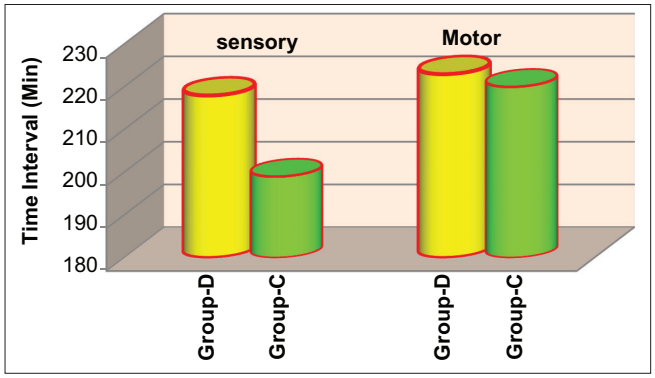

Figure 2: Time of sensory and motor recovery

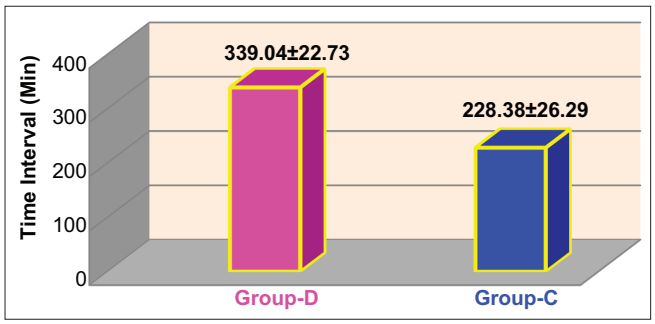

Figure 3: Time of first request of analgesic (min)

The mean sedation scores were higher in Group D than Group C (P = 0.003). In Group D, patients with sedation score >3 were 26 (65 %) and Group C was 12 (30 %) [Table 3].

There were no statistically significant side effects such as hypotension, bradycardia, nausea and vomiting, and respiratory depression, among the groups [Table 4].

DISCUSSION

Various adjuvants to local anesthetics have been tried in spinal anesthesia by intrathecal or by systemic routes to extend the duration and to improve the quality of spinal block and to produce post-operative analgesia and anxiolysis.

Alpha-2-adrenergic agonists such as dexmedetomidine and clonidine act by different mechanisms to produce analgesia, of which the central mechanism is attributed to their action at the spinal level where they act on laminae VII, VIII of the ventral horns of the spinal cord and action at the locus coeruleus and dorsal raphe nucleus is attributed to their action at the supraspinal level. They also act by peripheral mechanism and vasoconstricting effect on blood vessels.[17] These actions aid us to administer these drugs through various routes but produce similar effects irrespective of routes of administration.

The α2-adrenoreceptor agonists, namely, dexmedetomidine and clonidine as adjuvants to local anesthetics can be administered by epidural, intrathecal, caudal routes, and by peripheral nerve blocks. They have also been used as systemic adjuvants to local anesthetics and as premedicants by different routes to extend anesthesia and provide analgesia. There are studies about the use of intravenous dexmedetomidine and clonidine as systemic

Table 3: Ramsay sedation score

Score	Group D (n=40)	Group C (n=40)	P value
Sedation score (>3)	26 (65%)	12 (30%)	P=0.003*

Data expressed as mean (SD) or ratio or absolute numbers, *P<0.05 statistically significant

Table 4: Adverse events

Parameters	Data expressed as percentage or absolute numbers	
	Group D (n=40)	Group C (n=40)
Bradycardia	6 (15%)	4 (10%)
Hypotension	2 (5%)	2 (5%)
Nausea and Vomiting	1 (2.5%)	2 (5%)
Respiratory depression	0	0
Shivering	0	0

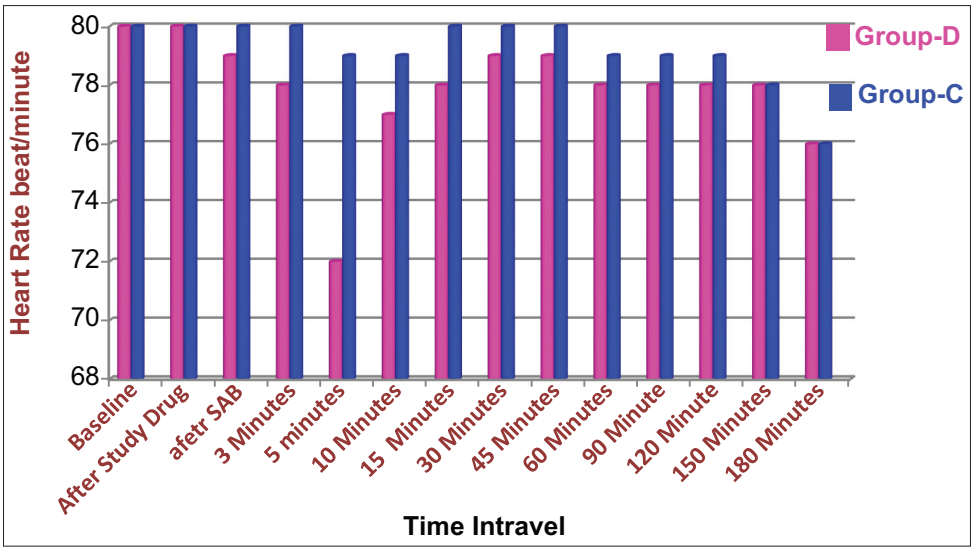

Figure 4: Comparison of heart rates

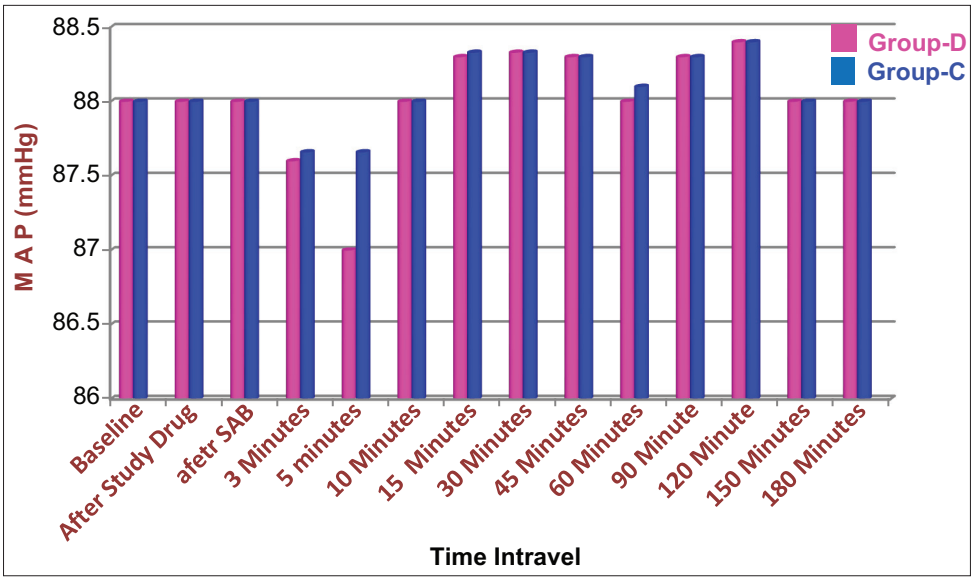

Figure 5: Comparison of mean arterial pressure (mmHg)

adjuvants for prolongation of spinal anesthesia. Rapid administration or infusion of these drugs might produce hypertension,[18] tachycardia, and bradycardia resulting in significant hemodynamic variability. To avoid these effects, we selected the intramuscular route for the administration of these drugs in our study.

In a study conducted by Aho *et al.*,[19] on the effect of intramuscular dexmedetomidine and clonidine on the attenuation of hemodynamic and stress response to gynecologic laparoscopy, the dose of IM clonidine used was 4.5 $\mu g/kg^{-1}$ and doses of IM dexmedetomidine used were 0.6 $\mu g/kg^{-1}$, 1.2 $\mu g/kg^{-1}$, and 2.4 $\mu g/kg^{-1}$. The higher doses were associated with significant hypotension and bradycardia and the lower doses were found ineffective. That is why we have taken dexmedetomidine 1 $\mu g/kg^{-1}$ and clonidine 2 $\mu g/kg^{-1}$ by the intramuscular route in our study.

Scheinin *et al.*,[20] in their study on pharmacological actions of intramuscular dexmedetomidine concluded that dexmedetomidine takes 60–150 min for its maximum effect after IM injection and according to Singh *et al.*,[21] intramuscular clonidine takes 30–60 min for its maximum effect after injection. Furthermore, hyperbaric bupivacaine gets fixed to the neural structures of the spine 30 min after injection. Because of the above effects, the IM injections were given 30 min before giving spinal anesthesia in our study.

In our study, intramuscular dexmedetomidine versus clonidine prolonged the duration of bupivacaine spinal

anesthesia and analgesia. The time of the first request for rescue analgesia was significantly prolonged in the dexmedetomidine group compared to the clonidine group that could be explained by the highly selective nature of dexmedetomidine for α-2-adrenoreceptors particularly α_{2A} and α_{2C} when compared to clonidine. The results of our study correlated with the study of Reddy *et al.*,[22] except that we used the intramuscular route in our study instead of the intravenous route, and also the dosages used in our study are double the doses used in their study.

Our study demonstrated the earlier onset times of sensory and motor block and prolonged duration of sensory block. However, the duration of the motor blockade was not effected, might be explained by direct suppression of impulse conduction in the large, myelinated A-alpha fibers. Our results are similar to the study conducted by Kaya *et al.*,[23] where there is no effect on the duration of the motor block with a single dose of 0.5 $\mu g/kg^{-1}$ of dexmedetomidine.

Dexmedetomidine is a highly selective α_2 agonist with α_2:α_1 binding ratio of 1620:1 whereas clonidine has a binding ratio of 220:1.[24] This property of dexmedetomidine accounts for its sedative and analgesic properties compared to clonidine. In our study, there is effective sedation with a score >3 noted by Ramsay's Sedation Scale in the dexmedetomidine group as the patients remained cooperative and easily arousable exempting the need for intra-operative sedation. These findings correlate with the findings of the study of Ustun *et al.*[25]

Hemodynamic stability was maintained throughout. Less than 20% fall from baseline in heart rate and MAP was observed among the groups. There is no excessive sedation, respiratory depression, or shivering noted in our study.

CONCLUSION

We conclude from our present study that, a single dose of dexmedetomidine 1 $\mu g/kg^{-1}$ given by intramuscular route preceding spinal anesthesia resulted in the rapid onset of sensory and motor block, extended the time of sensory recovery with prolonged post-operative analgesia, provided satisfactory sedation levels, with stable cardiovascular parameters, and without any adverse effects making it an effective adjuvant and remarkable alternative to intramuscular clonidine 2 $\mu g/kg^{-1}$ for lower limb orthopedic surgeries under Bupivacaine spinal anesthesia.

ACKNOWLEDGMENTS

We are grateful to all the staff of the Department of Orthopedics and Anaesthesiology Government General Hospital, Rangaraya Medical College, Kakinada, Andhra Pradesh, for extending their support and thankful for every patient for their active participation in this study.

REFERENCES

1. Metry AA, Nakhla GM, Wahba WZ, Wahba RM, Kamel IH. Abdominoplasty under spinal anesthesia: A feasibility study. Anesth Essays Res 2019;13:243-7.
2. Hohener D, Blumenthal S, Borgeat A. Sedation and regional anaesthesia in the adult patient. Br J Anaesth 2008;100:8-16.
3. Helgeson LE. Sedation during regional anaesthesia: Inhalational versus intravenous. Curr Opin Anaesthesiol 2005;18:534-9.
4. Gabriel JS, Gordin V. Alpha 2 agonists in regional anesthesia and analgesia. Curr Opin Anaesthesiol 2001;14:751-3.
5. Mauro VA, Brandão ST. Clonidine and dexmedetomidine through epidural route for post-operative analgesia and sedation in a cholecystectomy. Rev Bras Anestesiol 2004;4:1-10.
6. Strebel S, Gurzeler JA, Schneider MC, Aeschbach A, Kindler CH. Small-dose intrathecal clonidine and isobaric bupivacaine for orthopedic surgery: A dose-response-study. Anesth Analg 2004;99:1231-8.
7. Dobrydnjov I, Axelsson K, Thorn SE, Matthiesen P, Klockhoff H, Holmstorm B, *et al*. Clonidine combined with small-dose bupivacaine during spinal anesthesia for inguinal herniorrhaphy: A randomized double-blinded study. Anesth Analg 2003;96:1496-503.
8. Sethi BS, Samuel M, Sreevastava D. Efficacy of analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine. Indian J Anaesth 2007;51:415.
9. Agarwal A, Agarwal S, Payal YS. Comparison of block characteristics of spinal anesthesia following intravenous dexmedetomidine and clonidine. J Anaesthesiol Clin Pharmacol 2016;32:339-43.
10. Kumari R, Kumari A, Kumar S, Singh R. Intravenous dexmedetomidine as an adjunct to subarachnoid block: A simple effective method of better perioperative efficacy. J Anaesthesiol Clin Pharmacol 2017;33:203-8.
11. Jayaram L, Sinha A, Punhani D. A comparative study to evaluate the effect of intranasal dexmedetomidine versus oral alprazolam as a premedication agent in morbidly obese patients undergoing bariatric surgery. J Anaesthesiol Clin Pharmacol 2013;29:179-82.
12. Coursin DB, Maccioli GA. Dexmedetomidine. Curr Opin Crit Care 2001;7:221-6.
13. Bajwa SJ, Bajwa SK, Kaur J, Singh G, Arora V, Gupta S, *et al*. Dexmedetomidine and clonidine in epidural anaesthesia: A comparative evaluation. Indian J Anaesth 2011;55:116-21.
14. Schnaider TB, Vieira AM, Brandão AC, Lobo MV. Intraoperative analgesic effect of epidural ketamine, clonidine or dexmedetomidine for upper abdominal surgery. Rev Bras Anestesiol 2005;55:525-31.
15. Santpur MU, Kahalekar GM, Saraf N, Losari A. Effect of intravenous dexmedetomidine on spinal anaesthesia with 0.5% hyperbaric bupivacaine in lower abdominal surgeries: A prospective randomized control study. Anesth Essays Res 2016;10:497-501.
16. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health 1990;13:227-36.
17. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000;93:382-94.
18. Grant SA, Breslin DS, MacLeod DB, Gleason D, Martin G. Dexmedetomidine infusion for sedation during fiberoptic intubation: A report of three cases. J Clin Anesth 2004;16:124-6.
19. Aho M, Scheinin M, Lehtinen AM, Erkola O, Vuorinen J, Korttila K. Intramuscularly administered dexmedetomidine attenuates hemodynamic and stress hormone responses to gynecologic laparoscopy. Anesth Analg 1992;78:1065-75.
20. Scheinin H, Karhuvaara S, Olkkola KT. Pharmacodynamics and pharmacokinetics of intramuscular dexmedetomidine. Clin Pharmacol Ther 1992;52:537-46.
21. Singh M, Choudhury A, Kaur M, Liddle D, Verghese M, Balakrishnan I. The comparative evaluation of intravenous with intramuscular clonidine

for suppression of hemodynamic changes in laparoscopic cholecystectomy. Saudi J Anaesth 2013;7:181-6.
22. Reddy VS, Shaik NA, Donthu B, Sannala V, Jangam V. Intravenous dexmedetomidine versus clonidine for prolongation of bupivacaine spinal anesthesia and analgesia: A randomized double-blind study. J Anaesthesiol Clin Pharmacol 2013;29:342-7.
23. Kaya FN, Yavascaoglu B, Turker G, Yildirim A, Gurbet A, Mogol EB, *et al*. Intravenous dexmedetomidine, but not midazolam, prolongs bupivacaine spinal anesthesia. Can J Anaesth 2010;57:39-45.
24. Grewal A. Dexmedetomidine: New avenues. J Anaesthesiol Clin Pharmacol 2011;27:297-302.
25. Ustun Y, Gunduz M, Erdogan O, Benlidayi ME. Dexmedetomidine versus midazolam in outpatient third molar surgery. J Oral Maxillofac Surg 2006;64:1353-258.

How to cite this article: Bhashyam S, Kumar GP, Sagar TP, Gayathri S. Effects of Intramuscular Dexmedetomidine Versus Clonidine on the Duration of Subarachnoid Block and Analgesia for Lower Limb Orthopedic Surgeries. Int J Sci Stud 2020;8(4):142-148.

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