Original Article

Comparative Study of Dexmedetomidine and Magnesium Sulphate as Adjuvant to Epidural Bupivacaine in Lower Limb Orthopaedic Surgery

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ABSTRACT

Introduction: This prospective, randomized, double blind study was undertaken to establish the effect of addition of Dexmedetomidine or Magnesium sulphate as an adjuvant to epidural Bupivacaine in lower limb orthopaedic surgery.

Methodology: A total of 80 patients of American Society of Anaesthesiologists (ASA) physical status I and II aged 18-65 years of either sex were enrolled for elective lower limb orthopaedics surgery. All the study subjects received an epidural anaesthesia with 12 ml of 0.5% Bupivacaine alongwith either Magnesium sulphate (50 mg) (group BM) or Dexmedetomidine (0.5 µg/kg) (group BD) . The onset and duration of motor and sensory block, duration of analgesia, hemodynamic parameters, and any adverse events were monitored.

Results: Analgesia in the post-operative period was better in group BD (603.9±48.5 min v/s 276.7±46.9 min), onset of sensory and motor block were earlier in group BD, duration of sensory and motor blockade were significantly prolonged in group BD, and incidence of sedation was more in group BD.

Conclusion: Addition of Dexmedetomidine to Bupivacaine in epidural anaesthesia leads to faster onset of both sensory and motor block and prolongs the duration of sensory and motor block alongwith duration of post-operative analgesia with arousable sedation without any significant hemodynamic changes and side effects.

Keywords: Dexmedetomidine, Magnesium sulphate, epidural anaesthesia.

INTRODUCTION

Epidural anaesthesia is the most commonly used technique for providing not only peri-operative surgical anaesthesia but post-operative analgesia also in lower abdominal and limb surgeries.[1] It has been shown to blunt the stress response to surgery, decrease intraoperative blood loss, reduce the incidence of post-operative thromboembolic events, and decrease morbidity and mortality in high risk surgical patients. Alpha 2-adrenergic receptor agonists are being studied increasingly because of their sedative, analgesic, sympatholytic, anesthetic-sparing, and hemodynamic stabilizing properties.[2] Dexmedetomidine is a highly selective α-2 adrenergic agonist with an affinity eight times greater than that of clonidine[3,4] and selectivity ratio of 1600:1 (α2:α1). Because of its α-2 adrenoceptor agonist properties, Dexmedetomidine has a broad range of pharmacological properties, including sedation associated with arousability and orientation and without respiratory depression.[5,6]

Magnesium sulphate ($MgSO_4$) has anti-nociceptive effects primarily based on physiological calcium antagonism, that is voltage-dependent regulation of calcium influx into the cell, and non-competitive antagonism of N-methyl D-aspartate (NMDA) receptors thereby preventing central sensitization induced by peripheral nociceptive stimuli.[7,8] These effects have prompted the investigation of magnesium as an adjuvant agent for intra and post-operative analgesia as it is an inexpensive, relatively harmless molecule.[8] This study compared the efficacy of epidural Bupivacaine with Dexmedetomidine (0.5 µg/kg)

or Magnesium sulphate (50 mg) as adjuvant in American Society of Anaesthesiologists (ASA) I, II patients undergoing major lower limb orthopaedic surgeries.

METHODS

This randomized double blind study was approved by the institutional ethics committee. CTRI registration number of the study is: CTRI/2019/02/017780. All patients of either gender, aged 18-65 years, and ASA grade I and II scheduled for lower limb surgery under epidural anaesthesia who gave informed consent were eligible for the study. Exclusion criteria were patient refusal, history of adverse reaction to any study medication, spinal deformity, previous spinal surgery, pregnancy, and patient for whom central neuraxial block is contraindicated. Out of 100 subjects, 80 were selected and randomized (Figure 1). All patients had undergone pre-anaesthetic check-up and pre-operative fasting as per institutional guidelines.

All the patients had standard monitoring of their heart rate, NIBP, SpO2, and ECG and baseline values were recorded. An 18G intravenous (i.v.) cannula was inserted and preloading with lactated Ringer's solution 10 ml/kg was

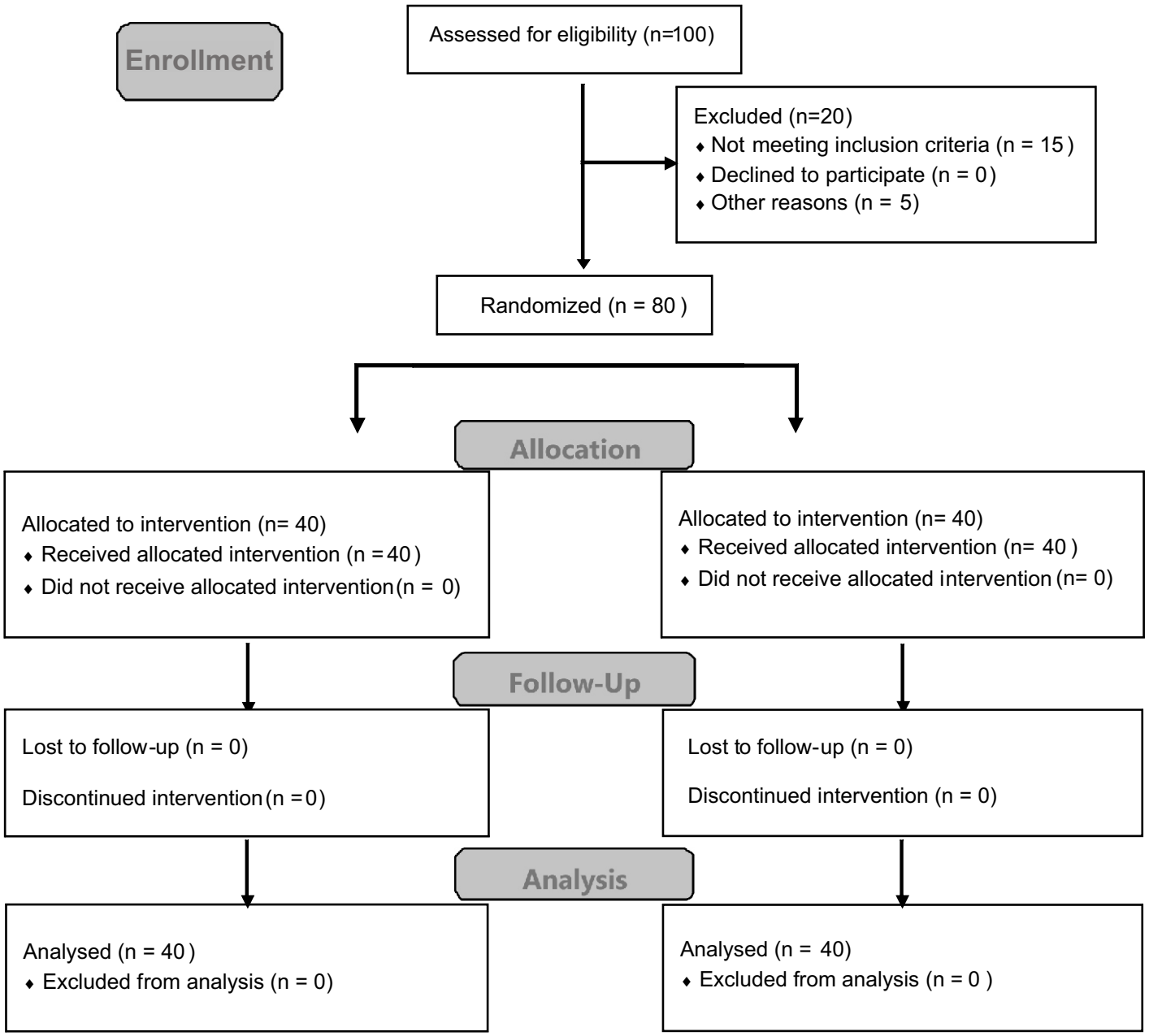

Figure 1: Consort flow chart.

done. Under aseptic conditions and infiltration of the skin with local anesthetic, an 18G Tuohy needle was used to identify the epidural space, by loss of resistance (LOR) technique, at L3-4 space in sitting position. A multiorifice epidural catheter was then advanced in epidural space after verification with test dose of 3 ml lignocaine 2% with adrenaline (1:200000). Subjects were randomized into groups BD and BM using a sealed envelope technique and received medication by epidural route as follows:

Group BD: Bupivacaine 0.5% (12 ml) + Dexmedetomidine 0.5 µg/kg (1 ml)

Group BM: Bupivacaine 0.5% (12 ml) + Magnesium sulphate 50 mg (1ml)

The sensory block was assessed using a short bevelled sterile 26G hypodermic needle along the midclavicular line bilaterally. The duration to achieve upto T10 level was noted. Modified Bromage scale was used to assess motor blockade:

0: No motor block,

1: Inability to raise extended leg; able to move knees and feet,

2: Inability to raise extended leg and move knee; able to move feet,

3: Complete block of motor limb.

Monitoring consisted of heart rate, non-invasive blood pressure, ECG, and SpO2 in both groups. The hemodynamic parameters and sedation were monitored continuously during the intraoperative period and recorded at time 5,10,15,20,25,30,45, and 60 minutes after giving block. Hypotension was defined as a systolic arterial blood pressure (SBP) < 90 mm of Hg or a decrease in SBP by 30% or more from baseline values and was treated by incremental doses of ephedrine 5 mg IV and IV fluid as required. Bradycardia was defined as fall in heart rate below 55 beats per minute or decrease in heart rate by 30% or more from baseline values and was treated with incremental doses of atropine 0.3 0.6 mg IV.

The patients were asked to evaluate their pain on standard 10 cm visual analogue pain scale. A bolus of epidural Bupivacaine 0.125% (12 ml) was administered by the anesthesiologist whenever VAS>3. Any side effects including hypotension, bradycardia, nausea, vomiting, sedation, and shivering were noted. Sedation was graded by using five point sedation scale;

Scale 1- Alert and wide awake,

Scale 2-Arousable to verbal command,

Scale 3-Arousable with gentle tactile stimulation,

Scale 4-Arousable with vigorous shaking,

Scale 5-Unarousable.

Statistical Analysis: A total sample size of 80 patients (n = 40 in each group) was calculated using power, and sample size calculator, α error of 0.05 and power of 80%. Nominal /categorical variables were summarized as frequency and percentage and were analyzed using Chi square test/ Fischer's Exact test as applicable. Continuous variables were summarized as mean and standard deviation and were analyzed using student t test and ordinal variables like VAS score were analyzed using Mann Whitney test. A p value < 0.05 was taken as statistically significant. All statistical analyses were done using Epi info version 7.2.1.0 and Open Epi version 3.

RESULTS

There were no statistical differences in age, sex, body weight, ASA class, and duration of surgery between the groups (Table 1).

The onset of sensory block (time to achieve sensory block to T10 level) was 13.5±2.1 minutes and 11.9±2.3 minutes for group BM and BD, respectively, being significantly earlier in group BD than group BM ($p<0.05$). The onset of

Table 1: Comparison of demographic data and duration of surgery in two groups

Parameters	Group BM (n=40)	Group BD (n=40)	p value
Age (years)	47.2 ± 14.6	42.3 ± 15.0	
Sex (Male/Female)	32/8	30/10	p >0.05
Weight (kgs)	54.53 ± 7.48	55.23 ± 8.81	
ASA (I/II)	34/6	35/5	
Duration of surgery (min)	53.62 ± 11.93	55.75 ± 19.4	

Table 2: Comparison of block characteristics in two groups

Block Characteristics (min)	Group BM (n=40)	Group BD (n=40)	p value
Onset of sensory block	13.5 ± 2.1	11.9 ± 2.3	0.0001
Onset of motor block	17.9 ± 1.8	15.7 ± 2.7	0.0001
Two segment regression	133.8 ± 4.3	134.9 ± 3.6	>0.05
Duration of sensory block	240.4 ± 28.75	306.1 ± 15.32	0.0001
Duration of motor block	191.7 ± 31.6	258.1 ± 15.95	0.0001
Duration of analgesia	276.7 ± 46.9	603.9 ± 48.5	0.0001

motor blockade (time to achieve motor blockade upto Bromage 3) was 17.9±1.8 minutes and 15.7±2.7 minutes for group BM, and group BD, respectively. Onset of motor block was significantly earlier in group BD than group BM ($p<0.05$) (Table 2). Both groups were similar in the maximum dermatomal height achieved (Table 3).

Preoperatively, immediately after drug delivery, at 5 minutes intervals for first 30 minutes and then 15 minutes intervals up to 60 minutes, heart rate and NIBP of patients were recorded. There was no statistically significant difference ($p > 0.05$) in the mean heart rate and mean arterial blood pressure of both groups at any time interval (Figure 2 and 3).

The two segment regression time was noted and found to be similar in both the groups. The duration of sensory block (time to regression sensory sensation up to S1 level) was 240.4±28.75 minutes and 306.1±15.32 minutes for group BM and group BD, respectively. The duration of sensory block was significantly longer in group BD than group BM ($p<0.05$) (Table 2). The duration of motor block (time from epidural medication to regression from Bromage 3) was 191.7±31.6 minutes for Magnesium group and 258.1±15.95 minutes for Dexmedetomidine group. The difference was statistically significant ($p<0.001$) (Table 2).

The mean sedation score was recorded at predefined time intervals. The mean sedation score in group BD was significantly higher during a time interval from 5 minutes to 1 hour intraoperatively as compared to group BM which had a mean sedation score of one throughout this period. The difference in mean sedation score was statistically highly significant ($p <0.0001$) with a maximum sedation score being 2.1±0.4 in group BD at 10 minutes intraoperatively. The duration of analgesia (time from epidural medication to first epidural top up) in Dexmedetomidine group (603.9±48.5 minutes) was statistically significantly prolonged compared to magnesium group (276.7± 46.9 minutes, $p <0.0001$) (Table 2).

The adverse effects were noted during intra-operative and

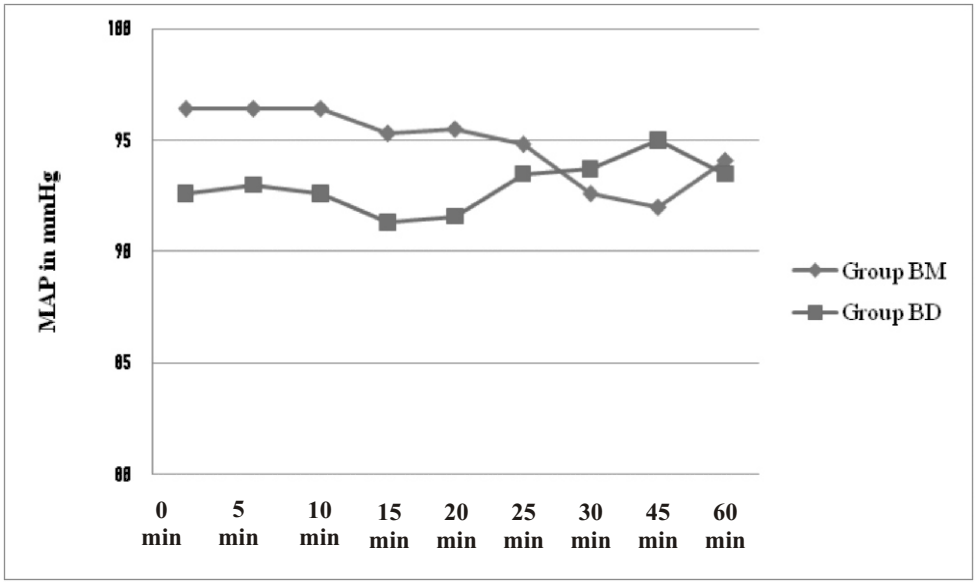

Figure 2: Comparison of mean arterial pressure (MAP) between the study groups.

Table 3: Maximum level of sensory blockade

Maximum sensory level	Group BM	%	Group BD	%
T6	0	0	2	5
T8	9	22.5	6	15
T10	31	77.5	32	
Total	40		40	80

post-operative period and found to be statistically not significant (Table 4).

DISCUSSION

The present study was designed with the aim of evaluating the addition of Dexmedetomidine or Magnesium sulphate to isobaric Bupivacaine 0.5% in epidural anaesthesia in orthopedic surgeries. We used 13 ml of study drug (0.5% Bupivacaine with magnesium sulphate 50 mg or 0.5% Bupivacaine with Dexmedetomidine 0.5 µg/kg) and found satisfactory results regarding onset of block and duration of analgesia which was comparable with a similar study done by Shahi et al[9] (2014) who had used 15 ml of study drug (0.5% Bupivacaine with Magnesium sulphate 50 mg and 0.5% Bupivacaine with Dexmedetomidine 0.5 µg/kg).

We have used a low dose of Dexmedetomidine (0.5µg/kg) in comparison to other studies, in order to reduce the risk of adverse effects. Shaikh et al[10] despite using a dose of 1µg/kg Dexmedetomidine found shorter duration of analgesia (342.97±18.03 minutes) and similar side effect profile, as compared to the present study.

In the present study, the mean onset of sensory block was significantly earlier in Dexmedetomidine group (11.9±2.3 minutes), when compared with Magnesium sulphate group (13.5±2.1 minutes). The mean onset of sensory block was found to be even earlier than the study done by Shahi et al[9], i.e. in Dexmedetomidine group (14.6±1.9 minutes) and in Magnesium sulphate group (15.4±2.1 minutes). Onset of sensory block was defined as the time from epidural injection to occurrence of sensory block at T10 dermatome in mid clavicular line. The mean duration of sensory block was significantly prolonged in Dexmedetomidine (306.±15.32 minutes) when compared to Magnesium group (240.4±28.75 minutes). The mean onset of motor block was significantly earlier in Dexmedetomidine group (15.7±2.7 minutes) than magnesium sulphate group (191±31.6 minutes). This was in accordance with studies done by Shaikh et al[10] and Mohanty et al.[11] The prolonged

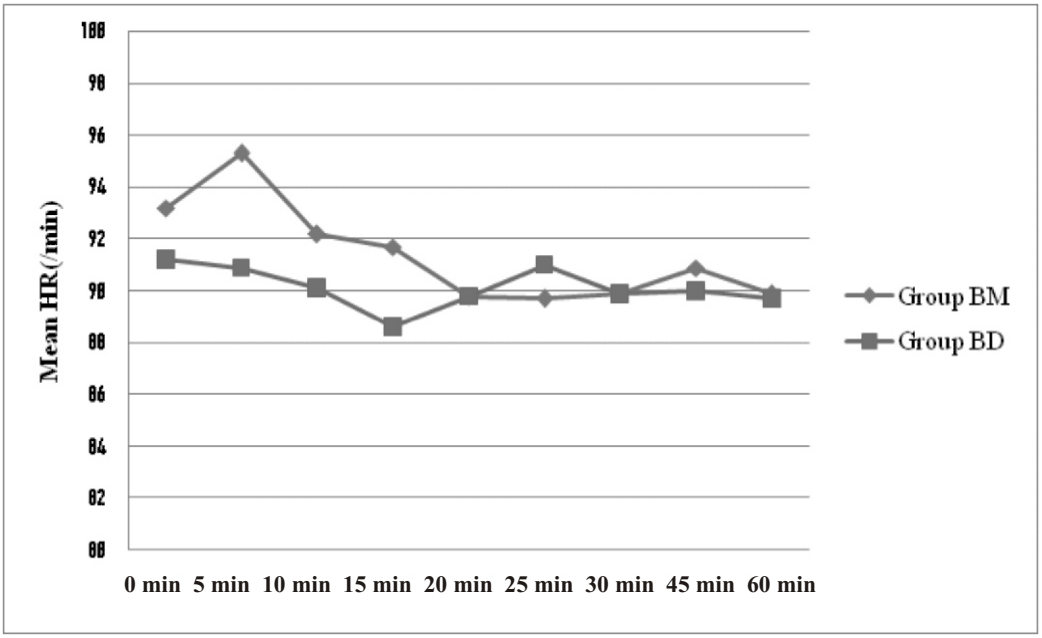

Figure 3: Comparison of intra-operative heart rate (HR) between the study groups.

Table 4: Comparison of side effects in two groups

Side effects	Group BM (n=40) n (%)	Group BD (n=40) n (%)	p value
Hypotension	2 (5%)	2 (5%)	
Bradycardia	0 (0)	4 (10%)	p >0.05
Nausea/vomiting	3 (7.5%)	6 (15%)	
Shivering	0 (0)	4 (10%)	

duration of block with Dexmedetomidine in epidural may be attributed to its synergistic effect with local anaesthetic. Dexmedetomidine is an α-2 adrenoceptor agonist which blocks conduction by binding to both pre-synaptic C-fibres and post-synaptic dorsal horn neurons in spinal cord; causing increased intensity of conduction block and analgesia.[12-16] Magnesium blocks NMDA channels in a voltage-dependent manner and produces a dramatic reduction in NMDA-induced currents.[17]

Duration of analgesia was significantly protracted in Dexmedetomidine group than Magnesium sulphate group. Dexmedetomidine has been proposed to provide analgesia by both spinal and supra-spinal mechanism. At spinal level it activates α-2a and α-2c adrenergic receptors mainly in lamina II thus reducing release of substance P and glutamate in primary afferent terminals. It also activates G-protein mediated potassium channels causing hyperpolarization of interneurons. Supraspinally, it causes suppression of neuronal firing in locus coeruleus by causing hyperpolarization of noradrenergic neurons, alongwith inhibition of nor epinephrine release in descending pathway terminating propagation of pain signals thus causing analgesia.[18,20] Neurophysiological studies have demonstrated that Magnesium is a physiological and pharmacological blocker of NMDA receptors in neuronal tissue. As the role of the NMDA receptor in pain perception has now become apparent, there is increasing use of Magnesium for the management of both acute[21] and chronic pain.[22] Magnesium non-competitively antagonizes NMDA receptors and blocks calcium influx in voltage dependent fashion, thus reducing NMDA induced currents and producing analgesia.[23]

Dexmedetomidine group shows considerable sedation without respiratory depression, in comparison to Magnesium sulphate group. The α_2 agonist causes sedation by its action on the locus coerulus. This mechanism acts in synergy with the sedation caused by epidural anaesthesia due to decreased afferent proprioceptor discharge. Sedation characteristics of Dexmedetomidine include a normal sleep pattern and calming effect on the patients who remain quiet but arousable and cooperative.[24]

A decrease in mean arterial blood pressure as well as heart rate was observed in both the groups after epidural injection which was not statistically significant at various time intervals (p >0.05). Bupivacaine is known to cause hypotension after neuraxial administration which can be explained by blockade of sympathetic vasoconstrictor pathways in the spinal cord and autonomic ganglia. The fall in blood pressure and heart rate due to Dexmedetomidine is attributed to its central action at the level of brain stem and inhibition of sympathetic out flow.[25,26] Magnesium, on the other hand also causes hypotension by reducing systemic vascular resistance with a compensatory increase in cardiac output. At higher plasma concentrations, it produces bradycardia. It has a major role in the management of rhythm disturbances.[26] The incidence of bradycardia and hypotension was not significant in study done by Shahi V et al.[9]

Shivering and bradycardia were common in Dexmedetomidine group, although statistically insignificant. This might be explained by hypothermia caused by local epidural anesthetic injection and thermal redistribution from the central to the peripheral region.[27]

The limitations of the present study were that the total analgesic requirement in first 24 hours was not included in this study and results cannot be generalized to ASA III and IV patients, as they were excluded from the study.

CONCLUSION

Dexmedetomidine 0.5 μg/kg seems to act as a better adjuvant than magnesium sulphate (50 mg) with 0.5% Bupivacaine, providing excellent postoperative analgesia

and superior sedative quality without undesirable side effects. Dexmedetomidine also provides early onset and prolonged duration of sensory and motor block, which may be useful during longer orthopaedics surgeries.

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