Section: Anesthesiology

Original Research Article

A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL COMPARING THE EFFICACY OF EPIDURAL BUPIVACAINE (0.5%) WITH DEXMEDETOMIDINE (0.5 µG/KG) AND MAGNESIUM SULPHATE (50 MG) AS AN ADJUVANT IN PATIENTS UNDERGOING MAJOR LOWER LIMB ORTHOPEDIC SURGERIES

R.Srilekha[1], R Ganessan[2], R.Iniya[3]

[1]Senior Assistant Professor, Department of Anesthesiology, Government Mohan Kumaramangalam Medical College and Hospital, Salem, Tamilnadu, India.
[2]Associate Professor, Department of Anesthesiology, KAPV Govt Medical College & Mgm Hospital, Tiruchirapalli, Tamilnadu, India.
[3]Assistant Professor, Department of Anesthesiology, Vinayaka Mission Medical College, Karaikal, Puducherry, India.

Received : 30/04/2023
Received in revised form : 08/06/2023
Accepted : 17/06/2023

Keywords:
Epidural bupivacaine, Dexmedetomidine, Lower limb, Orthopaedic surgery, Analgesia, Sedation score.

Corresponding Author:
Dr. R.Iniya
Email: iniya.special@gmail.com

DOI: 10.47009/jamp.2023.5.3.461

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (3); 2345-2350

Abstract

Background: Epidural anaesthesia is a recent evidence-based regimen for peri-operative and post-operative pain relief after surgeries. The study aimed to compare the efficacy of epidural bupivacaine (0.5%) with dexmedetomidine (0.5 µg/kg) or Magnesium sulphate (50 mg) as an adjuvant in American Society of Anaesthesiologists (ASA) I and II patients undergoing major lower limb orthopaedic surgeries. **Materials and Methods:** This prospective randomised control trial was conducted on 50 patients who came for elective lower limb surgeries at the Government Mohan Kumaramangalam Medical College and Hospital, Salem, Tamil Nadu, for two years. Subjects were randomised into groups BD and BM. Group BD: Bupivacaine 0.5% (12 ml) + Dexmedetomidine 0.5 µg/kg (1 ml), and Group BM: Bupivacaine 0.5% (12 ml) + Magnesium sulphate 50 mg (1ml). A detailed history of medical illness, prior surgeries, anaesthetic exposure, drug intake, allergies, premedication, monitoring of NIBP, ECG, SpO2, heart rate, and baseline cardio-respiratory parameters was recorded. **Results:** No significant difference in gender, ASA, age, weight, or duration of surgery between groups. Heart rate, SPO2, and MAP decreased gradually in both groups, with no significant difference. The dexmedetomidine group had longer sensory and motor block duration but no difference in time for sensory regression. Dexmedetomidine had a higher sedation score than magnesium sulphate, with 19 (76%) of the dexmedetomidine group having a sedation score >2. Bradycardia was only present in the dexmedetomidine group. **Conclusion:** Dexmedetomidine is a better adjuvant than magnesium sulphate with 0.5% bupivacaine, providing exceptional post-operative analgesia and superior sedative quality without side effects.

INTRODUCTION

Epidural anaesthesia is (peridural or extradural) obtained by blocking spinal nerves in the epidural space as the nerves emerge from the dura and then pass into vertebral foramina. It provides prolonged duration and differential blockade extended its use in post-operative analgesia and acute and chronic pain relief. But it has some disadvantages like patchy motor block and delayed onset than spinal anaesthesia. Various techniques are tried to overcome these points. Proper and non-complicated management of peri-operative and post-operative pain is crucial for ideal surgical patient care, decreasing hospital stay duration and increasing quality of life.[1-3]

Epidural anaesthesia is a recent evidence-based regimen for peri-operative and post-operative pain relief after surgeries. It has been found to reduce surgical stress, hemodynamic stability, recovery of gastrointestinal function, early ambulation, and thromboembolic events in high-risk patients. It provides more post-operative pain relief than systemic drugs and is safer with fewer systemic side effects.[4-5] Local anaesthetics are useful and effective in treating acute and chronic post-operative

pain. Still, the limitations like short duration of action and adverse effects on the Cardio-Vascular System (CVS)and Central Nervous System (CNS) curb its use in recent times.6 Adjuvants or additives are frequently used with local anaesthetics for their combined and additive effect by extending the period of sensory-motor block and restricting the increasing dose necessity of local anaesthetics.[7]

The collection of local anaesthetic adjuvants has progressed from opioids to an extensive collection of drugs with varying action mechanisms. A large range of opioids, from morphine, fentanyl and sufentanil to hydromorphone, buprenorphine and tramadol, was used earlier, which are restricted by their adverse effects like respiratory depression, nausea, vomiting and pruritus, especially with its neuraxial use. Alpha 2 adrenoreceptor antagonists like clonidine and dexmedetomidine are among the most extensively used local anaesthetic adjuvants. Other drugs like steroids (dexamethasone), anti-inflammatory agents (parecoxib and lornoxicam), midazolam, ketamine, magnesium sulfate and neostigmine have also been used with varied achievements. Local Anaesthetic peripheral nerve block adjuvants' success in prolonging analgesia is an extensively researched topic.[8] The apprehension concerning the safety outline of these adjuvants for prolongation of epidural analgesia demand further exploration in this track.

Dexmedetomidine, an α2 adrenergic receptor agonist, possesses hypnotic, sedative, anxiolytic, sympatholytic, and analgesic properties without producing significant respiratory depression. Its sympatholytic effect decreases mean arterial pressure (MAP) and heart rate (HR) by reducing norepinephrine release.[9-11] Dexmedetomidine has a broad range of pharmacological properties, including sedation associated with arousability and orientation and without respiratory depression.[12-14]

Magnesium sulphate (MgSO4) 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 sensitisation induced by peripheral nociceptive stimuli.[15]

This study aimed to compare the efficacy of epidural bupivacaine (0.5%) with dexmedetomidine (0.5 µg/kg) or Magnesium sulphate (50 mg) as an adjuvant in American Society of Anaesthesiologists (ASA) I and II patients undergoing major lower limb orthopaedic surgeries.

MATERIALS AND METHODS

This prospective randomised control trial was conducted at the Department of Anaesthesia, Government Mohan Kumaramangalam Medical College and Hospital, Salem, Tamil Nadu, for two years. It was done on 50 patients who came for elective lower limb surgeries. Institutional Ethical Committee approval was obtained before the start of the study. Informed written consent was obtained from each participant.

Inclusion criteria: Patients of either gender aged 18-65 years with ASA grade I & II and posted for elective lower limb surgery were included.

Exclusion criteria: Patients with a history of adverse reaction to any study drugs, spinal deformity, previous spinal surgery, any C/I to epidural anaesthesia like coagulation profile, with ASA II & IV, and patients who refused were excluded.

A detailed history of medical illness, present and past, along with a history of prior surgeries and anaesthetic exposure and their details, were recorded. History of drug intake and allergies to drugs and latex were recorded. Routine investigations and that on the surgery were done. General, systemic and thorough airway assessments of the patients were done. In the preoperative period, all patients were instructed about the benefits of epidural analgesia. Inj. Ranitidine and Inj. Metoclopramide was given as premedication. NIBP, ECG, SpO2, and heart rate were monitored continuously. 18G IV cannula were inserted and preloaded with RL 10 ml/kg.

Subjects were randomised into groups BD and BM. Group BD: Bupivacaine 0.5% (12 ml) + Dexmedetomidine 0.5 µg/kg (1 ml), and Group BM: Bupivacaine 0.5% (12 ml) + Magnesium sulphate 50 mg (1ml). Baseline cardio-respiratory parameters like heart rate, blood pressure, and oxygen saturation were recorded every 5 mins after administering study drugs.

The sensory block was assessed using a short bevelled sterile 26G hypodermic needle along the mid-clavicular line bilaterally, and the duration to achieve up to the T10 level was noted. A modified Bromage scale was used to assess motor blockades. Scale 0 indicated no motor block, scale 1 indicated the inability to raise an extended leg, able to move knees and feet, scale 2 indicated the inability to raise an extended leg and move knees, able to move feet, and scale 3 indicated a complete block of a motor limb.

Sedation was graded by using a five-point sedation scale. Scale 1 indicated alert and wide awake, scale 2 indicated arousable to verbal command, scale 3 indicated arousable with gentle tactile stimulation, scale 4 indicated arousable with vigorous shaking, and scale 5 indicated unarousable. 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 5, 10, 15, 20, 25, 30, 45, and 60 minutes after giving the block. Time in the operating room and duration of surgery were recorded. Any side effects, including hypotension, bradycardia, nausea, vomiting, sedation, and shivering, were noted.

Statistical analysis

Numerical variables like age, HR, NIBP, SPO2, time in the operating room, and duration of surgery

ISSN (O): 2687-5365; ISSN (P): 2753-6556

were represented in mean, median, mode and standard deviation. Categorical variables like gender and complications were expressed in frequencies and percentages. Pie charts and bar diagrams were used as appropriate.

When a numerical variable is associated with the numerical variables, such as Pearson's correlation test was used after checking for normality. When a categorical variable is associated with a categorical variable, the variables are represented in tables and bar diagrams. For the test of significance, the chi-square test was used. Fisher's exact test was used when more than 20% of the cell values have an expected cell value of less than 5. P-values less than 0.05 were considered statistically significant. Data were entered in an MS Excel sheet and analysed using SPSS software version 16. American Society of Anaesthesiologists (ASA) physical status classification system (ASAPS) was used.

RESULTS

Among the dexmedetomidine group, 5 (20%) were females, and 20 (80%) were males. Among the magnesium sulphate group, 8 (32%) were females, and 17 (68%) were males].

Table 1: Patient characteristics in the study

		Group BD	Group BM	P-value
Gender	Male	20 (80%)	17 (68%)	0.26
	Female	5 (20%)	8 (32%)	
ASA	I	18 (72%)	19 (76%)	0.50
	II	7 (28%)	6 (24%)	
Age		39.92 ± 7.921	39.92 ± 8.149	0.67
Weight		58.60 ± 4.778	58.40 ± 5.346	0.53
Duration of surgery		76.00 ± 9.372	75.76 ± 9.554	0.96

Among the Dexmedetomidine group, 18 (72%) patients belong to ASA I and 7 (28%) to ASA II. Among the Magnesium Sulphate group, 19 (76%) belong to ASA I, and 6 (24%) belong to ASA II. There is no significant difference in gender, ASA, age, weight, and the duration of surgery between groups (Table 1).

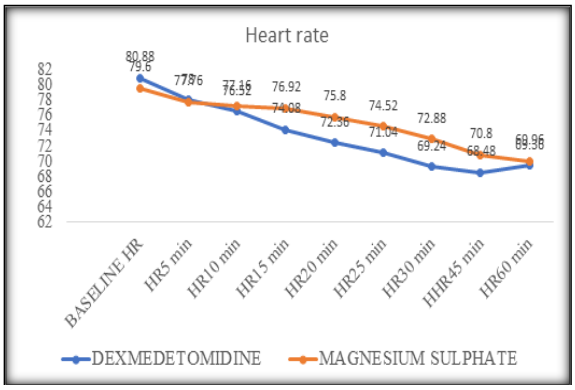

Figure 1: Heart rate between groups

The heart rate decreased gradually in both groups over time, with no significant difference between the two groups (Figure 1).

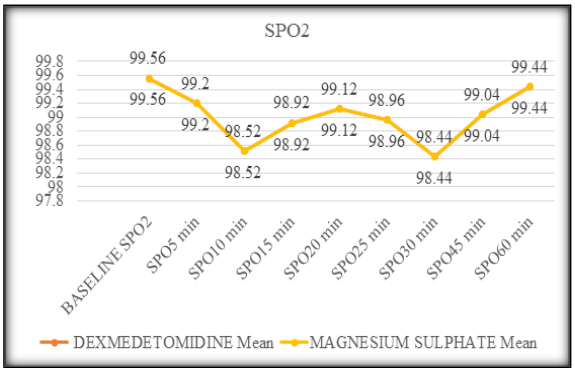

Figure 2: SPO2 between groups

The SPO2 among the groups at baseline to 60 minutes are equal among both groups (Figure 2).

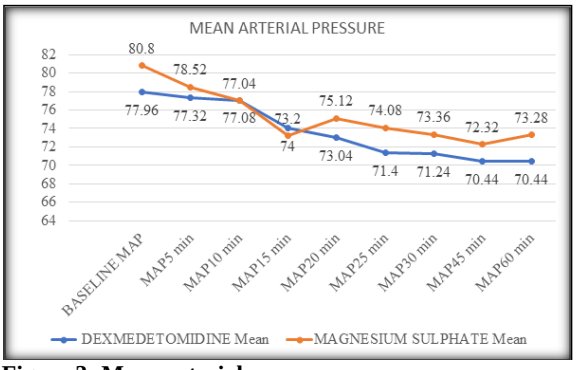

Figure 3: Mean arterial pressure

The MAP decreased gradually in both groups over time, with no significant difference between the two groups (Figure 3).

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 2: Association of intra-operative variables among groups

	Group BD	Group BM	P-value
Time of onset of sensory block	11.5 1.39	13.7 1.16	<0.001
Time of onset of motor block	15.420 1.38	17.640 .91	<0.001*
Duration of sensory block	304.96 6.23	245.64 10.68	<0.001*
Duration of motor block	258.08 6.66	190.52 16.01	<0.001*
Time of sensory regression to S1	133.86 1.47	133 1.83	0.07
Duration of analgesia	596.28 31.81	280.32 25.02	<0.001*

There was statistically significant showing early onset of sensory block and onset of motor block in the dexmedetomidine group. There was statistically significant showing a longer duration of sensory block and longer duration of motor block in the dexmedetomidine group.

No significant difference in time for sensory regression to the S1 level between groups. There was statistically significant showing longer duration of sedation in the dexmedetomidine group (Table 2).

Table 3: An adverse effect, a maximum level of sensory block, and sedation score between groups

		Group BD		Group BM	
The maximum level of sensory block	T10	16	64.0	15	60.0
	T6	3	12.0	-	-
	T8	6	24.0	10	40.0
Sedation score	1	6	24.0	17	68.0
	2	12	48.0	6	24.0
	3	7	28.0	2	8.0
Adverse effect	NIL	14	56.0	19	76.0
	Bradycardia	2	8.0	0	0
	Hypotension	2	8.0	2	8.0
	Nausea/Vomiting	4	16.0	3	12.0
	Shivering	3	12.0	1	4.0

Dexmedetomidine and magnesium sulphate had different sensory block levels, with dexmedetomidine having a higher sedation score than Magnesium sulphate. There was statistically significant, showing 19 (76%) of the dexmedetomidine group were having sedation score>2, and only 8 (32%) in the magnesium sulphate group had a sedation score >2 (p=0.006). This shows the good sedative effect of dexmedetomidine.

Among 25 subjects in the dexmedetomidine group. 14 (56%) had no adverse effects, 2 (8%) had bradycardia, 2 (8%) had hypotension, 4 (16%) had nausea and vomiting, and 3 (12%) had shivering. Among 25 study subjects in the magnesium Sulphate group, 19 (76%) had no adverse effect, 2 (8%) had hypotension, 3 (12%) had nausea and vomiting, and 1 (4%) had shivering. This was not statistically significant. Bradycardia was only present in the dexmedetomidine group (Table 3).

DISCUSSION

The study was done among 50 subjects, 25 in the dexmedetomidine group and 25 in the magnesium Sulphate group. The mean ± SD age in the dexmedetomidine group was 39.92 ± 7.92 years, and in the magnesium sulphate group was 39.92 ± 8.15 years. This was lesser compared to a study done by Mathur et al.[16] and lower than a study done by Yehia et al.[17] The mean ± SD weight in the dexmedetomidine group was 58.6± 4.78 Kg, and in the magnesium sulphate group was 58.4 ± 5.35 Kg, and this is higher than a study done by Mathur et al.[16] The result showed no significant difference for age and weight among the groups. The absence of significant difference indicates the success of randomisation, and this is similar to other studies.[16-19]

Our study shows no statistical significance between the groups in the case of surgery duration, which shows the accuracy of randomisation. This was similar to other studies where age, weight, ASA, gender, and duration of surgery were equally distributed among groups showing successful randomisation.[16,18,19] In our study, there was statistically significant showing early onset of sensory block in the dexmedetomidine group. The onset of sensory block was defined as the time from epidural injection to the occurrence of sensory block at the T10 dermatome in the mid-clavicular line. Yehia et al.[17] showed that the dexmedetomidine group showed superior analgesic criteria with onset at 8.25 ± 1.1 min versus 9.8 ± 1.5 min in the magnesium Sulphate group and 10.1 ± 1.3 min in group B (P=0.0002).

In our study, there was a statistically significant showing of early onset of motor block in the dexmedetomidine group and a statistically significant showing of longer duration of sensory block in the dexmedetomidine group. The mean ± SD duration of the motor block in the dexmedetomidine group was 258.08 ± 6.23 min, and the magnesium Sulphate group was 190.52 ± 10.68 min. This was statistically significant, showing a longer duration of motor block in the dexmedetomidine group. A study by Mathur et al.[16] showed that 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

ISSN (O): 2687-5365; ISSN (P): 2753-6556

group BM and BD, respectively. The duration of the motor block was 191.7 ± 31.6 minutes for the magnesium group and 258.1 ± 15.95 minutes for the dexmedetomidine group in their study. This concord with other studies where dexmedetomidine has shown longer sensory and motor block duration.[17-19]

The mean ± SD time for sensory regression to S1 level in the dexmedetomidine group was 133.86 ± 1.47 min, and the magnesium Sulphate group was 133 ± 1.83 min. This was not statistically significant. The mean ± SD duration of analgesia in the dexmedetomidine group was 596.28 ± 31.81 min, and the magnesium Sulphate group was 280.32 ± 25.02 min. This was statistically significant, showing a longer duration of sedation in the dexmedetomidine group ($p<0.001$).

Jain et al.21 and Shukla et al.22 observed that the duration of sensory and motor block times was significantly longer in the dexmedetomidine group than in the magnesium group. Dexmedetomidine can act as an α2-adrenoreceptor agonist in the peripheral and CNS. This analgesic effect of intrathecal dexmedetomidine occurs through inhibition of the release of C-fibre transmitters and hyperpolarisation of the postsynaptic dorsal horn neurons, which can explain the prolonged duration of a spinal block when dexmedetomidine was added to intrathecal anaesthetics.[19,23]

Duration of analgesia was significantly more protracted in the dexmedetomidine group than in the magnesium sulphate group. Dexmedetomidine has been proposed to provide analgesia by both spinal and supra-spinal mechanisms. At a spinal level, it activates α-2a and α-2c adrenergic receptors mainly in lamina II, thus reducing the release of P and glutamate in primary afferent terminals. It also activates G- protein-mediated potassium channels causing hyper-polarisation of interneurons. Supra spinally, it causes suppression of neuronal firing in locus coeruleus by causing hyper-polarisation of noradrenergic neurons and inhibiting norepinephrine release in descending pathways, terminating propagation of pain signals, thus causing analgesia.[16,18-20]

Among the dexmedetomidine group, 6 (24%) had a sedation score of 1, 12 (48%) had a sedation score of 2 and 7 (28%) had a sedation score of 3. Among the magnesium sulphate group, 17 (68%) had a sedation score of 1, 6 (24%) had a sedation score of 2 and 2 (8%) had a sedation score of 3. This was statistically significant, showing 19 (76%) of the dexmedetomidine group were having sedation score >2, and only 8 (32%) in the magnesium sulphate group had a sedation score >2. This shows the good sedative effect of dexmedetomidine ($p<0.006$). The dexmedetomidine group shows considerable sedation without respiratory depression compared to the magnesium sulphate group. The α2 agonist causes sedation by its action on the locus coeruleus. This mechanism synergises 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] Noxious stimulation releases glutamate and aspartate neurotransmitters, which bind to the NMDA receptor. Activation of these receptors leads to calcium entry into the cell. It initiates a series of central sensitisation such as wind-up and long-term potentiation in the spinal cord in the response of cells to prolonged stimuli. NMDA receptor signalling may be important in determining the duration of acute pain. Magnesium blocks calcium influx and non-competitively antagonises NMDA receptor channels.[25,26]

Among 25 subjects in the dexmedetomidine group. 14 (56%) had no adverse effects, 2 (8%) had bradycardia, 2 (8%) had hypotension, 4 (16%) had nausea and vomiting, and 3 (12%) had shivering. Among 25 study subjects in the magnesium Sulphate group, 19 (76%) had no adverse effect, 2 (8%) had hypotension, 3 (12%) had nausea and vomiting, and 1 (4%) had shivering. This was not statistically significant. Bradycardia was only present in the dexmedetomidine group. The fall in blood pressure and heart rate due to dexmedetomidine is attributed to its central action at the brain stem level and sympathetic outflow inhibition.[16,27,28]

Siddique et al.[18] found that dexmedetomidine as an adjuvant with hyperbaric bupivacaine leads to the earlier onset and prolonged sensory and motor block duration compared to magnesium sulfate. Mathur et al.[16] also found that the onset of sensory and motor block was earlier in group BD, the duration of sensory and motor blockade was significantly prolonged in group BD, and the incidence of sedation was more in group BD. Shahi et al.[20] did a study to establish the effect of adding magnesium or dexmedetomidine as an adjuvant to epidural bupivacaine in lower limb surgeries. They found that analgesia in the post-operative period was better in Group D, the sensory and motor blockade duration was significantly prolonged, and the incidence of sedation was more in Group D. Sayed et al.[19] also had similar findings. Tariq et al.[29] showed that post-operative analgesia was better in the Dexmedetomidine group with less rescue analgesic requirement and more incidence of sedation.

CONCLUSION

The study concludes that dexmedetomidine 0.5 µg/kg seems to act as a better adjuvant than magnesium sulphate (50 mg) with 0.5% bupivacaine, providing exceptional post-operative analgesia and superior sedative quality without undesirable side effects. Dexmedetomidine also provides early onset and prolonged sensory and motor block duration, which may be useful during

ISSN (O): 2687-5365; ISSN (P): 2753-6556

longer orthopaedics surgeries. The prevalence of adverse effects was more, and bradycardia as an adverse effect was present only in the dexmedetomidine group. Non-competitive NMDA antagonist magnesium sulfate, administered epidurally, also prolongs the duration of analgesia, but less than epidural dexmedetomidine.

Recommendation

Further studies with increased sample sizes matched for confounding factors in other settings, such as primary and secondary care, will represent the true nature of the study findings. Further studies are required to determine whether larger doses of epidural magnesium sulfate can produce greater potentiation of analgesia and reduce opioid requirements.

Limitations

The study's limitations are that confounding factors like systemic diseases were not studied, and the time for the first rescue analgesia was not analysed. A smaller sample size decreased the chance of generalisability. Hospital-based studies in a tertiary care setting may cause bias in the selection of patients.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556