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## A comparative study of epidural bupivacaine and epidural bupivacaine with magnesium sulphate for perioperative analgesia in patients undergoing lower limb surgery

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### Abstract

**Aims and objectives:** The aim of the study was to compare epidural plain bupivacaine and plain bupivacaine with magnesium sulphate in patients undergoing elective lower abdominal surgery.

**Methodology:** This Randomized parallel group double-blind controlled study was conducted on 60 patients of elective lower limb surgery. Group B received 0.5% bupivacaine +normal saline 1ml of 0.9% and Group BM received 0.5% bupivacaine+ magnesium sulphate (1ml) containing 50mg Bupivacaine.

**Results:** Both the drugs provided post-operative analgesia. Time for onset of sensory block in the two groups and there was significant difference between two groups in respect of onset of sensory block. The onset of block was significantly less in group BM compared to group B. The mean onset of sensory block (mean  $\pm$  SD) was Group B-15.57 $\pm$ 2.27 minutes and Group BM-12.93 $\pm$ 1.14 minute. The time for onset of motor block, duration of sensory block, duration of motor block and duration of analgesia in the two groups and there was no significant difference. Visual analogue scale (VAS) score, Verbal rating scale (VRS) score and no of rescue analgesia by the patients in the two groups and there was no significant difference.

**Conclusion:** Single dose epidural administration of 0.5% bupivacaine hydrochloride with 50mg magnesium sulphate produces predictable rapid onset sensory block with less side effect than plain 0.5% bupivacaine hydrochloride.

**Keywords:** Epidural bupivacaine, epidural bupivacaine, magnesium sulphate, perioperative analgesia, magnesium sulphate, perioperative analgesia

### Introduction

Epidural anaesthesia is a safe technique for surgical anaesthesia as well as for post operative analgesia. It has become a common practice to use polypharmacy approach for treatment of intra and post operative pain, because no drug has yet been identified that specifically inhibits nociception without associated side effects [1]. After sodium, potassium and calcium, magnesium is the most abundant cation in our body. It has antinociceptive effects in animal and human models of pain [2].

Noxious stimulus produces an influx of calcium ion through both voltage sensitive calcium channels that facilitates presynaptic release of neurotransmitters and post synaptic N-methyl D-aspartate calcium channels which triggers the sequence of events leading to cellular hyper excitability [3]. Studies in animal models of persistent pain in which central sensitization is present support this theory [4].

It is also known that bupivacaine hydrochloride is one of the most widely used long acting anaesthetic drug. When used in 0.5% and 0.75% concentration, it provides adequate surgical anaesthesia while analgesia can be obtained with concentrations as low as 0.125% to 0.25% [5]. It has been mentioned in systematic review that supplemental magnesium may provide perioperative analgesia, because this is a relatively harmless molecule, is not expensive and also because the biological basis for its potential antinociceptive effect is promising [6] these effects are primarily based on physiological calcium antagonism, that is voltage-dependent regulation of calcium influx into the cell, and noncompetitive antagonism of N-methyl D-aspartate (NMDA) receptors [7]. As, there is no ideal drug or combination of drugs for

perioperative epidural analgesia. Keeping these lacunae in mind, the present study was conducted to compare epidural plain bupivacaine and plain bupivacaine with magnesium sulphate in patients undergoing elective lower abdominal surgery.

### Aims and Objective

1. To evaluate onset, duration and height of sensory anesthesia between the study groups.
2. To evaluate the duration of analgesia between the study groups.
3. To evaluate the onset and duration of motor blockade between the study groups
4. To assess adverse side effects of these drugs between the study groups (if any).

### Materials and Methods

This Randomized parallel group double-blind controlled study was conducted on 60 patients of elective lower limb surgery. After the approval of the Institutional Ethics Committee of IMS & SUM Hospital, and permission of the SOA University, the present thesis work was carried out under the Department of Anaesthesiology, IMS & SUM Hospital, between April 2016 to July 2017.

Patients with ASA grade I and II, 20 to 60 years of either sex were included in the study. Local infection in the lumbar region, Known hypersensitivity to amide local anaesthetic, Bleeding diathesis, Spinal deformity, Diabetes Mellitus, Known neurological, cardiac, renal, metabolic and psychological disorder were excluded in the study. The patients who fulfilled the above inclusion criteria and had none of the exclusion criteria mentioned above were explained about the study and written informed consent was obtained. Patients thus enlisted for the study were randomly allocated into two groups using a computer generated randomization chart. Group B (n=30) patients with height >160cm received total volume of 20ml(19ml of plain 0.5% bupivacaine +normal saline 1ml of 0.9%) and those with height <160cm received a total volume of 15ml(14ml of 0.5% bupivacaine +normal saline 1ml of 0.9%). On the other hand Group BM (n=30) with height >160cm received a total volume of 20ml (19ml of 0.5% bupivacaine + magnesium sulphate (1ml) containing 50 mg) and those with height <160cm received a total volume of 15ml(14ml of 0.5% bupivacaine+ magnesium sulphate (1ml) containing 50mg) through the epidural route.

Patients were visited on the preoperative day for pre-anaesthetic checkup. Detailed history of present illness, any relevant past history of disease was recorded. Clinical examination of respiratory system, cardiovascular system and central nervous system was done. Vertebral spine was also examined. Laboratory investigations were noted. The patients were explained in detail about the procedure of lumbar epidural block. All their queries and doubts were answered to get their confidence and support.

All patients had an intravenous line with 18G cannula before arriving in the operation theater. Anaesthetic machine, breathing circuits and monitors were properly checked beforehand. Full range of drug and equipments including appropriate size laryngoscope blade, endotracheal tubes and airways were kept in hand. After arrival of patients in the operation theater a base line pulse rate, blood pressure, ECG, respiratory rate, SpO<sub>2</sub> were noted. All patients were preloaded with 15ml-20ml/kg of Ringer's

Lactate solution over 15 minutes before administering epidural block.

### Drugs kept ready for Epidural administration were

- 1 Injection bupivacaine hydrochloride 0.5% –20 ml vial – Two
- 2 Injection Magnesium Sulphate preservative free ampoule– one
- 3 Injection lignocaine hydrochloride 2% with adrenaline – 30 ml vial – one
- 4 Normal Saline Bottle - one

### Drugs of the same pharmaceutical brand were used in all patients

The drugs were prepared by an anaesthesiologist who was not involved in the study and the epidural anaesthesia was administered by the same anaesthesiologist in all the patients to minimize any operational bias. The patients were kept in sitting position. The overlying skin was prepared with spirit- povidone iodine -spirit, followed by antiseptic draping. After proper identification of space, 2ml of inj lignocaine 2% with adrenaline was used to infiltrate the skin and subcutaneous tissue at L<sub>2-3</sub> or L<sub>3-4</sub> interspace. For epidural anaesthesia 18G Tuohy needle was used. Epidural space was identified by loss of resistance to air technique. After negative aspiration test for blood and CSF, a test dose was administered with 3 ml of inj. Lignocaine hydrochloride 2% with adrenaline and monitoring was done to note any haemodynamic changes indicative of intravascular injection. After ensuring proper epidural placement of the needle tip, the study drug was slowly injected in small increments with repeated aspiration test as per protocol. After placement of study drug, epidural needle was removed; the puncture site was sealed with antiseptic dressing. Monitoring of vital signs was continued throughout the procedure. The patients were made supine. No other analgesic was given to the patients intraoperatively. The patients were administered O<sub>2</sub>, 3 L/min through face mask. The surgery was allowed after 20 minutes of epidural injection. The following parameters were noted:

- 1 Onset of Sensory Block: Assessed by pin prick method every 3 minutes. Time duration (minute) was assessed from local anaesthetic solution injection to start of loss of pain sensation to pin prick.
- 2 Duration of Sensory Block: Assessed every 15 minutes postoperatively by pin prick method. Time duration (minute) was assessed from onset of sensory block to regression of dermatome of two segments.
- 3 Duration of Analgesia:

### A. Assessed every 15 minutes postoperatively by four point verbal rating scale to record observer measurement of pain.

The scores are as follows:

1. Comfortable (no pain)
2. Mild pain (elicited only by close questioning)
3. Moderate pain (bothering the patients but often controlled by lying still, analgesic accepted gladly).
4. Severe pain (dominating consciousness and calling out for urgent relief).

Time duration (minute) was assessed from onset of sensory block to first request for rescue analgesic (i.e. pain score 3 or more).

Rescue analgesic injection Diclofenac sodium 1.5mg/kg was given intramuscularly. The number of rescue analgesics in 24 hours from administration of epidural anaesthesia was also noted.

### B. Assessed by 10 cm Visual Analogue Scale (VAS) at the time of request of analgesic by the patients.

- 1 Height of Block:** Assessed by pin prick method over dermatomal segments.
- 2 Postoperative Analgesia:** Assessed by using Four point Verbal Rating Scale and Visual Analogue Scale (VAS) which is essentially a numeric pain scale - 0 - 10. 0 - no pain, 10 - worst pain possible.
- 3 Onset of Motor Block:** Assessed every 3 minutes by modified Bromage scale as follows:
  0. no paralysis
  1. inability to raise extended leg 2- inability to flex knee
  2. Inability to flex ankle and first toe.

### Time duration (minute) was assessed from the time of injection of local anaesthetic solution to achieve motor scale 2 or more

- 1 Duration of Motor Block:** Assessed by modified Bromage scale every 15 minutes post operatively. Time duration (minute) was assessed from onset of motor block to regaining of full motor power and joint movement.
- 2 Haemodynamic parameters:** Heart rate, Systolic BP,

Diastolic BP, Respiratory rate were noted at 0, 15, 30, 60, 75, 90, 120, and at 240 mins from administration of epidural anaesthesia.

- 3 Side effects:** Nausea, vomiting, hypotension, shivering, headache, etc were noted.

### Statistical evaluation

Sample size calculation was done by taking duration of analgesia as primary outcome variable of interest. It was estimated that  $n = 26$  (recruitment target achieved -  $n = 30$  in each group) will be required per group to detect 60 minutes difference in this parameter with 80% power and 5% probability of Type I error. This calculation assumed a standard deviation of 75 minutes in duration of analgesia. For statistical analysis, raw data entered into a MS Excel spread sheet and analyzed by SPSS 20 (statistical software version 20). Unpaired student's  $t$ -test was used to compare normally distributed numerical variables. All analysis were two-tailed and  $p$  value  $<0.05$  was taken to be statistically significant.

### Results

Both groups were comparable in respect to mean age, sex, weight, height and duration of surgery. The mean duration of surgery in group A is  $96.83 \pm 17.93$  min. and of group (B) is  $96.66 \pm 19.71$  min. The difference is not statistically significant. Mean total duration of surgery is more or less same in both the groups.

**Table 1:** Outcome Parameters

	Group B	Group BM	P value
Onset of Sensory Block	$15.57 \pm 2.27$	$12.93 \pm 1.14$	0.001
Onset of Motor Block	$22.93 \pm 1.19$	$22.43 \pm 2.23$	0.38
Duration of Sensory Block	$137.17 \pm 22.4$	$142.17 \pm 20.71$	0.59
Duration of Motor Block	$191 \pm 15.16$	$192 \pm 15.06$	0.766
Duration of Analgesia	$236 \pm 21.28$	$241 \pm 10.62$	0.27

There was significant difference ( $p$  value  $< 0.0001$ ) among the study group (Gr. BM) and the control group (Gr. B) in respect to the time for onset of sensory block as shown in Table - 1. There was no significant difference ( $p=0.38$ ) among the study group (Gr. BM) and the control group (Gr. B) in respect to the time for onset of motor block as shown in Table 1. There was no significant difference ( $p=0.59$ ) among the study group (Gr. BM) and the control group (Gr. B) in respect to the duration of sensory block shown in the Table - 1. There was no significant difference ( $p=0.76$ ) among the study group (Gr. BM) and the control group (Gr. B) in respect to the duration of motor block as shown in Table - 1. There was no significant difference ( $p=0.27$ ) between the study group (Gr. BM) and the control group (Gr. B) in respect to the duration of analgesia as shown in Table - 1.)

**Table 2:** Pain parameters

	Group B	Group BM	P value
VAS score	$5.06 \pm 0.82$	$5.03 \pm 0.80$	0.87
VRS score	$3.36 \pm 0.49$	$3.2 \pm 0.40$	0.15
Rescue Doses	$2.6 \pm 0.82$	$2.5 \pm 0.78$	0.56

There was no significant difference ( $p=0.87$ ) among the study group (Gr. BM) and the control group (Gr. B) in respect to visual analogue score (VAS) at the time of

request of analgesic by the patient as shown in Table - 2. There was no significant difference ( $p=0.15$ ) among the study group (Gr. BM) and the control group (Gr. B) in respect to visual analogue score (VRS) at the time of request of analgesic by the patient as shown in Table - 2. There was no significant difference ( $p=>0.05$ ) between the study group (Gr BM) and control group (Gr B) with respect to total number of rescue doses required by the patient in the first 24 hours of administration of epidural anaesthesia as shown in Table 2. While the control group (Gr B) required an average of 2.6 doses, the study group (Gr BM) needed 2.5 doses in the said period. There was no significant difference between the patients of study group (Gr BM) and control group (Gr B) as per as Heart Rate, SBP, DBP and respiratory rate was concerned at any time in the study period. There was no significant difference in distribution of block height achieved in different patients between study (Gr BM) and control (Gr B) groups.

**Table 3:** comparison of incidence of side effects between groups

Side effects	Group B	Group BM	(P value)
Nausea and vomiting	4 (13.33%)	7(23.33%)	0.506
Shivering	2(6.67%)	3(10.00%)	1.000
Sedation	2(6.67%)	1(3.33%)	1.000
Headache	2(6.67%)	1(3.33%)	1.000

(Fisher's exact test 2 - tailed  $p$  value)

There was no significant difference in incidence of side effects between study (Gr BM) and control (Gr B) groups as shown in Table 3.

### Discussion

Epidural anaesthesia with local anaesthetics has the advantages of optimal perioperative conditions including analgesia with better postoperative outcome and lesser incidence of complications.

Many local anaesthetics have been used as for epidural anaesthesia, but bupivacaine is the most commonly used agent. Previously many drug has been added as an adjuvant with local anaesthetics. Till now very few studied magnesium as an adjuvant. IV MgSO<sub>4</sub> prolongs analgesia and lesser discomfort in post operative period [8, 9]. Intrathecal MgSO<sub>4</sub> also prolongs post operative analgesia [10] Mechanism of intrathecal MgSO<sub>4</sub> is postulated to be supraspinal. However KO *et al.* with 50mg/kg IV failed to demonstrate an increase in the CSF MgSO<sub>4</sub> level. Also they did not find any significant increase in the post operative analgesia [11]

In this perspective 50mg of epidural MgSO<sub>4</sub> is too small dose that should have any supraspinal effect after crossing the Duramater. Again the primary mechanism of action of MgSO<sub>4</sub> being antagonism of NMDA receptors, it can be postulated that quicker onset and relatively prolonged analgesia of MgSO<sub>4</sub> with bupivacaine may be due to their direct effects on the nerve roots in the epidural space alone.

The present study was framed to evaluate the efficacy of combination of epidural bupivacaine and MgSO<sub>4</sub> over bupivacaine alone in lower limb surgeries. The result of the study showed that addition of magnesium sulphate, a competitive NMDA receptor antagonist as adjuvant to epidural bupivacaine reduces the time of onset. This findings is corroborative with the study done by Ghatak *et al.* [12]

Magnesium blocks calcium influx and non-competitively antagonises NMDA receptor channels. Non-competitive NMDA receptor antagonists have an effect on pain, and they also accentuate the analgesic properties of opioids [13] Administered intravenously, intrathecally or epidurally, the true site of action of magnesium is probably at the spinal cord NMDA receptors [14] The duration and intensity of post-operative analgesia depends on the degree of inhibition of NMDA receptor signal transmission [14] Co-administration of epidural magnesium for post-operative patient-controlled epidural analgesia reduced fentanyl consumption without any side effects [15] Administration of epidural magnesium perioperatively was associated with less analgesic requirement in the post-operative period [14] Bilir *et al.* also reported reduction in post-operative fentanyl consumption without any side effects.

In this randomized parallel group double- blind controlled study, 60 adult patients of either sex having ASA physical status I or II, aged between 20-60 years were divided as per computerized randomized table into two groups – Group B and Group BM. Group B (n=30): received epidural 0.5% bupivacaine hydrochloride, Group BM (n=30): received epidural 0.5% bupivacaine hydrochloride plus 50mg Magnesium Sulphate

The volume of the drugs was calculated according to height of the patient (i.e. 150 -160 cm: 15 ml and 161 cm onwards: 20 ml). This was similar to the method used by Suraj Dhale and coworkers [16] who used 15 mls of 0.5% bupivacaine for

patients upto 160 cms height and 20 mls of 0.5% bupivacaine for patients having height greater than 160 cms. The demographic profile of the patients assigned to the two groups and the statistical test performed to determine the comparability between the two groups. There was no statistically significant difference between the groups in terms of age, sex, body weight and height and duration of surgery of the patients. Hence, the groups were comparable with respect to the demographic characteristics.

Time for onset of sensory block in the two groups and there was significant difference between two groups in respect of onset of sensory block. The onset of block was significantly less in group BM compared to group B. The mean onset of sensory block (mean  $\pm$  SD) was Group B-15.57 $\pm$ 2.27 minutes and Group BM-12.93 $\pm$ 1.14 minutes. Hasanein *et al.* concluded that magnesium sulphate in addition to bupivacaine and fentanyl for labour analgesia led to early onset, longer duration of action and reduced breakthrough pain [17].

The time for onset of motor block, duration of sensory block, duration of motor block and duration of analgesia in the two groups and there was no significant difference in the time of onset of motor block in the two groups.

Visual analogue scale (VAS) score, Verbal rating scale (VRS) score and no of resque analgesia at the time of request for rescue analgesic by the patients in the two groups and statistically there was no significant difference in the two groups. In the study by Sun *et al.* who found comparable effects of both epidural 500 mg and 3 mg morphine regarding analgesia in the first postoperative 6 h [18].

Different doses of epidural MgSO<sub>4</sub> had been tried; Bilir *et al.* [15] injected a bolus small dose of 50 mg followed by infusion of 100 mg, but Yousef and Amr used 500 mg MgSO<sub>4</sub> which is the maximum dose [15, 19] In this study, the used dose was the maximum dose but with continuous monitoring for the mother and fetus. In our study, the lower incidence of shivering in the magnesium group was because of the anti-shivering effects of magnesium which have been documented in previous studies that used magnesium intravenous and neuroaxial [20, 21]. They attributed the antishivering effect to the cutaneous vasodilatation preventing sensation of coldness, thus preventing the shivering reflex [21]. The comparable postoperative and intraoperative complication among both groups is because of the choice of intermediate dose. Reduced incidence of pruritis, nausea, vomiting, and hypotension was noted in the MgSO<sub>4</sub> group, but without clinical significance. It seems to be related to the reduction of postoperative fentanyl usage.

The haemodynamic parameters HR, SBP, DBP respectively compared between study and control groups. There was decreasing trend in heart rate, systolic and diastolic blood pressure in both the groups initially during intra operative period. But this fall were within normal range. No case of hypotension (reduction of blood pressure > 20% of base line) was found in our study. However hypovolemia was not allowed during perioperative period with infusion of Ringer's Lactate solution (as hypovolemia is not tolerated in patients with sympathetic block). The fall in blood pressure, often accompanied by reduction in heart rate, is usual after epidural block. The gradual fall of blood pressure in epidural block may be due to slow spread of block and there is more time for auto compensation to occur.

Respiratory rate and height of block between the two groups

during the perioperative period and there was no significant difference in respiratory rate in the two groups.

Hence it was observed in the study that addition of 50mg of MgSO<sub>4</sub> to 0.5% bupivacaine administered epidurally reduces the onset of sensory block up to 12.93±1.14 minutes compared to 15.57±2.27 minutes with epidural 0.5% bupivacaine alone. There were no significant change in duration of sensory and motor block. There were no significant change in blood pressure, pulse rate and respiratory rate. There was no significant increase in side effects.

Vital parameters were well maintained during intraoperatively and postoperative period. No significant difference in vital parameters was seen in the two groups.

Few minor side effects like nausea, vomiting, and shivering were found in our study groups but they were statistically not significant.

### Conclusion

In conclusion, a single dose epidural administration of 0.5% bupivacaine hydrochloride with 50mg magnesium sulphate produces predictable rapid onset sensory block with less side effect than plain 0.5% bupivacaine hydrochloride.

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