

# Comparison of the Effects of Magnesium Sulfate versus Clonidine as an Adjunct to Epidural 0.5% Ropivacaine in Lower Limb Surgeries in Adult Patients – A Prospective Double-blinded, Randomized, Controlled Study

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## Abstract

**Introduction:** Regional anesthesia is currently the most effective method of reducing the stress response and thereby pain, especially in patients with surgical procedures involving the lower body. Ropivacaine was studied both for surgical anesthesia and acute pain management. The aim of this study is to compare the effects of magnesium sulfate (50 mg) versus clonidine (150 mcg) as an adjunct to epidural 0.5% ropivacaine in lower limb surgeries in adult patients posted for lower limb procedures.

**Materials and Methods:** After institutional ethical committee approval and written, informed consent from the patient attendants, 75 patients undergoing elective surgeries under epidural anesthesia, aged 18–60 years of either gender, belonging to ASA Grades I and II were randomized for this study. Group N (Control): Patients were administered 19 ml of 0.5% ropivacaine with 1 ml of normal saline epidurally. Group M: Patients were administered 19 ml of 0.5% ropivacaine with 1 ml of magnesium sulfate (50 mg) epidurally. Group C: Patients were administered 19 ml of 0.5% ropivacaine with 1 ml of clonidine (150 mcg) epidurally. Groups were assessed for characteristics of sensory and motor blockade, hemodynamics, and side effects. Data were analyzed statistically.

**Observations and Results:** The duration of post-operative analgesia (time to the first request of pain relief) was significantly prolonged and highest in the clonidine group followed by magnesium group than the control group (Group C  $278 \pm 5.26$  min vs. Group M  $251 \pm 5.65$  min vs. Group N  $233.00 \pm 4.48$  min [ $P < 0.001$ ]).

**Conclusion:** Hence, magnesium sulfate has been proved to be a promising alternative as an adjuvant to regional analgesia in the perioperative period.

**Key words:** Analgesia, Clonidine, Epidural anesthesia, Magnesium sulfate, Ropivacaine

## INTRODUCTION

Pain during surgery is often underestimated and undertreated. Being purely subjective, pain and its intensity vary widely among patients. Regional anesthesia is currently the most

effective method of reducing the stress response and thereby pain, especially in patients with surgical procedures involving the lower body.<sup>[1]</sup> Ropivacaine the recently introduced propyl homolog of bupivacaine in a pure S (-) enantiomeric form associated with a reduced incidence of both cardiovascular and central nervous system toxicity, a concern with racemic bupivacaine.<sup>[2]</sup> In view of the wider application of regional anesthetic procedure in modern anesthesia practice, there is a need for local anesthetic with desirable properties such as longer duration of sensory blockade and lesser duration of motor paralysis. Ropivacaine was studied both for surgical anesthesia and acute pain management.<sup>[3,4]</sup> The onset, intensity, and duration of sensory block are, in general,

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similar to bupivacaine, but the depth and duration of motor block are less than with bupivacaine.<sup>[5,6]</sup> Various adjuvants such as fentanyl, morphine, clonidine, dexmedetomidine, and magnesium sulfate were added to ropivacaine in clinical trials to prolong the duration and improve the quality of pain relief.<sup>[7,8]</sup>

The aim of this study is to compare the effects of magnesium sulfate (50 mg) versus clonidine (150 mcg) as an adjunct to epidural 0.5% ropivacaine in lower limb surgeries in adult patients posted for lower limb procedures.

## MATERIALS AND METHODS

After institutional ethical committee approval and written, informed consent from the patient attendants, 75 patients undergoing elective surgeries under epidural anesthesia, aged 18–60 years of either gender, belonging to ASA Grades I and II were randomized for this prospective and controlled study. Randomization was done using computer-generated random numbers into three groups of 25 each.

All patients were subjected to epidural catheterization with 16/18 G size and given epidural anesthesia according to group allocation.

Group N (Control): Patients were administered 19 ml of 0.5% ropivacaine with 1 ml of normal saline epidurally.

Group M: Patients were administered 19 ml of 0.5% ropivacaine with 1 ml of magnesium sulfate (50 mg) epidurally.

Group C: Patients were administered 19 ml of 0.5% ropivacaine with 1 ml of clonidine 150 mcg) epidurally.

### Inclusion Criteria

ASA Grades I and II physical status, aged between 18 and 60 years, belonging to both the sexes undergoing lower limb surgeries.

### Exclusion Criteria

The following criteria were excluded from the study:

- Patients not willing to participate in the study
- Patients with ASA Grades III, IV, and V
- Patients with contraindication to regional anesthesia
- Those with known sensitivity to local anesthetics
- Patients with local infection at the site of injection
- Non-cooperative patients.

### Method

#### Pre-anesthetic evaluation

During pre-operative visit, patients' detailed history, general physical examination, and systemic examination

were carried out. Basic demographic data such as age, sex, height, and weight were recorded.

During pre-anesthetic check-up, the linear visual analog scale (VAS) was explained to all patients using 10 cm scale. Informed consent was obtained from all the 75 patients after the detailed explanation of the procedure to be performed. On the day of surgery, all patients were premedicated with 0.05–0.1 mg/kg of midazolam intramuscularly 45–60 minutes prior to the procedure. Baseline parameters of heart rate, blood pressure, respiratory rate, and SpO<sub>2</sub> were recorded before starting the case. Peripheral venous cannulation was done with 18G IV cannula and all the patients were preloaded with 500 ml Ringer's lactate solution. The patients were placed in the left lateral position and under strict aseptic precautions, after local infiltration with 1% xylocaine in the epidural space was identified with an 18G Tuohy needle at L3-L4 interspace, by "loss of resistance" technique. 18G epidural catheter was threaded through the needle into the epidural space for 4–5 cm and secured with adhesive tapes to the back. After negative aspiration for blood and cerebrospinal fluid, 3 ml of 1.5% lignocaine with 15 µg of adrenaline was given as test dose was given and the patient was turned to supine position. After 5 min, if there is no adverse reaction for the test dose, intravascular and intrathecal placement were ruled out, and the study and control drugs were administered as per the group allocation. The principal investigator loaded the study drugs as per group allocation and provided to the investigator who administered anesthesia just before administering epidural anesthesia in sealed covers.

Group N,  $n = 25$ , was given 19 ml of 0.5% ropivacaine and 1 ml of normal saline epidurally. Group M,  $n = 25$ , was given 19 ml of 0.5% ropivacaine and 1 ml of magnesium sulfate (50 mg) epidurally. Group C,  $n = 25$ , was given 19 ml of 0.5% ropivacaine and 1 ml of 150 mcg of clonidine epidurally.

In all the three groups, the onset of sensory blockade, onset of motor blockade, duration of analgesia, onset of two-segment regression, hemodynamic stability, and side effects are noted, systematically tabulated and statistically analyzed.

The level of sensory block was assessed by pinprick and the onset of blockade was noted. In all three groups, the time of injection was recorded as 0 h and onset of blockade, level (dermatomal) of sensory blockade, quality of motor blockade by modified Bromage scale [Table 1], two-segment regression time, and the time at which rescue analgesic given were noted. Continuously SpO<sub>2</sub> was monitored and pulse rate, respiratory rate, and blood pressure (non-invasive blood pressure) were

recorded every 5 min and urine output monitoring was done in both the groups and noted in the pro forma. Side effects such as nausea, vomiting, bradycardia, hypotension, respiratory depression, and shivering were noted in all the three groups.

Modified Bromage scale for the onset of motor blockade proposed by Bromage and modified by Logan-Wild Smith.

If the surgical procedure was long and patients required, the protocol was to administer further 10–12 ml of 0.5% bupivacaine by epidural route as top up. However, none of the patients required additional top up intraoperatively. Patients were administered rescue doses of 0.125% bupivacaine 10–12 ml if VAS  $\geq 4$  in the post-operative period. At the end of the surgery, the patients were shifted to post-operative ward, they were monitored for every 30 min for the first 6 h and thereafter every hour for 24 h period.

The time to first request analgesia (duration of post-operative analgesia) was recorded when the VAS reached 4 or more or when the patient complained of moderate-to-severe pain.

### Statistical Analysis

At the end of the study, all the data are compiled and statistically analyzed using:

- Descriptive data presented as mean  $\pm$  SD
- Continuous data analyzed by paired or unpaired *t*-test
- ANOVA after *t*-test for comparisons between groups and within groups.

## OBSERVATION AND RESULTS

All the 75 patients completed the study. The three groups were statistically comparable with respect to demographic data such as age, weight, height, male-to-female ratio, ASA grading, and duration of surgery as represented in Table 2. The types of lower limb procedures are presented in Table 3.

**Table 1: Bromage scale**

Scale	Criteria	Degree of block
0	Free movement of legs, feet with ability to raise extended leg	None
1	Inability to raise extended leg and knee flexion is decreased, but full extension of feet and ankles is present	Partial 33%
2	Inability to raise leg or flex knees; flexion of ankle and feet present	Partial 66%
3	Inability to raise leg, flex knee or ankle, or move toes	Complete paralysis

### Onset of Sensory Blockade

The mean time of onset of sensory block in Group N was  $12.38 \pm 0.88$  min, in Group M was  $5.96 \pm 0.73$  min, and in Group C was  $8.64 \pm 0.89$  min. The statistical analysis by ANOVA test showed that there was a statistically significant difference ( $P < 0.005$ ) between all the three groups, presented in Table 4.

### Two-Segment Regression Time

The two-segment regression time in Group N was  $106.24 \pm 2.47$  min, in Group M was  $113.28 \pm 1.92$  min, and in Group C was  $117.20 \pm 1.68$  min. The statistical analyses by ANOVA test showed that there was a statistically significant difference ( $P < 0.005$ ) between the three groups, presented in Table 4.

### Duration of Sensory Blockade

The mean duration of sensory blockade in Group N was  $215.92 \pm 5.21$  min, in Group M was  $236.00 \pm 5.68$  min, and in Group C was  $262.56 \pm 5.11$  min. the statistical analysis by ANOVA test showed that there is a statistically significant difference ( $P < 0.05$ ) in all the three groups, presented in Table 4.

### Onset of Motor Blockade

The mean duration of onset of motor blockade in Group N was  $24.58 \pm 1.77$  min, in Group M was  $13.26 \pm 1.28$  min, and in Group C was  $17.92 \pm 2.32$  min.

The statistical analysis by ANOVA test showed that there is a statistically significant difference ( $P < 0.05$ ) in all the three groups, presented in Table 4.

**Table 2: Demographic data**

Variable	Group N Mean/SD n=25	Group M Mean/SD n=25	Group C Mean/SD n=25	P value
Age in years	47/5.0	52/3.5	54/6.8	0.56
Weight in kg	58.96	53.28	56.94	0.44
Height in cm	155.76	155.32	155.48	0.34
Gender				
M:F ratio	12/13	13/12	14/11	
ASA grading				
I/II	14/11	15/10	13/12	
Duration of surgery	147/8	158/4	160/6	0.68

$P < 0.05$  considered not statistically significant. Data expressed as mean and standard deviation. Fisher's exact test

**Table 3: Types of surgeries**

Type of surgery	Group N n=25	Group M n=25	Group C n=25
IL nailing tibia	6	8	7
Tibial plating	6	6	5
ORIF femur	5	5	4
Dynamic hip screw	3	3	4
Adam Moore prosthesis	3	2	2
Total knee replacement	2	1	3

Data expressed in absolute numbers. ORIF: Open reduction and internal fixation

**Table 4: Characteristics of sensory and motor blockade**

Variable (time in min)	Group N Mean/SD n=25	Group M Mean/SD n=25	Group C Mean/SD n=25	ANOVA between groups (sum of squares)	Sig.
Mean onset of sensory block	12.38/0.88	5.95/0.73	8.64/0.89	519.88	0.01
Two-segment regression time	106.24/2.47	113.28/1.92	117.20/1.68	1542.08	0.001
Mean onset of motor block	24.55/1.77	13.26/1.28	17.92/2.32	1618.71	0.001
Duration of sensory block	215.92/5.21	236.00/5.68	262.56/5.11	27366.08	0.001
Duration of motor block	164.28/2.8	175.32/3.38	192.76/19.95	10309.54	0.001
Time to the first request analgesia	233/4.48	251/5.65	278/5.26	25657.14	0.01

Data expressed as mean and standard deviation

**Table 5: Intensity of motor blockade (modified Bromage scale)**

Grade	Group N n=25	Group M n=25	Group C n=25
0	2	1	2
1	20	21	19
2	3	3	4
3	0	0	0

Data expressed as absolute numbers

**Table 6: Intraoperative hemodynamics**

Groups	Mean PR	SD	Mean BP	SD	Mean RR	SD	Mean SpO <sub>2</sub>	SD
Group N	74	2	110	15	14	1.9	98	0.8
Group M	73	3	100	20	14	1.8	99	0.8
Group C	72	5	100	15	12	10.4	99	0.8

P&gt;0.05

**Duration of Motor Blockade**

The mean duration of motor blockade in Group N was  $164.28 \pm 2.80$  min, in Group M was  $175.32 \pm 3.38$  min, and in Group C was  $192.76 \pm 19.95$  min. the statistical analyses by ANOVA test showed that there is a statistically significant difference ( $P < 0.005$ ) between the three groups, presented in Table 4.

**Intensity of Motor Blockade**

The intensity of motor blockade evaluated by Bromage scale showed similar degree of block level of Grade 2 in all the three groups. The statistical analyses by Chi-square test showed that there was no statistical difference ( $P > 0.05$ ) between the three groups, presented in Table 5 and Figure 1.

**Intraoperative Hemodynamics**

In all the groups, there is no statistically significant difference in the hemodynamic variables. Mean systolic blood pressures and mean heart rates are represented in Table 6 and Figures 2 and 3.

**Duration of Post-operative Analgesia**

The duration of post-operative analgesia (time to the first request of pain relief) was significantly prolonged and highest in the clonidine group followed by magnesium

group than the control group. Group C  $278 \pm 5.26$  min versus Group M  $251 \pm 5.65$  min versus Group N  $233.00 \pm 4.48$  ( $P < 0.001$ ) are represented in Table 4 and Figure 4.

**Side Effects**

There were no statistical differences between clonidine group, magnesium group, and control group with respect to side effects such as hypotension, bradycardia, and shivering. About 40% of patients in clonidine group had sedation which is statistically significant when compared to other two groups, represented in Figure 5.

**DISCUSSION**

This study was undertaken to evaluate the effect of magnesium sulfate versus clonidine as an adjuvant to epidural ropivacaine compared with plain ropivacaine alone for lower limb surgeries.

Most of the previous studies proved that magnesium sulfate and clonidine have been associated with lesser analgesic requirements and less discomfort in the post-operative period when used systemically and also as adjuvants to regional anesthesia.<sup>[9,10]</sup> Recently, intrathecal and epidural administration of magnesium sulfate as an adjuvant to local anesthetics such as lignocaine, bupivacaine, levobupivacaine, and ropivacaine has been reported to produce effective and prolonged analgesia.<sup>[11,12]</sup>

N-methyl-D-aspartate (NMDA) receptor signaling may be important in determining the duration and intensity of acute post-operative pain. Magnesium sulfate is a competitive NMDA receptor antagonist and plays an important role in the prevention of central sensitization of pain in response to prolonged nociceptive stimuli.<sup>[13]</sup> Clonidine is an alpha-2 agonist, which induces dose-dependent antinociception at spinal level mainly through the stimulation of alpha-2 adrenoceptors in the dorsal horn.<sup>[14]</sup>

In our study, the mean time of the onset of sensory blockade in magnesium Group C is significantly less than clonidine group and control group

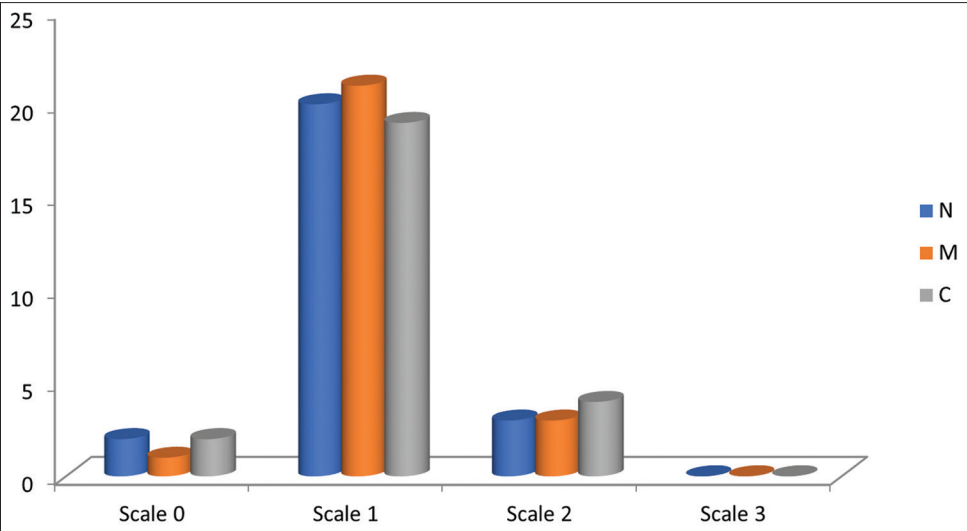


Figure 1: Intensity of motor blockade according to modified Bromage scale

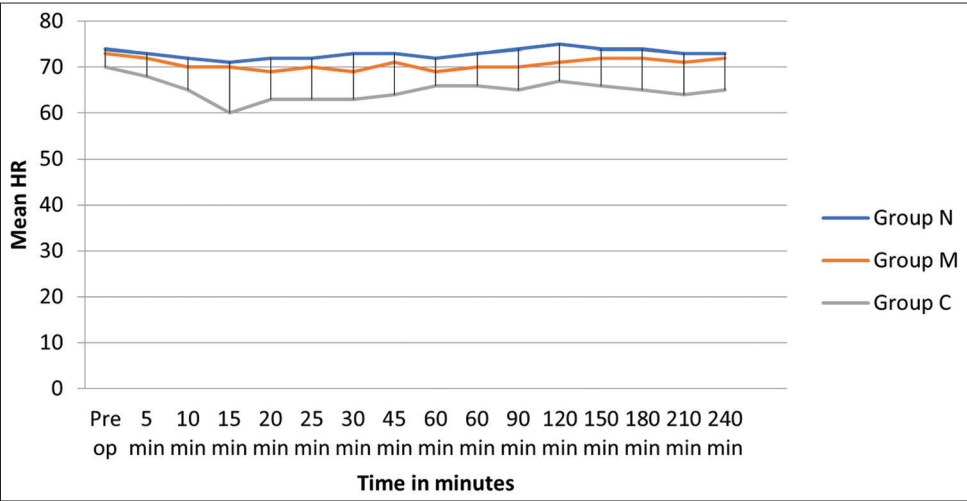


Figure 2: Intraoperative heart rate ( $P > 0.05$ )

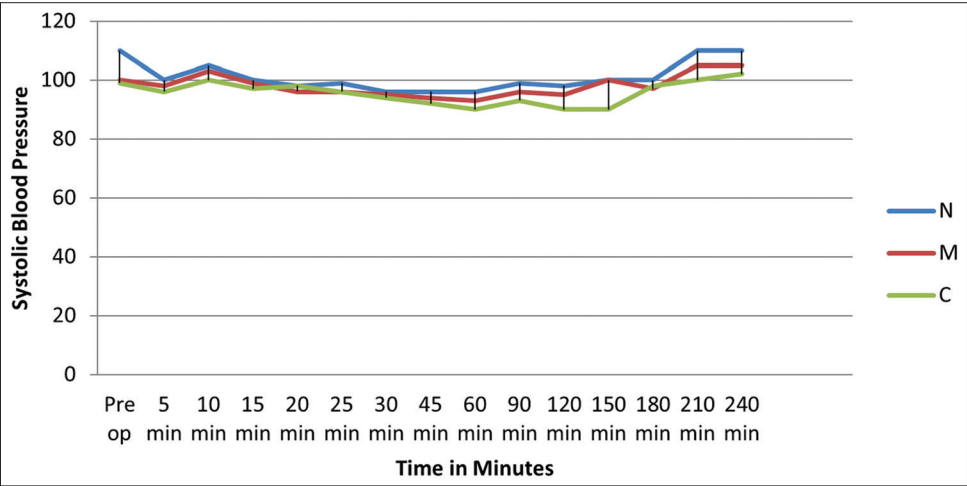


Figure 3: Systolic blood pressure ( $P > 0.05$ )



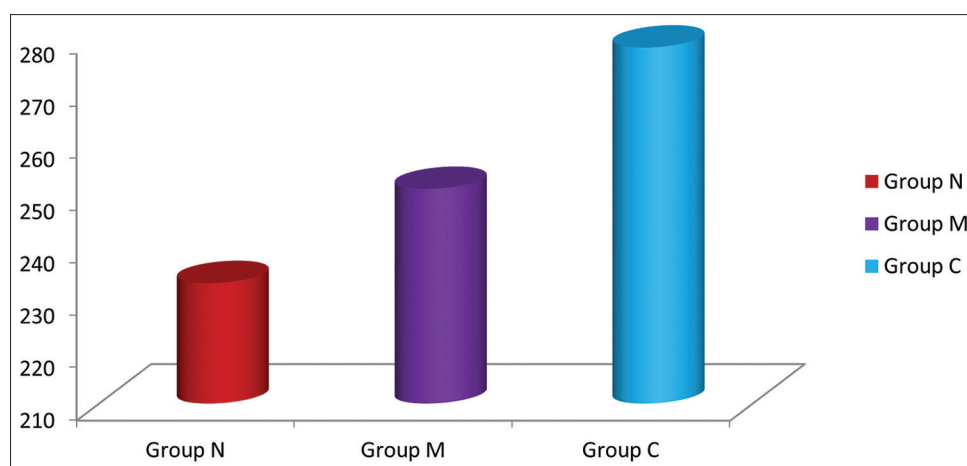


Figure 4: Time to the first request analgesia

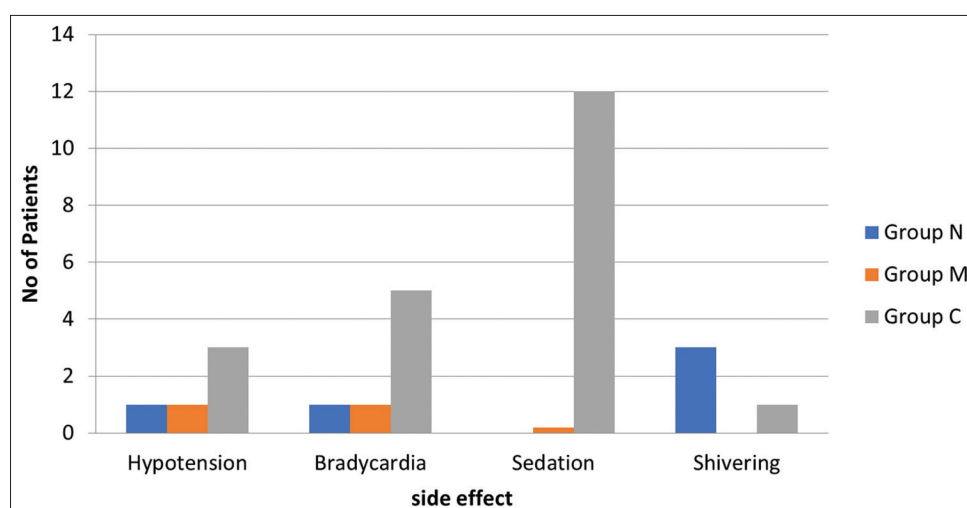


Figure 5: Incidence of side effects

(Group M  $5.96 \pm 0.73$  min vs. Group C  $8.64 \pm 0.89$  min vs. Group N  $12.38 \pm 0.88$  min,  $P < 0.005$ ).

In a study conducted by Ghatak *et al.*, epidural magnesium sulfate versus clonidine with bupivacaine showed that mean time of onset to T6 level for magnesium sulfate  $11.80 \pm 3.21$  min versus clonidine  $16.93 \pm 3.43$  min versus plain ropivacaine  $18.73 \pm 2.79$  min, ( $P < 0.001$ ), they correlated with the observations of this study.<sup>[15]</sup>

In our study, the two-segment regression time in magnesium group was significantly less than clonidine group but higher than control group (Group M  $113.28 \pm 1.92$  min vs. Group C  $117.20 \pm 1.68$  min vs. Group N  $106.24 \pm 2.47$  min [ $P < 0.001$ ]).

This finding also correlated with the above-mentioned study by Ghatak *et al.* (magnesium sulfate  $130.33 \pm 33.94$  min vs. clonidine  $145.33 \pm 27.74$  min vs. plain bupivacaine  $123.00 \pm 28.03$  min [ $P < 0.001$ ]).

The mean duration of sensory blockade in our study was significantly higher with clonidine group than magnesium and control groups (Group C  $262.56 \pm 5.11$  min vs. Group M  $236.00 \pm 5.68$  min vs. Group N  $215.92 \pm 5.21$  min [ $P < 0.001$ ]).

Mohammed *et al.* evaluated the efficacy and safety of epidural magnesium sulfate and clonidine as adjuvants to bupivacaine for post-thoracotomy pain relief and concluded that thoracic epidural analgesia using bupivacaine with clonidine is an efficient therapeutic modality for post-thoracotomy pain. Magnesium as an adjuvant provided quality post-operative analgesia decreasing the need for post-operative rescue analgesia and incidence of post-operative shivering without causing sedation.<sup>[16]</sup> The duration of post-operative analgesia is significantly prolonged in clonidine group in their study compared to magnesium and control groups comparable to the present study.

In a study conducted by Khalili *et al.*, who compared magnesium sulfate with bupivacaine versus plain

bupivacaine for lower extremity surgeries concluded that the duration of sensory blockade was significantly longer with magnesium sulfate group than in the control group (magnesium sulfate 106.5 min vs. control group 85.5 min [ $P < 0.001$ ]) which finding also is similar to this study.<sup>[17]</sup>

The mean time to onset of motor blockade in the present study was significantly less in magnesium group than clonidine group than control group (Group M  $13.26 \pm 1.28$  min vs. Group C  $17.92 \pm 2.32$  min vs. Group N  $24.58 \pm 1.77$  min [ $P < 0.001$ ]).

Similarly, the duration of motor blockade was significantly high in clonidine group than magnesium group and control group (Group C  $192.76 \pm 19.95$  min vs. Group M  $175.32 \pm 3.38$  min vs. Group N  $164.28 \pm 2.8$  min [ $P < 0.001$ ]).

The duration of post-operative analgesia (time to the first request of pain relief) was significantly prolonged and highest in the clonidine group followed by magnesium group than the control group (Group C  $278 \pm 5.26$  min vs. Group M  $251 \pm 5.65$  min vs. Group N  $233.00 \pm 4.48$  min [ $P < 0.001$ ]).

Shahi *et al.* did a comparative study on magnesium sulfate versus dexmedetomidine as adjuncts to epidural bupivacaine in lower limb surgeries and concluded that magnesium sulfate, administered epidurally, also prolongs the duration of analgesia, but less than epidural dexmedetomidine.<sup>[18]</sup> They reported that dexmedetomidine produced prolonged analgesia with arousable sedation.

Pradhan *et al.* conducted a comparative study on clonidine versus magnesium sulfate as adjuncts to epidural bupivacaine and concluded that magnesium sulfate was a better alternative to clonidine as an adjuvant to bupivacaine in epidural anesthesia in orthopedic lower limb surgeries for rapid onset of action, but clonidine has prolonged duration of action.<sup>[19]</sup> The observations of their study were comparable to the present study (Group M  $5.96 \pm 0.73$  min vs. Group C  $8.64 \pm 0.89$  min vs. Group N  $12.38 \pm 0.88$  min,  $P < 0.005$ , in the present study).

In our study, the intraoperative hemodynamic variables were more or less comparable in all the three groups except a few cases in the clonidine group had transient bradycardia ( $n = 5$ ) and hypotension ( $n = 3$ ) which were not statistically significant.

Only one patient had bradycardia and one patient had hypotension in both control and magnesium groups. Bradycardia and hypotension were treated with injection atropine 0.6 mg and IV crystalloid boluses, respectively.

Twelve patients of clonidine group had sedation in the perioperative period; they were awake but drowsy, calm, and easily arousable. None of the patients in all the three groups had any other side effects such as respiratory depression and dryness of mouth.

The results of our study suggest that epidural ropivacaine with clonidine produced significantly prolonged duration of post-operative analgesia with arousable sedation and minimal side effects when compared to epidural ropivacaine with magnesium sulfate and control groups, while magnesium sulfate produced shorter onset of sensory and motor blockade with significantly prolonged post-operative analgesia without sedation and side effects. Hemodynamics were comparable in all the groups. Hence, it can be concluded that magnesium sulfate may be a useful alternative as an adjuvant to epidural ropivacaine with safety and efficacy in the doses used.

The main limitation of this study is that the sample size is small. Most of studies were done with epidural bupivacaine.<sup>[20]</sup> There is a need for further clinical trials and research to be done with epidural ropivacaine and magnesium sulfate to establish the optimal and safe doses that can produce effective and prolonged duration of post-operative analgesia.

## CONCLUSION

Our study concluded that addition of magnesium sulfate to epidural ropivacaine produced earlier onset of sensory and motor blockade while significantly prolonging the post-operative analgesia when compared to control group but less duration of anesthesia when compared to clonidine group, without any significant side effects. Hence, magnesium sulfate has been proved to be a promising alternative as an adjuvant to regional analgesia in the perioperative period.

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