## **Original Research Article**

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# Comparative study of ropivacaine with ropivacaine-fentanyl and ropivacaine-fentanyl- magnesium sulfate in epidural anesthesia for lower limb surgeries

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#### **ABSTRACT**

**Background:** Epidural anesthesia is currently one of the most used technique for patients undergoing lower limb surgery. Dose sparing action of one adjuvant for another in epidural anesthesia with local anesthetic drugs for providing quality care to the patient remains controversial. Aims of the present study was to compare and study the properties 0.75% Ropivacaine alone (R) with 0.75% Ropivacaine-Fentanyl (RF) and 0.75% Ropivacaine-Fentanyl-Magnesium sulfate (RFM) in epidural anesthesia for lower limb surgeries. Study design was prospective randomized double blind study.

**Methods:** Patients between 18-60 years of age of ASA physical status class I and II undergoing lower limb surgeries were randomly allocated into 3 groups of 20 each. Total volume in epidural space given was 17ml in all 3 groups. Group R (n=20) received 15ml of 0.75% Ropivacaine with 2ml of normal saline, Group RF (n=20) received 15ml of 0.75% Ropivacaine with 50μg of fentanyl (1ml) and 1ml normal saline and Group RFM (n=20) received 15ml of 0.75% Ropivacaine with 50μg of fentanyl (1ml) and 100mg MgSO4 (1ml). Patients were then studied for hemodynamic profile, various block characteristics and side effects. Statistical analysis used was ANOVA, paired t-test, Chi-square and post hoc test were used. P <0.05 was considered significant.

**Results:** All three groups had stable hemodynamic parameters with Group RFM showing better block characteristics (p <0.001) in terms of time for achieving onset of analgesia, time for achieving T10 sensory blockade, time for requirement of first epidural top up, time for achieving motor Blockade, time for complete recovery of motor blockade with no significant differences in the side effect profile.

**Conclusions:** Epidural anesthesia for lower limb surgeries may have better block characteristic parameters if a combination of Ropivacaine-fentanyl-magnesium sulphate is used in comparison with ropivacaine-fentanyl or ropivacaine alone.

Keywords: Anesthesia, Epidural, Fentanyl, Lower extremity, Magnesium sulfate

### INTRODUCTION

Epidural anesthesia presently is one of the most useful techniques in modern Anesthesiology. Its versatility, gives anesthesiologist the opportunity to provide surgical anesthesia along with post-operative analgesia. As a sole regional anesthesia technique it is routinely used for abdominal and lower limb surgeries. For achieving desired per-operative anesthetic effect and to reduce the deleterious hemodynamic response of large volumes of local anesthetic agents, opioids and adjuvant drugs are routinely used in epidural space, but the exact volume and concentration required has not been validated yet.

Ropivacaine a new long-acting amide local anesthetic agent structurally related to bupivacaine is a pure S-enantiomer, with a high pKa and relatively low-lipid solubility. Ropivacaine has been the focus of intense interest because of its increased CNS and cardiovascular safety compared with bupivacaine.<sup>1</sup>

The addition of adjuvants like opioid to ropivacaine provides dose reduction and superior analgesia. Fentanyl is 800 times more lipophilic than morphine. It is rapidly absorbed from the epidural space and CSF. Due to its reduced cephalic spread the side effects are theoretically lesser than morphine.<sup>2</sup> It has a rapid onset of action of 15-30 minutes, and the duration of action of 2-5 hours. The initial bolus dose is usually 50-100 microgram. Respiratory depression at such doses is very rare and is usually associated with the use of other systemic opioids, or its accumulation from a prolonged infusion. Pruritus is the most common side effect whereas nausea and vomiting are rare.<sup>3</sup>

Magnesium is an N-methyl D-Aspartate (NMDA) receptor antagonist. Magnesium not only has its individual analgesic property but also has the analgesic property of opioids.<sup>4</sup> Magnesium supplementation potentiates the analgesic effect of opioids, while delays the development of its tolerance.<sup>5</sup> So using it as an adjuvant also reduces the requirement of opioids.

The aim of the present study was to evaluate the effect of Fentanyl and Magnesium Sulfate as adjuvant to 0.75% Ropivacaine in epidural anesthesia on block characteristics defined by onset of analgesia (in min), Time of achieving T10 sensory blockade (in min), maximum level of sensory blockade achieved, Time for achieving Motor Blockade (in min), Time for complete motor recovery (in min), Time for requirement of first epidural top up (in min), and hemodynamic parameters in patients undergoing lower limb surgeries. To the best in this knowledge there is currently no study comparing the efficacy of fentanyl and magnesium sulfate as adjuvant to 0.75% ropivacaine in epidural anesthesia in patients for lower extremity surgery.

#### **METHODS**

This prospective randomized double blind study was completed in operation theaters and post op ICU after getting approval from Institutional Ethical Committee (No.107/Ethics/R.Cell-17). Study duration was 1 year, starting from August 2016. A written informed consent was taken from patients.

Based on a previous study and considering 95% confidence interval and 80% power of study and adding for contingency of 10% a minimal sample size of 20 patients was found necessary for each group.<sup>6</sup>

Inclusion and exclusion criteria: 60 Patients between 18 and 60 years of age of the American Society of

Anesthesiologist (ASA) physical status class I and II, of either sex, posted for lower limb surgery were included in the study. Any contraindication to epidural anesthesia as local site infection, bleeding tendencies, vertebral anomalies, sepsis, raised intracranial pressure, allergy to local anesthetic agents, peripheral neuropathy, patient's refusal and physical dependence on narcotics were excluded from the study. Patients of renal, pulmonary, cardiovascular, neurological, neuromuscular diseases and deranged liver functions were also excluded from this study.

#### Randomization and blinding

The computer-generated simple random sampling procedure was used to allocate the subjects into three Groups R, RF, and RFM of 20 each. The study medication was prepared and administered by an anesthesiologist not involved in present study. Another anesthesiologist blind to the identity of study medication, monitored and managed the patients, and collected data.

Workup: Detailed preoperative assessment was done on the day before surgery, body weight, height, and vitals were recorded. All patients were advised overnight fasting. Aspiration prophylaxis was done with oral Ranitidine 150 mg on the night before surgery. Procedure was explained in full details to the patient and all doubts were adequately addressed. No anxiolytic was advised.

#### Anesthetic intervention

On the day of surgery in the operative room, an intravenous line of 20G was secured in the non-dominant hand under local anesthesia and preloading with 15ml/kg Ringer's lactate was done. Standard monitors such as Electrocardiography (ECG), pulse-oximetry, Noninvasive blood pressure (NIBP) were attached and base line vitals were recorded. Once the patient was comfortable to surroundings, under strict aseptic precautions, epidural (Perifix® ONE by B.Braun, Melsungen, Germany) was performed in sitting position at L3-L4 interspace in the midline using loss of resistance to air by 18 G tuohy needle under local anesthesia of skin. 20 G soft tip epidural catheter was introduced and secured at 4cm depth into epidural space after careful negative aspiration for blood and cerebrospinal fluid. After securing the catheter with sterile transparent dressing subject was made supine. A test dose of 3mL of 2% lignocaine hydrochloride with 1: 200000 adrenaline solution was given through epidural catheter. After 5 min of test dose epidural drug was administered in 3 groups.

- Group R (n=20): 15ml 0.75% Ropivacaine ± 2ml NS (total volume =17ml)
- Group RF (n=20): 15 ml 0.75% Ropivacaine ± 1 ml Fentanyl (50μg) ± 1ml NS (total volume =17ml)
- Group RFM (n=20): 15 ml 0.75% Ropivacaine ± 1 ml Fentanyl (50μg) ± 1 ml Magnesium Sulfate (100mg) (total volume =17ml)

Surgery was started once T10 dermatome block height was achieved. Sensory Block level was assessed using pinprick with 25G blunt needle in the mid clavicular line and the degree of motor block assessed according to the Modified Bromage score. O<sub>2</sub> at 4 L/min was administered through facemask. Heart rate, ECG, SpO<sub>2</sub>, and NIBP were recorded every 5 min for first 30 min, then at 15-min interval up to 60 min, then every half hourly for 4 hours or to the end of surgery.

#### Modified Bromage Scale

- Grade 0: Full flexion of knees and feet,
- Grade 1: Inability to raise extended leg, just able to flex knees with full flexion of feet
- Grade 2: Unable to flex knees, but some flexion of feet possible.
- Grade 3: Unable to move legs or feet.

The onset of sensory block was defined as the time between injection of epidural drugs and absence of pain at the L1 dermatome as assessed by sterile pinprick.

Time to complete motor block was defined as modified Bromage score of 3. Complete motor block recovery was defined when modified Bromage score was 0. Pain assessment was done using 100 point Visual analogue scale with VAS 0 = no pain and VAS 100 = worst possible pain.

In case of insufficient spread to T10 or VAS >40, bolus of epidural top up was administered (Top Up volume of 8ml of 0.75% Ropivacaine was given in all groups).

Hypotension was defined as mean arterial pressure values less than 65 mm of Hg and treated with Inj. mephentermine 6 mg i.v. bolus.

Tachycardia was defined as heart rate >100 /min and bradycardia as heart rate <45/min. Bradycardia was treated with 0.6mg inj. atropine i.v bolus.

Following block characteristics were recorded in every patient:

- Time of achieving onset of analgesia (in min)
- Time of achieving T10 sensory blockade (in min)
- Time for requirement of first epidural top up from initial medication (in min)
- Time for achieving Motor Blockade from medication (in min)
- Time for complete recovery of motor blockade (in min).
- Maximal and median level of sensory blockade achieved.

Any side effects including hypotension, bradycardia, shivering, sedation, nausea and vomiting was noted.

#### Statistical analysis

The statistical analysis of the data was done using SPSS (Statistical Package for Social Sciences) Version 16.0 statistical Analysis Software (Chicago, Inc., U.S.A.). The values were represented in Number (%) and Mean±SD. Qualitative data were expressed as a number. ANOVA, paired *t*-test, Chi-square and post hoc test were used. P <0.05 was considered significant.

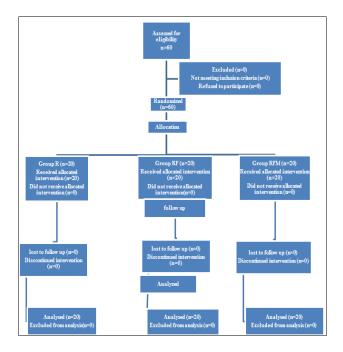


Figure 1: Consort flow diagram.

The consort flow diagram (Figure 1) illustrated the details of the participant progression during different trial phases. All 60 patients (20 in each group) completed the trial successfully and were analyzed as per the protocol.

#### **RESULTS**

Table 1: Demographic data.

	Group R	Group RF	Group RFM	P (ANOVA)
Age	34.75± 13.66	34.90± 14.23	35.65± 35.65	0.98
Male/ Female	12/8	16/4	14/6	0.38*
Height (cm)	158.30 ±5.51	165.97 ±8.70	160.99 ±8.06	0.06
Weight (kg)	55.55± 6.73	58.90± 8.44	57.10± 7.98	0.39
BMI (Kg/m2)	22.12± 1.67	21.51± 1.46	21.82± 1.65	0.48
Duration of surgery (in minutes)	186.25 ±31.49	199.25 ±53.7	173.95 ±31.21	0.14

Data are mean±SD (standard Deviation), P>0.05 = No significant difference, \* = chi-square test.

Table 1 depicts that all three groups were similar statistically in terms of demographic variables like age,

sex, height, weight, body mass index (BMI) and duration of surgery (P>0.05).

Table 2: Characteristics of epidural block.

Time in Minutes	Group R	Group RF	Group RFM	P (ANOVA)
Time for achieving onset of analgesia (L1)	$9.60 \pm 1.65^{\dagger}$	7.37±1.69 <sup>†</sup>	4.75±1.01 <sup>†</sup>	<0.001*
Time for achieving T10 sensory blockade	12.45±2.11 <sup>†</sup>	11.15±2.47 <sup>†,‡</sup>	7.28±1.34 <sup>‡</sup>	<0.001*
Time for requirement of first epidural top up	172.50±14.96 <sup>†</sup>	194.35±39.76‡	248.40±19.46 <sup>†,‡</sup>	<0.001*
Time for achieving Motor Blockade	24.40±3.71 <sup>†,‡</sup>	15.65±3.34 †	8.88±1.71 <sup>‡</sup>	<0.001*
Time for complete recovery of motor blockade	145.00±11.62 <sup>†</sup>	171.15±37.72‡	213.85±23.64 <sup>†,‡</sup>	<0.001*

Data are mean±SD (standard Deviation), \* Significant, †,‡ p= <0.001(Post-hoc tests)

Table 3: Comparison of adverse effects among the groups.

Adverse effects	Group	Group R		Group RF		RFM	D (Chi some we to st)
	No.	%	No.	%	No.	%	P (Chi-square test)
Hypotension	1	5.0	4	20.0	3	15.0	1.51
Nausea/ vomiting	0	0.0	2	10.0	1	5.0	3.5
Shivering	4	20.0	3	15.0	0	0.0	1.55
Bradycardia	0	0.0	0	0.0	0	0.0	-
Sedation	0	0.0	0	0.0	0	0.0	-

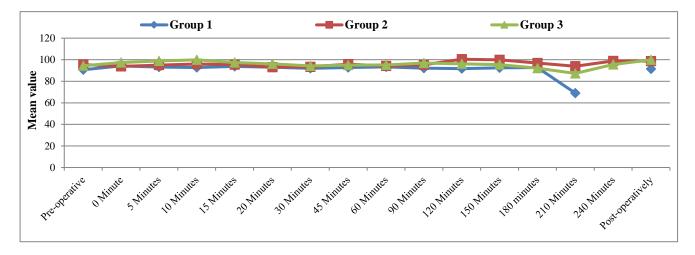


Figure 2: Comparison of mean arterial pressure amongst groups at various time intervals.

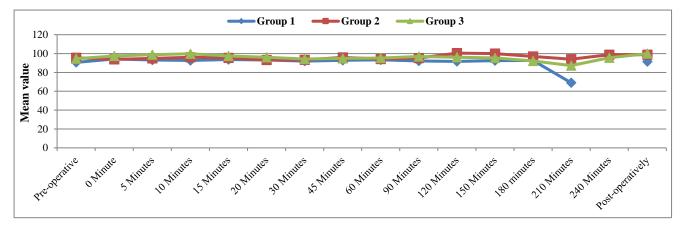


Figure 3: Comparison of heart rate among the groups at various time intervals.

Table 2 shows the various block characteristics measured were statistically significant between Group R, Group RF and Group RFM (p <0.001) in terms of time for achieving onset of analgesia (L1), time for achieving T10 sensory block, time for requirement of first epidural top up, time for achieving motor block, time for complete recovery of motor block.

Table 3 shows adverse effects amongst the groups, incidence of hypotension, nausea, vomiting and shivering was found to be statistically insignificant (p=1.51, p=3.5 and p=1.55) between groups. None of the patient in the present study was found to have pruritus, nausea and vomiting. The sedation score was in the range 0-1 in all three groups with no significant differences among the groups.

Figure 2 and Figure 3 shows the values of Mean arterial pressure and heart rate between the groups, which was statistically insignificant.

#### **DISCUSSION**

Epidural anesthesia is currently one of the most versatile practices in anesthesiology, but its early use date backs to 19<sup>th</sup> century when Physicians such as Corning published studies documenting success with neuraxial blocks in 1885.<sup>7</sup>

Local anesthetic agents are the mainstay of treatment in epidural anesthesia technique but at the same time are associated with major hemodynamic changes when used alone. So, many adjuvants like opioids, alpha-adrenergic agonists and magnesium sulfate have been added to reduce the concentration and the amount of local anesthetic agent used, thereby reducing the side effects. Ropivacaine, an analog of mepivacaine, has a lesser intense and shorter duration of motor block in addition to a lower toxicity profile than an equipotent dose of bupivacaine.<sup>8</sup>

This prospective randomized double blind study was done in patients scheduled for lower limb surgeries in epidural anesthesia to compare the block characteristics, hemodynamic profile and associated adverse effects, using 0.75% Ropivacaine (R), with 0.75% Ropivacaine-Fentanyl (RF) and 0.75% Ropivacaine-Fentanyl-Magnesium sulfate (RFM). No study comparing the epidural block characteristics and hemodynamic profile, using Ropivacaine with fentanyl and magnesium sulfate have been done till today to the best in this knowledge.

All the three groups were comparable in terms of demographic profile and duration of surgery. There was no statistical difference between Groups R, RF and RFM.

Mean time for achieving onset of analgesia from medication to L1 level was fast in Group RFM  $(4.75\pm1.01 \text{ minutes})$  than Group RF  $(7.37\pm1.69 \text{ minutes})$  and Group R  $(9.60\pm1.65 \text{ minutes})$ . The difference was

statistically significant (p<0.001) showing benefit of addition of magnesium sulfate on early onset. This study result was similar similar to previous studies.<sup>9,6</sup>

Mean Time of onset of T10 sensory block was fastest in Group RFM (7.28±1.34 minutes) as compared to Group R (12.45±2.11 minutes) and RF (11.15±2.47 minutes) and this was statistically significant (p<0.001), showing rapid onset of action produced by magnesium sulfate. This result was comparable to a previous study using bupivacaine and magnesium in epidural route. 10

Time for 1st epidural top up requirement in patients of Group R was earlier (172.50 $\pm$ 14.26 minutes) than that of Group RF (191.35 $\pm$ 33.08 minutes) and group RFM (248.40 $\pm$ 19.46 minutes) and the difference was statistically significant (p<0.001). Addition of magnesium with fentanyl as an adjunct to epidural ropivacaine provides excellent analgesia and delays the use for 1st epidural top up. This study result was comparable to previously done studies. 11.6

Time of onset of motor block in group RFM  $(8.88\pm1.71 \text{ minutes})$  was faster than Group RF  $(15.65\pm3.34 \text{ minutes})$  and R  $(24.4\pm3.71 \text{ minutes})$  which is statistically significant (p<0.001). In a previous study it was found that onset of motor blockade was  $16.92\pm3.84 \text{ minute}$  with epidural 20 ml ropivacaine 0.75% with 75 µg fentanyl in lower abdominal and lower limb surgeries. <sup>12</sup> Results in this study demonstrate that similar effect can be reached with lower volume of ropivacaine 0.75% and 50µg of fentanyl.

Time of complete motor recovery was earlier in group R  $(145.00\pm11.62~\text{minutes})$  than Group RF  $(171.15\pm37.72~\text{minutes})$  and Group RFM  $(213.85\pm23.64~\text{minutes})$  and the difference was statistically significant (p <0.001). Early recovery in Group R and group RF may be because of low volume of Ropivacaine used with prolonged effect in Group RFM due to magnesium sulfate.

Episodes of hypotension, nausea, vomiting and shivering were comparable in all the three groups. Previous study also observed that patients receiving 20ml 0.75% ropivacaine with 75 $\mu$ g fentanyl in epidural space had 40% incidence of nausea vomiting and 30% incidences of sedation. Lower incidences of nausea vomiting and sedation in current study were attributed to lower dose of fentanyl used as compared to above study.

There was no episode of bradycardia, sedation and respiratory depression in any of the groups. Hemodynamic parameters like mean arterial pressure and heart rate in all three groups were comparable and statistically insignificant during the course of surgery and post-operative period.

Limitation in this study it is the small sample size and future multicenter trials with larger sample size may be required for further validation in this finding.

#### **CONCLUSION**

Therefore, Authors can conclude that, combination of ropivacaine-fentanyl-magnesium sulfate in comparison to ropivacaine alone or ropivacaine-fentanyl, for epidural anesthesia in lower limb surgeries, provides better quality, early onset, prolonged duration of sensory and motor blockade with stable hemodynamic and fewer side effects.

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Ethical approval: The study was approved by the Institutional Ethics Committee (No.107/Ethics/R.Cell-17)

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