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A prospective, randomized, double-blinded clinical study of comparative evaluation of post operative analgesia with epidural ropivacaine 0.375% and epidural levobupivacaine 0.25% in lower limb orthopaedic surgeries

Harshitha MS[1], Pallavi SR[1] and Nagashree J Bharadwaj[2,*]

[1] Senior Resident, Department of Anesthesiology, Shimoga Institute of Medical Sciences, Shimoga, India.
[2] Senior Resident, Department of Anesthesiology, Dr. B R Ambedkar Medical College and Hospital, Bangalore.
* Correspondence: nagashree.brj@gmail.com

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Abstract: Background: Orthopaedic surgeries of lower limb are well suited for central neuraxial blockade. While the surgeries are done under spinal anesthesia, demand for post operative pain relief and need to reduce the use of systemic analgesics requires epidural analgesia in the post-operative period.
Objective: To evaluate and compare the duration of analgesia of 0.375% Ropivacaine and 0.25% Levobupivacaine given by epidural routes in lower limb orthopaedic surgeries in 24 hrs post operative period.
Material and Methods: In this prospective, randomized, double blinded clinical study, 60 adult patients of ASA I-II of both sexes were randomized into 2 groups(n=30). Patients received 7ml of 0.375% Ropivacaine in group R and 7ml of 0.25% Levobupivacaine in group L through epidural catheter.
Results: There was no significant difference between two groups with respect to demographic profile and ASA physical status. The mean duration (minutes) of analgesia after each epidural topup was significantly longer in group L (303.5±21.8) compared to group R (273.2±23.42) with p value 0.001. Total number of epidural topups were 5 for both the groups, rescue analgesics were needed in only 2 patients in each group. Quality of motor block was predominantly grade 0 of modified bromage scale in more than 80% patients in both the groups. Haemodynamic stability was well maintained and no adverse effects encountered in both the groups.
Conclusion: Epidural 0.25% Levobupivacaine and 0.375% Ropivacaine in their equipotent doses provided adequate post operative analgesia for lower limb orthopaedic surgeries. Levobupivacaine provided prolonged duration of analgesia compared to ropivacaine. But the total number of epidural topups, need for rescue analgesics and quality of motor block were similar for both the study drugs without any haemodynamic variations and adverse effects.

Keywords: Ropivacaine; Levobupivacaine; Lower limb orthopaedic surgery; Epidural; Post operative analgesia.

1. Introduction

Orthopaedic surgeries of lower limb are well suited for central neur-axial blockade. While most of these surgeries are done under spinal anesthesia, demand for post operative pain relief and the need to reduce the use of systemic analgesics requires epidural analgesia in the post operative period. Bupivacaine is the most commonly used local anaesthetic in epidural analgesia for labour pain relief and post operative pain relief in various surgeries [1].

The two S-enantiomers of racemic bupivacaine, levobupivacaine and ropivacaine appear to be ideal for post operative epidural analgesia as they have less potential for systemic toxicity [2]. Both drugs though structurally similar to the parent drug, have different potencies. Several studies have shown that while levobupivacaine may be as potent as bupivacaine (0.97:1) [3], ropivacaine is less potent(1.5:1) [2]. McDonald et al. [3] also showed that the relative potency of ropivacaine and bupivacaine is 1:2. The studies by Parpaglioni

et al. [4] and Lee YY et al. [5] comparing the ED50 of levobupivacaine and ropivacaine (10.8mg and 14.22mg respectively) revealed a potency ratio of 0.68 for ropivacaine/levobupivacaine5. Hence, the efficacy of these two drugs has to be evaluated considering their equipotent doses.

Levobupivacaine epidurally in various concentrations with or without opioids has been used for post operative pain relief in different surgeries6. Ropivacaine in concentrations ranging from 0.1% to 0.75% has tried intrathecally [7]. Murdoch JA et al. [8] has shown that epidural levobupivacaine 0.25% produces better analgesia as compared to 0.125% or 0.0625% solutions. Therefore, for this dose of levobupivacaine the equipotent dose of ropivacaine is 0.375%.Studies have shown the effectiveness of 0.375% ropivacaine through caudal epidural [9], cervival epidural [10] and thoracic epidural routes [11].

As there is a paucity of literature comparing equipotent doses of 0.25% levobupivacaine and 0.375% ropivacaine epidurally for post operative pain relief in orthopaedic surgeries, the present study is designed to evaluate these two drugs in equipotent doses of 0.25% and 0.375% respectively given via epidural route for post operative pain relief in lower limb orthopaedic surgeries.

2. Material and methods

Sixty subjects aged between 25 to 60 years of both sexes belonging to ASA Class I-II scheduled for elective lower limb orthopaedic surgeries at Krishna Rajendra Hospital attached to Mysore Medical College and Research Institute, Mysore will be selected for the study. The study will be conducted from November 2019 to September 2021.

2.1. Inclusion criteria

Adult subjects in the age group of 25 to 60 years, of both sexes, belonging to American Society of Anesthesiologists (ASA) physical status I -II, scheduled for elective lower limb orthopaedic surgeries will be included in the study.

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2.2. Exclusion criteria

Subjects belonging to the following classes:

1. Patients with spinal deformities
2. Local skin infection
3. Coagulation disorders
4. Impaired renal or liver functions
5. Neurological or mental disease
6. History of allergy to drugs to be used
7. Patients with Body Mass Index > 30 kg/m2
8. Height < 150cm

2.3. Method of Collection of Data:

Data will be collected in prescribed proforma meeting the objectives of the study. Adult subjects in the age group between 25-60 years, of both sexes, belonging to ASA class I-II posted for elective lower limb surgeries will be assigned randomly by simple shuffled sealed envelope technique into 2 groups (n=30):

Group R: will receive 7ml of 0.375% Ropivacaine through an epidural catheter route for post operative analgesia.

Group L: will receive 7ml of 0.25% Levo-bupivacaine through an epidural catheter route for post operative analgesia.

Preoperative assessment with required investigations will be done for each patient and patients with comorbid condition will be optimized. Written informed consent will be taken for each patient.

Patients will be instructed to fast for solids for 6 hrs and clear liquid for 2 hrs. All patients will be trained in the use of Visual Analog Scale (VAS) scoring to report pain in the post operative period on a scale of 0 to 10

where 0(=no pain),1 to3(=mild pain),4 to7(=moderate pain),8 to10(=severe pain,10 being the worst imaginable pain).

Patients will be premedicated on the night before surgery with Tablet Alprazolam 0.5mg. On the day of surgery, intravenous line will be obtained with 18 gauge cannula and patient will be preloaded with Ringer lactate 500ml half an hour before anaesthesia.

Monitoring will be done using multiparameter monitor having electrocardiography (ECG), non-invasive blood pressure (NIBP) and arterial pulse saturation (SPO2).Patients will be placed in sitting position with table kept flat. Under aseptic precautions, the skin over the second or third lumbar interspace is identified and will be infilterated with 2% lidocaine. The epidural space is located with 18G Tuohys needle using midline approach with loss of resistance to air technique. 20G epidural catheter will be inserted. After negative aspiration for blood and CSF, a test dose of 3ml 2% lidocaine with adrenaline 1:2,00,000 will be injected. The epidural catheter is secured and fixed. Lumbar puncture will be performed at the level of L3-L4 interspace through a midline approach using 25 G Quincke's spinal needle and sub arachnoid block will be achieved with 3ml of 0.5% bupivacaine heavy. The patient is made to lie down supine immediately after the block, with the operating table in the neutral position. Intra operatively patients' haemodynamic parameters(pulse rate, blood pressure and oxygen saturation) will be recorded.

At the end of surgery, or in the immediate post operative period, the patients' pain is assessed with VAS scoring. When patients complain of pain or VAS is more than 3, the epidural study drugs will be given according to randomization.

The study drugs will be prepared to a volume of 7ml by an anaesthesiologist in identical 10cc syringes and the observer will administer the epidural drug after negative aspiration for blood and CSF. The observer is blinded to the study drugs and will continue the further monitoring of the patients. Thus both observer and patient will be blinded to further clinical evaluation.

Haemodynamic parameters such as pulse rate, blood pressure and oxygen saturation will be continued to be monitored. The onset of epidural analgesia is the time taken for the relief of pain with VAS score becoming two or less. If within 15min of epidural dose, the patients complain of pain, paracetamol 15mg/kg i.v infusion is given as rescue analgesic.

The duration of post operative epidural analgesia is measured from the time of epidural drug injection to the next complaint of pain or VAS greater than 3. The total epidural dose requirement and the rescue analgesia required in 24 hours will be recorded. After each epidural top-up, the incidence of motor block will be recorded by assessing the motor power in the non operated leg using modified Bromage score as follows;

Bromage 0: subject is able to move the hip, knee and ankle and is able to lift his leg against gravity.
Bromage 1: subject is unable to lift his leg against gravity but is able to flex his knee and ankle.
Bromage 2: subject is unable to flex his hip and knee, but is able to flex his ankle.
Bromage 3: subject is unable to flex his hip, knee and ankle, but is able to move his toes.
Bromage 4: complete paralysis.

All subjects will be monitored during the surgery and perioperative period till complete sensory and motor recovery, employing multi parameter monitors which displays heart rate, systolic blood pressure(SBP), diastolic blood pressure(DBP), mean arterial pressure(MAP), ECG and SPO2.

A total sample size of 56 patients will be required to detect a presumed minimum clinically significant difference of 10% in the duration of post op analgesia. Allowing for patients lost to analysis, 60 patients are selected and 30 patients will be randomly allocated into two equal groups (30 patients each).

2.4. Statistical Analysis

Quantitative variables will be analyzed and reported as mean and standard deviation. Categorical variables will be analyzed using the Chi-square test. Statistical significance among the groups will be evaluated using one-way analysis of variance (ANOVA) followed by application of Bonferronis t test to look for intergroup comparisons. A $p<0.05$ is considered statistically significant and $p < 0.001$ as statistically highly significant.

3. Results

All patients enrolled in the present study were in the age group of 25-60 years. The mean age in group L was 40.07±4.7 years and in group R was 40.77±6.112 years. There was no statistically significant difference found between two groups with respect to age (p=0.601). The two groups were more or less homogeneous with respect to age. In group L, 8 were female and 22 were male patients. In group R, 9 were female and 21 were male patients. There was no statistically significant difference found between two groups with respect to sex distribution (p= 1). In both the groups, there is a predominance of male patients.

Table 1. ASA Physical status distribution

ASA	Group L No. of patients(%)	Group R No. of patients(%)	Total No of patients(%)
I	25	25	50
	83.3%	83.3%	83.3%
II	5	5	10
	16.7%	16.7%	16.7%
Total	30	30	60
	100.0%	100.0%	100.0%

In group L, 25 patients were ASA I and 5 patients were ASA II. In group R, 25patients were ASA I and 5 patients were ASA II. There was no statistically significant difference found between two groups with respect to ASA (p=1). Hence, both groups were comparable.

Comorbidities distribution in both the groups. In group L, 2 patients had DM, 3 patients had HTN and remaining 25 patients had no comorbidities. In group R, 2 patients had HTN, 3 patients had DM and remaining 25 patients had no comorbidities. There was no statistically significant difference found between two groups with respect to Comorbidities (p=1). Hence, both the groups patients were comparable.

Mean height of patients in both the groups. The mean height in group L is 162±5.573 cms and in group R is 162.33±5.809 cms. There was no statistically significant difference found between two groups with respect to height (p=0.876).

Mean weight of patients in group L and R. The mean weight in group L was 64.50±6.101kgs and in group R was 64.17±4.178kgs. There was no statistically significant difference found between two groups with respect to weight (p=0.806).

Mean Heart rate distribution in bpm between two groups. Basal and values measured at 15th minute after each epidural topups were compared. Mean basal HR were comparable. There was no statistically significant difference found between two groups with respect to HR at 15th minute after each epidural topup doses except at fourth epidural dose which is statistically significant but clinically none of the patients showed bradycardia or tachycardia.

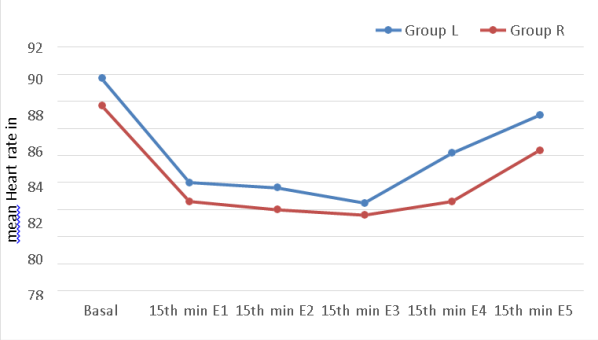

Figure 1. Mean heart rate distribution between two groups at various time intervals

Basal and values measured at 15th minute after epidural topups were compared. The SBP at basal levels were comparable. Statistically significant difference in SBP was observed between the two groups 15 minutes

after each epidural topup doses except at third epidural dose but clinically none of the patients developed hypotension or hypertension.

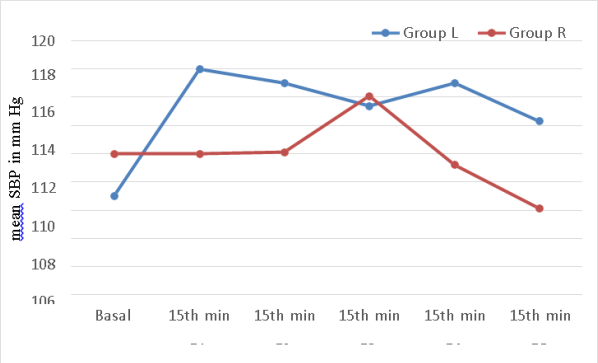

Figure 2. Mean SBP distribution between two groups at various time intervals

Table 2. Mean DBP distribution between two groups at various time intervals

DBP in mm Hg	Group L Mean±SD	Group R Mean±SD	Pvalue
Basal	65.33±4.1	66.7±4.2	0.340
15th min E1	70.8±3.9	66.9±3.8	<0.001
15th min E2	70.5±3.9	67.2±4.5	0.004
15th min E3	69.6±3.9	68.5±3.5	0.225
15th min E4	69.2±3.4	66.9±5.8	0.069
15th min E5	68.0±3.1	65.7±4.7	<0.001

Basal and 15th minute after epidural top ups were compared. Mean basal DBP values were comparable.

There was no statistically significant difference found between two groups with respect to mean DBP at 15th minute after each epidural top up doses E3,E4 but mean DBP at 15th minute after each epidural top up doses E1,E2, E5 showed highly significant difference but clinically none of the patients developed hypotension or hypertension.

Mean basal MAP values were comparable. Statistically significant difference in MAP was observed between two groups 15 min after each epidural topup doses except at third epidural dose but clinically none of the patients developed hypotension or hypertension.

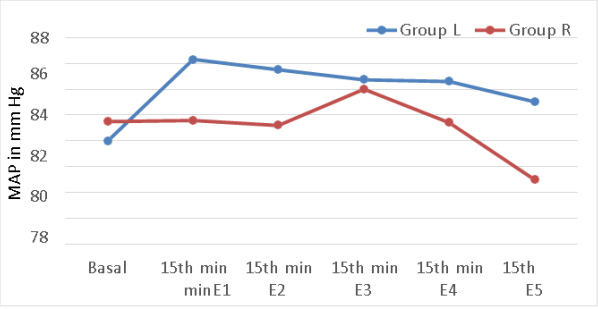

Figure 3. MAP distribution between two groups at various time intervals

Table 3. Mean VAS score distribution between two groups at various time intervals

	Group L1 Mean±SD	**Group R Mean±SD**	**P value**
Pre VAS score E1	3.9±0.3	4.0±0	0.155
Post VAS score E1	0.6±1.3	0.4±0.5	0.354
Pre VAS score E2	4.0±0	4.0±0	–
Post VAS score E2	0.3±0.4	0.6±1.3	0.219
Pre VAS score E3	4.0±0.2	4.0±0	0.322
Post VAS score E3	0.7±0.9	0.4±0.5	0.386
Pre VAS score E4	4.0±0	4.0±0	–
Post VAS score E4	0.3±0.5	0.3±0.5	1.00
Pre VAS score E5	4.0±0	4.0±0	–
Post VAS score E5	0.3±0.5	0.4±0.5	0.325

Before each epidural topup in both the groups, VAS score was predominantly more than 3. After each epidural topup, the VAS score reduced to less than 2. Hence, there is no significant difference between the two groups with respect to VAS score.

Mean onset time of analgesia distribution in minutes between two groups after each epidural top ups. The onset time of analgesia in both the groups was comparable. There was no statistically significant difference in onset time of analgesia.

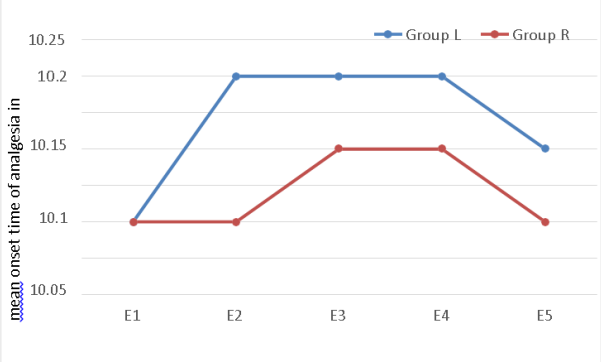

Figure 4. Mean onset time of analgesia distribution between two groups at various time intervals

Table 4. Mean Duration of analgesia distribution between two groups at various time intervals

Duration of analgesia in minutes	**Group L Mean±SD**	**Group R Mean±SD**	**P value**
E1	294.9±29	251.5±12.4	<0.001
E2	310.4±21.1	263.0±26.1	<0.001
E3	295.4±27	273.4±24.3	<0.001
E4	308.7±12.5	273.2±28.3	<0.001
E5	308.2±19.8	304.9±30	0.634

The epidural levobupivacaine produced consistently prolonged analgesia compared to epidural ropivacaine except after the fifth epidural E5 topup, where duration of analgesia was similar.

Table 5. Motor blockade distribution using modified bromage scales between two groups

	Modified Bromage Scale	Group			
		L		R	
		N	%	N	%
E1	Grade 0	25	83.3%	25	83.3%
	Grade 1	3	10.0%	5	16.7%
E2	Grade 0	26	86.7%	28	93.3%
	Grade 1	2	6.7%	0	.0%
E3	Grade 0	24	80.0%	22	73.3%
	Grade 1	4	13.3%	6	20.0%
E4	Grade 0	25	83.3%	22	73.3%
	Grade 1	3	10.0%	6	20.0%
E5	Grade 0	25	83.3%	28	93.3%
	Grade 1	3	10.0%	0	.0%

Motor blockade produced by repeated epidural doses in both the groups were predominantly modified bromage grade 0 and there is no significant difference between the two groups.

Mean rescue analgesia requirement distribution between two groups. In Group L, 2 subjects required 4 doses of Rescue analgesia and in Group R, 2 subjects required 3doses of Rescue analgesia in 24 hours post operative period. Remaining 28 patients in both the groups did not require the rescue analgesia throughout the study. There was no statistically significant difference between both the groups with comparable mean rescue analgesia requirement.

4. Discussion

The commonly used long acting amide local anaesthetic, Bupivacaine with low cc/cns ratio threshold and difficult to reverse cardiovascular collapse, the S-enantiomers of racemic bupivacaine like levobupivacaine and ropivacaine were used with reduced potential systemic toxicity due to isomerism. Ropivacaine being less lipophilic compared to bupivacaine, accounts for its reduced propensity to block larger myelinated motor nerve fibers and thus has better sensory motor differentiation. Several studies have shown that levobupivacaine: bupivacaine potency ratio is (0.97:1)5 and Ropivacaine: bupivacaine is (0.65:1) [2,5].

Parpaglioni et al. [4] and Lee YY et al. [5] observed that the relative potency ratio of Ropivacaine/Levobupivacaine is 0.68 taking into account their ED50 dose (14.22mg for ropivacaine and 10.8mg for levobupivacaine). While higher concentrations, like 0.5% or 0.75% may be required for intra-operative analgesia, to provide post- operative analgesia with minimal muscle relaxation, lower concentrations of LA's needed.

For levobupivacaine, Murdoch JA et al. [8] study have used 0.25% solution to provide adequate post operative analgesia. Equipotent dose of ropivacaine for this levobupivacine 0.25% concentration is 0.375%. Hong JM et al. [11] in their observations on haemodynamic changes after epidural ropivacaine concluded that ropivacaine in doses more than 0.375%.

administered epidurally may be assosciated with significant hypotension specially in elderly patients. Hence, in the present study we used this safe concentration of 0.375% ropivacaine given epidurally. However, there is paucity of literature comparing equipotent doses of 0.25% levobupivacaine & 0.375% Ropivacaine for post operative analgesia in lower limb orthopaedic surgeries.

The assessment of post-operative pain which is highly subjective can be done using different scales like- Maunuksela score, VAS score, Numerical rating scale, McGill Questionnaire. Since our study population are from lower socio-economic strata who may not co-operate in assessing pain using complex pain assessment scales for the present study, we used the VAS score which has advantages of easy bedside assessment and simple grading of pain. The VAS score of 3 or more was considered as need for epidural top up or rescue analgesic in the present study. This correlates with the similar VAS score levels in their studies like- Mehta S et al. [12] , Korula S et al. [13]. The onset of epidural analgesia was taken as VAS score becoming 2 or less or patient getting pain relief. This is similar to study protocol in the study by Mehta et al. [12].

The present study showed that epidurally administered 0.25% levobupivacaine produced significantly prolonged duration of analgesia of about 303.5±21.8 minutes compared to equipotent dose of 0.375% ropivacaine after each intermittent bolus dose administration.

Crews JC et al. [14] demonstrated that 0.25% levobupivacaine alone produced post operative analgesia for 4.26± 0.54 hours which is similar to our findings. Nasreen F et al. [6] showed that caudal epidural with 0.25% levobupivacaine alone produced analgesia of 348±37 minutes which is similar to our findings.

In the present study intermittent boluses of epidural ropivacaine 0.375% produced analgesia of 273.2± 23.42minutes. At similar epidural concentrations of the drug Conceicao et al. [9] showed that the duration of analgesia was 5±3.2hours which is similar to our findings.

Both levobupivacaine and ropivacaine at equipotent doses were able to provide adequate post operative analgesia at lower concentrations used. Our findings correlate with those of Murdoch JA et al[8] study on post operative epidural analgesia after orthopaedic surgery observed that 15mg/hr levobupivacaine(0.25% 6ml/hr) produced adequate analgesia in first 24hours with 47% subjects requiring no rescue analgesics and there were no PCA requests per hour.

In the present study, the rescue analgesic was used if within 15minutes of epidural dose did not produce adequate pain relief to the patients. Paracetamol 15mg/kg i.v infusion was administered as rescue analgesic. Epidural LAs in our study were given as intermittent boluses without any baseline or continuous infusions. Inspite of this, only two patients in levobupivacaine group (patient no. 22and 27) required rescue analgesic after the 1st epidural dose and two patients in ropivacine group (patient no. 61and 62) required rescue analgesic after the 2nd epidural dose.

Rescue analgesic requirement after epidural ropivacaine was needed in 16 out of 50 patients in a study by Mehta S et al. [12] This large number may be due to lower concentration of ropivacaine (0.2%) used by them.

In our study both levobupivacine 0.25% and ropivacaine 0.375% given as epidural boluses did not produce any significant motor blockade. All the patients had the motor block of grade 0 or 1 in the modified bromage score after each epidural top up in the 24 hours period. Thus, 0.25% levobupivacaine or 0.375% ropivacaine produce adequate analgesia with minimal motor blockade in post operative period.

Our observations with respect to motor blockade by levobupivacaine 0.25% are similar to the findings of Murdoch JA et al. [8] study and our observations of moto blockade with ropivacaine 0.375% are similar to the findings of Elsafty O et al. [15] and Conceicao et al. [9] studies.

In our study, there was a significant difference in SBP, DBP and MAP in the post operative period between group L and group R with reduction in values in group R. But none of the patients in both groups did not need any vasopressors and difference between the groups was clinically not significant. These findings corelate well with Raj AD et al. [16] , Hong J M et al. [11] and Scott D A et al. [17] studies.

In our study both Levobupivavine 0.25% and Ropivacaine0.375% did not produce any significant changes in heart rate before and after 15 minutes of epidural topup. These findings are similar to observations of Mehta S et al. [12] study.

5. Conclusion

Epidural 0.25% Levobupivacaine and 0.375% Ropivacaine in their equipotent doses for lower limb orthopaedic surgeries provide adequate post operative analgesia with Levobupivacaine shown to provide prolonged duration of analgesia compared to Ropivacaine. But the total number of epidural topups, need for rescue analgesics and quality of motor block were similar for both the study drugs without any significant haemodynamic variations and adverse effects.

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Conflicts of Interest: The authors declare that they do not have any conflict of interests.

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