A randomized, double-blind interventional study comparing the effect of levobupivacaine versus ropivacaine with fentanyl as an adjuvant in thoracic epidural analgesia for post-thoracotomy pain relief

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Context
Majority of studies have compared the clinical efficacy of levobupivacaine or ropivacaine with bupivacaine. Therefore, new and safer anesthetic agents ropivacaine and levobupivacaine have been introduced and are commonly used nowadays.
Aims
To assess and compare the effect of levobupivacaine versus ropivacaine with fentanyl as an adjuvant in thoracic epidural analgesia for post-thoracotomy pain relief.
Settings and design
The study was conducted in the Department of Anesthesia, Cardiothoracic and Vascular OT.
Study design
Hospital-based randomized, double-blind interventional study.
Patients and methods
After obtaining the Institutional Ethics Committee approval and written informed consent, 60 patients aged between 18 and 60 years of either sex, with American Society of Anesthesiologist status II/III, with weight more than 45 and less than 65 kg and height between 152 and 182 cm, scheduled to undergo surgeries with thoracotomy were enrolled for the study. The patients were randomized to receive injection levobupivacaine (0.2%) or ropivacaine (0.2%) 6 ml in 20 ml normal saline with injection fentanyl 20 μg bolus in the epidural space followed by injection levobupivacaine 0.1% or ropivacaine 0.1% with fentanyl 2 μg /ml at a rate of 0.1 ml/kg/h thoracic epidural infusion till 24 h postoperatively.
Statistical analysis used
Independent *t* test and analysis of variance test were used to compare the continuous variable and χ^2 test was used for categorical variables.
Results
The demographic and preoperative hemodynamic and respiratory parameters were comparable in both the groups.
The postoperative hemodynamic variables, respiratory parameters, and pain scores were also comparable in both the groups. In visual analog scale score, statistically significant difference was observed at 20, 24, and 28 h. Patients receiving levobupivacaine required rescue analgesia later (31.78±15.22 h) than patients receiving ropivacaine (23.16±13.67 h) and were extubated earlier with lesser duration of ICU and hospital stay.
Conclusions
We concluded that the duration of analgesia was longer with levobupivacaine with fentanyl as compared with ropivacaine with fentanyl as need for first rescue analgesia was later in the levobupivacaine group. In the levobupivacaine group patients were extubated earlier and had a lesser stay in ICU and hospital.

Keywords:
fentanyl, levobupivacaine, ropivacaine, thoracic epidural analgesia, thoracotomy

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Introduction

Post-thoracotomy pain harmfully distress pulmonary function by impairing deep breathing and active coughing, resulting in retention of secretions, atelectasis, and pneumonia [1]. Thus, suitable

postoperative pain management is necessary to speed up functional recovery, as well as for enabling early ambulation and the quick return of patients to their normal activities and subsequent discharge from the hospital.

Epidural anesthesia is one of the most versatile and extensively used regional anesthetic techniques that emerged as the gold standard for post-thoracotomy pain control [2].

Various local anesthetics have been used in varying concentrations to provide effective postoperative analgesia. Although bupivacaine remains the most widely used long-acting local anesthetic, it can impair myocardial performance and conduction when systemic toxicity occurs. Ropivacaine and levobupivacaine are enantiomers of bupivacaine that have been compared extensively when administered in neuraxial blocks or other peripheral nerve blocks [3].

Although the combination of epidural opioid with local anesthetics is known to provide superior analgesia in the postoperative period, epidural ropivacaine has not been evaluated in combination with low-dose opioid for postoperative analgesia. Therefore, this randomized, double-blind study is designed to evaluate the comparative effect of fentanyl as an adjuvant to levobupivacaine versus ropivacaine in thoracic epidural analgesia for post-thoracotomy pain relief.

Patients and methods

Study location

The study was conducted in the Department of Anesthesia, Cardiothoracic and Vascular OT.

Study design

Hospital-based, randomized, double-blind interventional study.

Sample size

A sample size of 30 cases was calculated for 95% confidence and 80% power to verify the expected difference of 1.27±1.03 in time duration for need of first rescue analgesia in both groups. It was further enhanced to 32 cases in each of the two groups assuming 10% attrition, dropout, and failed procedure.

Sampling technique

Randomization was done by the sealed envelope method. In all, 60 eligible cases were randomly allocated into two study groups using the sealed envelope technique. In this technique, 60 envelopes equally divided in two groups were prepared and mixed. After fulfilling the inclusion and exclusion criteria, one envelope was picked by the anesthesiologist and accordingly treatment was given.

Double blinding

The anesthesiologist who prepared and administered the anesthetic agent was different from the anesthesiologist who observed the study variables. The patient was told that some analgesic agent would be given for pain but the type of analgesic agent was not told.

Study groups

The study was conducted in the following two groups of patients. Each group consisted of 32 patients (n=32/group).

Group A: patients received injection levobupivacaine (0.2%) 6 ml in 20 ml normal saline with injection fentanyl 20 μg bolus in the epidural space followed by injection levobupivacaine 0.1% with fentanyl 2 μg/ml at a rate of 0.1 ml/kg/h for 24 h.

Group B: patients received injection ropivacaine (0.2%) 6 ml in 20 ml normal saline with injection fentanyl 20 μg bolus in the epidural space followed by injection ropivacaine 0.1% with fentanyl 2 μg/ml at a rate of 0.1 ml/kg/h for 24 h.

Patients of either sex undergoing thoracotomy, willing to give written informed consent, age between 18 and 60 years, weighing 45–65 kg, normal mental status, ASA grades II and III, and height 152–182 cm were included in the study. Patient refusal, inability to understand visual analog scale (VAS), allergic to the drugs involved in the study, bleeding disorders or on anticoagulants, infection at the local site and thoracic spine deformity were excluded.

After obtaining approval from the University Hospital Ethics Committee and written informed consent, 64 patients were included in the study. At the time of preoperative visit, patients were familiarized with a 10-cm VAS scale for pain assessment (0=no pain at all, 10=worst imaginable pain), and peak expiratory flow rate (PEFR) was noted using a Rossmax Peak Flowmeter. On arrival to the operation theater, fasting status, written informed consent, and PAC were checked. All routine monitors were attached: pulse rate (PR), systolic blood pressure, diastolic blood pressure, mean arterial pressure, and SpO_2 were noted. Intravenous line with 18 G cannula was secured and intravenous fluid RL was started at 5 ml/kg/h.

Patients were allocated to levobupivacaine with fentanyl (group A) or ropivacaine with fentanyl (group B) groups using the sealed envelope method. Under all aseptic precautions and sterile draping, intervertebral space T_4–T_5 or T_5–T_6 was identified. After infiltration of local anesthetic, a 18-G Tuohy needle was inserted via the paramedian approach with a 10 ml syringe with 5 ml air. The Tuohy needle was advanced slowly with repeated checking whether the epidural space has been reached using loss of resistance technique. On reaching the epidural space, after a negative aspiration test, a test dose of 3 ml of 2% injection lignocaine with adrenaline 1 in 200 000 was injected to confirm the epidural space. Patient's vitals were monitored for 15 min. An epidural catheter of 20 G was inserted through it after flushing it with saline. Internal jugular vein and femoral arterial cannulation was done under local anesthesia.

The patient was induced with injection midazolam intravenous (0.05 mg/kg), injection propofol intravenous (2 mg/kg), injection fentanyl intravenous (2 mcg/kg), injection rocuronium intravenous (0.9 mg/kg), which were given as a muscle relaxant to facilitate endotracheal intubation. The patient was ventilated with 100% oxygen for 3 min and under direct laryngoscopy the patient was intubated with the appropriate size ETT. Bilateral air entry was checked and the tube was fixed. The surgery was allowed to start and anesthesia was maintained with 100% oxygen, 1% sevoflurane, and intermittent injection atracurium intravenous (0.1 mg/kg).

At the end of surgery, as per the allocated group, a bolus dose of 0.2% levobupivacaine or 0.2% ropivacaine 6 ml in 20 ml normal saline with injection fentanyl 20 μg followed by injection levobupivacaine 0.1% or injection ropivacaine 0.1% with injection fentanyl 2 μg/ml at a rate of 0.1 ml/kg/h was started. The patient was shifted to the ICU with IPPV and taken on a ventilator. When the patient gained consciousness, hemodynamically stable, and fulfilled the criteria of extubation, the patient was extubated. In the ICU patient's hemodynamic parameters were monitored hourly; the time of extubation was noted.

After extubation, VAS score and PEFR was noted at different time intervals and the time of first need of rescue analgesia (injection diclofenac intravenous) was noted when the VAS score was more than 3. The epidural infusion was continued till 24 h postoperatively following which the epidural catheter was removed and the duration of ICU and hospital stay was noted.

VAS was assessed at the time of extubation, and then every 4 h till 48 h. Patients was allowed to receive rescue analgesics on a VAS score of more than 3. Injection diclofenac (50 mg) was given intravenous as rescue analgesia. This time from the stopping of epidural infusion to first administration of rescue analgesic (total duration of analgesia) was noted. The patient was monitored for 48 h for any adverse effects.

Statistical analysis

The questionnaires were initially checked for completeness, and data was cleaned for errors and missing values. The corrected data was then entered into Microsoft Excel after preparing a master chart. After entering data of every 10 questionnaires, one random form was picked and data entry was rechecked. An independent person verified the data entry of two randomly chosen forms after entry of every 15th questionnaire.

Data analysis was done using licensed SPSS software, version 21.0 (SPSS Inc., Chicago, Illinois, USA). Univariate analyses were done initially and the results were presented with the help of tables, text, bar diagrams and pie charts. Descriptive statistics were used to calculate frequencies of categorical variables, and measures of central tendencies and dispersion were used to describe continuous variables. Independent *t* test and analysis of variance test were used to compare the continuous variable and χ^2 test was used for categorical variables. Nonparametric Mann–Whitney test and Kruskal–Wallis test were used in the case of data that did not follow a normal distribution. Data are presented as mean (SD) or number or proportions.

A *P* value less than 0.05 was considered as statistically significant.

Outcome variables

(1) Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, SpO_2.
(2) Time of extubation.
(3) Time of first rescue analgesia.
(4) VAS scores and Ramsay scores.
(5) PEFR.
(6) Duration of ICU and hospital stay.

Ethical issues

Approval from the Institutional Ethics Committee was taken before the start of the study. Written and informed consent was obtained from the participants before proceeding with the study. Each eligible participant was explained about the purpose of the

study by the investigator and an informed and written consent was obtained before inclusion. They were assured of complete confidentiality of information, and the option of withdrawing from the study at any point of time. The study did not involve any method that puts the patients, family members, or the investigator at risk.

Results

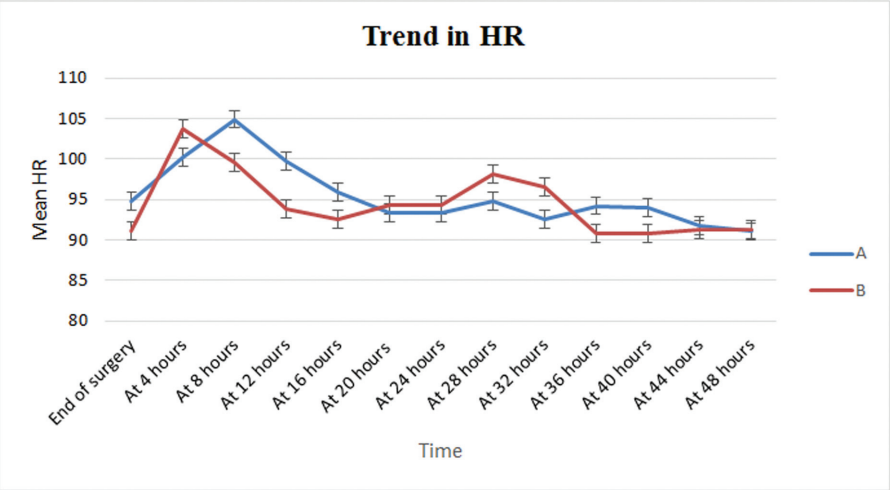
All the patients enrolled in either group after the randomization and were subjected to statistical analysis. The demographic and the preoperative hemodynamic and respiratory parameters were comparable in both the groups, as depicted in Table 1 and Figs 1 and 2 showing trends of heart rate and mean arterial pressure in both the groups. Table 2 shows the trend of mean VAS score among both the groups. Statistically significant difference was observed at 20, 24, and 28 h. The mean VAS score at 20 h in group A and group B is 2.37±0.81 and 2.83 ±0.70, at 24 h it is 2.43±0.9 and 2.93±0.64, and at 28 h it is 2.47±0.9 and 3.07±0.58, respectively. It shows that the patient in group A had comparatively less mean VAS than patients in group B ($P>0.05$). At all other time intervals, the mean VAS score difference between the two groups is nonsignificant, suggesting better pain relief with levobupivacaine. Table 3 shows the trend of Ramsay sedation score among both the groups. There is a statistically significant difference among the two groups at 8, 12, 16, 20, 24, 28, and 48 h ($P<0.05$). In group A Ramsay sedation score is higher than group B at certain point of time which means patients are more sedated in group A than in group B. Figure 3 shows the comparison of the trend of PEFR among both the groups from the time of extubation till 48 h postextubation. It was observed that there is no significant statistical difference at any point of time ($P>0.05$).

Table 4 shows the mean duration of extubation, need of first rescue analgesia, mean duration of ICU, and

Table 1 Demographic data

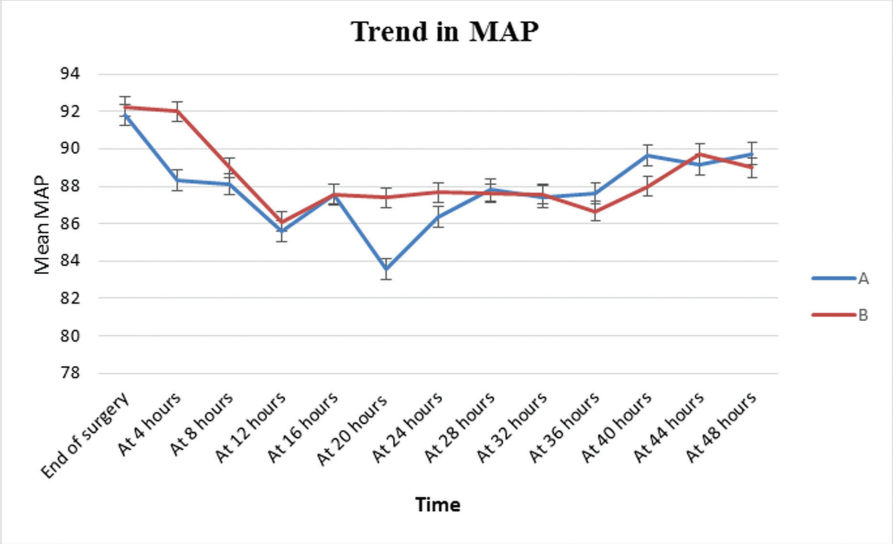
	Factor	Group A	Group B	*P* value	Significance
Age distribution	Mean	31.500	34.533	0.331	Nonsignificant
	SD	10.754	13.098		
Sex distribution	Male	16	18	0.795	Nonsignificant
	Female	14	12		
Weight distribution	Mean	55.1	54.667	0.961	Nonsignificant
	SD	7.6083	12.6449		
Height distribution	Mean	163.6	163.9	0.882	Nonsignificant
	SD	7.87226	7.76975		
BMI distribution	Mean	20.62	20.6	0.993	Nonsignificant
	SD	2.764	5.338		

Figure 1



Comparison of trend of heart rate among both the groups.

Figure 2



Comparison of trend of mean arterial blood pressure among both the groups.

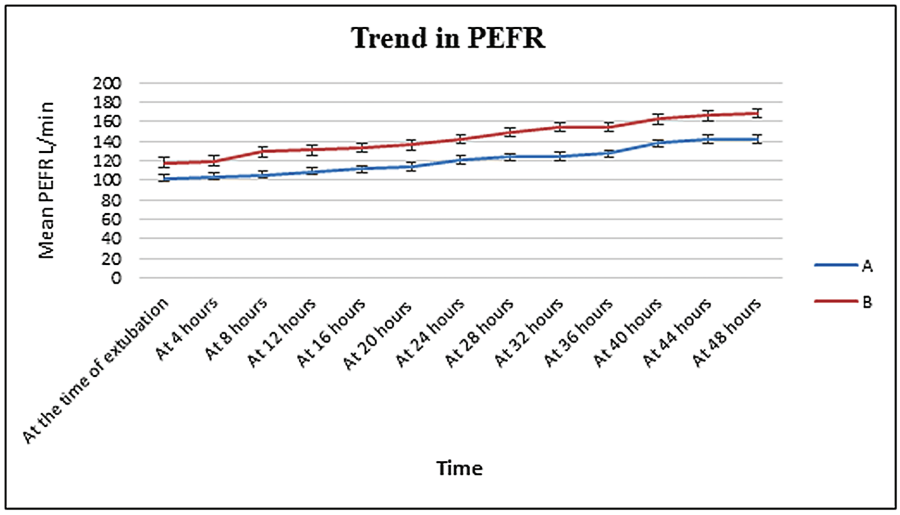
Table 2 Mean of postoperative visual analog scale score at different time intervals among both groups

Groups	A		B		*P* value	Significance
	Mean	SD	Mean	SD		
At the time of extubation	2.9	0.76	2.93	0.78	0.868	Nonsignificant
At 4 h	2.87	0.82	2.93	0.78	0.749	Nonsignificant
At 8 h	2.8	0.76	2.87	0.73	0.730	Nonsignificant
At 12 h	2.6	0.77	2.83	0.7	0.224	Nonsignificant
At 16 h	2.5	0.82	2.83	0.65	0.086	Nonsignificant
At 20 h	2.37	0.81	2.83	0.7	0.020	Significant
At 24 h	2.43	0.9	2.93	0.64	0.016	Significant
At 28 h	2.47	0.9	3.07	0.58	0.003	Significant
At 32 h	2.67	0.84	2.83	0.38	0.330	Nonsignificant
At 36 h	2.63	0.85	2.83	0.46	0.263	Nonsignificant
At 40 h	2.57	0.68	2.73	0.45	0.267	Nonsignificant
At 44 h	2.633	0.56	2.67	0.48	0.805	Nonsignificant
At 48 h	2.77	0.63	2.67	0.48	0.490	Nonsignificant

Table 3 Mean of postoperative Ramsay sedation score at different time intervals among both groups

Groups	A		B		*P* value	Significance
	Mean	SD	Mean	SD		
At the time of extubation	2.53	0.86	2.47	0.9	0.77	Nonsignificant
At 4 h	2.53	0.86	2.43	0.9	0.661	Nonsignificant
At 8 h	2.53	0.78	2.13	0.73	0.044	Significant
At 12 h	2.73	0.52	2.2	0.71	0.002	Significant
At 16 h	2.63	0.61	2.23	0.68	0.020	Significant
At 20 h	2.83	0.38	2.17	0.7	0.001	Significant
At 24 h	2.77	0.57	2.03	0.61	0.001	Significant
At 28 h	2.77	0.57	2.17	0.59	0.001	Significant
At 32 h	2.53	0.73	2.37	0.49	0.304	Nonsignificant
At 36 h	2.47	0.73	2.4	0.56	0.694	Nonsignificant
At 40 h	2.73	0.45	2.6	0.5	0.281	Nonsignificant
At 44 h	2.93	0.25	2.83	0.38	0.235	Nonsignificant
At 48 h	2.77	0.57	3	0	0.032	Significant

Figure 3



Comparison of trend of peak expiratory flow rate among both the groups.

Table 4 Mean duration of extubation time (h), need for first rescue analgesia (h) of ICU stay (h), duration of hospital stay (in days) among both the groups

	Factor	Group A	Group B	*P* value	Significance
Duration of extubation (h)	Mean	4.210	8.540	0.007	Significant
	SD	3.420	7.800		
Need for first rescue analgesia (h)	Mean	31.78	23.16	0.027	Significant
	SD	15.22	13.67		
ICU stay (h)	Mean	18.97	25.43	0.001	Significant
	SD	5.25	7.71		
Hospital stay (days)	Mean	7.61	9.20	0.037	Significant
	SD	2.17	3.41		

hospital stay, all of which are significant. The mean duration of extubation of groups A and B are 4.21±3.42 and 8.54±7.8 h, respectively, suggesting that patients receiving levobupivacaine were extubated earlier. The mean value of time of first rescue analgesia in groups A and B is 31.78±15.22 and 23.16±13.67 h, respectively. The mean value of duration of ICU stay in groups A and B is 18.97±5.25 and 25.43±7.71 h, respectively, and the difference is statistically significant ($P<0.05$). The mean value of duration of hospital stay in groups A and B is 7.61±2.17 and 9.20±3.41 days, respectively, and this difference is statistically significant ($P<0.05$).

Discussion

Epidural analgesia has been shown to promote early mobilization, reduce the time for tracheal extubation, reduce pulmonary morbidity, reduce the rehabilitation time, and reduces the length of hospital stay [4]. Among the most commonly used pain-relieving techniques, there is evidence that the epidural local anesthetic or local anesthetic–opioid combinations are the most effective in providing pain relief after major surgical procedures [5,6].

The demographic and hemodynamic variables were comparable in the two groups.

In our study, we used levobupivacaine with fentanyl and ropivacaine with fentanyl epidural infusion; we did not find any statistically significant difference in PEFR at all time intervals during the postoperative period till 48 h. In a study conducted by Macias *et al.* [7], they compared plain ropivacaine with ropivacaine+fentanyl and bupivacaine+fentanyl in different concentrations of local anesthetics. They observed that patients in the ropivacaine group experienced more pain and performed worse in spirometry than patients who received epidural fentanyl along with local anesthetics. There was no significant difference in motor block among the three groups. Expectations of less motor block with ropivacaine were not fulfilled; therefore, the only reason to replace bupivacaine would be the better toxicity profile of ropivacaine (less cardiac and CNS toxicity).

Weakness in the intercostal muscle is induced by the epidural local anesthetic in high concentration. Deterioration of pulmonary mechanics in the early postoperative period is thought to be caused mainly by respiratory effects of severe postoperative pain, so the slightly worse performance in spirometry in group R may be explained by worse pain control.

In our study at 20, 24, and 28 h, the VAS score in group A was 2.37±0.81, 2.43±0.9, and 2.47±0.9 and in group B was 2.83±0.7, 2.93±0.64, and 3.07±0.58, respectively (Table 2). The VAS score was more in group B (ropivacaine+fentanyl) than group A (levobupivacaine+fentanyl). This difference was statistically significant. These results are in contrast with the study of Lakshmi *et al.* [8] and it can be explained by longer duration of action of levobupivacaine as compared with ropivacaine due to its biphasic absorption profile.

In a study by Gandhi *et al.* [9], the duration of analgesia was 382±18.63 min in group A (levobupivacaine +fentanyl) and 382±15.98 min in group B (ropivacaine+fentanyl), which was statistically comparable. This study was not similar with our study as at some time interval we found significant difference in VAS score (at 20, 24, and 28 h in the postoperative period).

We compared our study with a study by Saroa *et al.* [3], who used the same drugs for paravertebral postoperative analgesia. They demonstrated that both the local anesthetics, that is levobupivacaine and ropivacaine at a concentration of 0.2% were equally efficacious in providing pain relief. Although the time of first analgesic requirement was more in group levobupivacaine, the overall analgesia consumption was similar in both the groups. Similarly in our study, duration of requirement of first rescue analgesia was more in group A (31.78 ±15.22 h) than group B (23.16±13.67 h). This difference is statistically significant.

Ramsay sedation score was calculated every 4 h, till 48 h after extubation and it was significant at 8, 12, 16, 20, 24, 28, and 48 h (Table 3). The mean values for group A and group B was statistically significant at the above-mentioned time intervals ($P<0.05$). In a study conducted by Kulkarni *et al.* [10], it has been observed that the patients in group BF were found to be slightly more sedated immediately after operation up to 6 h as compared with group RF, but this difference was statistically not significant.

The current study revealed that the need of first rescue analgesia (in h) was higher in group A compared with group B, that is the mean value of time of first rescue analgesia in groups A and B is 31.78±15.22 and 23.16 ±13.67 h respectively, and the difference is statistically significant (Table 4). This is supported by a study conducted by Athar *et al.* [11] in which the duration of analgesia was also significantly longer in group levobupivacaine (309.83±36.45) than in group ropivacaine (249.50±22.83, $P<0.0001$).The mean value of duration of extubation in groups A and B is 4.21±3.42 and 8.54±7.8 h (Table 4), respectively, and the P value is 0.007, which is statistically significant ($P<0.05$), which implies that patients receiving epidural infusion of levobupivacaine with fentanyl were extubated earlier than those receiving ropivacaine with fentanyl. The mean value of duration of hospital stay in groups A and B is 7.61 ±2.17 and 9.20±3.41 days, and the mean value of duration of ICU stay is 18.97±5.25 and 25.43 ±7.71 h, respectively, and these differences are statistically significant ($P<0.05$). In contrast to this, a study by Senard *et al.* [12] found the mean duration of hospital stay in the levobupivacaine group to be 14.2 ±6.4 and in ropivacaine group to be 13.6±4.8 days, which was higher compared with our study, and it was statistically not significant between both the groups ($P>0.05$).

The most dreaded complication of epidural technique is accidental dural puncture, spinal cord hematoma, spinal infection, or abscess. We were fortunate enough that we did not face any of these complications. The most feared side effect and complication of thoracic epidural anesthesia using local anesthetics with opioids is respiratory depression, pruritus, nausea, and vomiting. But in our study these complications were not encountered.

Limitations

(1) Sample size of the study was less.
(2) Pharmacokinetic characteristics of the drugs were not evaluated.

Conclusion

In this study, we concluded that the duration of analgesia was longer with levobupivacaine with fentanyl as compared with ropivacaine with fentanyl as the need for first rescue analgesia was later in the levobupivacaine group. In the levobupivacaine group, patients were more sedated but extubated earlier. The

ICU and hospital stay was less in the levobupivacaine group.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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