A prospective randomized study for comparison of epidural 0.5% levobupivacaine with 0.5% racemic bupivacaine using fentanyl as common adjuvant in lower limb orthopedic surgeries

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Abstract

Background: Levobupivacaine, an S(-) isomer of bupivacaine, has been shown a lower risk of cardiovascular and central nervous system toxicity than bupivacaine. This study was aimed to compare racemic bupivacaine and levobupivacaine in epidural anesthesia for lower limb orthopedic surgeries using fentanyl as a common adjuvant.

Methods and Material: A randomized prospective study was planned on sixty patients of ASA grade I and II who were admitted for elective lower limb orthopedic surgeries under epidural anesthesia. Patients were randomly divided into two Groups, Group B (n=30) received bupivacaine 0.5% (13ml) and fentanyl 100 µg, Group L (n=30) received levobupivacaine 0.5% (13ml) and fentanyl 100 µg. In both the Group's onset of sensory and motor block, highest level of sensory block, duration of sensory and motor block, degree of motor block and hemodynamic parameters and complications were assessed perioperatively.

Results: Mean duration of onset of sensory block was 9.54±1.03 and 9.85±0.97 min for Group B and Group L respectively and onset of motor block for Group B was 19.48±1.58 min and for Group L was 19.01±1.30 min, which were comparable for both Groups (P >0.05). Mean duration of sensory block was 371.33±13.23 min and 366.17±5.83 min in Group B and L respectively and mean duration of motor block was 273.0±11.0 min and 274.9±18.45 min in Group B and L respectively which were comparable in both Groups, (P > 0.05). The degree of motor block assessed by modified bromage scale was higher in Group B than Group L. Hemodynamic changes and complications having no significant differences between two Groups, (P > 0.05).

Conclusion: The combination of levobupivacine and fentanyl is equipotent to bupivacaine and fentanyl in epidural anesthesia. Rather it seems to be a better alternative local anesthetic agent in epidural anesthesia for lower limb orthopedic surgeries.

Keywords: Bupivacaine, Levobupivacaine, Fentanyl, Epidural, Orthopedic surgeries.

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Introduction

Epidural anesthesia is the most commonly used technique for providing perioperative surgical anesthesia and postoperative analgesia in lower limb orthopedic surgeries. In orthopedic surgeries, early postoperative mobilization with minimal pain is desirable for early rehabilitation and return to normal activities which can be provided using epidural anesthesia and adjuvants.(1)

Bupivacaine, levobupivacaine, and ropivacaine are commonly used local anaesthetic (LA) agents for epidural block and provide good quality of anesthesia and analgesia. Bupivacaine is used as a racemic mixture, but racemic bupivacaine is found more toxic to both the central nervous system and the cardiovascular system. Levobupivacaine is an amide type of local anesthetic agent which is the pure S (-) enantiomer of bupivacaine and because of its significantly less cardiovascular and central nervous system toxicity, levobupivacaine seems to be a better alternative to bupivacaine.(2,3,4,5,9)

Opioid analgesics are commonly used as adjuvants to local anesthetics in epidural anesthesia. Opioid analgesics when used as an adjuvant, accelerates the onset, improve the quality of the block along with reduced effective dose of local anesthetic and prolong the duration of anesthesia and analgesia. Fentanyl, an opioid analgesic, is a highly lipid-soluble with a rapid onset and short duration of action. The rationale for using fentanyl as an adjuvant with a local anesthetic agent is to alleviate pain by their synergistic mechanism of action as the local anesthetic agent act upon nerve terminals and the opioids at the spinal cord receptor simultaneously. Fentanyl is also known to reduce the minimum effective local anesthetic or analgesic concentration of bupivacaine and levobupivacaine due to its dose sparing effect, thereby reducing their side effects.(1,6,7)

Various studies have undergone to compare these two drugs in labour analgesia, gynecological, abdominal and other surgeries but the literature showed limited evidence about comparison of these two drugs in epidural anesthesia for lower limb orthopedic surgeries.(8) We hypothesized that 0.5%

levobupivacaine would be comparable to 0.5% racemic bupivacaine regarding various block characterstics when used epidurally along with fentanyl as an adjuvant and it would prove to be beneficial in patients with limited cardiac reserve because of its reported lesser cardiotoxicity and neurotoxicity or better safety profile as compared to racemic bupivacaine. Therefore this study was undertaken to compare the onset and duration of motor & sensory block, degree of motor block, hemodynamic changes, intraoperative and postoperative complications in epidural anesthesia with levobupivacaine *vs* bupivacaine using fentanyl as a common adjuvant in patients undergoing lower limb orthopedic sugeries.

Subjects and Methods

This prospective randomized study was conducted in Department of Anesthesiology, JLN Medical College, Ajmer, during a period of 18 months (July 2014 to December 2015) after approval from institutional ethical committee and written and informed patient's consent including sixty patients of ASA physical status I or II aged 18 to 60 years undergoing elective lower limb orthopedic surgeries under epidural anesthesia. Among the selected individuals, those fulfilling the inclusion criteria were included in the study. Exclusion criteria were known hypersensitivity to study drugs, ASA physical status III or above, patient refusal, general contraindications for epidural anesthesia, morbid obesity and patients with coagulation abnormalities.

The study population was randomly allocated into 2 Groups with 30 patients in each Group according to computer generated random number table and allocation concealment was done using sequentially numbered closed opaque sealed envelope technique. A trained anesthesiologist, who was not involved in the study process, prepared the syringes for epidural injection for the purpose of blinding so both the patient and the investigator who assessed the results were blinded. Group B received 13ml of 0.5% bupivacaine with 2ml (100 µg) of fentanyl (total volume-15ml) and Group L recieved 13ml of 0.5% levobupivacaine with 2ml (100 µg) of fentanyl (total volume-15ml).

After arrival in the operation theatre, all routine investigations, preanesthetic evaluation and patient's consent form was checked. All the patients in the study were hydrated with 10ml/kg Ringer's lactate intravenously before the procedure. All baseline hemodynamic parameters, HR (Heart rate), NIBP (Non-invasive blood pressure), SpO_2 (Oxygen saturation) and ECG (Electrocardiogram) were recorded.

Under all aseptic precautions, lumbar area of patient's back was painted and draped. An 18 G Touhy's epidural needle was introduced into L3-L4 epidural space using loss of resistance to air technique. Epidural catheter was inserted 4 cm into the epidural space and 3 ml of 1.5% lignocaine with adrenaline (1:2,00,000) was given as a test dose. Continuous cardiopulmonary monitoring was done and the study drug was injected into the epidural space. The time of administration of the study drug was considered as zero time to assess the duration of blockade.

The hemodynamic parameters were monitored every 5 minutes until 30 minutes of epidural drug administration and every 30 minutes thereafter till the completion of the surgical procedure. The various complications (nausea, vomiting, hypotension, urinary retention, arrhythmia and pruritus) were assessed perioperatively.

Onset of sensory block at T10 dermatome i.e. time interval between the end of administration of the anesthetic drug and the onset of cutaneous analgesia at T10 was evaluated using midline bilateral pin prick method every minute till complete loss of cutaneous sensation at T10 level was noted. Degree of motor block was assessed by Modified Bromage Scale(0 = no block, 1= inability to raise extended leg, 2=inability to flex the knee, 3= inability to flex ankle and foot).[19] The primary outcome of the study was to compare the onset and duration of sensory blockade of levobupivacaine and bupivacaine for their anesthetic and analgesic effects as we hypothesized that both drugs are equipotent. The secondary outcomes were to compare the onset and duration of motor blockade, degree of motor blockade, height of sensory blockade, hemodynamic parameters and complications associated with study drugs.

Statistical analysis

The sample size was calculated to be 30 in each Group to demonstrate 40% difference in time of onset and duration of sensory blockade in two Groups with power of 0.8 and type I error of 0.05. We had set α=0.05 and β=0.2 and used a large magnitude of effect (effective size 0.8) to estimate a sufficient sample size. The analysis done showed that 30 patients in each Group would be sufficient to compare various block characteristics however it might be smaller for evaluation of safety profile of these two drugs. The sample size was also based on previous studies done to compare these two drugs. All the values were expressed as Mean±SD or percentage. Qualitative data (ASA grade, degree of motor block and complications) were compared using Chi-square test incorporating Fishers exact test and quantitative data (age, weight, heart rate, blood pressure, onset of sensory and motor block, duration of sensory and motor block) were compared using unpaired and paired t-test. Significance is assessed at 5% level of significance. The data was subjected to statistical analysis using statistical package for social science (SPSS) version 20.0. A P value of > 0.05 was considered as not significant and a value of $P < 0.05$ was considered as significant.

Results

Both the Groups were comparable in terms of demographic profile and duration of surgery. (Table 1)

The onset of sensory block was 9.54±1.03 and 9.85±0.97 min for Group B and Group L respectively and onset of motor block for Group B was 19.48±1.58 min and for Group L was 19.01±1.30 min. Patients in both Groups were comparable with respect to onset of sensory and motor block (P >0.05). (Table 2)

In patients belonging to Group L, 63.3% attained T6 level, 30% attained T7 level and 6.7% attained T10 levels, whereas in Group B, 60% attained T6 levels, followed by 30% attaining T7 level and 10% attaining T10 level. There was no significant difference in the highest level of sensory block achieved in both Groups. (Table 2)

The duration of motor block was 273.0±11.0 min and 274.9±18.45 min in Group B and L, respectively and duration of sensory block was 371.33±13.23 min and 366.17±5.83 min in Group B and L respectively. Patients in both Groups were comparable with respect to duration of motor and sensory block (P >0.05). (Table 2)

Degree of motor block was assessed by modified bromage scale showed that in Group B,46.67% of patients had grade 2 and 33.33% of patients had grade 3 degree of motor block, whereas in Group L only 33.33% of patients had grade 2 and 26.67% of patients had grade 3 degree of motor block. The degree of motor block was higher in Group B. (Table 2)

Baseline heart rate, systolic blood pressure, diastolic blood pressure and oxygen saturation in Group B and Group L were comparable. These parameters were also remained stable throughout the duration of block in both the Groups, (P >0.05). (Fig. 1, 2, 3)

In our study, in Group B, 5 patients experienced nausea, 1 patient had vomiting, 4 patients had hypotension and 4 patients had pruritus whereas in Group L 4 patients experienced nausea, 1 patient had vomiting, 5 patients had hypotension and 5 patients had pruritus. Thus both Groups were comparable regarding complications (P >0.05). We did not observe arrhythmia, urinary retention and respiratory depression in any of the patient in both Groups. (Table 3),(Fig. 4)

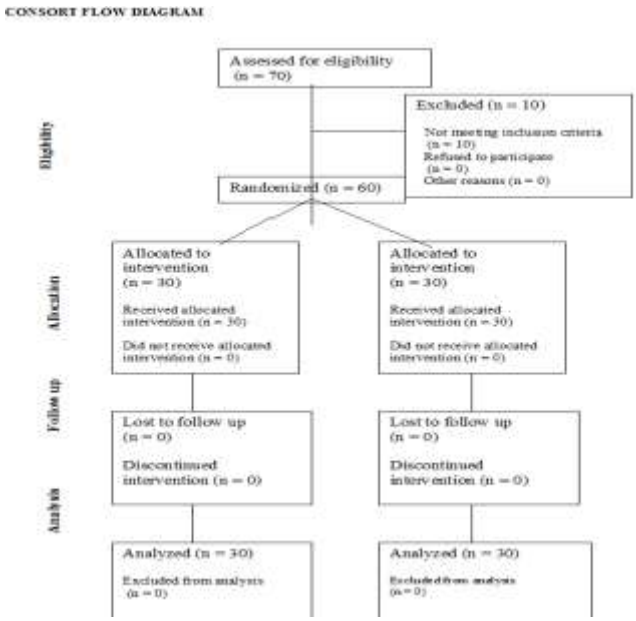

Table 1: Demographic profile of the patients and mean duration of surgery in both Groups

Demographic profile	Group B (n=30)	Group L (n=30)	P value
Weight (kg)	65.36±7.65	66.28±5.65	>0.05
Age (year)	43.79±5.90	42.51±5.59	>0.05
Male/Female (M/F)	14 /16	13/17	>0.05
Mean duration of surgery (min)	76±23	74± 44	>0.05

* Values are expressed as Mean± SD and numbers.

* P value >0.05 not significant

Table 2: Comparison of sensory and motor block characteristics in both Groups

Block characteristics	Group B (n=30)	Group L (n=30)	P value
Onset of sensory block(min)	9.54±1.03	9.85±0.97	>0.05
Highest level of sensory block	T6-60% T7-30% T10-10%	T6-63.3% T7-30% T10-6.7%	-
Duration of sensory block(min)	371.33±13.23	366.17±5.83	>0.05
Onset of motor block(min)	19.48±1.58	19.01±1.30	>0.05
Duration of motor block(min)	273.0±11.0	274.9±18.45	>0.05
Degree of motor block (Grades 0-3)	Grade 2-46.67% Grade 3-33.33%	Grade 2-33.33% Grade 3-26.67%	-

*values are expressed as Mean±S.D. and percentage (%)
*P >0.05, not significant, p<0.05, significant

Table 3: Perioperative complications in both Groups

Complications	Group B (n=30)		Group L (n=30)	
	No.	%	No.	%
Nausea	5	71.43	4	57.14
Vomiting	1	14.29	1	14.29
Hypotension	4	57.14	5	71.43
Urinary retention	0	0.00	0	0.00
Arrythmia	0	0.00	0	0.00
Pruritus	4	57.14	5	71.43

*Group B- Bupivacaine+fentanyl, Group L- Levobupivacaine+fentanyl

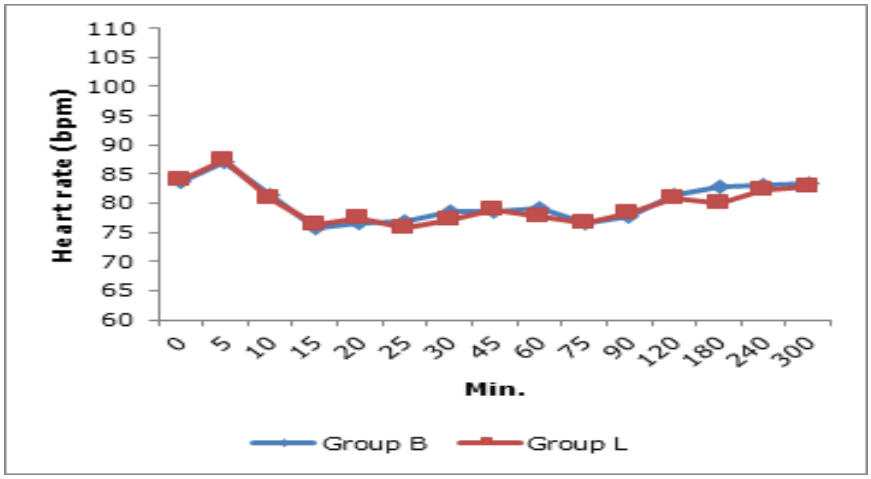

Fig. 1: Comparison of heart rate (bpm) in both Groups
*Group B- Bupivacaine+fentanyl, Group L- Levobupivacaine+fentanyl

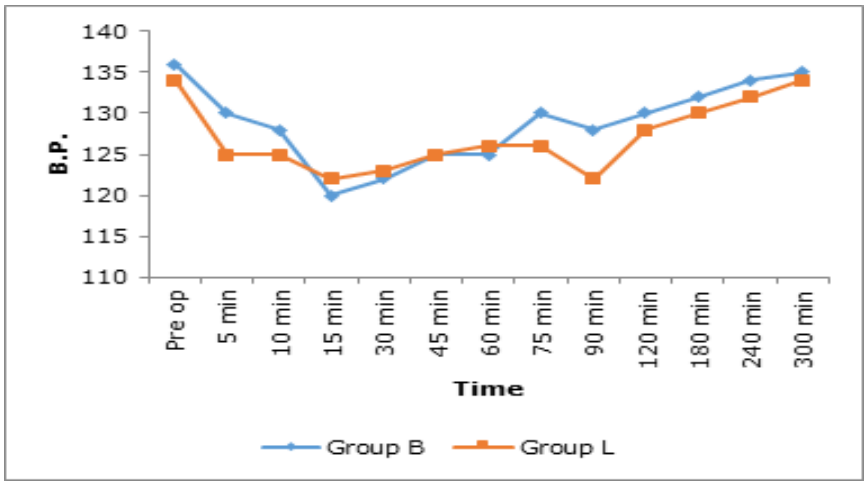

Fig. 2: Comparison of systolic blood pressure (SBP) in both groups (mm Hg)
*Group B- Bupivacaine+fentanyl, Group L- Levobupivacaine+fentanyl

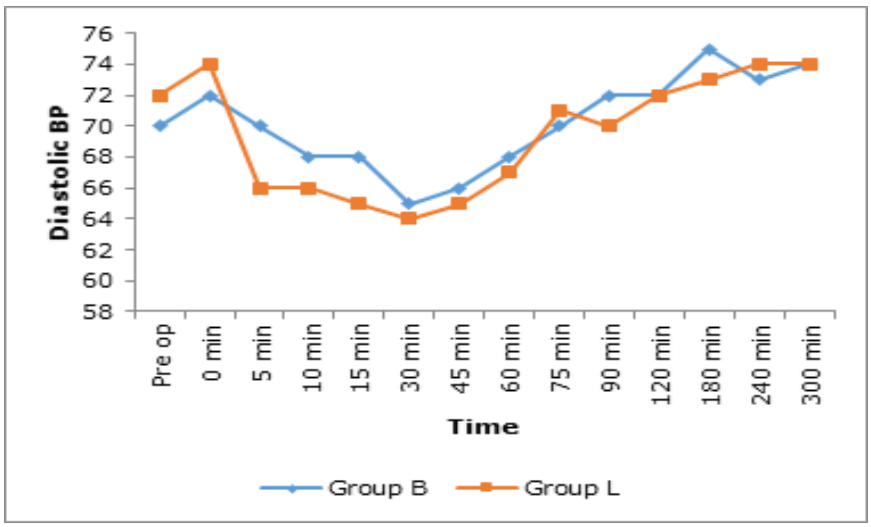

Fig. 3: Comparison of diastolic blood pressure (DBP) in both Groups (mm Hg)
*Group B- Bupivacaine+fentanyl, Group L- Levobupivacaine+fentanyl

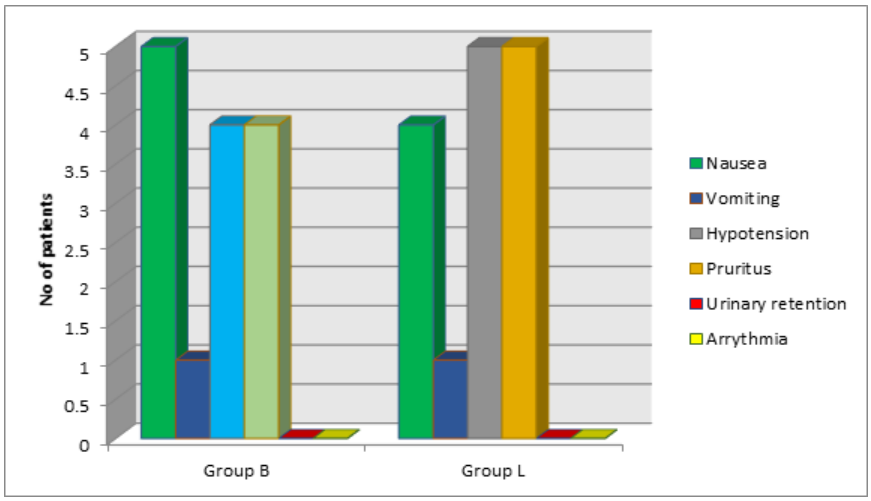

Fig. 4: Distribution of perioperative complications in both Groups
*Group B- Bupivacaine+fentanyl, Group L- Levobupivacaine+fentanyl

Discussion

Epidural anesthesia provides excellent pain relief with early mobilization of patients particularly when a local anesthetic agent is combined with an adjuvant like opioids. The addition of adjuvants in epidural anesthesia accelerates the onset of sensory blockade but also decreases the effective dose of local anesthetic agent i.e. dose sparing effect. The synergistic mechanism between local anesthetic agents and opioids is well established for epidural anesthesia and it proved to be beneficial for patients in terms of early rehabilitation and recovery due to adequate analgesia devoid of any side effects associated with local anesthetics.[1,9]

Bupivacaine is associated with a number of side effects like unwanted motor blockade, neurotoxicity and cardiotoxicity which may cause death due to its systemic side effects after accidental intravenous injection and warrants continued search for new and safer local anesthetic agent. Levobupivacaine have been developed as an alternative to bupivacaine after the evidence of its cardiotoxicity and it seems to have less toxic effects on cardiovascular and central nervous system.[10]

The mean time of onset of sensory and motor block was statistically not significant between the two Groups, (P >0.05). The previous studies have also demonstrated that levobupivacaine and bupivacaine were similar in terms of onset of sensory blockade, regardless of the type of surgery.[8]

Kara F et al[11] who compared the effects of epidural 0.5% bupivacaine and 0.5% levobupivacaine administration on anaesthesia quality, incidence of side effects in hip and lower extremity surgery and Cox CR et al[12] who compared 0.5% bupivacaine and 0.5% levobupivacaine administered epidurally for lower limb surgeries found no significant difference in the onset of sensory and motor blockade, which may be due to the same concentration (0.5%) of local anesthetic used in our study also.

The duration of motor block was assessed by onset of motor block to complete recovery (Bromage scale-0). In our study there was no significant difference in duration of motor block in both the Groups (P > 0.05). Similar to our study a study done by Casimiro C et al[8] who compared levobupivacaine plus fentanyl and racemic bupivacaine plus fentanyl in epidural anesthesia for lower limb surgeries and in another study by Kara F et al[11] compared the effects of epidural 0.5% bupivacaine and 0.5% levobupivacaine administration on epidural anesthesia found that there was no significant difference in duration of motor blockade with both drugs (P > 0.05) and Kopacz et al[13] who compared epidural 0.75% levobupivacaine with racemic bupivacaine for lower abdominal surgeries found similar duration of motor block in both Groups (P > 0.05).

However in contrast to our study Garcia et al[14] compared 0.5% levobupivacaine with 0.5% bupivacaine in epidural anesthesia for caesarean delivery, found a longer duration of motor block with levobupivacaine. The doses used in our study were same as that used in study by Garcia et al but have longer duration of motor block with levobupivacaine have no clinical significance and could not be explained as far as the dose is concerned.

In our study mean duration of sensory block was comparable in both Groups (P >0.05). The results of our study are similar to the study done by Casimiro C et al[8] who concluded that levobupivacaine plus fentanyl versus racemic bupivacaine plus fentanyl in epidural anaesthesia for lower limb surgeries produced sensory blockade of similar duration. And also in a study done by Kara F et al[11] who compared the effects of epidural 0.5% bupivacaine and 0.5% levobupivacaine in hip and lower extremity surgery found no significant difference in duration of sensory blockade with both drugs.

In contrast Cox CR et al[12] compared levobupivacaine (two different dosage) with bupivacaine (one dosage) administered epidurally for lower limb surgeries found a significantly longer duration of sensory block with one of dosages of levobupivacaine 0.75% than bupivacaine 0.5%, this may be due to different dosages used in both studies. The concentration of levobupivacaine used in our study was 0.5%, but in Cox`s study the concentration of levobupivacaine used were 0.5% and 0.75%, i.e. two different doses. So the results were similar with 0.5% concentration of levobupivacaine in between two Groups.

These results regarding mean duration of sensory blockade depicted the association between the dose and concentration of local anesthetic used and duration of blockade.[8,17] The longer duration of sensory blockade with levobupivacaine (0.75%) can be explained by the higher concentration of levobupivacaine used in study by Cox et al.

The degree of motor block was significantly more in Group B as compared to Group L. Similar to our study Casimiro C et al[8] found that the proportion of patients with motor blockade as determined by the modified Bromage scale was statistically different; patients allocated to levobupivacaine Group showed a higher proportion of lack of motor blockade than bupivacaine. The decreased motor block seen with levobupivacaine may be due to decreased potency of levobupivacaine as compared to bupivacaine.[15,16] However in another study, Kara F et al[11] found that there was no statistically significant difference between the Groups in terms of quality or degree of motor block for both Groups (P > 0.05). Further research should be done to determine the difference in motor block at higher concentration of local anesthetics. The differential blockade might see with low dose of levobupivacaine (0.5%) as we have used and probably

may not appreciated at higher doses of levobupivacaine (0.75%).

Hypotension is always expected to be accompanied with epidural anesthesia due to sympathetic blockade however it can be prevented by preloading with crystalloids. Hemodynamic parameters in both Groups did not differ significantly with respect to heart rate and blood pressure at any time interval, which is consistent with the study done by Kara F et al[11] on comparison of epidural 0.5% bupivacaine and 0.5% levobupivacaine administration on epidural anesthesia quality found no significant changes in the hemodynamic variants for bupivacaine and levobupivacaine, and also supported by Casimiro et al.[8] The stable hemodynamic parameters can be explained by lower volume of local anesthetic agent used along with fentanyl as an adjuvant which has a dose sparing effect. However fentanyl may increase the incidence of pruritus, nausea, vomiting, respiratory depression and urinary retention, which were comparable between two Groups.[1]

In contrast Kopacz et al[13] reported that hypotension was the most common side effect and was experienced by a similar proportion of patients in both treatment Groups at the start of surgery (21% levobupivacaine, 18% bupivacaine) and during surgery (32% in both treatment Groups). This may be due to use of higher concentration (0.75%) of levobupivacaine and bupivacaine in their study.

In another study done by Kara F et al[11] compared the effects of epidural 0.5% bupivacaine and 0.5% levobupivacaine administration on quality of anesthesia, incidence of side effects, and time for requirement of analgesia in hip and lower extremity surgery found no significant difference in side effect profile in both Groups.

In previous studies as by Gristwood RW et al[5] showed levobupivacaine has lesser side effect profile than bupivacaine, demonstrated that levobupivacaine could be a safer alternative local anaesthetic drug to bupivacaine, as far as cardiotoxicity is concerned.

Limitations

Although we were not able to reveal the safety profile of these two drugs in emergent cardiac situations produced as a result of cardiotoxicity due to smaller sample size in our study however this was not a primary objective of our study. So it might be possible that a larger sample size than our study could reveal significant differences in the safety profile of these two drugs. The differential effect or the dose dependent effect of these two study drugs could be better appreciated in further studies or clinical trials using higher doses or different doses. These may be the limitations of our study.

Conclusion

In our study we concluded that combination of levobupivacine and fentanyl is equipotent to bupivacaine and fentanyl in epidural anesthesia for lower limb orthopedic surgeries as both provided stable hemodynamics with adequate sensory and motor anesthesia devoid of any significant adverse effects. Rather it seems to be a better alternative local anaesthetic agent in epidural anesthesia. Although in our study we failed to demonstrate a better safety profile of levobupivacaine than bupivacaine due to smaller sample size.

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