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Original Article

Randomized Clinical Comparison of Epidural Bupivacaine with Fentanyl and Epidural Levobupivacaine with Fentanyl in Patients Undergoing Total Abdominal Hysterectomy

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Abstract

Background: Levobupivacaine is a relatively new local anesthetic agent with minimal side effects compared to bupivacaine.

Aim: To compare the post-operative analgesic effects of epidural levobupivacaine with fentanyl and epidural bupivacaine with fentanyl in patients undergoing abdominal hysterectomy.

Materials and Methods: Single randomized study was conducted in 60 ASA Grades I or II patients undergoing elective abdominal hysterectomies using combined spinal epidural technique. All patients received subarachnoid blockade with 3 ml of 0.5% bupivacaine. Regression of sensory blockade level to T8 is noted. Now, Group A (n = 30) patients received epidural top up with 10 ml of 0.5% bupivacaine with 20 mcg fentanyl. Group B (n = 30) patients, received epidural top up with 10 ml of 0.5% levobupivacaine with 20 mcg fentanyl. The time of onset of analgesia and duration of effective analgesia are noted.

Results: Duration of complete analgesia postoperatively, in Group A patients, was 75.50 ± 23.13 min, while in Group B patients, the duration was found to be 128.00 ± 22.98 min. Effective analgesia, in Group A patients, lasted for an average duration of 134.50 ± 29.26 min, while it lasted for an increased average duration of 181 ± 23.94 min in Group B patients.

Conclusion: Levobupivacaine forms a suitable alternative and provides prolonged post-operative analgesia compared to bupivacaine.

Key words: Cardiotoxicity, Epidural, Hysterectomy, Levobupivacaine

INTRODUCTION

Total abdominal hysterectomy is a relatively common gynecological procedure, routinely done under neuraxial blockade. Epidural anesthesia will take care of the post-operative pain relief and can also be used intraoperatively to supplement anesthesia if insufficient. Racemic bupivacaine is the commonly used local anesthetic for epidural infusion. However, its prolonged or continuous use can lead to severe cardiotoxic and central nervous system (CNS) side effects. Levobupivacaine, S-enantiomer of bupivacaine has been found to be associated with a better pharmacological profile and much less side effects compared to bupivacaine.[1] The high lipid solubility and plasma protein binding of this drug results in less free fraction of the drug available to produce toxicity. Combining an opioid with the local anesthetic agent has become a widely accepted practice for epidural top up or infusion. Their combination limits the regression of the sensory block seen with local anesthetics alone and improves the quality of dynamic pain relief.[2] Hence, we determined to postoperatively compare the analgesic and hemodynamic effects of epidural bupivacaine-fentanyl and levobupivacaine-fentanyl solutions.

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MATERIALS AND METHODS

After approval of the study by our institutional ethical committee, the study was conducted in 60 ASA Grades I or II patients undergoing elective abdominal hysterectomies using combined spinal epidural technique. The age of the patients ranged from 18 to 60 years, weighing 35-65 kg and height ranging from 155 to 160 cm. Informed written consent was obtained after explaining the procedure. Exclusion criteria included patients with coagulation disorders, cardiac failure, liver failure, renal failure, neurological and mental illness, deformity of spinal column, patients with allergy to local anesthetics, infection at the site of injection, surgeries lasting for more than 4 h duration. Visual analog scale (VAS) was explained to all patients. The patients were shown a 10 cm long scale marked 0-10 on a blank paper and told that 0 represents "no pain" and 10 represents worst possible pain. On the day of procedure, baseline hemodynamic parameters were noted. The patients were randomized into two groups by drawing of lots.

After shifting, the patient to the operating room, electrocardiograph (ECG), pulse oximetry, and noninvasive blood pressure monitors were connected. Intravenous access obtained with 18G intravenous cannula. Pre-operative vital signs: Pulse rate, systolic and diastolic blood pressure, and oxygen saturation were noted. Under sterile aseptic precautions, epidural catheterization was performed at L1-L2 space with 16G Tuohy needle by loss of resistance technique. A 20G epidural catheter was introduced and 5 cm of catheter kept inside. Subarachnoid blockade was performed in L3-L4 space using 25-gauge Quincke needle. After free flow of CSF, 3 ml of 0.5% hyperbaric bupivacaine injected in both groups at a rate of 0.2 ml/s. Immediately, the patients were turned on their back to supine position. The sensory blockade level is assessed at the end of 5th min and thereafter every 15 min. Regression of the sensory blockade level to T8 is noted. Now, the patients randomized to Group A, received epidural top up with 10 ml of 0.5% bupivacaine with 20 mcg fentanyl after negative aspiration for CSF or blood. The patients randomized to Group B, received epidural top up with 10 ml of 0.5% levobupivacaine with 20 mcg fentanyl after negative aspiration for CSF or blood. Hemodynamic parameters were monitored after giving the block. The onset of loss of pinprick discrimination at the level of T6 was noted as - "the time of onset of analgesia" this was monitored every 5 min up to a maximum of 25 min. The maximal level of sensory blockade at 25 min after the epidural top up was noted. "Block failure" was defined as onset of loss of pinprick sensation more than 25 min at T6 lever or inadequate blockade. These patients were excluded from the study. Intraoperative pulse rate, systolic and diastolic blood pressure, and oxygen saturation were monitored. Any intraoperative pain at the site of surgery or intraoperative increase in pulse rate or blood pressure >20% from the baseline is regarded as exclusion criteria, and these patients were excluded from the study. These patients were given general anesthesia using injection glycopyrrolate 0.2 mg/kg, injection fentanyl 2 μ/kg, injection thiopentone 5 mg/kg, and injection atracurium 0.6 mg/kg. Intraoperative complications such as hypotension, bradycardia, or ECG abnormalities were noted. After the conclusion of the surgery, immediate post-operative VAS score was noted. The patient was shifted to post-anesthesia care unit and monitored for 12 h after which they were shifted to their respective wards. In the PACU, vital parameters and VAS score were recorded. VAS score was recorded for every 15 min up to 4 h. "The duration of effective analgesia" was defined as the duration until which the patient had a VAS score ranging from 0 to 2. "The duration of complete analgesia" was defined as the duration until which the patient had a VAS score of 0. VAS score of >4 was an exclusion criteria and patients with an immediate post-operative VAS score >4 were excluded from study. Rescue analgesia for those patients were given using injection tramadol 100 mg i.v. or injection fentanyl 50 mcg, followed by 8 ml of 0.25% bupivacaine. Side effects like hypotension was managed with intravenous fluids and incremental doses of injection ephedrine 6 mg and bradycardia were managed with injection atropine 0.6 mg.

Descriptive statistics was done for all data and suitable statistical tests of comparison were done. Continuous variables were analyzed with the unpaired *t*-test and categorical variables were analyzed with the Chi-square test and fisher exact test. Statistical significance was taken as $P < 0.05$. The data were analyzed using Epi Info software (7.1.0.6 version; Center for disease control, USA) and Microsoft Excel 2010. The sample size was determined on the basis of a pilot study in which the reduction in post-operative pain score (VAS) was measured as 15%. We calculated a minimum sample size of 24 patients was required in each group, assuming a type 1 error (two-tailed) of 0.05, and a margin of error of 10%. Therefore, the final sample selected was $n = 30$ in Group A and $n = 30$ in Group B.

RESULTS

Group A patients ($n = 30$) received epidural top up of 10 ml of 0.5% bupivacaine with 20 mcg fentanyl, while Group B patients ($n = 30$) received epidural top up of 10 ml of 0.5% levobupivacaine with 20 mcg of fentanyl. Both groups were compared with respect to age and body mass index (BMI) distribution.

By conventional criteria, the association between the treatment groups and age was considered to be not statistically significant since $P > 0.05$.

By conventional criteria, the association between the treatment groups and BMI is considered to be not statistically significant since $P > 0.05$.

Both the groups were compared on the hemodynamic changes that occurred 5 min and 10 min after spinal blockade and every 5 min after epidural blockade up to 25 min. Statistically no significant changes in pulse rate was observed with a $P > 0.05$.

Both the groups were compared on the basis of blood pressure parameters. Statistically no significant changes in blood pressure were found with a $P > 0.05$.

The time of onset of analgesia was compared in both the groups after epidural top up. The mean onset time of analgesia in Group A was 11.33 ± 3.46 min, while in Group B, it was 13.00 ± 4.28 min showing no statistical significance with a $P = 0.10$.

The duration of complete analgesia for which the patients showed a VAS score of 0 was compared in both groups. Group A patients showed an average duration of 75.50 ± 23.13 min, while in Group B patients, the duration was found to be 128.00 ± 22.98 min. The difference was statistically significant with a $P < 0.05$.

Table 1: Comparison of study patients age

Group	Mean±SD	P
Group A	45.43±6.46	0.822
Group B	45.07±6.11	

SD: Standard deviation

Table 2: Comparison of study patients BMI

Group	N	Mean±SD	P
Group A	30	24.39±1.10	0.432
Group B	30	24.16±1.21	

SD: Standard deviation

Table 3: Hemodynamic changes in study patients

Pulse rate	Mean±SD		P
	Group A	Group B	
Baseline	80.73±6.79	80.33±4.89	0.794
5 Min after SAB	68.8±4.95	65.37±3.48	0.547
10 min after SAB	63.8±5.85	62.43±4.35	0.308
5 min after epidural	62.77±8.65	62.8±8.85	0.988
10 min after epidural	61.97±10.55	64.53±11.21	0.364
15 min after epidural	62.43±13.13	64.07±11.72	0.613
20 min after epidural	63.67±9.72	64.07±8.64	0.866
25 min after epidural	66.43±11.52	65.57±11.65	0.773

SD: Standard deviation

The duration of effective analgesia for which the patients showed a VAS score of 0 to 2 was compared in both the groups. Effective analgesia in Group A patients lasted for an average duration of 134.50 ± 29.26 min, while it lasted for an increased average duration of 181 ± 23.94 min in Group B patients. This difference was statistically significant with a $P < 0.05$.

Side effects like hypotension occurred in three patients in each group and were treated with injection ephedrine 6 mg, while bradycardia occurred in three patients in Group A and were treated with injection atropine 0.6 mg. (Tables 1-6)

Table 4: Comparison of blood pressure

Types of blood pressure	Mean±SD		P
	Group A	Group B	
Systolic			
Baseline	126.03±6.3	125.67±5.82	0.815
5 Min after SAB	111.77±8.01	114.47±10.64	0.271
10 Min after SAB	109.93±10.74	111.73±11.97	0.542
5 Min after Epidural	110.3±10.59	108.27±8.78	0.421
10 Min after Epidural	110.43±11.64	106.43±10.11	0.160
15 Min after Epidural	109.87±11.2	105.27±10.9	0.112
20 Min after Epidural	110.87±12.62	104.7±10.92	0.477
25 Min after Epidural	107.83±11.88	105±10.6	0.333
Diastolic			
Baseline	78.37±6.6	77.9±5.45	0.766
5 min after SAB	73.07±7.07	72.7±7.63	0.847
10 min after SAB	71.47±8.59	70.27±7.5	0.566
5 min after epidural	68.07±8.4	67.73±8.44	0.878
10 min after epidural	67.1±8.41	65.43±8.5	0.448
15 min after epidural	64.9±9.09	63.33±8.08	0.483
20 min after epidural	63.73±9.07	61.97±8.14	0.430
25 min after epidural	63.9±8.16	64.83±8.49	0.665

SD: Standard deviation

Table 5: Comparison of mean arterial pressure

Mean arterial pressure	Mean±SD		P
	Group A	Group B	
Baseline	90.77±6.01	89.8±7.24	0.575
5 min after SAB	85.96±6.56	86.62±7.85	0.722
10 min after SAB	84.29±8.23	84.09±8.21	0.925
5 min after epidural	82.14±8.12	81.24±8	0.667
10 min after epidural	81.54±8.18	79.1±8.52	0.261
15 min after epidural	79.89±8.34	77.31±8.34	0.236
20 min after epidural	79.44±8.91	76.21±8.14	0.147
25 min after epidural	78.55±8.36	78.22±8.33	0.881

SD: Standard deviation

Table 6: Comparison of analgesic effect

Analgesic effect	Mean±SD		P
	Group A	Group B	
Time of onset of analgesia after epidural	11.33±3.46	13±4.28	0.102
Duration of complete analgesia	75.5±23.13	128±22.98	<0.0001
Duration of effective analgesia	134.5±29.26	181±23.94	<0.0001

SD: Standard deviation

DISCUSSION

Combined spinal epidural technique for abdominal hysterectomy has been found to provide adequate blockade in terms of height and duration than spinal anesthesia alone.[3,4] This is in accordance with Mihic *et al.*,[5] who concluded that combined spinal epidural technique was the superior technique for abdominal hysterectomy.

Traditionally, racemic bupivacaine has been the most commonly used anesthetic agent in spinal and epidural anesthesia for lower abdominal surgeries. It has found to be effective for both sensory and motor blockade intraoperatively and for sensory analgesia postoperatively. However, one of the most feared side-effects of racemic bupivacaine is its cardiotoxicity. Racemic bupivacaine causes blockade of the sodium channel, prolonging the diastolic period. This can predispose to the formation of re-entrant arrhythmias. Bupivacaine also causes blockade of potassium channels, resulting in prolongation of QTc interval. It has been found, that it is pronounced more with R(+) enantiomer, hence the S(-) enantiomer (levobupivacaine) has been developed as an anesthetic agent.[6] Levobupivacaine was found to cause smaller changes in indices of cardiac contractility and the QTc interval of the electrocardiogram and also to have less depressant effect on the electroencephalogram.[7] The negative inotropic effect was found to be less with levobupivacaine, compared to bupivacaine.[8] Since levobupivacaine has a lower risk of cardiovascular and CNS toxicity compared to racemic bupivacaine, we decided to compare its effectiveness in providing sensory analgesia with bupivacaine in patients undergoing abdominal hysterectomy.

Both the groups showed no statistical difference with respect to age, BMI, and ASA physical status. Hemodynamic changes with respect to pulse rate and blood pressure in both the groups were also of no clinical significance with a $P > 0.05$ in all parameters. The time of onset of analgesia after epidural top up in Group A was around 11.33 ± 3.46 min, while in Group B, it was 13.00 ± 4.28 min, showing no statistical significance with a $P = 0.10$. This shows that both bupivacaine and levobupivacaine almost have same potency with regard to the time of onset of analgesia.

However, the duration of complete analgesia for which the patients showed a VAS score of 0, was prolonged in the levobupivacaine group (128.00 ± 22.98 min), while in the bupivacaine group, the duration was found to be 75.50 ± 23.13 min. Similarly, the duration of effective analgesia, for which the patients showed a VAS score of 0-2, was also prolonged in the levobupivacaine group with an average duration of 181 ± 23.94 min, while it lasted for 134.50 ± 29.26 min in the bupivacaine group patients. This difference was statistically significant with a $P < 0.05$. The above observation shows that levobupivacaine, prolongs sensory analgesia duration, when compared to bupivacaine. This is in accordance with the studies conducted by Foster *et al.*[6] He observed that sensory block tended to be longer with levobupivacaine than bupivacaine, amounting to a difference of 23 to 45 min with epidural administration and approximately 2 h with peripheral nerve block. With epidural administration, levobupivacaine produced less prolonged motor block than sensory block.[9] Further, higher doses of levobupivacaine can be used to prolong duration of sensory blockade without any incidence of side effects.[10] Foster *et al.* also further added that levobupivacaine had a less negative inotropic effect and at doses <75 mg, produced less prolongation of the QTc interval, when compared to bupivacaine. Further addition of fentanyl to levobupivacaine reduces the stress response to surgery, prolongs post-operative analgesia, rather than when levobupivacaine alone was used.[11,12]

CONCLUSION

Our study results show that levobupivacaine is equipotent to bupivacaine in providing analgesia, with a much more prolonged duration. At the same time, it is associated with less side effects than compared to bupivacaine. We conclude that levobupivacaine is a much more suitable alternative to bupivacaine in neuraxial blockade for abdominal and lower limb surgeries.

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