

A clinical comparative study of 0.2% levobupivacaine with 25 mcg fentanyl versus 0.2% ropivacaine with 25 mcg fentanyl for post-operative epidural analgesia in patients undergoing lower limb orthopaedic surgeries

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Received: 03rd October, 2016

Accepted: 05th October, 2017

Abstract

Objectives: The objectives of our study were to compare the efficacy and safety of 0.2% Levobupivacaine with 25 mcg Fentanyl and 0.2% Ropivacaine with 25 mcg Fentanyl given epidurally for post-operative analgesia in patients who were operated electively for lower limb orthopaedic conditions under spinal anaesthesia.

Materials and Methods: Sixty patients belonging to American Society of Anaesthesiologists (ASA) Class I and II of both sexes, of age within 20 - 60 years were included in the study after obtaining institutional ethical committee clearance.

Patients were divided randomly into 2 groups: Group - LF which received 8 ml of 0.2% Levobupivacaine with 25 mcg Fentanyl and Group - RF which received 8 ml of 0.2% Ropivacaine with 25 mcg Fentanyl. Surgery was conducted under spinal anaesthesia. Later 8 ml of the test drug combination was given epidurally in the post-operative period when the patient complained of pain (VAS score > 4) and the parameters were recorded periodically until pain reappeared (VAS score > 4).

Results: In both the groups mean duration of surgery, changes in haemodynamics and demographic profiles were comparable. However the total duration of post-operative analgesia in Levobupivacaine group was 325 +/- 63.06 minutes and in Ropivacaine group was 210 +/- 24.91 minutes respectively and this appeared to be statistically significant.

Conclusion: Compared to 0.2% Ropivacaine with 25 mcg Fentanyl, 0.2% Levobupivacaine with 25 mcg Fentanyl provides intense and longer duration of post-operative analgesia with similar haemodynamic stability.

Keywords: Levobupivacaine, Ropivacaine, Fentanyl, Post-operative analgesia, Local anaesthetics.

Introduction

Epidural analgesia has various advantages in post operative pain management like early mobilization, decreasing rehabilitation time, reduction of pulmonary complications, reduction of cardiac ischaemia and dysrhythmia in high risk patients thereby reducing incidence of post operative myocardial infarction and also reduces postoperative ileus thereby minimising hospital stay.¹

Bupivacaine is known to cause cardiotoxicity when injected intravenously in high concentration.²

Among local anaesthetics, bupivacaine belongs to long acting group. It was first used in 1970's. It is composed of two isomers: S(-) and R(+). It is widely used in central neuraxial blockade and other field blocks. It causes various adverse effects, among which cardiac adverse effects predominate. Literature shows cardiac adverse effects because of inadvertent intravascular injection of bupivacaine lead to high mortality. So, the search for newer agents continued. As a result of this extensive research, two drugs – Levobupivacaine and Ropivacaine having lesser cardiac adverse effects compared to Bupivacaine have been developed.³

When multimodal approach is used for achieving better pain relief postoperatively, it helps in good recovery of the patient. Hence we can combine two

drugs so that their concentration can be reduced, thereby decreasing lethal adverse effects they would cause if used individually at a higher concentration.⁴

Hence in our study we have compared Levobupivacaine plus Fentanyl with Ropivacaine plus Fentanyl injected epidurally in patients undergoing elective lower limb orthopaedic surgeries.

Objectives

Comparing the effectiveness of 0.2% Levobupivacaine with 25 mcg Fentanyl in a single dose versus 0.2% Ropivacaine with 25mcg Fentanyl in a single dose injected epidurally in the post-op period in patients who undergo elective lower limb orthopaedic surgeries regarding:

1. Postoperative analgesia duration.
2. Haemodynamic parameters such as Heart rate and Blood pressure.

Materials and Methods

Source of Data: Sixty patients both male and female, aged between twenty to sixty years, falling under ASA Class I and II, posted for elective lower limb orthopaedic surgeries. The study was conducted for a period of 1 year.

Inclusion Criteria: Both male and female patients, aged between twenty to sixty years, categorized as ASA

Class I and II, posted for elective lower limb orthopaedic surgeries were considered for our study.

Exclusion Criteria:

1. Patients having BMI > 27 kg/m².
2. Patients height < 150 cms and > 170 cms.
3. Patients on anticoagulants, bleeding disorders, raised intracranial pressure, severe hypovolemia, infections at the site of epidural catheter insertion.

Method of collection of data:

1. STUDY DESIGN: Randomized, prospective study.
2. SAMPLE SIZE CALCULATION:
 Z^2pq/d^2 Z = Standard normal deviate (1.96)
 p = Prevalence (0.04)
 q = 1-p = 1 - 0.04 = 0.96
 d = Error margin (0.05)
 = 1.96 x 1.96 x 0.04 x 0.96 / 0.05 x 0.05
 Approximately 60

The study population was divided by computer generated numbers randomly into two groups and each group was allotted thirty patients (n=30).

Group LF: Received 8ml of 0.2% Levobupivacaine with 25 mcg Fentanyl.

Group RF: Received 8ml of 0.2% Ropivacaine with 25 mcg Fentanyl.

Each patient was assessed pre-operatively and a written informed consent taken. Surgery was scheduled only after all patients underwent pre-operative preparations. 18 gauge IV canulae were used to obtain IV lines and patients were administered RL 500 ml before administering epidural anaesthesia in order to preload them.

Under strict asepsis, epidural space was identified at L₂ - L₃ interspace using 20 G Tuohy's needle by loss of resistance to air technique in sitting position, midline approach; epidural catheter passed subsequently and fixed 3 cm inside epidural space. Then surgery performed under spinal anaesthesia. Later patient shifted to post-op room after completion of surgery. Visual Analogue Scale (VAS) was used to assess the pain (0 = no pain till 10 = maximum pain).

Test drug was injected through epidural catheter as soon as VAS score became 4. Subsequently patient was evaluated for post-op pain using VAS score noted every 1 minute for 10 mins, every 3 mins for a duration of next 15 mins and every 30 mins thereafter. Changes in

Results

Table1: Age distribution

Age (years)	Group LF		Group RF	
	Number	Percentage	Number	Percentage
20-29	8	26.7	9	30.0
30-39	6	20.0	8	26.7
40-49	8	26.7	5	16.7
50-59	8	26.7	8	26.7
Total	30	100	30	100

the haemodynamics were noted every 5 mins upto 30 mins and every half hour thereafter.

Total duration of post-operative analgesia was calculated based on the time taken for the VAS score to resume as 4 after injecting the study drug.

Definitions

Peak of post-operative analgesia: Zero or One VAS Score.

Duration of Post-operative analgesia: Total time taken since injecting the study drug till the patient complains of pain assessed by VAS Score of 4.

Changes in Haemodynamics:

1. **Hypotension:** A fall in Systolic Blood Pressure (SBP) less than 90 mm Hg or a reduction in SBP by more than 25% below the base line is considered as hypotension. It will be treated by allowing more IV fluid infusions initially, if persistent fall in SBP noticed then Inj Mephenteramine given IV as 3 mg increments.

2. **Bradycardia:** A heart rate < 60 beats/min is considered as Bradycardia. It will be treated using Inj of Atropine 0.6 mg IV.

Adverse effects: Any adverse changes in HR, Rhythm and BP and any signs or symptoms like circumoral numbness, tremors, muscle twitches, depression (sedation, clouding of consciousness, apnoea), any signs of allergic reactions to the drug will be considered as adverse effects and monitored closely.

Visual analogue pain scale: Pain intensity in patients was analysed using Visual Analogue Scale. Patient was asked to point out the scores on the scale after giving the test drug.



Statistical significance (P) for the results obtained from the above study were analysed using:

1. Descriptive statistics.
2. t-test = Independent samples.
3. t-test = Paired samples.
4. Repeated measure ANOVA.

Using SPSS for Windows (version 20.0)

The mean age in group LF is 42.3 years and group RF is 40.7 years. No significant statistical difference was noted as far as age of patients in both groups is considered. Both groups looked similar in respect to age distribution.

Table 2: Sex distribution

Sex	Group LF		Group RF	
	Number	Percentage	Number	Percentage
Male(M)	24	80	23	76.7
Female(F)	6	20	7	23.3
Total	30	100	30	100

Though there seemed to be a predominance of male patients in both the groups, yet it was not statistically significant as far as sex distribution of patients in each group.

Table 3: Duration of Post-Operative Analgesia

	Mean (min)	Standard Deviation (SD)	Mean Difference	p-Value	Significance
Group LF	325.0	63.06	115.0	< 0.05	Significant
Group RF	210.0	24.91			

The mean duration of postoperative analgesia in Levobupivacaine group (group LF) was 325± 63.06 minutes, whereas in Ropivacaine group (group RF) it was 210± 24.9 minutes. The p-value was < 0.05, indicating that the difference was highly significant (Table 3). This shows that Levobupivacaine group had a longer duration of post-operative analgesia in comparison with Ropivacaine group

Table 4: Variation in Heart Rate

Time (min)	Group LF		Group RF		Mean Difference	p-Value	Significance
	Mean (bpm)	Standard Deviation (SD)	Mean (bpm)	Standard Deviation (SD)			
Basal	90.20	12.209	90.00	12.183	0.200	0.950	Ns
5	91.10	13.042	90.80	12.893	0.300	0.929	Ns
10	93.13	13.610	92.70	13.139	0.433	0.901	Ns
15	94.90	13.538	94.00	13.125	0.900	0.795	Ns
20	92.90	13.327	92.50	13.528	0.400	0.909	Ns
25	92.67	13.730	92.00	13.636	0.667	0.851	Ns
30	91.87	13.605	91.70	13.155	0.167	0.962	Ns
60	91.17	13.488	90.67	13.118	0.500	0.885	Ns
90	90.37	12.995	90.23	13.690	0.133	0.969	Ns
120	90.13	13.685	90.00	11.968	0.133	0.968	Ns
150	90.20	13.700	89.87	12.280	0.333	0.921	Ns
180	90.00	12.529	89.87	13.172	0.133	0.968	Ns

At an interval of 0, 5, 10, 15, 20, 25, 30, 60, 90, 120, 150, 180 minutes, the mean heart rate in the two groups was compared (Table 4). No statistically significant difference in the mean heart rate was noticed in either of the groups and there was no incidence of bradycardia in any patients in both groups.

Table 5: Variation in Systolic Blood Pressure

Time (min)	Group LF		Group RF		Mean Difference	p-Value	Significance
	Mean (mm Hg)	Standard Deviation (SD)	Mean (mm Hg)	Standard Deviation (SD)			
Basal	120.0	7.683	121.06	7.624	-1.066	0.591	Ns
5	117.93	8.178	118.93	6.902	-1.0	0.611	NS
10	114.06	8.212	115.93	6.917	-1.86	0.345	NS
15	111.13	8.768	112.06	6.877	-0.93	0.648	NS
20	106.06	8.590	106.93	6.741	-0.86	0.665	NS
25	105.0	7.588	107.93	7.510	-2.93	0.138	NS
30	107.93	6.485	109.0	7.348	-1.06	0.553	NS
60	109.13	6.532	110.06	6.857	-0.93	0.591	NS
90	110.20	6.244	112.20	6.288	-2.0	0.221	NS
120	112.13	5.894	112.86	6.185	-0.73	0.640	NS
150	112.33	5.920	113.0	6.297	-0.66	0.674	NS
180	114.13	5.917	114.93	6.230	-0.80	0.612	NS

At an interval of 0, 5, 10, 15, 20, 25, 30, 60, 90, 120, 150, 180 minutes, the mean systolic blood pressure was compared between two groups. (Table-5). There was no statistically significant difference in the mean systolic blood pressure (SBP) between groups at various intervals. However 4 patients in group LF and 3 patients in group RF developed hypotension. It was treated with intravenous fluids and 3 mg increments of Inj. Mephentaramine IV.

Table 6: Variation in Diastolic Blood Pressure

Time (min)	Group LF		Group RF		Mean Difference	p-Value	Significance
	Mean (mm Hg)	Standard Deviation (SD)	Mean (mm Hg)	Standard Deviation (SD)			
Basal	75.33	5.785	74.87	6.118	0.467	0.763	Ns
5	70.87	4.776	70.93	5.533	-0.067	0.960	Ns
10	68.87	5.348	68.20	5.467	0.667	0.635	Ns
15	65.40	6.328	65.53	6.361	-0.133	0.935	Ns
20	65.60	5.289	65.73	4.601	-0.133	0.917	Ns
25	66.27	4.660	65.87	4.953	-0.400	0.749	Ns
30	67.80	5.714	68.33	5.511	-0.533	0.714	Ns
60	69.00	6.319	69.60	6.066	-0.600	0.709	Ns
90	70.13	5.728	71.00	5.675	-0.867	0.558	Ns
120	71.67	5.898	72.40	6.066	-0.733	0.637	Ns
150	72.47	5.888	73.67	5.307	-1.200	0.410	Ns
180	72.13	5.655	72.87	5.296	-0.733	0.606	Ns

The mean of the diastolic blood pressures (DBP) was compared between the two groups at 0, 5, 10, 15, 20, 25, 30, 60, 90, 120, 150, 180 minutes. No significant statistical difference was noted. However 4 patients in group LF and 3 patients in group RF developed hypotension which was treated with intravenous fluids and inj. mephentamine 3 mg increments IV.

Discussion

60 patients of ASA class I and II, posted for various elective lower limb orthopaedic surgeries were

grouped randomly into either Levobupivacaine (LF) group or Ropivacaine (RF) group after obtaining a written informed consent. After identification of epidural space with loss of resistance technique and introduction of epidural catheter, 8ml of the test drug combination was injected and various parameters were studied.

Hypothesis for the present study is 0.2% Levobupivacaine produces more intense & long lasting postoperative analgesia compared to 0.2% Ropivacaine

as Ropivacaine is less potent due to its lesser lipid solubility.⁷

Review of randomised control trials done by Casati et al., reported that differences in potency exist among the local anaesthetics and ranked the potency in descending order: racemic bupivacaine > levobupivacaine > ropivacaine.⁷

This is also evidenced by other studies; comparable results were found by many studies using low concentrations of Levobupivacaine and high concentrations of Ropivacaine. Peduto et al,⁸ (epidural levobupivacaine 0.5% vs epidural ropivacaine 0.75%), Casati et al,⁹ (PCEA levobupivacaine 0.125% vs PCEA ropivacaine 0.2%), Rao et al,¹⁰ (epidural levobupivacaine 0.5% vs epidural ropivacaine 0.75%).

Smet et al¹¹ concluded in their study that epidural Ropivacaine 0.165% was inferior to Levobupivacaine 0.125% in providing longer duration of post-operative analgesia in patients undergoing lower limb orthopaedic surgery.

Goyagi et al¹² concluded in their study that epidural 0.24% Levobupivacaine is superior to the 0.19% Ropivacaine in providing postoperative analgesia in patients undergoing the gynecological abdominal surgery.

Drugs selected for the study

Since there are many evidences of severe cardiotoxicity and neurotoxicity with Bupivacaine, two new drugs Levobupivacaine and Ropivacaine, both long acting were developed as alternatives.⁷

In 2009, Ropivacaine came to use in India and has found its place in labour analgesia. More recently in 2012, Levobupivacaine was introduced in India and was rarely used for postoperative analgesia. Studies comparing the post operative analgesic effects & haemodynamic changes of Levobupivacaine and Ropivacaine are not many in the present scenario. Hence Levobupivacaine and Ropivacaine were selected.

Multimodal analgesia involves combination of analgesic agents, in the present study local anaesthetics have been combined with opioid to achieve maximal therapeutic effect and minimal adverse effect. Fentanyl was selected among opioids because it causes less respiratory depression, 100 times more potent than morphine, wide usage and cost-effectiveness.

Concentration of the drugs selected

Studies using the minimal local anaesthetic concentration (MLAC) design, which calculate the ED50 dose for a predefined endpoint, suggest that ropivacaine and levobupivacaine have different potencies. Despite this, in most clinical randomized trials, aiming at administering effective doses for the majority of patients, it appeared difficult to find significant differences between the newer local anaesthetics and racemic bupivacaine. As a

consequence, there lies a dilemma in deciding what concentrations of local anaesthetic to select and how to interpret the results while performing comparative studies.¹¹

However, for postoperative epidural infusions, dose-ranging studies established that 0.2% ropivacaine was a suitable concentration. Therefore, most investigators compare infusions of bupivacaine or levobupivacaine at 0.1% or 0.125% with ropivacaine 0.2%, which removes any imbalance in comparative potency at different concentration.¹³ Hence, a concentration of 0.2% was selected for both drugs.

Demography data

Demographic data comparing age, sex, weight, height shows no statistically significant difference among both the groups.

Postoperative analgesia

In general, loss of pain occurs before loss of sensory and autonomic function and loss of motor function but this is dependent upon the physicochemical properties of the drugs used and the site to which it is given.¹⁴

In our study, the duration of analgesia for group LF is 325+/-63.06 mins & group RF is 210+/-24.91 mins, which is statistically significant. This can be evidenced by the fact that equal doses of both Levobupivacaine and Bupivacaine provide same duration of analgesia (4-6hr) but with a better clinical safety with Levobupivacaine.¹⁶ However, the median duration of analgesia when 0.5% Ropivacaine was injected for surgery was 1.7-4.2 hours.²² This can be further substantiated by studies conducted by Peduto et al⁸ Kara et al²¹ Senard et al²³ Rao et al¹⁰ Brown et al²⁴ Morrison et al¹⁸ where the duration of analgesia produced by Ropivacaine is much lesser in comparison to Levobupivacaine.

In our study significant longer duration of analgesia has been obtained with Levobupivacaine. This can be attributed to the higher potency and lipid solubility of Levobupivacaine because equipotent concentration of both local anaesthetics were not selected for the study.

Role of fentanyl: In our study Fentanyl was added as an adjuvant as it gives a dose sparing effect and also the duration and quality of analgesia is also increased.

The total effective dose of local anaesthetics for postoperative analgesia will be reduced and its quality will be increased on addition of opioids (Fentanyl, Morphine).¹⁶

The quality of pain relief from low-dose epidural infusions of plain local anaesthetic consistently benefits from the addition of adjuvants such as opioids (Hubler et al, 2001,²⁵ Senard et al 2002²³) or alpha-2 adrenoceptor agonists. Potential dose-sparing benefits are more obvious for local anaesthetic side effects

(hypotension and motor block) than for opioid-related side effects.

Haemodynamic changes

In the present study, at any given interval of time there was no significant difference in the heart rate between the two groups. Episodes of bradycardia too weren't noticed in either group. Further it was noted that either statistically or clinically there were no significant changes in mean systolic or diastolic blood pressures at any interval of time. Hypotension was experienced by 4 patients in Levobupivacaine group and 3 patients in Ropivacaine group. It was corrected by 3 mg incremental doses of Inj. Mephentermine IV.

The study done by Casati et al⁹ Senard et al²³ Rao et al¹⁰ also found insignificant changes in haemodynamic parameters on using comparable concentrations of levobupivacaine and ropivacaine in their studies.

Complications and drugs used

Complications observed were hypotension, shivering, nausea and vomiting.

Hypotension was defined as reduction in blood pressure by 20% from baseline and was treated by inj. Mephentermine. Nausea and vomiting were treated by inj. Ondansetron 4mg I.V, inj. Ranitidine 50mg I.V, Shivering was treated by inj. Tramadol 20-25mg I.V.

Table 7: Complications observed

Complications	Group LF	Group RF
Hypotension	4	3
Shivering	7	5
Nausea	3	2
Vomiting	3	2

Conclusion

0.2% Levobupivacaine with 25 mcg Fentanyl is more effective, provides long lasting intense post-operative analgesia compared with 0.2% Ropivacaine with 25 mcg Fentanyl without any significant haemodynamic alterations.

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