Original Article

Comparing the effects of three local anaesthetic agents on cardiac conduction system - A randomised study

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ABSTRACT

Background and Aims: This study aimed to compare the effects of three local anaesthetic (LA) agents, namely bupivacaine, levobupivacaine, and ropivacaine, on the cardiac conduction system as assessed by corrected QT (QTc) and P wave dispersion (PWD) intervals in lower limb orthopaedic surgeries and to find the most suitable LA agent that can be used for a long duration. **Methods:** The study included 75 patients with American Society of Anesthesiologists physical status I and II of either gender in the age group of 18–65 years undergoing elective lower limb orthopaedic surgeries under epidural anaesthesia. These were allocated to groups B (bupivacaine), L (levobupivacaine), and R (ropivacaine). We observed blood pressure, heart rate, respiratory rate, PWD, and QTc intervals from baseline value through Holter monitoring, pain assessment by visual analogue scale, and demand and total volume of LA consumed by patient-controlled analgesia devices. The repeated measures of ANOVA were carried out to find the effect of time and time-to-group interaction among the groups across the periods. **Results:** On intergroup comparison of QTc and PWD, no significant difference among groups was observed, but on intragroup analysis, a statistically significant increase in QTc and PWD from baseline was observed for each of groups B, L, and R at all time intervals. However, the mean increase in QTc and PWD recorded for Group B was higher than in groups L and R. **Conclusions:** Bupivacaine has the maximal tendency to prolong QTc and PWD. All three agents showed comparable haemodynamic effects and time to onset of sensory and motor blockade.

Keywords: Bupivacaine, heart conduction system, levobupivacaine, lower extremities, orthopaedic procedures, P wave dispersion, QT, ropivacaine

INTRODUCTION

The cardiotoxicity of local anaesthetic (LA) agents has been one of the most significant concerns while using them either in higher doses or for a prolonged duration.[1] Epidural anaesthesia has the potential to provide optimal operating conditions with the advantage of prolonged postoperative pain relief.[2] In epidural anaesthesia, to achieve the desired effect, a large volume of LA is required compared to other regional anaesthesia techniques and for a longer time stretching into the postoperative period, which increases the possibility of LA toxicity.

Different LA agents are used for epidural anaesthesia, the most popular being lidocaine and bupivacaine.[3] Bupivacaine, being longer acting among the two, is more popular for regional anaesthesia and postoperative pain relief. However, it is associated with side effects such as central nervous system (CNS) toxicity and cardiotoxicity.[4] These toxicities had been attributed to the R (+) isomer, which has a higher affinity to the

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sodium channels than the S(-) isomer. Levobupivacaine is a pure S (+) enantiomer of bupivacaine with the advantage of lesser CNS toxicity and cardiotoxicity. Ropivacaine, an optically pure S (-) enantiomer of propivacaine, also shares similar LA properties while having lesser potential for systemic toxicities.[5]

The primary objective of our study was to compare the effects of bupivacaine, levobupivacaine, and ropivacaine on cardiac conduction in surgeries conducted under epidural anaesthesia. The secondary objectives were to compare the effects of these three LA agents on the onset and the quality of analgesia provided to the patient following lower limb surgeries.

METHODS

This randomised study was conducted at a tertiary care centre from January 2019 to December 2021. The institutional ethical committee approved the study protocol (vide approval number IEC no.: 62/17, dated 3rd Feb 2018), and it was registered in the Clinical Trials Registry-India (CTRI/2018/09/015812 dated 24th Sep 2018, accessible at https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2018/09/015812). Written informed consent was obtained from the patients to participate in the study and use the patient data for research and educational purposes. The study was carried out using the principles of the Declaration of Helsinki, 2013, and good clinical practice.

Seventy-five patients with American Society of Anesthesiologists (ASA) physical status I and II of either gender in the age group of 18–65 years undergoing elective lower limb orthopaedic procedures under epidural anaesthesia and postoperative epidural analgesia through patient-controlled anaesthesia (PCA) were included. Patients with hypersensitivity to the amide group of LA agents, pregnancy, raised intracranial pressure, neurological or neuromuscular diseases, congenital spinal anomalies, scoliosis, post-traumatic vertebral injuries, cardiovascular diseases, severe renal, hepatic or respiratory diseases, severe hypovolaemia, haemorrhagic and hypovolaemic shock, severe anaemia, coagulopathy and systemic or local infection, or receiving antiarrhythmic or any other drugs that are known to cause alteration in cardiac conduction system were excluded.

In this study, the anaesthesiologist, who was not part of the study team, decided on the LA agent, either bupivacaine, levobupivacaine, or ropivacaine, by drawing lots. The three groups were Group B—patients who received 0.5% bupivacaine, Group L—0.5% levobupivacaine, and Group R—0.75% ropivacaine. A blinded anaesthesiology resident, who was not involved in the intraoperative or postoperative care of the patients, collected the data. Figure 1 shows the flowchart showing the workflow of the study.

The instructions about using the PCA pump (CADD-Legacy Ambulatory Infusion pump, Smiths Medical), the Holter monitor (BPL TRAK48 ECG Holter Machine, BPL Medical Technologies Pvt Ltd, Bengaluru, India), and the visual analogue scale (VAS) were explained in detail to all the enroled patients during preoperative visits. Premedication and preoperative advice were given as per standard guidelines. The Holter monitor was attached 30 minutes before the surgery in the preoperative room, and recording was started. The Holter recording was done throughout the intraoperative period and continued till 24 hours of the postoperative period.

In the operation theatre, baseline blood pressure (BP), heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SpO_2), and electrocardiography (ECG) were recorded. The best inter-lumbar space between L1 and L4 was identified, and 2% lignocaine with adrenaline was infiltrated. 18G epidural needle was inserted into the epidural space and confirmed by loss of resistance to saline injection. A 20-G epidural catheter was threaded through the 18-G Tuohy needle so that 5 cm of catheter remained in the epidural space. A bacterial filter was attached to the hub of the catheter. A test dose of LA (3 mL of 2% lignocaine with 1:2,00,000 adrenaline) was administered via the catheter to rule out inadvertent intravascular or intrathecal placement of the catheter. If there were no signs of motor block (intrathecal placement) or tachycardia (intravascular placement) for 5 minutes, the patient was turned supine. Surgical anaesthesia was achieved by initial epidural bolus injection of 15 mL LA agent, depending upon the allocation of the group. If the block was not achieved up to the desired dermatome level, incremental doses of 4 mL were given after 15 minutes of bolus dose. The onset of sensory block was tested at 1-minute intervals by using the pinprick method with a 27-G hypodermic needle at the anterior axillary line on both sides. The absence of pain from a pinprick at the T10 level was recorded as the onset time of the sensory block. The end of the bolus injection of the study drug was termed as 'time 0' for subsequent patient assessment. The parameters observed and recorded were blood pressure, HR, RR,

and SpO_2 at baseline (on arrival in OT), 0 minute (at the end of epidural bolus), 5 and 10 minutes, then at every 10 minutes intervals for the first 60 minutes and every 30 minutes till completion of surgery. Further measurements were recorded in the postoperative period at 2, 4, 8, 12, 16, 20, and 24 hours after epidural injection of LA.

As the expected average duration of surgery in all patients of each group was 90–120 minutes, the epidural PCA pump device was instituted 2 hours after the epidural bolus in all the patients. All patients received 1 g paracetamol intravenously every 8 hours. In the event of inadequate analgesia (VAS score exceeding 7), 75 mg of diclofenac sodium was provided intramuscularly.

For postoperative pain relief, patients of groups B, L, and R received infusions of 0.125% bupivacaine, 0.125% levobupivacaine, and 0.2% ropivacaine, respectively. The PCA pumps were programmed to provide an infusion rate of 4 mL/hour, a demand dose of 4 mL, a lockout interval of 15 minutes, and a maximum number of demand doses/hour set at three.

The primary outcomes measured were corrected QT interval (QTc) and P-wave dispersion (PWD) at baseline, 5, 10, 20, 30, 40, 50, 60, 90 minutes and 2, 4, 8, 12, 16, 20, and 24 hours. QTc was calculated using Bazett's formula, QT_C = QT/RR, where QT is the QT interval and RR is the RR interval. PWD is the difference between the widest and the narrowest P-wave duration recorded from the 12 ECG leads. The secondary outcomes measured were the time to onset of sensory block (T10 level), motor block after administration of epidural anaesthesia, the demand dose, and total doses of LA agents consumed by the patients through the PCA pump. In addition, the VAS score was measured at 2, 4, 6, 8, 12, 16, 20, and 24 hours postoperatively.

The 12-lead Holter monitor was attached to the patient in the preoperative period for 24-hour follow-up. Any significant change in QTc and P-wave dispersion (PWD) and QTc intervals from baseline value and intergroup analysis was done using appropriate statistical methods to see which group had more significant changes in these parameters. Holter monitoring was assessed for any occurrence of episodes of arrhythmia.

As no previous study examined the effects of three long-acting LA agents on QTc or PWD following their epidural administration, we settled on a sample size of convenience and decided to recruit 25 patients in each of the three groups. All the analyses were carried out using a statistical package for social sciences (SPSS) 16.0 version (Chicago, Inc., USA). The results are presented in frequencies, percentages, and mean [standard deviation (SD)]. The Chi-square test was used to compare the categorical variables, such as gender, ASA class, and VAS score. The one-way analysis of variance (ANOVA) followed by Tukey's post-hoc tests was used to compare continuous variables, such as age, body mass index (BMI), HR, BP, QT interval, onset of effect epidural block, and volume of LA agent consumed, among the groups. The repeated measures of ANOVA were carried out to find the effect of time and time-to-group interaction among the groups across the periods. P values < 0.05 were considered significant.

RESULTS

A total of 75 patients in the 18–65 age group undergoing elective lower limb orthopaedic surgeries under epidural anaesthesia were enroled in the study. The mean age of the patients, distribution of males and females, distribution of ASA classes, and BMI were comparable in all three groups [Table 1]. There was no significant difference in HR and mean arterial pressure among the three groups from baseline until 24 hours [Figures 2 and 3].

The intragroup analysis of QTc values showed a statistically significant ($P < 0.05$) increase from baseline for all the groups at each time interval [Table 2]. However, the mean increase in QTc intervals recorded for Group B was higher than for groups L and R. On intragroup analysis of PWD, there was a statistically significant ($P < 0.05$) increase in groups B and L from 30 minutes to 24 hours. In

Table 1: Comparison of the demographic data of the three groups

Parameter	Group B (*n*=25)	Group L (*n*=25)	Group R (*n*=25)
Age (years)	42.84 (11.35)	44.04 (10.41)	41.96 (13.16) (36.8, 47.11)
Gender (male/female)	14/11	15/10	13/12
ASA class (I/II)	15/10	11/14	13/12
BMI (kg/m^2)	21.75 (2.05)	20.91 (1.58)	22.09 (1.57)

Data expressed as mean (standard deviation) (95% confidence interval), ASA: American Society of Anesthesiologists functional class, BMI: Body mass index

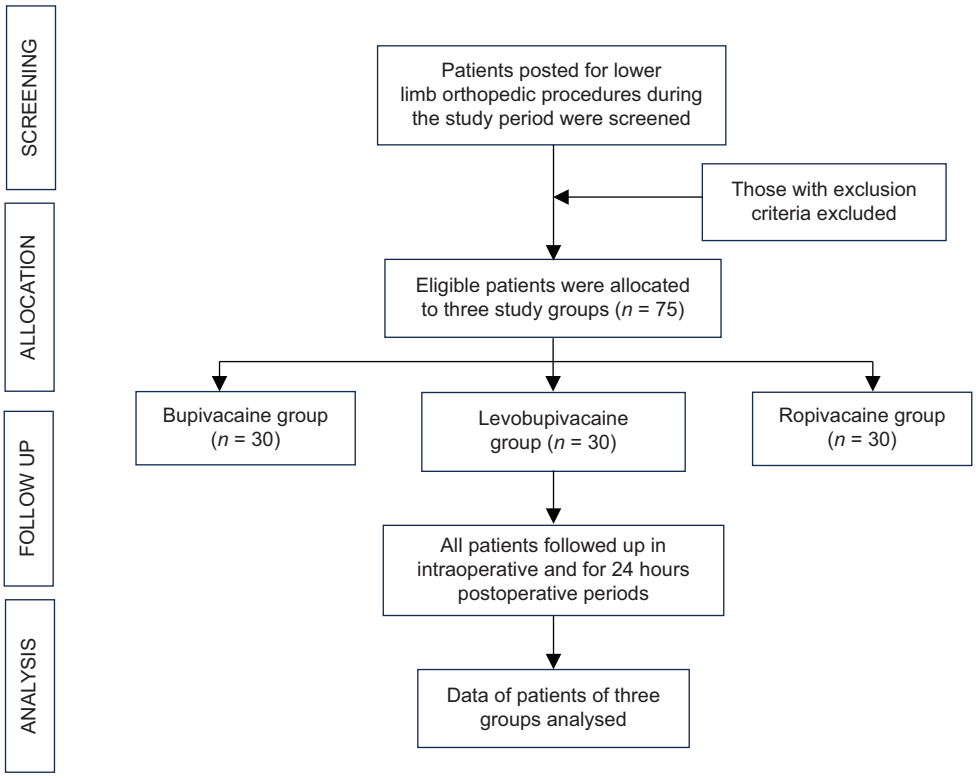

Figure 1: Flow chart of participants recruitment

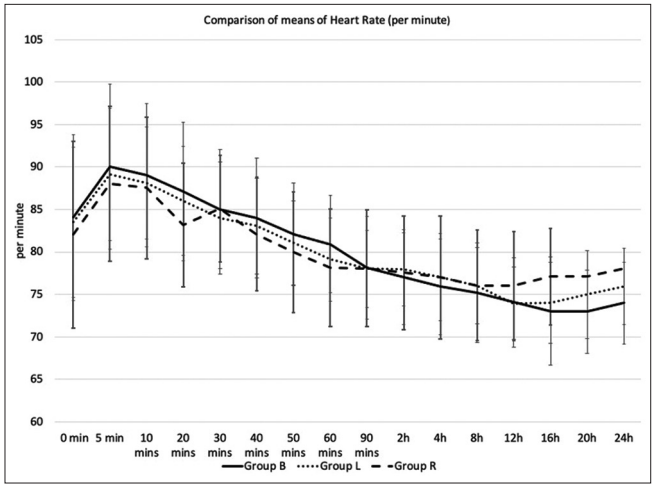

Figure 2: Comparison of heart rate

contrast, there was a significant increase in Group R from 90 minutes to 20 hours. The highest mean value of PWD was observed at 16 hours postoperatively in groups B and L, whereas in Group R, the highest value was observed at 12 hours. Although the mean increase in PWD for Group B was higher than for groups L and R, the difference was not statistically significant [Table 2].

The three groups had comparable differences in the time of onset of sensory and motor blocks [Table 3]. The demand dose and total doses of LA agents consumed through the PCA pump by the patients in either of the three groups were comparable [Table 3]. The VAS was comparable among the groups at different postoperative periods until 24 hours [Table 4].

DISCUSSION

We observed a statistically significant increase in QTc and PWD from baseline for each of the three groups at all time intervals. However, the mean increase in QTc and PWD recorded for Group B was higher than that of groups L and R. All three agents showed comparable haemodynamic effects, time to onset of sensory and motor blockade, and quality of postoperative analgesia.

It was reported that when bupivacaine or levobupivacaine was used for subarachnoid block, the QTc was comparable between the two groups till 10 minutes of administration. However, there was a trend of shortening of QTc.[6] These findings were at variance with our findings, possibly because the doses used were lesser (10 mg of either of the two LA agents) than what we used.

In a study that compared the effects of 7.5 mL of a single bolus of 0.5% bupivacaine and 0.75% ropivacaine on QTc in patients who underwent lung

Table 2: Intragroup comparison of the change in mean corrected (QTc) and P-wave dispersion (PWD) intervals from baseline at different time points

Time from baseline	Group B				Group L				Group R			
	QTc (ms)		PWD (ms)		QTc (ms)		PWD (ms)		QTc (ms)		PWD (ms)	
	Mean Difference from baseline	*P*	Mean Difference from baseline	*P*	Mean Difference from baseline	*P*	Mean Difference from baseline	*P*	Mean Difference from baseline	*P*	Mean Difference from baseline	*P*
0 min	4.72 (6.35, 3.08)	<0.001*	0.52 (4.81, −3.77)	1.00	6 (6.71, 5.28)	<0.001*	−1.72 (1.62, −5.06)	1.00	4 (5.24, 2.75)	<0.001*	−1.6 (1.05, −4.25)	1.00
5 min	5 (7.84, 2.16)	<0.001*	2.88 (7.55, −1.79)	1.00	6.92 (8.99, 4.85)	<0.001*	−0.96 (2.19, −4.11)	1.00	6.88 (9.16, 4.59)	<0.001*	−0.56 (2.64, −3.76)	1.00
10 min	6.16 (10.23, 2.09)	<0.001*	3.48 (8.62, −1.66)	1.00	5.28 (8.83, 1.72)	1.00	0.52 (3.97, −2.93)	1.00	5.96 (10.66, 1.25)	0.03*	−0.08 (3.35, −3.51)	1.00
20 min	10.56 (17.41, 3.7)	<0.001*	4.88 (10.1, −0.34)	0.10	9.88 (13.98, 5.77)	<0.001*	1 (4.06, .−2.06)	1.00	4.92 (8.34, 1.49)	0.001*	−0.08 (3.19, −3.35)	1.00
30 min	15 (22.0, 7.99)	<0.001*	6.88 (11.64, 2.11)	<0.001*	13.92 (19.6, 8.23)	<0.001*	2.88 (5.7, −0.05)	0.04*	6 (9.57, 2.42)	<0.001*	1.52 (4.92, −1.88)	1.00
40 min	18.76 (26.0, 11.51)	<0.001*	7.04 (12.4, 1.67)	0.02*	17.24 (24.68, 9.79)	<0.001*	3.52 (6.55, −0.48)	0.009*	8.84 (12.72, 4.95)	<0.001*	1.44 (5.56, −2.68)	1.00
50 min	20.6 (29.01, 12.18)	<0.001*	8.12 (13.17, 3.06)	<0.001*	19 (25.05, 12.94)	<0.001*	3.48 (7.02, −0.06)	0.06	9.2 (14.22, 4.17)	<0.001*	2.48 (6.24, −1.28)	1.00
60 min	23.4 (35.16, 11.63)	<0.001*	8.08 (13.81, 2.34)	0.01*	21.04 (29.27, 12.80)	<0.001*	3.92 (6.81, −1.02)	0.01*	11.36 (15.69, 7.03)	<0.001*	1.96 (5.78, −1.86)	1.00
90 min	24.76 (35.47, 14.04)	<0.001*	9.96 (17.15, 2.76)	0.01*	22.84 (31.35, 14.32)	<0.001*	5.92 (8.84, −2.99)	<0.001*	13.48 (20.28, 6.67)	<0.001*	4.52 (8.75, 0.28)	0.025*
Postoperative period												
2 h	24.96 (35.14, 14.77)	<0.001*	10.92 (18.23, 3.6)	<0.001*	23 (31.04, 14.97)	<0.001*	6.96 (11.95, 1.96)	0.01*	13.76 (20.64, 6.87)	<0.001*	5.48 (9.37, 1.58)	0.001*
4 h	25.76 (36.3, 15.21)	<0.001*	11.48 (17.49, 5.46)	<0.001*	23.92 (33.41, 14.42)	<0.001*	6.92 (10.49, 3.34)	<0.001*	15.2 (24.09, 6.31)	<0.001*	6.04 (10.45, 1.62)	0.001*
8 h	27.48 (38.27, 16.68)	<0.001*	11.84 (17.86, 5.81)	<0.001*	24.4 (33.63, 15.16)	<0.001*	7.48 (12.67, 2.28)	0.01*	16.32 (25.07, 7.57)	<0.001*	6.52 (11.07, 1.96)	0.001*
12 h	27.96 (38.66, 17.25)	<0.001*	12.08 (18.28, 5.87)	<0.001*	26 (34.82, 17.17)	<0.001*	8 (13.82, 2.17)	0.01*	16.24 (24.79, 7.69)	<0.001*	7 (12.42, 1.57)	0.002*
16 h	28.28 (39.63, 16.92)	<0.001*	12.4 (18.75, 6.04)	<0.001*	26.52 (36.78, 16.25)	<0.001*	8.16 (13.62, 2.69)	<0.001*	16.2 (24.75, 7.64)	<0.001*	6.92 (12.06, 1.78)	0.001*
20 h	28.68 (40.56, 16.79)	<0.001*	12 (19.04, 4.95)	<0.001*	27.04 (37.0, 17.07)	<0.001*	7.84 (13.0, 2.67)	<0.001*	16.04 (24.07, 8.0)	<0.001*	6.56 (11.63)	0.002*
24 h	28.88 (40.04, 17.72)	<0.001*	11.44 (18.55, 4.32)	<0.001*	27.04 (38.92, 15.78)	<0.001*	7.08 (11.84, 2.34)	<0.001*	15.96 (24.26, 7.65)	<0.001*	6.32 (12.96, 0.32)	0.08

Data expressed as mean difference (95% confidence interval), QTc: Corrected QT interval, PWD: P wave dispersion, MD: Mean difference, ms: milliseconds, *significant

Table 3: Comparison of onset of sensory block (T10), motor block, demand dose, and total dose of local anaesthetic consumed through PCA pump among the groups

	Group B	Group L	Group R	*P*
Onset of sensory block T10 (minutes)	10.44 (2.90) (9.3, 11.57)	11.20 (3.00) (10.02, 12.37)	10.96 (2.8) (9.86, 12.05)	0.64
Onset of motor block (minutes)	21.76 (4.75) (19.89, 23.62)	22.52 (4.51) (20.75, 24.28)	22.32 (4.06) (20.72, 23.91)	0.82
Demand dose (ml)	15.48 (4.00) (13.91, 17.04	18.04 (4.29) (16.35, 19.7	16.12 (3.80) (14.63, 17.61)	0.07
Total dose (ml)	149.24 (9.79) (145.4, 153.07)	157.08 (10.26) (153.05, 161.1)	153.84 (9.16) (150.24, 157.43)	0.06

Data expressed as mean (standard deviation) (95% confidence interval). PCA = Patient controlled analgesia

Table 4: Comparison of mean visual analogue score (VAS) among the groups at different times in the postoperative period

Mean VAS score	2 hours	4 hours	8 hours	12 hours	16 hours	20 hours	24 hours
Time in the postoperative period							
Group B	0.48 (0.77) (0.17, 0.78)	0.76 (0.83) (0.43, 1.08)	1.16 (0.62) (0.91, 1.4)	1.52 (0.71) (1.24, 1.79)	1.96 (0.94) (1.59, 2.32)	2.28 (0.98) (1.89, 2.66)	2.56 (1.00) (2.16, 2.95)
Group L	0.44 (0.65) (0.18, 0.69)	0.80 (0.76) (0.5, 1.09)	1.20 (0.65) (0.94, 1.45)	1.48 (0.71) (1.2, 1.75)	1.92 (0.86) (1.58, 2.25)	2.28 (0.98) (1.89, 2.66)	2.56 (1.00) (2.16, 2.95)
Group R	0.44 (0.71) (0.16, 0.71)	0.72 (0.74) (0.5, 1.09)	1.24 (0.78) (0.93, 1.54)	1.56 (0.71) (1.28, 1.83)	1.88 (0.97) (1.5, 2.26)	2.24 (0.83) (1.91, 2.56)	2.48 (0.82) (2.15, 2.8)
P	0.06	0.06	0.08	0.07	0.06	0.07	0.09

Data expressed as Mean (standard deviation) (95% confidence interval). VAS = Visual analogue score

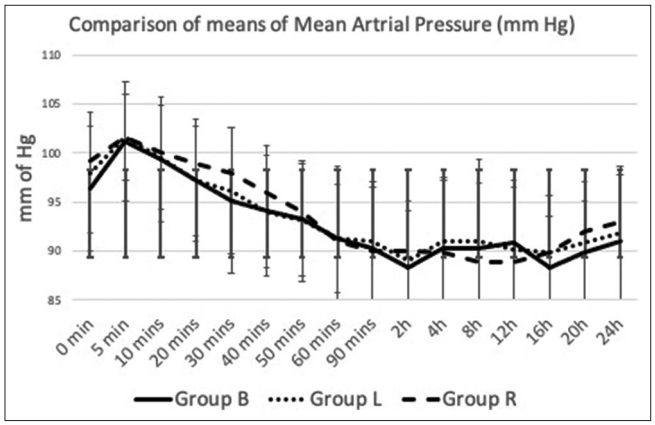

Figure 3: Comparison of mean arterial pressure

resection under thoracic epidural analgesia (TEA) and general anaesthesia (GA), the authors reported that the QTc interval after LA injection was more prolonged in patients receiving bupivacaine than those receiving ropivacaine.[7] In TEA, administration of LA alters the QT interval depending upon the level of the epidural block, that is, whether cardiac sympathetic nerves were blocked or not (T1-T4 or below).[8] Moreover, propofol has also been independently implicated in prolonging QTc.[9] Thus, it is difficult to ascribe the prolongation of QTc to the LA agent when GA is also administered. When 20 mL of 0.75% ropivacaine and 0.5% bupivacaine were administered through the lumbar epidural route, followed by infusion via a PCA pump, there was no difference in QTc interval between the two groups nor the number of patients with QTc interval exceeding 440 ms.[10,11]

The LA agents administered into the epidural space are gradually absorbed into the systemic circulation, and the increased plasma concentration leads to CNS and cardiac toxicities.[12]

The normal value of PWD is 29 (9) ms. PWD ≥40 ms indicates the presence of heterogeneous electrical activity in different regions of the atrium and is a strong predictor of atrial tachyarrhythmias, particularly atrial fibrillation.[13] In a previous study, when bupivacaine or levobupivacaine was used for subarachnoid block, the authors did not report any significant rise in PWD from baseline or significant difference between the groups that received bupivacaine or levobupivacaine.

In our study, although the time taken for the onset of sensory block till T10 level and motor block was comparable in the three groups and all three agents showed good sensory block capability, patients in Group R reported lower VAS postoperatively compared with groups B and L, but the difference was statistically insignificant.

We used bupivacaine and levobupivacaine at 0.5% concentrations and ropivacaine at 0.75% because it was shown that when used in sub-arachnoid block (SAB) for lower limb surgeries, the relative anaesthetic potency ratios were 0.97 for levobupivacaine/bupivacaine, 0.65 for ropivacaine/bupivacaine, and 0.68 for ropivacaine/levobupivacaine. Hence, levobupivacaine and bupivacaine were almost

equipotent, and ropivacaine was 0.4–0.7 times less potent than bupivacaine and levobupivacaine.[13]

The strength of our study is that we compared three LA agents involving higher doses administered over 24 hours through the epidural route to see changes in cardiac conduction (QTc and PWD). However, our study has several limitations; for example, we did not correlate QTc and PWD intervals with serum concentrations of LA agents, and it was a single-centre study. Future studies may examine any correlation between QTc and PWD and serum concentrations of LA agents.

CONCLUSION

Bupivacaine has the maximal tendency to prolong cardiac conduction (as evidenced by corrected QT interval and P-wave dispersion) among bupivacaine, levobupivacaine, and ropivacaine when administered through epidural route for 24 hours.

Statement on data sharing

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' Institution policy.

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Conflicts of interest

There are no conflicts of interest.

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