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Comparison of Intra-Operative ECG Variations (QRS and PR Interval Prolongation) Between 0.25% Ropivacaine and 0.25% Bupivacaine in Patients Undergoing Lower Limb Surgery under Epidural Blockade

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ABSTRACT

Background: *Ropivacaine, new aminoamide local anaesthetic (LA) drug, is chemically homologous to bupivacaine. The lower lipid solubility and higher clearance of ropivacaine compared with bupivacaine is presumed to retard penetration of myelin sheaths, leading to a decreased potential for neural and cardiac toxicity. This may offer an advantage in terms of systemic toxicity. Experimental studies and case reports confirm this hypothesis, showing that ropivacaine causes fewer cardiotoxic effects and is better alternative to bupivcaine.*

Material & Method: *Thirty ASA grade I and II patients of either sex, aged between 20 -50 years undergoing elective lower limb surgeries were enrolled in each group using double-blind randomization. Each group received 0.25%, 25 ml of either bupivacaine or ropivacaine with 18 G needle as single shot epidural injection. A sensory level of T_{10} was achieved. Variations in heart rate, arterial blood pressure and ECG (P-R interval & QRS prolongation, ectopics, arrhythmias) were recorded before epidural injection, 10 minutes after epidural injection and thereafter every 10 minutes interval till the end of surgery.*

Result: *This study showed that epidural ropivacaine produced ECG changes which were substantially similar to those produced by equipotent concentrations and doses of bupivacaine.*

Conclusion: *ECG changes in terms of ventricular arrhythmias, QRS and P-R interval were clinically similar in both groups.*

Keywords: *Epidural anaesthesia, cardiotoxicity, bupivacaine, ropivacaine.*

INTRODUCTION

Epidural anaesthesia is versatile mode of anaesthetic technique, widely accepted both for elective and emergency lower abdomen and lower limb operations. Bupivacaine, a traditional local anaesthetic (LA) of amide group, widely accepted for epidu-ral anaesthesia, in spite of its known cardiotoxicity. The description of several cardiac arrests following an accidental intravenous injections or a pronounced overdose of bupivacaine during periph-eral nerve blockade or epidural anaesthesia have led to development of a more recently introduced long acting local anaesthetic, ropivacaine.

Ropivacaine, chemically homologous to bupivacaine, is the first enantiomercially pure anaesthetic and exists as the S- enantiomer [1]. It is less arrhythmogenic and less potent than bupivacaine in depressing electrophysiologic variables [2]. The lower lipid solubility and higher clearance of ropivacaine compared with bupivacaine is presumed to retard penetration of myelin sheaths[3], leading to a decreased potential for neural and cardiac toxicity. This study was designed to comparing intraoperative electrocardiographic changes in terms of QRS and P-R interval prolongation, arrhythmias and ectopics obtained with 0.25% ropivacaine and 0.25% bupivacaine in equipotent concentration for lower limb surgeries under epidural anaesthesia.

MATERIAL & METHOD

Following hospital Ethical Committee approval and written informed patient consent, 30 ASA grade I and II patients of either sex, aged between 20 years to 50 years undergoing elective lower limb sur-geries were enrolled in each group using sealed envelope method. The study was designed as a prospective, randomized, double- blind clinical trial. Exclusion criteria considered were contraindications to epidu-ral anaesthesia: severe cardiopulmonary, renal, hematological or hepatic diseases, pre-existing neurological or psychiatric illnesses, chronic pain syndromes, alcohol or drug abuse, obesity, drug allergy and mental retardation.

In operation theatre, preloading was done with an infusion of Ringer's lactate (RL) at a rate of 10 ml/kg twenty minutes before epidural anaesthesia. Injection Tramadol 100 mg had been added to preloading RL fluid. Followed by routine, continuous monitoring consisting of non- invasive blood pressure (NIBP), electrocardiography(ECG), heart rate(HR), SpO2 monitoring (Drader- infinity vista) intra-operatively. All solutions were prepared in an adjacent room by paramedics, not involved in the subsequent evaluation of the patients. After skin infiltration with 2 ml of 2% lidocaine with adrenaline, 25 ml of 0.25% concentration of either study drug was injected through 18 G epidural needle as single shot epidural in between L2-3 or L3-4 space using standard protocol in sitting position. A sensory level of T10 was achieved. If no sensory-motor blockade achieved within 20 minutes of epidural injection, patients were excluded from the study. Four patients(1 bupivacaine, 3 ropivacaine) were excluded from the study due to technical failure of the block. Patients were given injection midazolam 2mg as loading dose and then sedation was maintained with 3 mg/hr infusion of midazolam.

Variations in HR, systolic, diastolic and mean arterial blood pressure(SBP, DBP & MAP), SpO2 and ECG(QRS width, PR interval, ventricular arrhythmias and ectopics) were recorded before epidural injection, 10 minutes after epidural injection and thereafter every 10 minutes till the end of opera-tion. Any hypotension (SBP <100 mmHg) or a decrease of more than 30% from baseline) or bradycardia(HR < 50/min) was treated with IV fluid and 3 mg of IV mephenteramine or atropine 0.5 mg increments as or when required. Oxygen was administered with face mask at a rate of 5 L/min throughout the perioperative period. A decrease in SpO2 to <95% was de-fined as hypoxia and treated with supplemental oxygen via a Venturi- mask 40% at 10 L/min. The assessment of ECG was done by investigator not aware of study solution used.

STATISTICAL ANALYSIS & RESULTS

The data obtained from the sixty patients entered in Microsoft excel sheet, checked for miss-ing errors using SPSS v-18 software. For continuous variables the unpaired student's t -test was used whereas chi- square test was used for categorical data.The demographic characteristics and ASA physical status in the two groups were comparable. Duration of surgery showed statistically significant difference between study groups.(Table 1) Four patients(one in bupivacaine group and three in ropiva-caine) required general anaesthesia, hence were excluded from the study.

Changes in heart rate were not different between the two groups ($p>0.05$) preoperatively.As we know that both bupivacaine and ropivacaine drugs produces bradycardia in the intraoperative period. The fall in the mean heart rate was seen more in the bupivacine group from their baseline values while the rise in heart rate was seen in the ropiva-caine groups and this difference was statistically significant.(Table 2) No 'p ' value was calculated at 90 min as the standard deviation(SD) of 6 patients in bupivacaine and 3 patients in ropivacaine group is zero.

The preoperative and intraoperative mean SBP and DBP in the two groups was not showing significant difference statistically($p>0.05$). The fall in SBP may be due to the inbuilt property of the regional anaesthetic drugs given epidurally to produce hypotension. Although bupivacaine group was thought to be produce more hypotension in the intraoperative period than the ropivacaine drug. (Table 2 & 3) Because of the inherent property of epidural anaesthetic drugs to produce hypotension on being administered; there had been seen decrease in the mean MAP in both the groups at various intraoperative time, except at 80min and 90 min and the difference in mean MAP was observed to be significant statistically($p<0.05$)(Table 3).

As both the bupivacaine and ropivacaine are cardiodepressant anaesthetic drugs, the cardiodepression is seen less in ropivacaine drug because of its less lipophilic property. But the width of mean ORS interval as well as mean P-R interval at different intraoperative periods from their baseline values remained almost same and the difference in both the groups remained statistical-ly insignificant, except at 90min intraoperative period few patients showed statistically significant in both the groups.(Table 4) Sedation required in ropivacaine group was higher than in bupivacaine group. No ECG ab-normalities like ventricular arrthymias and ventricular ectopics had been seen in any group during preoperative and intraoperative period. Also, none of the patients in both the groups experienced nausea/vomiting as the side effects of the anaesthesia.

Table 1: Baseline characteristics in the 2 groups of patients

Baseline parameters	Number	Bupivacaine group	Ropivacaine group	P* value
Mean Age (in years)	30	33.50 ± 6.4 (26 to 45yrs)	37.53 ± 7.81 (22 to 50yrs)	0.480
Mean weight (in kg)	30	59.30 ± 6.75 (49 to 70kg)	59.80 ± 5.93 (48 to 69kg)	0.762
Sex (M/F)	30	18/12	16/14	0.602
ASA (I/II)	30	12/18	12/18	1.000
DOS (Duration of surgery) in min	30	72.0 ± 14.95	62.0 ± 16.69	0.018

*using student's t test and Chi sq test

Table 2: Changes in the mean HR and mean SBP in the intraop period in the 2 groups

Parameters	Preop/intraop time intervals	Mean ± SD (Bupivacaine gp)	Number	Mean ± SD (Ropivacaine gp)	Number	P** value
HR(beats/min)	Preop	80.27 ± 7.0	30	80.27 ± 8.03	30	1.000
	10 min	77.93 ± 4.80	29	83.40 ± 7.37	27	0.001
	20 min	75.83 ± 6.36	29	84.53 ± 6.34	27	0.001
	30 min	77.93 ± 4.80	29	84.87 ± 4.78	27	0.001
	40 min	78.0 ± 5.30	29	86.20 ± 5.74	27	0.001
	50 min	77.93 ± 4.80	29	85.75 ± 5.05	24	0.001
	60 min	80.57 ± 7.79	23	84.78 ± 4.56	18	0.037
	70 min	80.0 ± 3.55	20	86.15 ± 3.11	13	0.001
	80 min	78.59 ± 0.94	17	88.50 ± 3.16	8	0.001
	90 min	78.0 ± 0.0	6	88.0 ± 0.0	3	-*
SBP (mm Hg)	Preop/intraop time intervals	Mean ± SD (Bupivacaine gp)	Number	Mean ± SD (Ropivacaine)	Number	P** value
	Preop	121.50 ± 5.52	30	122.33 ± 6.48	30	0.594
	10 min	121.47 ± 4.67	29	120.93 ± 6.25	27	0.709
	20 min	120.07 ± 5.77	29	120.60 ± 6.20	27	0.731
	30 min	120.07 ± 4.74	29	119.80 ± 5.83	27	0.847
	40 min	117.67 ± 4.96	29	118.87 ± 5.96	27	0.400
	50 min	119.13 ± 4.16	29	120.33 ± 4.74	24	0.523
	60 min	119.39 ± 1.95	23	119.89 ± 5.72	18	0.698
	70 min	117.30 ± 3.63	20	119.54 ± 5.55	13	0.170
	80 min	121.65 ± 4.32	17	120.50 ± 5.63	8	0.579
	90 min	120.0 ± 2.83	6	116.67 ± 9.24	3	0.419

*no p value is calculated as the SD of 6 patients in bupivacaine and 3 patients in ropivacaine group is zero

**using student's t test

Table 3: Changes in the mean DBP and mean MAP in the 2 groups at different intraop time intervals

Parameters	Preop/intraop time intervals	Mean ± SD (Bupivacaine gp)	Number	Mean ± SD (Ropivacaine gp)	Number	P* value
DBP(mm Hg)	Preop	87.73 ± 8.49	30	82.27 ± 5.53	30	0.802
	10 min	81.40 ± 7.78	29	80.27 ± 5.43	27	0.515
	20 min	82.23 ± 6.90	29	80.33 ± 5.41	27	0.240
	30 min	79.20 ± 5.47	29	80.60 ± 4.58	27	0.287
	40 min	80.80 ± 8.15	29	79.07 ± 4.95	27	0.323
	50 min	78.73 ± 7.38	29	79.75 ± 4.62	24	0.539
	60 min	78.0 ± 5.72	23	79.22 ± 4.56	18	0.463
	70 min	76.90 ± 3.87	20	79.23 ± 4.66	13	0.129
	80 min	80.24 ± 7.97	17	80.25 ± 4.83	8	0.996
	90 min	80.67 ± 3.27	6	78.0 ± 8.72	3	0.654
MAP (mm Hg)	Preop/intraop time intervals	Mean ± SD (Bupivacaine gp)	Number	Mean ± SD (Ropivacaine)	Number	P* value
	Preop	92.17 ± 1.84	30	101.73 ± 2.16	30	0.092
	10 min	90.80 ± 1.63	29	99.97 ± 2.16	27	0.001
	20 min	91.0 ± 1.98	29	98.53 ± 2.08	27	0.001
	30 min	91.73 ± 1.64	29	98.30 ± 2.0	27	0.001
	40 min	86.80 ± 1.69	29	96.57 ± 1.99	27	0.001
	50 min	87.97 ± 1.61	29	93.17 ± 1.66	24	0.001
	60 min	90.09 ± 0.60	23	91.61 ± 1.88	18	0.001
	70 min	90.0 ± 3.64	20	93.0 ± 2.04	13	0.005
	80 min	93.24 ± 6.22	17	93.13 ± 4.88	8	0.965
	90 min	91.0 ± 7.54	6	90.33 ± 8.96	3	0.909

*student's t test

Table 4: ECG changes in the 2 groups at different intraop periods

ECG Parameters	Preop/intraop time intervals	Mean ± SD (Bupivacaine gp)	Number	Mean ± SD (Ropivacaine gp)	Number	P* value
QRS (sec)	Preop	0.1158 ± 0.0106	30	0.1215 ± 0.017	30	0.142
	10 min	0.1158 ±0.0106	29	0.1215 ± 0.017	27	0.142
	20 min	0.1158 ± 0.0106	29	0.1215 ± 0.017	27	0.142
	30 min	0.1158 ± 0.0106	29	0.1215 ± 0.017	27	0.142
	40 min	0.1158 ± 0.0106	29	0.1215 ± 0.017	27	0.142
	50 min	0.1158 ± 0.0106	29	0.1160 ± 0.013	24	0.943
	60 min	0.1154 ± 0.011	23	0.1158 ± 0.013	18	0.921
	70 min	0.12 ± 0.012	20	0.12 ± 0.016	13	0.183
	80 min	0.12 ± 0.013	17	0.11 ± 0.017	8	0.397
	90 min	0.12 ± 0.0	6	0.10 ± 0.006	3	0.038
P-R (sec) interval	Preop/intraop time intervals	Mean ± SD (Bupivacaine gp)	Number	Mean ± SD (Ropivacaine)	Number	P* value
	Preop	0.2297 ± 0.018	30	0.2307 ± 0.019	30	0.843
	10 min	0.2297 ± 0.018	29	0.2307 ±0.019	27	0.843
	20 min	0.2267 ± 0.015	29	0.2307 ± 0.019	27	0.389
	30 min	0.2297 ± 0.018	29	0.2307 ± 0.019	27	0.843
	40 min	0.2297 ± 0.018	29	0.2307 ± 0.019	27	0.843
	50 min	0.2297 ± 0.018	29	0.2267 ± 0.020	24	0.575
	60 min	0.2300 ± 0.018	23	0.2261 ± 0.019	18	0.518
	70 min	0.2325 ± 0.044	20	0.2323 ± 0.018	13	0.964
	80 min	0.2282 ± 0.021	17	0.2338 ± 0.023	8	0.570
	90 min	0.2100 ± 0.0	6	0.2333 ± 0.011	3	0.001

*student's t test

DISCUSSION

Most studies, comparing ropivacaine with bupivacaine in many clinical trials of regional anaesthesia, have shown that the onset, potency and duration are very similar to those of bupivacaine [4] .The sensory block provided by ropivacaine is similar to that produced by equivalent dose of bupivacaine in epidural anaesthesia [3]. However, ropivacaine offered a slower onset and a shorter duration of motor block, as well as faster resolution of sensory block compared with the bupivacaine as has been demonstrated in clinical epidural and volunteer studies [5],[6].

As we know that both bupivacaine and ropivacaine drugs produce bradycardia in the intraoperative period [1]. In our study, the fall in the HR was seen more in the bupivacine group from their baseline values while the rise in HR was seen in the ropivacaine groups($p<0.001$). All LAs drugs are known to depress Vmax in a dose –dependent manner depending on the membrane potential and rate of stimulation [7]. But, epidural anaesthesia technique require relatively larger doses and volume of local anaesthetics for their adequacy. Bupivacaine depresses Vmax consideraby more than lignocaine and results in slowed conduction of the cardiac action potential which is manifested by prolongation of the P-R and QRS intervals in the ECG. Studies suggest that the bupivacaine has been found to be more cardiotoxic than equivalent doses of lignocaine or ropivacaine in the isolated perfused rabbit heart [3],[8,][9].

After extradural administration the pharmacokinetic profile of the two drugs were similar to those determined in animal studies [3]. Our study shows that the epidural administration of either 25ml bupivacaine or 25ml ropivacaine as 0.25% was well tolerated without complications and an adequate block for lower limb surgery was achieved in all; except one in bupivacaine group and three in ropivacaine group patients. The fall in blood pressure may be due to the inbuilt property of the regional anaesthetic drugs given epidurally. Although bupivacaine group is thought to be produce more hypotension in the intraoperative period than the ropivacaine drug as ropivacaine is

said to have some vasoconstrictor capabilities [10]. (Table 2 & 3) Regression of block occurs due to diffusion of the LAs away from the site of action, which in turn depends upon the vascularity of that particular tissue. Greater vascularity resulted in earlier block regression because of rapid washout of the drug from the epidural space. The lower lipid solubility and higher clearance of ropivacaine compared with bupivacaine is presumed to retard penetration of myelin sheaths leading to a decreased potential for neural and cardiac toxicity [3]. Studies of lumber extradural bock in humans have confirmed that equal volumes and concentrations of ropivacaine and bupivacaine produce a similar pattern of sensory block [11]. But, when bupivacaine is bound to cardiac muscle, recovery from block is slow [3]. This might be the reason for statistically significant decrease in mean arterial blood pressure(MAP) between two groups intraoperatively.($p<0.001$) (Table 3)

Local anaesthetics exert their direct toxic effects on the heart by blocking sodium influx through sodium channels [12]. This causes depression of the maximal rate of increase (Vmax), of the cardiac action potential and results in delayed conduction, seen on the ECG as prolongation of the P-R interval and QRS complex. Re-entrant phenomena and ventricular arrhythmias may occur [12]. Ropivacaine depresses Vmax less than bupivacaine and recovery is quicker after ropivacaine [13]. In animals, ropivacaine causes less prolongation of the QRS complex and at supraconvulsant doses is less arrhythmogenic [12]. As other LAs, ropivacaine has the potential to induce CVS toxicity (e.g. arrhythmias, reduced myocardial conductivity & contractility) and CNS toxicity (e.g.seizures) at high plasma concentration. But, the peak plasma concentration of ropivacaine was below the concentration associated with systemic toxicity in animals. But, the risk of these toxicities increases following accidental intravascular administration [3]. In a previous study, a cardiovascular symptoms were associated with higher peripheral venous plasma concentrations of ropivacaine than bupivacaine. The lower lipid solubility and higher clearance of ropivacaine compared with bupivacaine may offer an advantage in terms of systemic toxicity [3], [12]. That's why ropivacaine has been shown to have an increased therapeutic index in human volunteer studies.

At low concentrations, bupivacaine blocks sodium channels in a slow-in slow-out manner and at high concentrations the channels is blocked in a 'fast-in, slow-out' manner which causes difficulty in resuscitation when ventricular fibrillation has occurred. Studies suggest that the cardiotoxicity of bupivacaine results from its high lipid solubility [14]. The development of ECG disturbances and severe myocardial depres-sion was more rapid with bupivacaine than ropivacaine.

In our study, we didn't see any significant changes in QRS and P-R interval between two study groups . The incidence of ropivacaine induced cardiovascular symptoms may be age-related. This might be explained on the basis of that epidural administration of ropivacaine for surgery generally produced dose-dependent adverse events similar to those observed with equal doses of bupivacaine. Secondly, we had enrolled ASA grade I & II healthy patients in our study using a drug concentration of 0.25%.

However, some studies, particularly those utilizing the concept of Minimum Local An-algesic Concentration (MLAC) in epidural analgesia, have questioned whether the difference in cardiotoxicity seen between the two agents is in fact a result of an absolute difference in potency [15], [16]. The suggestion is that the therapeutic ratio of the two may be the same. Such concerns must be viewed against the important basic principle that the local, and subsequent systemic, dynamics of a particular local anaesthetic will depend on the site of injection [17]. Again, ropivacaine is less potent and less toxic than bupivacaine at equal mg/kg dosages, but there is no apparent differ-ence in toxicity at equipotent dosages. Insufficient data are available to allow a reason-able comparison between ropivacaine and bupivacaine in terms of safety and effi-cacy.

Despite the differences observed in the MAP values in two groups the hypotension produced by both the drugs is not more so there is no specific vasopressor agent is required. Also, the patients in both the groups experienced no nausea/vomiting as the side effects of the anesthesia.

CONCLUSION

Our study showed that the ECG changes in terms of arrhythmias, widen QRS com-plexes, wide P-R interval were clinically similar in both the groups without the oc-currence of significant adverse effects. The clinical and experimental studies have also shown that epidural anaesthesia with ropivacaine has been proven less cardiotoxic and better alternative to bupivacaine in all aspects because of its higher therapeutic index. The rationale for replacing bupivacaine with ropivacaine is to provide a wider margin of safety with the same analgesic efficacy and less postoperative motor block. But, to reach to a solid conclusion, this study needs to be done with large sample size.

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