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COMPARISON OF CARDIOVASCULAR SAFETY OF BUPIVACAINE AND ROPIVACAINE ADMINISTERED BY SUPRACLAVICULAR BLOCK IN PATIENTS UNDERGOING UPPER ARM SURGERY

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ABSTRACT

Bupivacaine and Ropivacaine were widely used long acting local anesthetic agents in regional anesthesia. Though efficacious, cardiovascular adverse drug reactions are known safety concerns with use of long acting local anesthetic agents, especially with Bupivacaine. The aim of this study was to compare the cardiovascular safety of Bupivacaine and Ropivacaine in patients receiving supraclavicular brachial plexus block for upper arm surgery. It was a randomized, double blind, controlled, prospective study. Screened patients fulfilling the inclusion and exclusion criteria were randomized to receive supraclavicular block using nerve locator with 40 ml of either Bupivacaine 0.5% or Ropivacaine 0.5%. Parameters under study such as pulse rate, blood pressure, electrocardiogram recordings such as PR interval, QRS duration and QT interval were compared from the start of the study to regular intervals such as during the study, post operatively and at follow up using paired T test and intergroup comparison were made using unpaired T test. It was observed that the pulse rate, blood pressure, PR interval, QRS duration and QT interval didn't differ significantly from the baseline when compared to various intervals such as during surgery, post operatively and at follow up (p value>0.05). There was no significant difference between the pulse rate, blood pressure, PR interval, QRS duration and QT interval on intergroup comparison (p value > 0.05). In the present study, both the local anesthetic agents Bupivacaine and Ropivacaine did not produce any cardiovascular changes in patients receiving supraclavicular block using nerve locator.

KEYWORDS: ***Bupivacaine, Ropivacaine, pulse rate, blood pressure, PR interval, QRS duration, QT interval.***

INTRODUCTION

Regional anesthesia using long acting anesthetic agents is widely practiced method for anesthesia and pain management in surgeries. However, accidental intravascular injection or abnormal rapid absorption of local anesthetic agents from the site of administration results into systemic adverse reactions.[3] Systemic toxicity of local anesthetic agents involves the Central Nervous System (CNS) and Cardiovascular System (CVS) (Cox B et al. 2003; Dippenaar JM. 2009). Direct and indirect effects of local anesthetic agents on myocardium are responsible for the cardiovascular toxicity. Direct effect such as negative inotropy is due to decreased

released calcium release from sarcoplasmic reticulum, disturbance in Na^{+}/Ca^{+2} pump function, altered mitochondrial energy transduction and decreased cAMP production. Indirect effect of local anesthetics was due to blocking the impulse conduction from nucleus tractus solitarius located in the medulla oblongata (Cox B et al. 2003; Dippenaar JM. 2009). Racemic Bupivacaine, an amide local anesthetic belonging to the pipecoloxylidide group has been the most widely used longer acting local anesthetic agent. Bupivacaine induced cardiac toxicity is a concentration related phenomenon. It depresses the intra – atrial, AV nodal, intra – ventricular conduction and myocardial contractility in a concentration dependant manner due to its ability to block fast sodium channels in nerves and cardiac tissues (De Segura G et al. 2002; Ryu YH et al. 2007). Ropivacine is an enantiomerically pure (S – enantiomer), pipecoloxylidide and amide local anesthetic agent with a longer duration of action. Previous experimental and clinical studies have shown that Ropivacaine caused less prolongation of QRS duration and required higher doses in comparison with Bupivacaine to produce cardiac effects respectively (Scott DB et al. 1989; Groban L and Dolinski S. 2001; Kuthiala G et al. 2011). However, limited data was available comparing the cardiovascular safety of these drugs when administered by supraclavicular brachial plexus block method using nerve locator. The present study was conducted to compare the cardiovascular changes produced by equal volumes and concentration of Bupivacaine and Ropivacaine when administered by supraclavicular brachial plexus block using nerve locator in patients undergoing upper arm surgeries.

MATERIALS AND METHODS

Study design, screening, inclusion and exclusion criteria

This study was an open labeled, randomized, prospective clinical study involving 30 patients. Institute Ethics committee approval for conducting this study was obtained. This study was conducted in a tertiary set up in collaboration with orthopedic and anesthesia departments. Patients scheduled for elective upper arm surgery using supraclavicular block were selected after screening them for inclusion and exclusion criteria. These patients were evaluated by an anesthesiologist. Inclusion criteria for the selecting patients for study were adults equal to or above 18 years of age, either sex, scheduled for elective surgery to upper extremities, eligible for anesthesia using supraclavicular brachial plexus block, fulfilling American society of Anesthesiologist (ASA; 2014 available from www.asahq.org/resources/clinical-information/asa-physical-status-classification-system) physical status criteria I and II and those who were willing to give informed consent. Patients with concomitant illness such as diabetes or hypertension were allowed to continue their relevant medications. Patients were excluded from the study if they were suffering from any untreated chronic illness, abnormal ECG findings, suffering from cardiac and renal diseases, pregnant, lactating, bronchopulmonary disease, known allergy to study drugs, smoking or any other form of drug dependence.

Administration of Local anesthetics agents under study and study parameters

Following the screening procedure, 60 selected patients were randomized into two groups A and B using computer generated randomization chart. Group A and Group B patients received 40 ml injection of 0.5% concentration of Bupivacaine hydrochloride and Ropivacaine hydrochloride respectively. The baseline investigations of selected patients were done at the time of admission, after surgery and on follow up. Vital parameters such as pulse rate, blood pressure and respiratory rate as well as an electrocardiogram (ECG) parameters such PR interval QRS duration and QT interval were noted during admission, one hour before the surgery, while administering the drug, during surgery at regular intervals of 5 minutes, post operatively, one day after surgery and finally one week after surgery during follow up. On the day of surgery, patients were evaluated again and under aseptic conditions, the brachial plexus was identified at the supraclavicular region using Stimuplex nerve locator. On the appearance of muscle twitches at upper arm, the needle was fixed and 40ml study drugs were injected only after confirming that the needle was not intravascular. Use of pre anesthetic medications was allowed. Use of adrenaline along with local anesthetic drugs was not allowed. While injecting, the pulse rate and blood pressure were recorded. Following this the surgery was conducted after confirming the loss of sensory functions such as touch and complete loss of motor activity. The pulse rate and blood pressure were recorded every 5

minutes during the surgery till 40 minutes. Postoperatively, pulse rate, blood pressure and ECG parameters such as PR interval, QRS duration and QT interval were recorded. Similar recordings were taken after a week during follow up. Development of any adverse effects or symptoms during the period of study was recorded.

Analysis and Biostatistics

The pulse rate, systolic blood pressure and diastolic blood pressure, ECG parameters such as PR interval, QRS duration and QT interval obtained before the administration of study drugs were compared with the findings obtained during the time of administration, during the surgery, postoperatively and during follow up using paired "T" test to check for level of significance. The findings of group A were compared with group B with the help of unpaired "T" test. The difference in the values when compared were considered as significant if the p value obtained was less than 0.05, whereas, it was considered insignificant if the p value was more than 0.05.

RESULTS

In the present study, sixty patients were posted for elective upper arm surgeries were selected after the screening process. These patients were equally randomized to either group A (receiving Injection Bupivacaine 0.5%) or group B (receiving injection Ropivacaine 0.5%) using computer generated randomization technique. These baseline parameters didn't show any significant variations and all the baseline investigations were normal. Mean age of patients in group A was 38 years and in group B was 39 years.

Pulse rate

Mean pulse rate of patients of group A taken on admission, before the procedure, during procedure, post – operatively, next day of surgery and on follow up after one week of surgery are 73.2, 73.3, 73.2, 73.7, 74 and 74.4 respectively. The mean pulse rate in the group A increased after injecting Bupivacaine during procedure from 73.2 per minute up to 1 – week after surgery i.e. 74.4 per minute. However, on applying "paired T – test" between the baseline pulse rate i.e. before procedure and pulse rate at various intervals, there was no difference statistically ($P > 0.05$). Mean pulse rate of patients of group B taken on admission, before procedure, during procedure, post – operatively, next day of surgery and on follow up after one week of surgery are 72.8, 72.9, 72.8, 72.8, 72.8 and 72.8 respectively. The mean pulse rates of patients in group B taken at various intervals however did not changed statistically from the baseline pulse rates by applying "paired T – test" ($P > 0.05$). When the mean values of pulse rates of Group A and Group B were compared using 'unpaired t – test', there was no statistical significance ($P>0.05$). Table 1 shows the comparison of pulse rate at various intervals in both the groups A and B.

Table 1

Comparison of mean Pulse rate in both the Groups at various intervals

Pulse Rate (per minutes)	Group A (Mean ± S.D.)	Group B (Mean ± S.D.)	P Value #
On Admission	73.2 ± 6.1	72.8 ± 5.9	> 0.05
Before Procedure	73.3 ± 6.1 *	72.9 ± 5.4 *	> 0.05
During Procedure	73.2 ± 5.1 *	72.8 ± 5.8 *	> 0.05
Post operatively	73.7 ± 3.4 *	72.8 ± 4.5 *	> 0.05
1 – day after Surgery	74.0 ± 4.5 *	72.8 ± 5.2 *	> 0.05
1 – week after Surgery	74.4 ± 4.1 *	72.8 ± 5.6 *	> 0.05

(* - P value > 0.05; not significant)

Blood Pressure

Mean values of systolic blood pressure (in mm of Hg) in group A during admission, before surgery, after drug administration (after 5, 10, 15, 20, 30 and 40 minutes), post operatively, one day after surgery and one week after surgery were 128.1, 126.9, 125.8, 126.1, 125.7, 125.5, 124.7, 125.6, 127, 126.1 and 125.5 respectively. Mean values of diastolic blood pressure (in mm of Hg) in group A during admission, before surgery, after drug administration (after 5, 10,

15, 20, 30 and 40 minutes), post operatively, one day after surgery and one week after surgery were 77, 77.5, 77.5, 77, 76.8, 77.5, 77.1, 77.2, 77.2, 76.8 and 77.4 respectively. Mean values of systolic blood pressure (in mm of Hg) in group B during admission, before surgery, after drug administration (after 5, 10, 15, 20, 30 and 40 minutes), post operatively, one day after surgery and one week after surgery were 127.1, 127.2, 126.5, 126.2, 126.2, 126.2, 126.7, 126.3, 125.3, 125 and 125.1 respectively. Mean values of diastolic blood pressure (in mm of Hg) in group B during admission, before surgery, after drug administration (after 5, 10, 15, 20, 30 and 40 minutes), post operatively, one day after surgery and one week after surgery were 77, 77.3, 76.6, 76.7, 76.1, 77.5, 77.1, 77.4, 76.8, 77.1 and 76.4 respectively. It was observed that the blood pressure decreased in both the groups during the procedure, but on applying 'paired t – test' and compared the mean systolic and diastolic blood pressure values at each interval with the baseline value i.e. before surgery (126.9 mm Hg and 77.5 mm Hg for Group A; 127.2 mm Hg and 77.3 mm Hg for Group B respectively) within groups there was no statistical significance (P>0.05). When the mean values of systolic and diastolic blood pressures of Group A and Group B were compared using 'unpaired t – test', there was no statistical significance (P>0.05). Table 2 shows the comparison of mean systolic and diastolic blood pressure between group A and Group B.

Table 2

Comparison of mean Blood Pressure in both the Groups at various intervals

Intervals		Group A		Group B		P value#
		Mean sBP	Mean dBP	Mean sBP	Mean dBP	
Admission		128.1	77.0	127.1	77.0	> 0.05
Before Surgery		126.9	77.5	127.2	77.3	> 0.05
After Drug Administration	**5min**	125.8*	77.5*	126.5*	> 0.05	> 0.05
	10min	126.1*	77.0*	126.2*	> 0.05	> 0.05
	15min	125.7*	76.8*	126.2*	> 0.05	> 0.05
	20min	125.5*	77.5*	126.2*	> 0.05	> 0.05
	30min	124.7*	77.1*	126.7*	> 0.05	> 0.05
	40min	125.6*	77.2*	126.3*	> 0.05	> 0.05
Post operatively		127.0*	77.2*	125.3*	76.8*	> 0.05
1 day after Surgery		126.1*	76.8*	125.0*	77.1*	> 0.05
1 week after Surgery		125.5*	77.4*	125.1*	76.4*	> 0.05

*(sBP – systolic blood pressure; dBP – diastolic blood pressure; *P value > 0.05; Not significant statistically on comparison With respective baseline value in groups.#P value on intergroup comparison not significant.)*

ECG parameter (PR interval, QRS duration and QT interval)

PR interval in both the groups during the course of a study remained constant i.e. 0.16 mm, QRS interval remained constant (0.08 mm) in Group A during the course of study, whereas in group B the QRS interval decreased to 0.08 at post operative period but remained constant (0.08 mm) during rest of the study course. In Group A, QT interval remained constant (0.39 mm) throughout study, except after 1 – week of surgery where it increased to 0.40 mm. In Group B, QT interval remained constant (0.39 mm) but slightly increased at post operative period (0.40 mm).However on applying 'paired t – test', the mean PR interval, mean QRS interval and mean QT interval within both the groups did not differ significantly (P>0.05). On applying 'unpaired t – test', there was no statistical difference in the mean PR interval, mean QRS interval and mean QT interval between the two groups (P>0.05). Table 3 shows the comparison of ECG parameters at regular interval in both the groups. There were no adverse drug reactions reported by patients receiving either Bupivacaine or Ropivacaine.

Table 3

Comparison of mean values of PR interval, QRS duration and QT interval in both the Groups at various intervals

	Group A			Group B			P value#
	PR	QRS	QT	PR	QRS	QT	

Admission	0.16*	0.08*	0.39*	0.16*	0.09*	0.39*	> 0.05
Before Surgery	0.16*	0.08*	0.39*	0.16*	0.09*	0.39*	> 0.05
Post - operatively	0.16*	0.08*	0.39*	0.16*	0.08*	0.40*	> 0.05
1 day after Surgery	0.16*	0.08*	0.39*	0.16*	0.09*	0.39*	> 0.05
1 week after Surgery	0.16*	0.08*	0.40*	0.16*	0.09*	0.39*	> 0.05

(*P value > 0.05; not significant statistically on comparison with respective baseline value in groups.
#P value on intergroup comparison not significant.)

DISCUSSION

Local anesthetic agents have a prominent affect on central nervous system and cardiovascular system owing to its pharmacodynamic property of blocking peripheral fast voltage gated sodium channels on neuronal axons (Graf BM. 2001). Long acting local anesthetic agents such as Bupivacaine and Ropivacaine produces cardiac actions at higher concentration due to its ability to block voltage gated ion channels and intracellular enzyme systems, leading to reduced cardiac membrane potential and intracellular metabolism. The cardiovascular effects seen are reduced cardiac output, ventricular rhythm abnormalities, contractile failure, vasodilation and cardiovascular collapse at doses higher than the recommended therapeutic doses (Graf BM et al. 2002). In the present study, sixty patients were randomly and equally distributed in two groups. The baseline characteristics of both the groups were matched. Equal volume (40ml) and similar concentration (0.5%) of Bupivacaine hydrochloride and Ropivacaine hydrochloride were administered through supraclavicular brachial plexus block using nerve locator to facilitate the administration to the plexus proximity as much as possible. Use of adrenaline along with these local anesthetic agents were avoided as adrenaline is a sympathomimmetic drug and affect the basic study parameters.

Pulse rate

It was seen in the study that the mean pulse rate of patients in either group did not change significantly from the time of admission till after one week follow up. Slight rise in the mean pulse rate was observed in Bupivacaine group next day of surgery and after one week, but it was statistically insignificant (p value > 0.05). Inter group comparison also did not show any significant variation in the mean pulse rate from the day of admission till the completion of study (p value > 0.05). In a study conducted by Knudsen K et al (1997), it was seen that the pulse rate was increased by 12 % in subjects receiving both Bupivacaine and Ropivacaine which was highly significant. However, study involved healthy volunteers as study participants and the drugs were administered intravascularly (Knudsen K et al. 1997). In another study conducted by Hamaji A et al (2013), patients treated with Bupivacaine and Ropivacaine showed significant reduction in the pulse rate postoperatively when compared with preoperative value, but when compared with each other, the difference was insignificant. In the present study, despite an insignificant rise in the pulse rate in patients treated with Bupivacaine, the two groups didn't differ significantly with each other (p value > 0.05) (Hamaji A et al. 2013). However, this finding from present study was in accordance to the findings obtained in the study conducted by Kooloth RA et al (2015). In the present study, there was no significant difference in the mean blood pressure values before the administration of either study drugs when compared with the values after administration (p < 0.05). Intergroup comparison did not show any significant difference in the preoperative and postoperative values after administration of either drug (p > 0.05). This finding from present study is in accordance with the findings from a study conducted by Kooloth RA et al (2015). In the study conducted by Hamaji A et al (2013), rise in systolic and diastolic blood pressure was observed in patients administered with Ropivacaine. In the present study, it was observed that the ECG parameters such as PR interval, QRS duration and QT interval did not differ significantly in either group when comparison was made between before procedure mean values to after procedure mean values. Intergroup comparison of mean values before the procedure and after the procedure showed that ECG parameters such as PR interval, QRS duration and QT interval did not vary

significantly. These findings from the present study were not in agreement with findings from study conducted by Hamaji A et al (2013). It was seen that QRS duration was significantly reduced in patients administered Bupivacaine (p value < 0.001), however, intergroup comparison with Ropivacaine administered patients were not significant. There were few incidences of supraventricular arrhythmias reported in the study conducted by Hamaji A et al (2013).

CONCLUSION

The present study concludes that long acting amide local anesthetic agents Bupivacaine and Ropivacaine when administered in patients undergoing upper arm surgery under supraclavicular brachial plexus block using nerve locator at equal volume and concentration did not affect cardiovascular activity.

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