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SCIENTIFIC ARTICLE

Comparative Study Related to Cardiovascular Safety between Bupivacaine (S75-R25) and Ropivacaine in Brachial Plexus Block

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Abstract

Background and objectives: Bupivacaine is a first choice for regional anesthesia considering its effectiveness, long duration and less motor blockade. Bupivacaine (S75-R25) is a mixture of optical isomers containing 75% levobupivacaine (S-) and 25% dextrobupivacaine (R+) created by a Brazilian pharmaceutical company. This investigation compared cardiac safety and efficacy of bupivacaine S75-R25 with vasoconstrictor and ropivacaine for brachial plexus blockade.

Methods: Patients were randomized to receive brachial plexus anesthesia with either bupivacaine S75-R25 with epinephrine 1:200,000 (bupi) or ropivacaine (ropi), both at 0.50%, in 30 mL solution. We registered a continuous Holter ECG throughout the procedure, as well as the Lovett scale of force in addition to monitoring (heart rate, pulse oximetry and non-invasive blood pressure). The incidence of adverse events was compared with the chi-square or Fisher test.

Results: We allocated forty-four patients into two groups. They did not show any difference related to age, weight or height, gender, as well as for surgical duration. Supraventricular arrhythmias were not different before or after the plexus blockade, independent of the local anesthetic chosen. Loss of sensitivity was faster for the bupivacaine group (23.1 ± 11.7 min) compared to the ropivacaine one (26.8 ± 11.5 min), though not significant (p = 0.205, Student *t*). There was a reduction in the cardiac rate, observed during the twenty-four-hour Holter monitoring.

Conclusions: This study showed similar efficacy between bupivacaine S75-R25 for brachial plexus blockade and ropivacaine, with similar incidences of supraventricular arrhythmias.

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Introduction

Bupivacaine has an asymmetric or chiral carbon that gives it the property of optical isomers, the form R(+) or dextrorotatory and the form S(-) or levorotatory. Local anesthetics formulated with bupivacaine use a racemic mixture with 50% of each of the isomers. Due to its widespread use, there were reports of important cardiac and neurological toxicity that took place mostly from accidental intravascular injections [1].

Drug research introduced two comparable levorotatory compounds, the levobupivacaine isomer, a purified (S-) bupivacaine, and the ropivacaine. Clinical studies showed similar efficacy of sensory block for the sciatic nerve [2,3], spinal blockade [4-6], and epidural [7,8], both in intensity and duration when comparing levobupivacaine with racemic bupivacaine. However, its motor blockade seemed inferior [8]. Ropivacaine, on the other hand, appears to have slightly lower anesthetic potency than levobupivacaine or the racemic bupivacaine, including a lower motor blockade [8]. Ropivacaine reached the equivalence of levobupivaine in interscalene brachial plexus block [9], and sciatic nerve [3,10]. Its cardiac and neurological toxicity are apparently lower than the other two anesthetics [11,12]. Lethal intravenous doses of levobupivacaine and ropivacaine in pigs were equivalent and about two times higher than racemic bupivacaine [13]. The cardiac toxicity induced by intracoronary injection in sheep was similar for the three drugs [14]. These three drugs produced a QRS widening in isolated rabbit hearts, and the racemic bupivacaine was 2 to 3 times more toxic [15]. Also, ropivacaine required a higher dose to induce asystole in rats [16].

Levobupivacaine and ropivacaine are less neurotoxic than racemic bupivacaine in producing seizures in rats [16,17]. In sheep, the seizure threshold is always lower among the pregnant animals. Ropivacaine is safer than levobupivacaine, which in turn is safer than bupivacaine [18].

Although *in vitro* studies have shown that the two isomers of bupivacaine are equipotent in promoting motor block [19], the dextrorotatory form is more potent than the levorotatory in inhibiting sodium channels [20], which justifies a reduced motor block when using the mixture with a higher concentration of the isomer (S-). Brazilian pharma introduced an enantiomeric mixture of optical isomers containing 75% of levobupivacaine (S-) and 25% of dextrobupivacaine (R+), a bupivacaine (S75-R25). Studying the effectiveness of levobupivacaine and the bupivacaine (S75-R25) in epidural anesthesia, we found a reduction in the incidence of cardiac and neurological adverse events and the adequacy of sensory and motor blockade [21,22].

This study compared cardiac safety and efficacy of anesthetic bupivacaine S75-R25 with vasoconstrictor and ropivacaine for brachial plexus blockade (BPB) for upper limb surgery, considering the technique may infuse large doses of local anesthetic.

Methods

After approval from the Ethical Review Board, patients of both sexes aged between 18 and 40 years with an indication for elective unilateral forearm, wrist or hand procedures were invited to participate. They constituted a convenience sample with group allocation determined by a computerized table to receive either bupivacaine S75-R25 (bupi group) or ropivacaine (ropi group).

According to the American Society of Anesthesiologists (ASA), all patients were considered ASA I or II. Those showing local anesthetic hypersensitivity, intolerance or allergy to any of the drugs used in this protocol, as well as patients with multiple trauma or acute injuries like spinal cord injuries, peripheral neuropathy or other neurological disorders were excluded. Exclusion criteria have also been myocardial infarction less than 6 months prior, dementia and other cognitive matter, abuse of alcohol and antiretroviral drug use. We excluded patients who signed the consent but would show any significant changes in the baseline Holter monitoring, an hemoglobin < 10 $g.dL^{-1}$, leukocytosis higher than 14,000; an INR > 1.3, persistent atrial fibrillation or the presence of ventricular extrasystoles.

We used the "Holter" ECG GE model MARS 5000. The Visual Analog Scale (VAS) for pain assessed patients in the postoperative [23,24]. The Lovett scale of force was used to assess strength, based on subjective evaluation with 6 degrees (6 – Normal: force; 5 - Good: muscle wins gravity but strength is reduced; 4 - Reasonable: the muscle is able to overcome gravity and perform partially normal movements; 3 - Weak: small movements can be executed but do not win gravity; 2 - Trait: there is muscle contraction but no movement; 1 - Paralysis: no contraction or movement is observed).

After the consent and one week before patients collected laboratory exams, a resting ECG was registered and they were placed in Holter monitoring (preop) to capture a baseline tracing. The perioperative Holter monitoring (postop) was installed in the operating room. We used the following monitoring devices: pulse oximeter, non-invasive arterial pressure monitor and electrocardiography. A nasal cannula for administration of oxygen (2 $L.min^{-1}$) was offered. Patients received midazolam 0.05 to 0.3 $mg.kg^{-1}$ (maximum at 15 mg) intramuscular before the procedures.

The axillary artery was identified by palpation, followed by the insertion of the electrically isolated needle on the medial side of the arm in a 45-degree angle to the skin. Electrical stimulation pulses with a duration of 0.1 - 0.2 ms, frequency 1 to 2 Hz were used to promote motor response in order to guide the progression and direction of the needle. After the identification of suitable location for the injection of local anesthetics in territories of nerves radial, median and musculocutaneous, a test for the prevention of intravascular injection with 3 mL of sodium chloride with 15 mcg of adrenaline was done.

Patients received an infiltration of 30 ml of anesthetic - either the bupivacaine S75-R25 solution at 0.50% (bupi) or ropivacaine at 0.50% (ropi), according to protocol selection of unidentified ampoules. These were prepared as 20 mL of ropivacaine and 20 mL of bupivacaine S75-R25 with epinephrine 1:200,000, that remained sealed throughout the study and were open only after collecting all information from medical records. Whenever a partial failure was detected, the protocol allowed the use of fentanyl 1 $mcg.kg^{-1}$ and a continuous target-infusion of propofol of up to 3 $mcg.mL^{-1}$, both intravenously. In the case of total failure, the procedure would be directed to general anesthesia.

The following parameters were evaluated every five minutes: skin conductance by patch clamping, motor blockade (Lovett), heart rate, blood pressure and hemoglobin saturation (oximeter). After 30 minutes of blockade infiltration, if there was a partial or total failure of anesthesia, the anesthesiologist had to decide the procedure to be adopted and the data collected were discarded as not suitable for the investigation. Patients received 100 mg of ketoprofen and 2,000 mg of dipyrone right after the end of surgery and tramadol 100 mg was prescribed on demand. They were assessed after six and 24 hours of injection of the anesthetic, when the Holter was removed and the patient questioned about adverse events and tolerability.

Statistical analysis was done using STATISTICA version 5.0 (Statsoft Inc, Tulsa, USA) with a significance level of 0.05. Quantitative variables are represented by mean and standard deviation, median and minimum and maximum values, compared by analysis of variance with repeated measures. We represent qualitative variables such as incidence of adverse events with absolute (n) and relative (%) numbers, compared using the chi-square or Fisher test.

Results

Forty-four patients signed the informed consent and were allocated into the two groups. They did not show any difference related to age, weight, height, or gender nor in surgical duration (Table 1). The procedures performed - arthrodesis and arthroplasty, neurolysis, Kirschner wire removal, tenolysis, fracture fixation and carpal tunnel release surgery - were fairly distributed among the two groups. Both groups lost one patient's data due to inappropriate Holter records.

All patients showed responses related to electrical stimulation of nerves radial, median and musculocutaneous. They have their heart rate reduced from preoperative measurements compared to surgery under the brachial plexus blockade ($p < 0.0001$), a reduction that was not different between the groups ($p = 0.997$). The number of QRS complex was also reduced ($p < 0.0001$) from preoperative during the surgery, but was not different between the groups ($p = 0.585$). Independent of which local anesthetic was used, the number of supraventricular arrhythmias was not different before or after the plexus blockade. The differences among these results showed a lower heart rate, a lower maximum heart rate, a reduced number of QRS. The number of supraventricular arrhythmias remained the same (Table 2).

The loss of sensitivity was faster for the bupivacaine (23.1 ± 11.7 min) compared to the ropivacaine group (26.8 ± 11.5 min), though not significant ($p = 0.205$, Student *t*). Motor blockade was significantly lower (better level of block) among patients under bupivacaine from the 35th minute and beyond. Two patients from the bupivacaine group and four from the ropivacaine experienced insufficient anesthetic blockade ($p = 0.66$, Chi-square), receiving propofol (bupivacaine, n = 7; ropivacaine, n = 3) and/or fentanyl (bupivacaine, n = 4; ropivacaine, n = 1). Four patients from the bupivacaine

Table 1 – Patient characteristics and surgery duration (min) (mean ± SD).

	Bupivacaine S75-R25 (n = 22)	Ropivacaine (n = 22)	p value
Age	40.6 ± 11.4	40.9 ± 11.3	0.936*
Weight	78.7 ± 19.2	72.6 ± 15.5	0.254*
Height	1.70 ± 0.10	1.60 ± 0.10	0.070*
BMI	27.6 ± 6.7	27.1 ± 5.6	0.795*
Surgery duration	74.5 ± 51.8	94.5 ± 53.1	0.211*
Gender (male/female)	9/13	7/15	0.754**

*Student t; ** Chi-Square.

Table 2 – Holter (mean ± SD).

		Bupivacaine S75-R25 (n = 21)	Ropivacaine (n = 21)	p value
Heart rate	preoperative	81.3 ± 10.7	84.9 ± 9.4	0.997
	postoperative	72.4 ± 8.0	68.5 ± 10.9	
		P < 0.0001		ANOVA
QRS (n)	preoperative	4,660.5 ± 545.6	4,726.3 ± 541.3	0.585
	postoperative	4,277.2 ± 502.8	4,037.1 ± 668.3	
		p < 0.0001		ANOVA
SV arrhythmias (n)	preoperative	2.0	0.0	0.659
	postoperative	1.0	1.0	0.163
		p = 0.139	p = 0.916	M-W
	Pre-Intra Diff			M-W
Heart Rate		8.9 ± 7.3	19.3 ± 9.1	0.005
Maximum HR		14.3 ± 10.8	18.1 ± 7.7	0.045
QRS		383.3 ± 357.9	689.2 ± 590.2	0.045
SV arrhythmias		-3.7 ± 8.8	-0.1 ± 4.6	0.339

SV: Supraventricular; M-W: Mann-Whitney; HR: heart rate; Diff: difference.

Table 3 – Brachial Blockade findings (mean ± SD) (median [min-max]).

	Bupivacaine S75-R25 (n = 22)	Ropivacaine (n = 22)	p value
Loss of sensitivity (min)	23.1 ± 11.7	26.8 ± 11.5	0.205*
Lovett scale	2.8 ± 1.1	2.1 ± 0.9	0.032*
	3.0 [1-5]	2.0 [1-4]	0.070*
Insufficient blockade (n)	2	4	0.660**
Propofol, total infusion range (mg)	50-250	20-100	
Fentanyl, total infusion range (mcg)	50-100	50-100	
Tramadol (n)	4	7	0.486**

*Student *t*; ** Chi-Square.

group requested tramadol during the postoperative period, whereas seven did so in the ropivacaine group (p = 0.48, Chi-square) (Table 3).

Discussion

This study showed a similar efficacy of bupivacaine S75-R25 with epinephrine and ropivacaine in brachial plexus block, without a higher incidence of supraventricular arrhythmias and a reduced cardiac rate during a 24-hour Holter monitoring.

Although the advantages of upper extremity blockade are well established, the cardiotoxicity is, perhaps, the most severe complication associated with the use of long-acting local anesthetics. A previous study of interscalene BPB with patients under a holter monitoring showed prolongation of PQ interval with racemic bupivacaine, but not with ropivacaine [25]. Also, no cardiovascular toxicity – such as changes in QRS complex, PQ interval and AV dissociation – was registered with a combination of prilocaine and ropivacaine in the blockade [26].

The anesthetic efficacy of levobupivacaine in BPB has been reportedly similar to the racemic bupivacaine for latency, failure rate, and motor blockade [27]. In addition, both anesthetics offered prolonged postoperative analgesia compared to ropivacaine for BPB and for femoral nerve block, although ropivacaine block installed faster [28]. Notwithstanding, the literature seems to have no register of studies addressing cardiovascular toxicity with levobupivacaine during a brachial plexus blockade.

This report showed that both bupivacaine S75-R25 and ropivacaine had a comparable mean time to promote anesthesia. The motor blockade reached the "trace" level in the Lovett scale (evidence of slight contractility) faster with ropivacaine. This finding was in accordance with a previous report suggesting ropivacaine to be a faster anesthetic drug [28], and with a slightly better sensory as well as motor blockade than levobupivacaine, while duration was similar [29].

Four patients that received ropivacaine and two that received bupivacaine S75-R25 had partial incomplete blockade. All of them were treated with 100 mcg of fentanyl intravenously and a target-infusion propofol. Compared to the bupivacaine S75-R25 blockade (8.9 ± 7.3), patients in the ropivacaine group also showed a higher reduction in cardiac rate during surgery in relation to the preoperative measurement (19.3 ± 9.1). It is also interesting to notice that both systolic (136.8 ± 17.4 *vs* 126.7 ± 16.2) and diastolic pressure (76.9 ± 11.8 *vs* 69.1 ± 8.7) were higher with ropivacaine. These results suggest that both ropivacaine and bupivacaine S75-R25 are good options for BPB having the advantage of a low cardiotoxicity. They may also be adequate for hypertensive patients, since regional anesthesia could prevent the "tourniquet hypertension", although ropivacaine may otherwise bring some additional risk of not counteracting this phenomenon [30,31].

Finally, a limitation in this research was the lack of follow-up for analgesia duration with the use of a visual analogic scale. Nevertheless, a previous study with equal masses of ropivacaine and levobupivacaine suggested the latter may reach a greater duration of sensory analgesia - up to 15 hours - but with a longer motor blockade [32]. There was no consumption of non-steroidal analgesics during post-anesthesia care unit, as well as no register of post-operative nausea or vomiting, even with a similarly lower demand for tramadol.

In conclusion, this study suggests both bupivacaine S75-R25 and ropivacaine were not associated with cardiac toxicity during brachial plexus blockade within 24 hours of surveillance, but it seems advisable to point out that ropivacaine should be under careful consideration for hypertensive patients.

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