A multicentre trial of ropivacaine 7.5 mg·ml^{-1} *vs* bupivacaine 5 mg·ml^{-1} for supra clavicular brachial plexus anesthesia

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Purpose: To compare the efficacy of ropivacaine 7.5 mg·ml^{-1} with bupivacaine 5.0 mg·ml^{-1} for subclavian perivascular brachial plexus block.

Methods: After informed consent, 104 ASA I-III adults participated in a randomized, double-blind, multi-center trial to receive 30 ml of either ropivacaine 7.5 mg·ml^{-1} or bupivacaine 5.0 mg·ml^{-1} for subclavian perivascular brachial plexus block prior to upper limb surgery. Onset and duration of sensory and motor block in the distribution of the axillary, median, musculo-cutaneous, radial and ulnar nerves were assessed.

Results: Onset times and duration of sensory and motor block were similar between groups. Mean duration of analgesia for the five nerves was between 11.3 and 14.3 hr with ropivacaine and between 10.3 and 17.1 hr with bupivacaine. Quality of muscle relaxation judged as excellent by the investigators was not significantly different (ropivacaine - 35/49, bupivacaine - 30/49). The median time to first request for analgesia was comparable between the two groups (11-12 hr). One patient developed a grand mal seizure shortly after receiving bupivacaine and recovered consciousness within 30 min. There were no serious adverse events in the ropivacaine group.

Conclusions: Thirty ml ropivacaine 7.5 mg·ml^{-1} (225 mg) produced effective and well tolerated brachial plexus block of long duration by the subclavian perivascular route. In this study, the results were similar to those of 30 ml bupivacaine 5.0 mg·ml^{-1}.

Objectif : Comparer l'efficacité de 7,5 mg·ml^{-1} de ropivacaïne avec 5,0 mg·ml^{-1}de bupivacaïne dans le cas d'un blocage périvasculaire sous-clavier du plexus brachial.

Méthode : Ayant été bien informés, 104 adultes ASA I-III ont consenti à participer à un essai multicentrique, randomisé et en double aveugle et ont reçu 30 ml de ropivacaïne 7,5 mg·ml^{-1} ou de bupivacaïne 5,0 mg·ml^{-1} pour un blocage périvasculaire sous-clavier du plexus brachial, précédant une intervention au membre supérieur. On a noté le début et la durée du blocage sensitif et moteur selon la distribution des nerfs axillaire, médian, musculo-cutané, radial et cubital.

Résultats : Le début et la durée du blocage sensitif et moteur ont été similaires dans les deux groupes. La durée moyenne de l'analgésie pour les cinq nerfs se situait entre 11,3 et 14,3 h avec la ropivacaïne et entre 10,3 et 17,1 h avec la bupivacaïne. La qualité du relâchement musculaire, jugée excellente par les chercheurs, n'a pas présenté de différence intergroupe significative (ropivacaïne - 35/49, bupivacaïne - 30/49). Le temps moyen écoulé jusqu'à la première demande d'analgésique a été comparable également (11-12 h). Un patient a subi une crise d'épilepsie peu après avoir reçu la bupivacaïne et est redevenu conscient en moins de 30 min. Il n'y a pas eu d'incident défavorable important dans le groupe ropivacaïne.

Conclusion : Trente millilitres de ropivacaïne 7,5 mg·ml^{-1} (225 mg) ont produit un blocage du plexus brachial efficace, de longue durée et bien toléré, par voie périvasculaire sous-clavière. Les résultats ont été similaires à ceux de 30 ml de bupivacaïne 5,0 mg·ml^{-1}.

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Funded by a research grant from Astra Pharma Inc.

Accepted for publication July 10, 1999

ROPIVACAINE is a new long-acting local anesthetic available as a pure S-enantiomer. It exhibits less CNS and cardio-toxicity[1-2] than bupivacaine and is effective when used for brachial plexus anesthesia.[3-4] Brachial plexus block with a solution of ropivacaine 2.5 mg·ml^{-1} frequently required supplementation[4] while ropivacaine 5.0 mg·ml^{-1} was comparable to bupivacaine 5.0 mg·ml^{-1}.[3] We hypothesized that a further increase in the ropivacaine dose would result in increased efficacy and duration for brachial plexus anesthesia.

This study investigated the efficacy of ropivacaine 7.5 mg·ml^{-1} compared with bupivacaine 5.0 mg·ml^{-1} for brachial plexus blocks.

Methods

Five centres participated in this randomised, double blind, parallel group study. After institutional review board approval and informed consent 104 adults scheduled for elective orthopedic surgery of the hand or arm were studied. All patients had a routine physical examination and baseline ECG performed within 14 days of surgery. Inclusion criteria were: ASA I-III, age 18-75 yr and weight 50-100 kg. Exclusion criteria were: allergy to study medications, contraindication to brachial block, heart conduction block, significant neurological disease in the arm, advanced diabetes with neurological signs, renal disease, psychiatric history, inability to comply with the study assessments and pregnancy. Patients who met the inclusion criteria were randomised to receive a subclavian perivascular brachial plexus block with 30 ml ropivacaine 7.5 mg·ml^{-1} or 30 ml bupivacaine 5 mg·ml^{-1} (Astra Pharma Inc, Mississauga, Ontario, Canada). Upon arrival in the operating room/ block room, an intravenous infusion was established and standard monitors (ECG, BP, and oximeter) were applied. Premedication consisted of 1-2 mg midazolam *iv* and/or 50-100 µg fentanyl *iv* administered as necessary. The patient was placed in the dorsal recumbent position with the head turned away from the site of injection. Lidocaine was used for skin infiltration prior to block placement at the discretion of the anesthesiologist. The block was performed according to the method described by Winnie.[5] A 22-25 gauge, short bevel needle was employed and as soon as paresthesia below the shoulder was obtained, following aspiration, a test dose of 2-4 ml of the study drug was injected rapidly to elicit 'pressure paresthesia' and thereby confirm proper needle placement. In some centres, a nerve stimulator was used to locate the brachial plexus employing single nerve localization with the threshold current of 0.5 to 1.0 mA (Table II). The remaining 26-28 ml of the study drug were then injected slowly in an incremental fashion and the needle withdrawn.

Assessment of motor function was performed before the block and every 10 min after injection for up to 50 min. Surgery commenced as soon as pin prick analgesia was established in the operative field.

TABLE I Demographic data (mean ± SD)

Variable	*Ropivacaine Group (n=52)*	*Bupivacaine Group (n=51)*
Age (yr)	46 ± 15	51 ± 16
Height (cm)	170 ± 9	168 ± 10
Weight (kg)	74 ± 13	73 ± 13
Sex (M/F)	32/20	23/28
ASA (I/II/III)	22/25/5	13/32/6

TABLE II Anesthetic technique for brachial plexus block performance and location of paraesthesia. (More than one can be selected)

	Ropivacaine Group (n=49)	*Bupivacaine Group (n=49)*
Method of plexus identification:		
Paraesthesia	20	23
Pressure parasthesia	4	4
Nerve stimulator	29	25
Other	2	-
Location of paraesthesia:		
Below shoulder	22	18
Median area	18	19
Ulnar area	15	11
Radial area	21	21
Other	9	7

TABLE III Median amounts of adjunctive medications given during surgery (Fentanyl= µg·hr^{-1}; midazolam= mg·hr^{-1}; propofol= mg·hr^{-1}).

Therapy	*Dose Median(Range)*	*Group*	*N*	
Fentanyl	0-100	Ropivacaine	12	46(16-98)
		Bupivacaine	14	48(12-69)
	>100-200	Ropivacaine	1	157(157-157)
Midazolam	0-5	Ropivacaine	6	0.9(0.5-3.5)
		Bupivacaine	4	0.9(0.2-1.0)
	>5-10	Ropivacaine	2	8.3(7.9-8.7)
	>10	Bupivacaine	1	18(18-18)
Propofol	0-100	Ropivacaine	5	57(25-64)
		Bupivacaine	3	37(32-100
	>100-200	Ropivacaine	1	138(138-138)
		Bupivacaine	4	132(106-160)
	>200	Ropivacaine	3	228(225-240)
		Bupivacaine	2	653(533-774)

Sensory and motor assessments were continued at 4,6,8,10,13,16,19 and 22 hr after injection or until the block completely regressed. Sensory block was evaluated by pin prick using a blunt 20 G dental needle in the cutaneous areas supplied by the axillary, radial, ulnar, musculo-cutaneous and median nerves. Motor block of the same nerves was graded on a scale of 0-2 (0= no block, 1= partial block, 2= full motor block). The quality of analgesia and muscle relaxation was assessed by the surgeon and investigator at the end of surgery as excellent, satisfactory or unsatisfactory. The presence or absence of tourniquet pain was also recorded when a pneumatic tourniquet was used. If adequate analgesia did not occur in the area of surgery at 50 min, the patient was to be given general anesthesia. In order to standardise adjunctive medications during surgery, propofol and midazolam were allowed for sedation and fentanyl for breakthrough pain. Local supplementation was not permitted because of the risk of confusing postoperative sensory assessments of the block.

Other assessments included heart rate and blood pressure before block placement and at 10 min intervals after injection until 60 min. Thereafter, measurements were recorded every 30 min for up to four hours. All adverse events were also documented.

All data were entered into a spread sheet database and analyzed by Astra Pharma Inc using SAS^R. Efficacy variables, block onset, duration and regression were compared using survival function (Kaplan-Meier). Differences between groups were estimated using confidence intervals (bootstrap method) and the log-rank test. A P value of <0.05 was considered significant. The sample size was based on the confidence interval width of 10-15 min for the median time to onset of analgesia with ropivacaine for each nerve.[3] It was assumed that the present study would have the same underlying variability of medians and a 95% confidence interval for the difference between the medians of approximately 20.5. In order to have an expected width of approximately 16 min for such an interval, 50 patients in each treatment group were required.

Results

A total of 104 patients were randomised (ropivacaine group=53, bupivacaine group=51). Four patients were deleted from the ropivacaine group (three due to technical failure and one for not receiving any medication) and two from the bupivacaine group (one technical failure and one adverse event) leaving 49 completed patients per group. Patient demographic data are summarized in Table I. All patients underwent elective hand surgery and the median durations

TABLE IV Onset and duration of sensory block (mean ± SD)

Variable	*Ropivacaine group*	*Bupivacaine group*
Onset analgesia (min)		
Axillary nerve	13 ± 11	15 ± 12
Median nerve	12 ± 12	12 ± 8
M-cutaneous nerve	11 ± 10	13 ± 10
Radial nerve	11 ± 9	12 ± 9
Ulnar nerve	9 ± 6	13 ± 10
Onset anesthesia (min)		
Axillary nerve	21 ± 10	23 ± 14
Median nerve	18 ± 10	25 ± 16
M-cutaneous nerve	18 ± 11	22 ± 15
Radial nerve	16 ± 10	21 ± 14
Ulnar nerve	19 ± 11	23 ± 16
Duration anesthesia (hr)		
Axillary nerve	8 ± 4	9 ± 5
Median nerve	9 ± 3	11 ± 4
M-cutaneous nerve	10 ± 3	12 ± 5
Radial nerve	10 ± 3	12 ± 4
Ulnar nerve	9 ± 3	11 ± 5
Duration analgesia (hr)		
Axillary nerve	11 ± 5	12 ± 7
Median nerve	14 ± 5	15 ± 6
M-cutaneous nerve	14 ± 6	15 ± 7
Radial nerve	14 ± 6	16 ± 6
Ulnar nerve	14 ± 4	14 ± 7

M-cutaneous = Musculocutaneous nerve

TABLE V Onset and duration of motor block (mean ± SD)

Variable	*Ropivacaine group*	*Bupivacaine group*
Onset partial block (min)		
Axillary nerve	7 ± 4	9 ± 6
Median nerve	10 ± 8	14 ± 11
M-cutaneous nerve	8 ± 7	10 ± 9
Radial nerve	9 ± 6	11 ± 9
Ulnar nerve	9 ± 7	12 ± 9
Onset complete block (min)		
Axillary nerve	14 ± 10	19 ± 13
Median nerve	16 ± 10	23 ± 15
M-cutaneous nerve	15 ± 11	20 ± 12
Radial nerve	15 ± 10	18 ± 11
Ulnar nerve	13 ± 7	18 ± 14
Duration complete block (hr)		
Axillary nerve	11 ± 4	12 ± 4
Median nerve	10 ± 3	12 ± 4
M-cutaneous nerve	12 ± 3	14 ± 3
Radial nerve	11 ± 3	14 ± 5
Ulnar nerve	10 ± 3	12 ± 4
Duration partial block (hr)		
Axillary nerve	14 ± 5	16 ± 5
Median nerve	13 ± 3	15 ± 6
M-cutaneous nerve	14 ± 5	16 ± 5
Radial nerve	14 ± 4	17 ± 5
Ulnar nerve	14 ± 4	15 ± 6

M-cutaneous = Musculocutaneous

TABLE VI Quality of analgesia, muscle relaxation and tourniquet pain as assessed by investigator

Variable	*Ropivacaine group (n=49)*	*Bupivacaine group (n=49)*
Analgesia		
Excellent	33	26
Satisfactory	2	6
Unsatisfactory	14	17
Muscle relaxation		
Unassessed	0	1
Excellent	35	30
Satisfactory	2	4
Unsatisfactory	12	14
Tourniquet pain		
Unassessed	15	18
Absent	31	25
Present	3	6
Time to tourniquet pain(hr)*	(n=3) 2(0.6-2.3)	(n=6) 1.6(1.2-2.6)
Time to first analgesia request (hr)*	(n=44) 11(1.7-19.5)	(n=41) 12.2(2.4-25.2)

* Median (Range)

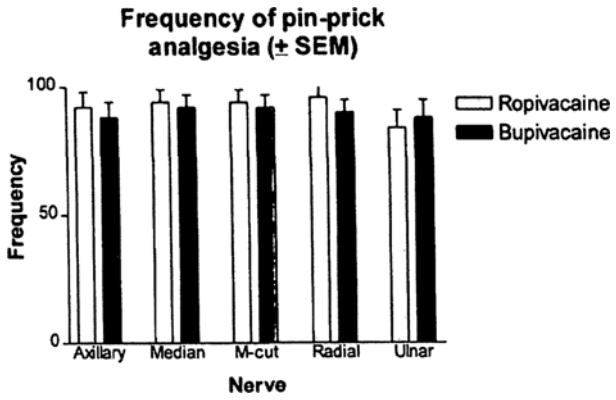

FIGURE 1 The frequency of analgesia was higher than 84% in all five nerves and did not differ between the two local anesthetic agents. (M-cut = musculocutaneous)

were 73 and 67 min for the ropivacaine and bupivacaine groups respectively. Anesthetic techniques for the brachial plexus block and location of paresthesia are summarized in Table II. The entire study drug was injected in both groups over a median time of three minutes. The overall use of adjunctive sedatives/analgesics (midazolam, fentanyl and propofol) was similar in both groups (Table III). Conversion to general anesthesia was required in 14 patients in the ropivacaine group and nine patients in the bupivacaine group. Onset and duration of sensory block (Table IV) and motor block (Table V) were not different between the two groups. The frequency of patients with a complete sensory or motor block was also not different between groups (Figures 1-3). There was no difference in the quality of muscle relaxation, analgesia and tourniquet pain (Table VI). The median time to first analgesic request was 11 and 12 hr in the ropivacaine and bupivacaine groups respectively, and, was not different. Both groups were also similar with respect to blood pressure and pulse measurements.

The most common adverse events were nausea (ropivacaine - 33%, bupivacaine - 28%), vomiting (ropivacaine - 8%, bupivacaine - 14%) and Horner's syndrome (ropivacaine - 8%, bupivacaine - 6%). One male, ASA I patient aged 30 yr (weight: 77 kg, height: 162 cm) in the bupivacaine group developed a grand mal seizure eight minutes after study drug injection suggestive of systemic toxicity. There was no blood aspirated prior to drug injection and with supramaximal electrical stimulation, biceps twitching was evident during injection. The patient was treated with 6 mg midazolam *iv* and the airway was supported with an oral airway and bag-mask ventilation. Spontaneous respiration was restored in five minutes and the patient regained consciousness in 30 min. At the time of the seizure, the patient was monitored with ECG which showed sinus tachycardia. A 12 lead ECG was not done since there was no sign of ventricular arrhythmia and the hemodynamics were not affected. The patient made a full recovery without residual side effects.

Discussion

This study compared the efficacy of 30 ml ropivacaine 7.5 $mg \cdot ml^{-1}$ with 30 ml bupivacaine 5.0 $mg \cdot ml^{-1}$ for subclavian perivascular brachial plexus block (SPBPB). Both agents were found to have similar effects, with no differences in terms of onset and duration of sensory analgesia and anesthesia, and, partial and complete motor block. The frequency of adverse events was also identical but one patient in the bupivacaine group developed a grand mal seizure that was causally related to injection of the local anesthetic. There were no serious adverse events in the ropivacaine group.

Previous studies have demonstrated that 0.5% solutions (175 mg) of ropivacaine and bupivacaine are equally effective for subclavian perivascular brachial plexus anesthesia.[3] It is recognized that volumes of at least 40 ml of local anesthetic are more commonly used when performing a SPBPB.[4,5] In the present study a volume of 30 ml of local anesthetic was chosen by consensus in order to ensure that the study did not expose patients in the lower weight ranges to an unacceptably

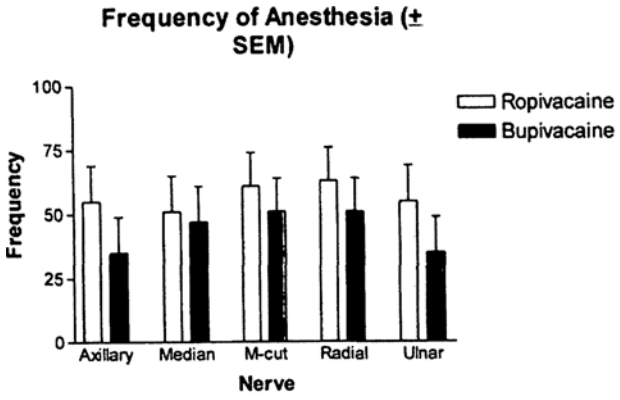

FIGURE 2 The frequency of surgical anesthesia was between 51% to 63% in the ropivacaine group and between 35% to 51% in the bupivacaine group and did not differ. (M-cut = musculocutaneous)

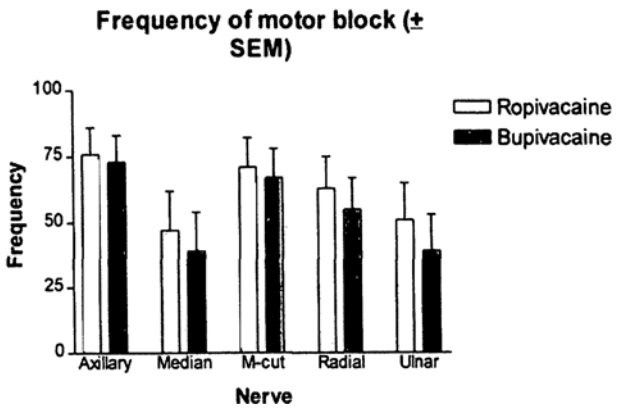

FIGURE 3 The frequency of motor block ranged from 47% to 76% in the ropivacaine group and from 39% to 73% in the bupivacaine group and was not different. (M-cut = musculocutaneous)

high dose of bupivacaine and to facilitate blinding. Such limitations did not allow us to explore fully the greater margin of safety of ropivacaine by employing at least 40 ml of solution. Future studies in this area may be needed to explore the safety and efficacy of ropivacaine to a fuller extent by employing 40 ml of the 7.5 $mg \cdot ml^{-1}$ or, possibly, the 10 $mg \cdot ml^{-1}$ solutions.

When compared with earlier studies[3] with 32 ml ropivacaine 5 $mg \cdot ml^{-1}$, the differences in efficacy were relatively small. The mean onset times for analgesia and anesthesia with ropivacaine 7.5 $mg \cdot ml^{-1}$ were 9-13 min and 16-21 min respectively. Comparable times reported for ropivacaine 5 $mg \cdot ml^{-1}$ were 8-15 min and 13-28 min when used for SPBPB.[3] The mean duration of sensory block with ropivacaine 7.5 $mg \cdot ml^{-1}$ in the present study was 11-14 hr and that reported for ropivacaine 5 $mg \cdot ml^{-1}$ was 13-14 hr.[3] The mean times to onset and duration of motor block with ropivacaine 7.5 $mg \cdot ml^{-1}$ in this study were 7-10 min and 13-14 hr respectively while comparable times reported for ropivacaine 5.0 $mg \cdot ml^{-1}$ were 3-11 min and 13-14 hr. Thus, this historical comparison indicated that ropivacaine 7.5 $mg \cdot ml^{-1}$ provided a similar efficacy to ropivacaine 5.0 $mg \cdot ml^{-1}$ when administered for SPBPB. More recently, our findings have been confirmed for interscalene brachial plexus block using 30 ml ropivacaine 5.0 $mg \cdot ml^{-1}$, ropivacaine 7.5 $mg \cdot ml^{-1}$ or bupivacaine 5.0 $mg \cdot ml^{-1}$ by Klein *et al.* [6] Onset time to motor and sensory block was <6 min in all three groups and there was no difference in efficacy between the groups.

The frequency of successful analgesia, anesthesia and motor block (Figures 1-3) was comparable between ropivacaine 7.5 $mg \cdot ml^{-1}$ and bupivacaine 5.0 $mg \cdot ml^{-1}$ in spite of a trend in favour of ropivacaine 7.5 $mg \cdot ml^{-1}$. These frequencies with ropivacaine 7.5 $mg \cdot ml^{-1}$ are, however, less than those obtained with 32 ml ropivacaine $mg \cdot ml^{-1}$ as reported by Hickey *et al.*[3] The frequency of motor block was also lower than the 83-91% reported by Hickey *et al.*[3] Possible reasons for a lower efficacy in this study are: variations in technical proficiency among a much larger group of anesthesiologists (12 *vs* 2), fewer patients blocked per anesthesiologist, differences in nerve localisation techniques between anesthesiologists, a slightly lower volume used in the present study (30 *vs* 32 ml), and a slightly different method of recording successful analgesia and anesthesia (nerves *vs* dermatomes). In the study by Hickey *et al.*[3] needle localization was exclusively determined by eliciting paresthesia. In spite of this it is important to note that the majority of patients had successful anesthesia in the relevant dermatomes to allow surgery to proceed without resort to general anesthesia. Fourteen patients in the ropivacaine group and nine patients in the bupivacaine group required conversion to general anesthesia. In addition, because we did not restrict our study to a limited number of anesthesiologists and we allowed both methods of nerve localization, it could be suggested that our study may have greater generalizability to other institutions.

Previous studies have reported a high frequency of Horner's syndrome with bupivacaine 0.5% after SPBPB.[3] The present study did not confirm these findings and the frequency of this adverse event was comparable in both groups. Thus, a differential effect on sympathetic nerves

of the head and neck does not seem to be evident with this concentration of ropivacaine. In addition, both sensory and motor block with ropivacaine 7.5 $mg \cdot ml^{-1}$ lasted 13-14 hr, suggesting that sensory-motor separation as seen with lower concentrations of epidural ropivacaine[7–8] is not evident with brachial plexus anesthesia and this strength of ropivacaine.

One serious adverse event (a grand mal seizure) occurred in the bupivacaine group shortly after block completion in spite of careful aspiration before injection. The patient made a full recovery with no residual effects. Accidental intravascular injection of local anesthetic is a problem in spite of meticulous technique and is particularly worrisome when large volumes of anesthetic are required for efficacy. It is suggested that the lower CNS and cardiotoxicity of ropivacaine in such circumstances may help in reducing the risks to the patient.[9]

In conclusion, 30 ml ropivacaine 7.5 $mg \cdot ml^{-1}$ or bupivacaine 5.0 $mg \cdot ml^{-1}$ for subclavian perivascular brachial plexus block produced satisfactory and comparable sensory and motor block.

Acknowledgments

The authors thank their co-investigators and research coordinators for help with the study and Sergio Escobedo of Astra Pharma Inc for statistical help.

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