A double-blind comparison of ropivacaine 0.5%, 0.75%, 1.0% and bupivacaine 0.5%, injected epidurally, in patients undergoing abdominal hysterectomy

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Purpose: *Ropivacaine is a new long-acting, injectable local anaesthetic currently undergoing clinical investigation world wide. It is structurally very similar to bupivacaine, but with less potential for central nervous system or cardiac toxicity. The purpose of this double-blind study was: to investigate the dose-response relationship of increasing doses of ropivacaine on the quality of anaesthesia and the duration of both motor and sensory blockade, and to compare these results with an established local anaesthetic, bupivacaine.*

Methods: *One hundred and twenty five patients were randomly assigned to one of four treatment groups and 116 completed the study. Epidural anaesthesia was established using 25 ml test solution, injected over three minutes following a satisfactory test dose. Sensory onset, spread and duration, using the pin prick method, and motor scores using a modified Bromage scoring system were compared.*

Results: *A dose/response relationship was observed with increasing doses of ropivacaine for all variables tested except analgesia and muscle relaxation ($P < 0.01$). There were differences in: (i) motor onset (Levels 1 and 2), when ropivacaine 1.0% was compared with ropivacaine 0.75% and 0.5% ($P < 0.05$); (ii) in sensory duration at all levels except T_6 when ropivacaine was compared with ropivacaine 0.5% ($P < 0.05$); (iii) differences in sensory duration at T_{12} and S_1 when ropivacaine 1.0% was compared with bupivacaine 0.5% ($P < 0.05$); (iv) differences in motor duration at all levels when ropivacaine 1.0% was compared with ropivacaine 0.5% ($P < 0.05$). No serious adverse events were reported in this study.*

Conclusion: *Increasing doses of ropivacaine were associated with an increased clinical effect. The most consistent differences occurred when ropivacaine 1.0% was compared with 0.5% and the least consistent between ropivacaine 0.5%, 0.75% and bupivacaine 0.5%. The main difference between ropivacaine 1.0% and bupivacaine was in sensory duration. No serious adverse events were reported.*

Objectifs: *La ropivacaïne est un nouvel anesthésique local injectable à longue durée d'action qui subit des essais cliniques partout dans le monde. Sa structure ressemble beaucoup à celle de la bupivacaïne mais son potentiel de toxicité pour le système nerveux central est moindre. Les objectifs de cette étude en double aveugle étaient de rechercher la relation dose-effet de doses croissantes de ropivacaïne sur la qualité de l'anesthésie et la durée des bloc sensitif et moteur, et de comparer ces résultats avec un anesthésique local établi, la bupivacaïne.*

Méthodes: *Cent vingt-cinq patients ont été assignés aléatoirement à un de quatre groupes et 116 ont complété l'étude. L'anesthésie épidurale a été réalisée avec une solution test de 25 ml, injectée en trois minutes après une dose-test satisfaisante. L'installation sensorielle, la propagation et la durée, mesurés avec la méthode de la piqûre, et les scores de motricité mesurés sur une échelle de Bromage modifiée ont été comparés.*

Résultats: *Une relation dose-effet a été observée avec l'augmentation des doses de ropivacaïne pour toutes le variables*

Key words
ANAESTHETIC TECHNIQUES: epidural;
ANAESTHETICS LOCAL: ropivacaine, bupivacaine;
SURGERY: gynaecology.

This was a multi-centre trial conducted in the Departments of Anaesthesia at the Universities of Alberta, Toronto and Ottawa in Canada. This study was supported by a grant from Astra Pain Control AB, Södertälje, Sweden.

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testées excepté l'analgésie et la relaxation musculaire ($P < 0,01$). Les différences suivantes ont été notées pour: (i) l'installation motrice (niveaux 1 et 2), lorsque la ropivacaïne 1,0% était comparée avec la ropivacaïne 0,75% et 0,5% ($P < 0,05$); (ii) la durée sensorielle à tous les niveaux excepté T_6 quand la ropivacaïne 0,5% ($P < 0,5$); (iii) des différences de durée sensorielle à T_{12} et S_1 quand la ropivacaïne 1,0% était comparée à la bupivacaïne 0,5% ($P < 0,05$); (iv) des différence de durée pour la motricité à tous les niveau quand la ropivacaïne 1,0% était comparée avec la ropivacaïne 0,5% ($P < 0,05$). Aucun effet défavorable n'est survenu pendant l'étude.

***Conclusions**: L'augmentation des doses de ropivacaïne a été associée à une augmentation de l'effet clinique. Les différences les plus importantes sont survenus quand la ropivacaïne 1,0% était comparée à 0,5% et les moins importantes entre la ropivacaïne 0,5%, 0,75% et la bupivacaïne 0,5%. La différence principale entre la ropivacaïne 1,0% et la bupivacaïne portait sur la durée sensorielle. Il n'y a pas eu d'effets secondaires graves.*

Ropivacaine (1-propyl-2', 6'-pipecoloxylidide hydrochloride monohydrate) is a new, long-acting, injectable, local anaesthetic, structurally very similar to other pipecholoxylidine derivatives, synthesized by Ekenstam.[1] However, it is the first local anaesthetic to be presented as an almost pure enantiomer (>99% pure). It exists primarily as the S-enantiomer (rotates polarized light to the left). Physical-chemical properties of ropivacaine are similar to bupivacaine; however, lipid solubility of ropivacaine is 2.9 compared with 39 to bupivacaine (partitioning between N-heptane and phosphate buffer at pH 7.4 and 37°C).[2]

The objectives of this study were to test the dose/response relationship of increasing doses of ropivacaine on the duration and quality of epidural anaesthesia, and to compare these effects with an established control (bupivacaine).

Methods

This was a double blind, randomized, multi-centre trial, carried out in three university centres in Canada. The clinical effects of three different concentrations of ropivacaine (0.5%, 0.75%, and 1%) were compared, when injected epidurally, for abdominal hysterectomy which, in turn, were compared with an established treatment, bupivacaine 0.5%.

The study protocol was approved by the respective Institutional Review Boards in the three medical centres and written informed consent was obtained from all participants, before the study.

Healthy patients, (ASA 1–2) scheduled for routine abdominal hysterectomy with the following characteristics: age between 18–60 yr, weight between 50–90 kg, and height 150 cm, were considered eligible for the study. The following patients were excluded – those with a known allergy to local anaesthetics, a history of drug or alcohol dependence, mental illness (depression or schizophrenia), communication or language barriers, currently participating in other trials, receiving treatment for cardiac arrhythmias and those in whom epidural anaesthesia was contraindicated.

All participants received diazepam 10 mg *po* before commencing the study. An intravenous infusion was established and 1000 ml balanced salt solution were infused over 30 min before insertion of the epidural injection. Vital signs (blood pressure (BP), heart rate (HR), and respiratory rate (RR)) were recorded at five minute intervals and both ECG and pulse oximetry were monitored continuously from the commencement of the study until discharge from the post anaesthesia recovery room (PARR). Patients were positioned in the lateral decubitus position and a 16 or 17 gauge Tuohy needle was advanced into the epidural space, at either the L_{2-3} or L_{3-4} interspace, using the loss of resistance technique (to air). A test dose, of 3 ml lidocaine 1.5%, with epinephrine 1:200,000 was administered, through the Tuohy needle, and three minutes were allowed to elapse, for detection of signs of an intravascular or subarachnoid injection. If the test dose was negative, 25 ml of the study drug were then injected intermittently through the needle, over three minutes. The patient was then placed in the supine position, in preparation for clinical assessment.

Clinical assessment

SENSORY ANALGESIA

Sensory variables were assessed at five minute intervals for the first 30 min, then every 15 min until the first hour had elapsed, then every 30 min for the next five hours, then hourly, until full return of sensation. Sensory impairment was tested using a blunt tipped, short bevelled 27 gauge needle. If the sensory spread had not extended to T_6 within one hour, general anaesthesia was electively induced.

MOTOR BLOCKADE

Motor blockade was assessed at similar intervals, using a modified Bromage scoring system:

0 = No motor paralysis
1 = Unable to raise extended leg
2 = Unable to flex knee
3 = Unable to flex ankle
4 = Unable to move toes.

QUALITY OF ANALGESIA AND ABDOMINAL WALL RELAXATION

At the end of the surgery, the quality of analgesia and abdominal wall relaxation was recorded as satisfactory, satisfactory until a specified time or unsatisfactory as judged by the investigator and surgeon.

ADVERSE EVENTS

Adverse events were defined as any unfavourable event temporarily associated with the administration of the study drug whether or not there was any causal relationship between the event and the administration of the study drug.

CARDIOVASCULAR VARIABLES

Heart rate and systolic and diastolic readings were recorded at five minute intervals throughout the procedure until discharge from the PARR, and then, at hourly intervals until the block had regressed fully. Definitions were arbitrarily established for hypotension, hypertension, bradycardia and tachycardia. Hypotension was defined as a systolic blood pressure (SBP) ≤90 mmHg or a ≥25% decrease in SBP compared with the ward measurement made before surgery. Hypertension was defined as a SBP 180 mmHg. Bradycardia was defined as a HR ≤40 BPM (or a ≥25% decrease in heart rate compared with the ward measurement made before surgery). Tachycardia was defined as a HR ≥130 BPM.

DATA ANALYSIS

The following data were analyzed and compared: patient demographic variables; onset, duration, and regression of both motor and sensory analgesia; adequacy of epidural blockade; quality of surgical anaesthesia; degree of motor and sensory separation; cardiovascular variables; and, adverse events. Duration was defined as the time interval between complete onset and complete recovery. Regression was defined as the time from completion of injection until full recovery. Data are presented using median values and the interquartile range (Q1, Q3, max. min.). (Figures 1, 2, 3 and 4).

Statistical methods

Pairwise comparisons of the four groups were performed using the Cochran-Mantel-Haenszel tests which are in effect ANOVAs, with the added advantage of controlling for the centre effect. When significance occurred in any of these comparisons, an adjustment was made using the Bonferroni procedure. In addition, a dose/response relationship between the three ropivacaine groups was evaluated by fitting of linear regression lines. Separate regression lines were calculated at each sensory and motor variable. Whenever the slope was considered statistically significant, a dose response relation was concluded. The centre adjusted Mantel-Haenzel test was used to calculate the dose/response differences between ropivacaine groups in relation to analgesia and muscle relaxation. The bupivacaine group was then compared with each ropivacaine group using the same procedure.

TABLE I Demographics

Variable	*R 0.5%*	*R 0.75%*	*R 1.0%*	*B 0.5%*
Age (yr)	44.7 ± 5.9	39.6 ± 6.0	38.1 ± 7.6	43.9 ± 7.3
Wt. (kg)	68.8 ± 11.7	66.1 ± 9.7	65.4 ± 8.4	65.6 ± 9.6
Ht. (cm)	162.0 ± 6.7	162.1 ± 7.7	161.2 ± 5.7	162.1 ± 4.4
ASA I/II	16/11	20/10	20/10	22/7
	27	30	30	29

Values are means ± S.D.

TABLE II Upper sensory distribution

Variable	*R 0.5%*	*R 0.75%*	*R 1.0%*	*B 0.5%*
Upper level (Median)	T_4(8)	T_6(9)	T_4(16)	T_6(12)
Range	(C_4–T_{10})	(C_4–T_8)	(C_2–T_{11})	C_2–T_{10}
	27	30	30	29

Results

One hundred and twenty-five patients agreed to participate in this study. Eight were considered technical failures, two because of dural taps, six because there was no evidence of epidural anaesthesia following injection of local anaesthetic solution, and one additional patient was excluded because the surgical procedure was delayed. Therefore, 116 patients met the protocol requirements.

Demographic comparisons

Age, wt, ht and ASA status were compared and there were no differences among the groups (Table I).

Sensory onset

Pairwise comparisons between the groups revealed some statistical differences, however, the clinical importance of these differences was inconsequential (Figure 1).

Sensory distribution

The total number of dermatomes blocked did not differ among the groups, nor did the maximal upward spread of sensory analgesia (Table II).

Sensory duration

In contrast to sensory onset and distribution, marked dif-

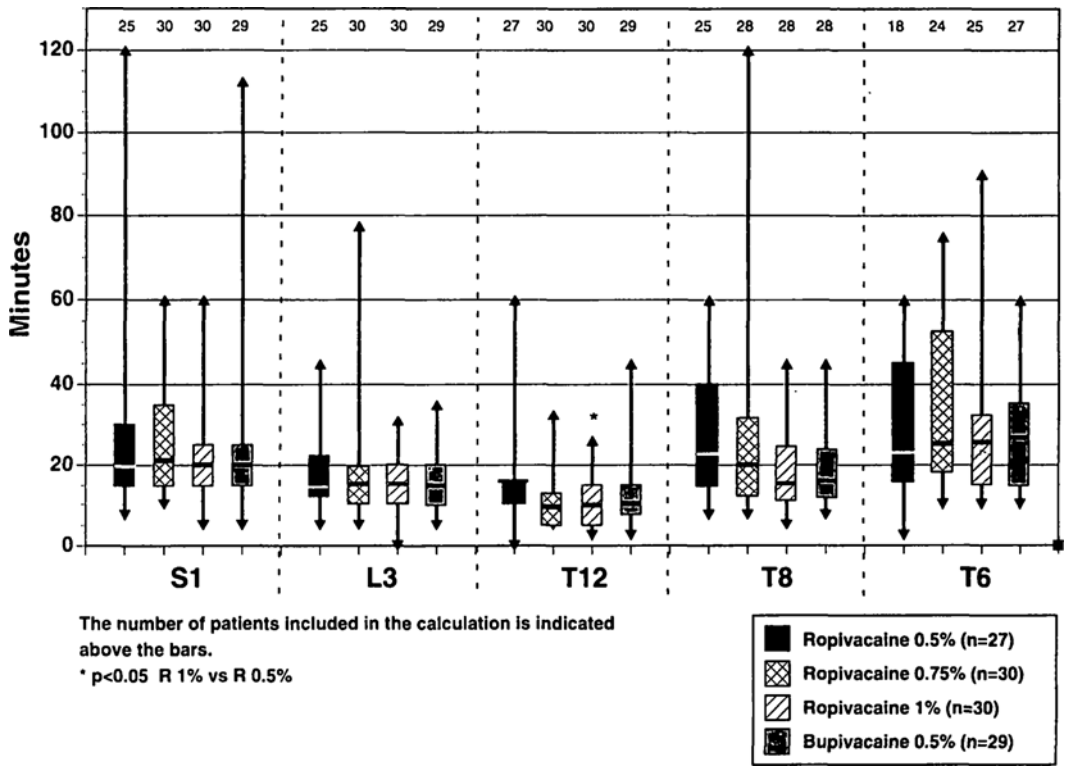

FIGURE 1 Sensory onset.

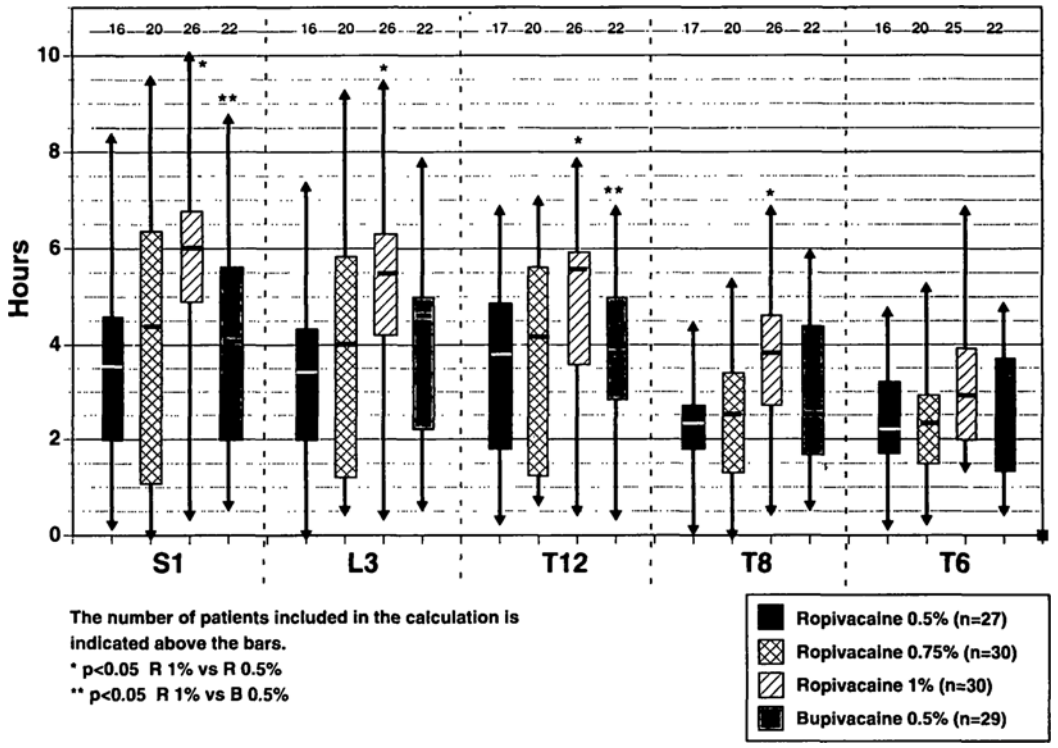

FIGURE 2 Sensory duration.

ferences were observed in the duration of sensory analgesia between the groups with median values ranging between two and six hours depending upon the dermatome observed. Differences were observed at various points and the most consistent differences were observed when comparing ropivacaine 1% with ropivacaine 0.5% (Figure 2). Sensory duration of ropivacaine 1.0% at S_1 was six hours compared with four hours for bupivacaine 0.5% ($P < 0.05$). Significant differences were also noted at T_{12}.

DOSE/RESPONSE ANALYSIS

The dose/response analysis of the effects of ropivacaine on the duration of sensory analgesia revealed significance at all levels except T_6 ($P < 0.01$).

MOTOR ONSET

Pairwise comparisons among groups revealed clinically and statistically significant differences. Onset to level 2 motor blockade (knee) ranged between 15 and 30 min (median value) depending upon the group. The most notable differences were observed when comparing ropivacaine 0.5% with ropivacaine 1%, where the differences were significant ($P < 0.05$) at all levels except at the toes (Figure 3). Pairwise comparisons among other groups also revealed some significant differences.

Motor duration

The median duration of motor blockade ranged between 168 min and 288 min at the hip depending upon the group (Figure 4). The greatest differences in duration were noted when comparing ropivacaine 1% and 0.5% ($P < 0.05$). Differences in motor duration were also noted between ropivacaine 1.0% and 0.75%.

DOSE/RESPONSE EVALUATION

The dose/response effect on motor duration by increasing doses of ropivacaine was marked at all levels ($P < 0.01$).

EFFICACY EVALUATION

Of the original 116 patients who met the protocol requirement, 32 required general anaesthesia, 14 because the block did not reach T_6 in one hour, and 18 because of inadequate surgical anaesthesia, (Table III).

QUALITY OF ANALGESIA AND MUSCLE RELAXATION

No differences were noted in pairwise comparisons or dose/response effects on the quality of analgesia or muscle relaxation. A dose response effect was noted in the degree of motor blockade achieved. All patients in the ropivacaine 1.0% study achieved a level 3 motor blockade. Twenty-one patients out of a total of 29 in the bupivacaine 0.5% study achieved a level 3 motor blockade. These differences were not significant.

Adverse events

The most common adverse events reported were nausea, vomiting, hypotension, headache and backache (Table IV). There were no differences among the groups. There were two dural punctures but neither patient received the study drug. There were no reported cases of systemic toxicity. There were no serious adverse events in this study.

Discussion

A dose response relationship was observed with increasing doses of ropivacaine ($P < 0.01$) in all variables tested except for the quality of analgesia and abdominal wall relaxation. Multiple pairwise comparisons among the groups revealed that the onset of motor and the duration of both motor and sensory anaesthesia were enhanced by increasing the mass of ropivacaine ($P < 0.05$), and the most consistent differences were observed when ropivacaine 1.0% was compared with ropivacaine 0.5%.

Ropivacaine is the first long acting, injectable local anaesthetic to undergo testing in more than 20 yr. Although identified as a local anaesthetic in 1957, ropivacaine testing did not begin until 1988 when Albright observed that accidental intravascular injections of bupivacaine resulted in serious cardiac toxic effects with poor outcomes.[3] Initial studies in animals suggested that ropivacaine was less likely to induce cardiac toxic effects when injected intravenously.[4–7] Intravenous infusions of ropivacaine in human volunteers resulted in fewer central nervous system effects or cardiac abnormalities than did bupivacaine.[8] *In vitro* studies in isolated vagus nerve preparations demonstrated that ropivacaine and bupivacaine were equally potent in their ability to block C-fibre activity, but ropivacaine was less effective in blocking larger motor fibres (Aα).[9] This observation was also verified in intact animals undergoing spinal and epidural anaesthesia.[10] Therefore, based on preliminary data, it appeared that ropivacaine had a pharmacodynamic profile very similar to that of bupivacaine with a reduced potential for cardiac toxicity. For these reasons, ropivacaine was clinically tested in humans. Ropivacaine has been tested clinically in more than 2000 patients and volunteers world-wide since 1988.* This was the first study to test the efficacy of ropivacaine when injected epidurally for major abdominal surgery.

*Data on file at ASTRA, Södertälje, Sweden.

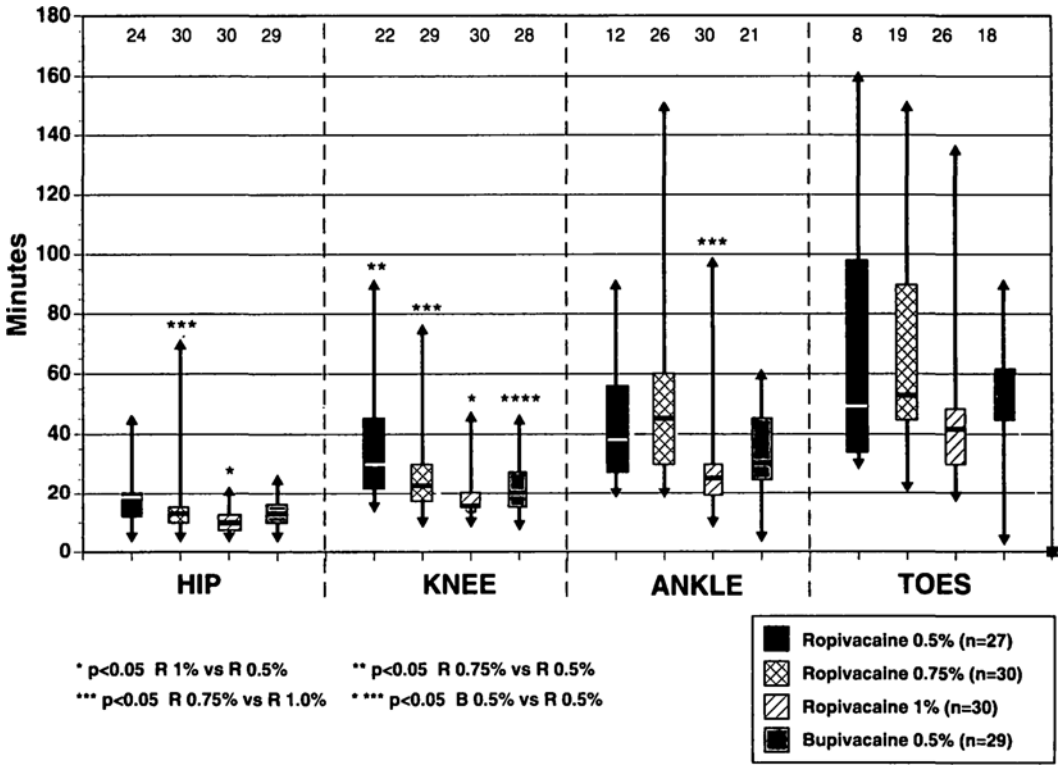

FIGURE 3 Onset of motor blockade.

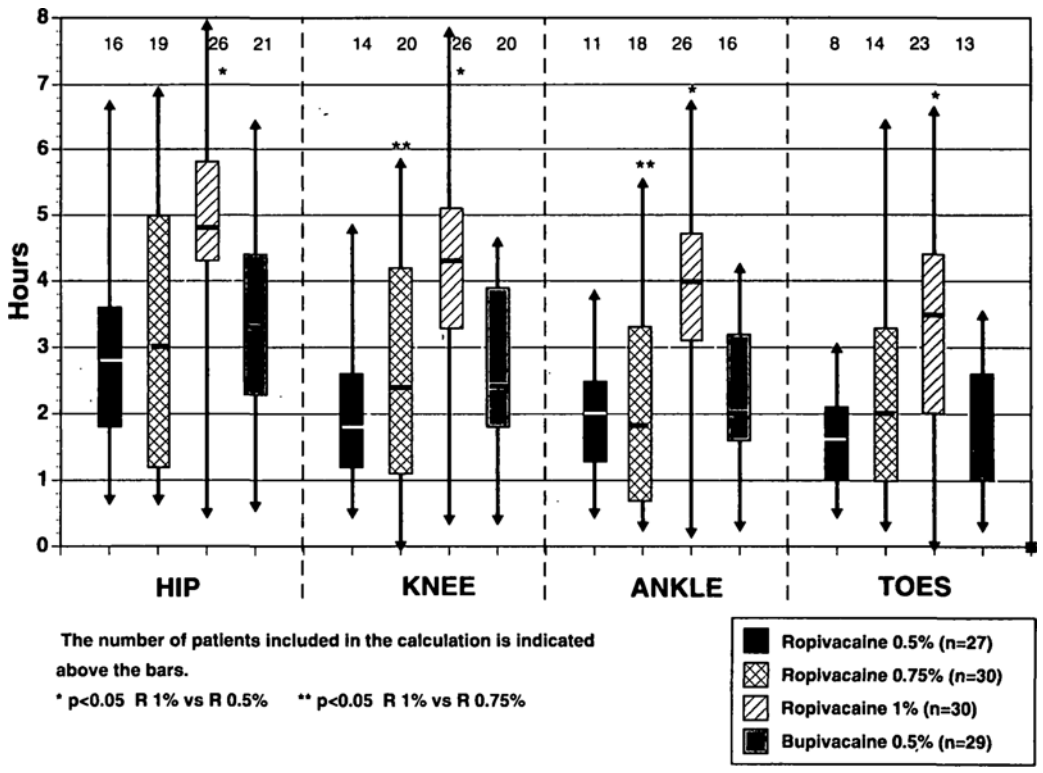

FIGURE 4 Duration of motor blockade.

TABLE III Clinical efficacy

Result	*R 0.5%*	*R 0.75%*	*R 1.0%*	*B 0.5%*	*Total*
GA ($\downarrow T_6$)	4	5	3	2	14
GA	6	6	1	5	18
Epidural	17	19	26	22	84
Total	27	30	30	29	116

TABLE IV Adverse events

Symptom/signs	*R 0.5%*	*R 0.75%*	*R 1.0%*	*B 0.5%*
Hypotension	7	10	15	10
Nausea	15	24	23	17
Vomiting	6	7	9	8
Headache	3	3	4	3
Backache	1	6	4	4

A single injection technique was selected in an effort to minimize technical variations which are more likely to occur with catheter techniques. It was surprising to note that when the mass of local anaesthetic was doubled, there was little influence on the onset and overall spread of sensory anaesthesia. (Figure 1 and Table II). In contrast, the onset of motor blockade was greatly influenced by the mass of ropivacaine administered. The onset of a level 2 motor blockade was halved by doubling the mass of ropivacaine (15 min vs 30 min, Figure 3). All patients in the ropivacaine 1.0% group achieved a level 3 motor blockade with median onset times of 25 min. There was a reduced incidence of level 3 blocks in the three remaining groups. A dose response effect was evident in the ropivacaine groups. This may have clinical implications in surgical procedures requiring moderate to profound degrees of motor blockade in the early stages of a procedure, such as abdominal hip or knee surgery. Thus ropivacaine 1.0% may be a desirable concentration for major surgery performed under epidural anaesthesia alone. It is difficult to explain why different concentrations of local anaesthetic had little influence on the onset of action of sensory anaesthesia yet had a marked effect on the onset of motor blockade. This difference may reflect the lack of sensitivity of sensory testing using the skin prick method.

The relatively high failure rate noted in this study deserves some comment. Of the 116 patients who satisfied the protocol requirements, 32 required general anaesthesia, 14 because the block did not reach T_6, and 18 because of inadequate surgical or anaesthesia conditions intraoperatively. This represents an overall failure rate of 27% which is high by any standards. However, one would anticipate a higher failure rate than usual in any study of this nature (dose/finding). Forty percent of these failures were because of failure to reach a T_6 sensory level. In retrospect, a catheter technique may have been more desirable because it would have enabled introduction of local anaesthetic solutions into the epidural space at a higher level. Sample size prevented us from drawing any conclusions about failure rates in the pairwise comparisons.

No serious adverse events were noted in this study. Two patients incurred accidental dural puncture, however, neither received ropivacaine, nor did they develop headaches. The definition of tachycardia was perhaps too liberal, however, median changes in heart rate varied no more than ±10% from base line in any of the group comparisons and there were no differences noted between the groups.

A Bonferroni correction was performed because multiple pairwise comparisons were made. The Bonferroni correction has the disadvantage of being overly conservative; therefore, true differences may not have been detected. However, statistical differences were still noted in many of the pairwise comparisons following this correction.

The majority of ropivacaine clinical trials todate (>70), involved epidural administration. This study is unique in that it was the only study in which 250 mg ropivacaine were administered epidurally. Thirty patients received this mass of ropivacaine epidurally which amounted to 5 $mg \cdot kg^{-1}$ in some cases. In the two other studies comparable in design to this one,[11,12] the results were remarkably similar. All three studies showed that the onset and spread of sensory anaesthesia appeared to be uninfluenced by the mass of local anaesthetic injected. Furthermore, all three showed that by increasing the mass of local anaesthetic, the duration of both motor and sensory anaesthesia was prolonged and the intensity of motor blockade was increased which confirmed that ropivacaine was pharmacodynamically similar to other long acting agents.

In conclusion, a clear dose response effect was evident with increasing doses of ropivacaine. In the pairwise comparisons, the most consistent differences were noted between ropivacaine 1.0% and 0.5% and the least consistent between ropivacaine 0.5%, 0.75% and bupivacaine 0.5%. The main difference between ropivacaine 1.0% and bupivacaine was in sensory duration. No serious adverse events occurred in this study.

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