Spinal anaesthesia for elective surgery: a comparison of hyperbaric solutions of racemic bupivacaine, levobupivacaine, and ropivacaine

J. F. Luck†*, P. D. W. Fettes† and J. A. W. Wildsmith†

University Department of Anaesthesia, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK

*Corresponding author. E-mail: johnfluck@gmail.com

Background. The aim of this study was to compare the clinical effects of ‘hyperbaric’ bupivacaine for spinal anaesthesia with those of similar preparations of levobupivacaine and ropivacaine.

Methods. Sixty ASA grade I–II patients undergoing elective surgery under spinal anaesthesia were randomized to receive 3 ml of bupivacaine, levobupivacaine, or ropivacaine, each at 5 mg ml$^{-1}$ and made hyperbaric by the addition of glucose 30 mg ml$^{-1}$. A standard protocol was followed after which a blinded observer assessed the sensory and motor blocks. The level and duration of sensory (pinprick) block, intensity and duration of motor block, and time to mobilize and to micturate were also recorded.

Results. One patient (ropivacaine group) required general anaesthesia because of technical failure, but all the other blocks were adequate. There were no significant differences between the groups with regard to the mean time to onset of sensory block at T10, the extent of spread, or mean time to maximum spread. Regression of sensory block in the ropivacaine group was more rapid as demonstrated by duration at T10 ($P<0.0167$) and total duration of sensory block ($P<0.0167$). Patients in the ropivacaine group had more rapid recovery from motor block ($P<0.0167$) and shorter times to independent mobilisation ($P<0.0167$). There were no significant differences between the bupivacaine and the levobupivacaine groups.

Conclusions. ‘Hyperbaric’ ropivacaine provides reliable spinal anaesthesia of shorter duration than bupivacaine or levobupivacaine, both of which are clinically indistinguishable. The recovery profile of ropivacaine may be useful where prompt mobilization is required.

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The impetus for the development of the newer stereoselective, single enantiomer amide local anaesthetic agents, ropivacaine and levobupivacaine, came from reports of fatal cardiac toxicity in pregnant women receiving epidural bupivacaine and etidocaine for Caesarean section. Although these concerns are not clinically relevant to spinal anaesthesia because of the smaller doses required, there has, nevertheless, been interest in the potential of these agents for intrathecal use. Although neither ropivacaine nor levobupivacaine are licensed for this route in the UK, ropivacaine was approved for intrathecal administration by the European Union in 2004.

Both ropivacaine$^{2–5}$ and levobupivacaine$^{6–9}$ have been studied to some degree for spinal anaesthesia. Ropivacaine is well tolerated after intrathecal use,$^{10}$ and was found to have a shorter duration of action than bupivacaine, making it a possible alternative to lidocaine for ambulatory surgery because of the low incidence of transient neurological symptoms (TNS).$^{11}$ Racemic bupivacaine and levobupivacaine, its S enantiomer, appear to produce a very
similar pattern of the block.\textsuperscript{8,9} However, we are not aware of any study comparing all three drugs directly in the non-obstetric setting without concurrent use of adjuncts. The aim of this prospective, randomized, double-blinded study was to do this in elective surgical patients using equal doses (as per the expressed formulations for commercial use) of hyperbaric solutions of similar density.

**Methods**

Sixty patients of ASA grade I–II undergoing elective lower abdominal, perineal, or lower-limb surgery under spinal anaesthesia gave written informed consent to participate in the study, which was approved by the local research ethics committee. Premedication consisted of oral temazepam 0–20 mg which was administered at the discretion of the clinician responsible.

On arrival in the anaesthetic room, routine monitoring with ECG, non-invasive arterial pressure, and pulse oximetry were commenced, and venous access secured. No fluid was administered and the patient was placed in the left lateral decubitus position for lumbar puncture, which was performed using a mid-line approach at the second or third lumbar interspace. A 25 swg Whitacre needle (VYGON, UK) was inserted with the distal port facing laterally, and the appropriate anaesthetic solution injected over 10–15 s. Each of the 60 patients was randomized (sealed, shuffled, numbered, and opaque envelopes) to one of the three groups of 20 patients. Each of the patients enrolled in the study received 3 ml of one of the three solutions: bupivacaine (Svedocain: bupivacaine hydrochloride, Inibsa laboratorios, Spain) 5 mg ml\textsuperscript{-1}, levobupivacaine (Chirocaine: levobupivacaine hydrochloride, Abbot Laboratories, UK) 5 mg ml\textsuperscript{-1}, or ropivacaine (Naropin: ropivacaine hydrochloride, AstraZeneca, Sweden) 5 mg ml\textsuperscript{-1}, each with glucose 30 mg ml\textsuperscript{-1} (Table 1). All solutions were prepared aseptically by the anaesthetist administering the spinal block immediately before injection. The patient was turned supine immediately after the injection, the time of which was defined as ‘zero’.

Thereafter, an investigator, blinded to the identity of the solution administered, assessed the upper and lower limits of sensory block (analgesia to pinprick using the short bevel end of a 27 swg dental needle: caudad limit of sensory block assessment, S2), the degree of motor block (modified Bromage scale: 0, no motor block; 1, inability to raise extended leg, able to bend knee; 2, inability to bend knee, can flex ankle; and 3, no movement), and recorded the heart rate and arterial pressure 2, 5, 10, 15, 20, 25, and 30 min after injection. The patients were then transferred into the operating theatre and, if they wished, received sedation by a target-controlled infusion of propofol titrated to maintain verbal contact throughout. Assessments were continued at 30 min intervals thereafter until complete motor and sensory (beyond S2) blocks regression. Hypotension (defined as $>$30% decrease in systolic arterial pressure from baseline) was treated with i.v. ephedrine 3 mg. I.V. fluids were administered only to replace estimated intraoperative losses.

Once sensory block had fully regressed, patients were encouraged to mobilize carefully under supervision. Bladder catheterization was performed when surgically indicated and time to micturition was recorded in all other patients. Patients were visited or telephoned 24 h and 3–7 days later to identify any adverse sequelae.

The sample size was chosen to be consistent with our previous experience and studies\textsuperscript{2–4} so as to maintain the overall alpha error $<$0.05 and power (1–beta) $>$0.9 and to provide useful additional safety and tolerability data. Data are presented as median (range), mean (SD), or frequencies as appropriate. Binomial data were compared using $\chi^2$ or Fisher’s test. Block characteristics were compared using the Kruskal–Wallis one-way analysis. In the event of a significant difference, post hoc comparisons were performed using the two-tailed Mann–Whitney U-test with a Bonferroni correction for multiple two-way testing. A $P$-value of $<$0.0167 was considered statistically significant. Data were analysed using a standard computer-based statistics package (StatsDirect statistical software version 2.5.5).

**Results**

The groups were comparable with respect to age, weight, and ASA status (Table 2). There was a difference in height between the bupivacaine and the ropivacaine

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Bupivacaine ($n=20$)</th>
<th>Levobupivacaine ($n=20$)</th>
<th>Ropivacaine ($n=19$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61 (29–73)</td>
<td>57 (26–73)</td>
<td>59 (37–75)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165 (8)</td>
<td>169 (10)</td>
<td>173 (11)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75 (19)</td>
<td>82 (12)</td>
<td>83 (18)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>8/12</td>
<td>11/9</td>
<td>14/5</td>
</tr>
<tr>
<td>ASA III</td>
<td>4/16</td>
<td>8/12</td>
<td>5/14</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>49 (13–98)</td>
<td>44 (20–67)</td>
<td>49 (15–115)</td>
</tr>
</tbody>
</table>

**Table 1** Density of 5 mg ml\textsuperscript{-1} solutions of bupivacaine, levobupivacaine, and ropivacaine with 30 mg ml\textsuperscript{-1} dextrose at 37°C. Data represent mean (SD).

**Table 2** Patient characteristics and type of surgery performed. Data are presented as median (range), mean (SD), or frequencies.
groups (mean 8 cm, sampling probability <0.05), a higher proportion of male to female patients in the ropivacaine group (14/5), compared with the others (levobupivacaine 11/9 and ropivacaine 8/12).

One patient was withdrawn due to technical failure and received a general anaesthetic leaving 19 patients in the ropivacaine group. All the other blocks were adequate for surgery.

No statistically significant differences were observed between the three groups with respect to times [in min; median (range)] to onset of analgesia to pinprick at T10 [bupivacaine 5 (2–5), levobupivacaine 5 (2–15), and ropivacaine 5 (2–15)] and maximum cephalad spread [bupivacaine 25 (10–30), levobupivacaine 25 (10–30), and ropivacaine 20 (2–30)], or in maximum upper sensory block level [bupivacaine T3 (T2–T8), levobupivacaine T4 (T2–T8), and ropivacaine T4 (T2–T10)] (Table 3 and Figs 1 and 2).

The times of sensory block regression, both to T10 [bupivacaine 129 (58–178), levobupivacaine 131 (50–205), and ropivacaine 84 (45–145)] and complete regression, were shorter in the ropivacaine group than the other two. The difference between the ropivacaine group and the others was statistically significant beyond the 90 min time point (Fig. 1). There was no significant difference in the pattern of sensory regression between the bupivacaine and the levobupivacaine groups.

The degree and duration of motor block were significantly less in the ropivacaine group compared with the other two groups (Table 3 and Fig. 3). Thus, patients in the ropivacaine group mobilized significantly sooner than patients in the other two groups. There was no statistically significant difference between the bupivacaine and the levobupivacaine groups.

The nature of the surgery (i.e. gynaecological or urological) required that a number of the patients electively had urethral catheterization. Thus, the numbers available to analyse the time to micturition were reduced. The median time to micturition was shortest in the ropivacaine group, although this difference did not achieve statistical significance.

Cardiovascular changes were unremarkable, with no statistically significant differences between the groups in heart rate, systolic arterial pressure (Fig. 4), or the incidence of hypotension (Table 4).

Follow-up at 24 h and at 3–7 days after operation revealed no major sequelae (Table 4). Two patients (one in the bupivacaine group and one in the ropivacaine group) had symptoms of headache (unrelated to posture) during the first 24 h, but these symptoms had resolved completely at the 3–7 day follow-up.

**Table 3** Characteristics of intrathecal blocks for bupivacaine (B), levobupivacaine (L), and ropivacaine (R). Data are presented as median (range). *A significant result with P-value of <0.0167

<table>
<thead>
<tr>
<th>Sensory block</th>
<th>Bupivacaine (n=20)</th>
<th>Levo Bupivacaine (n=20)</th>
<th>Ropivacaine (n=20)</th>
<th>P-value</th>
<th>Kruskal–Wallis P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset to T10 (min)</td>
<td>5 (2–15)</td>
<td>5 (2–15)</td>
<td>5 (2–15)</td>
<td>0.65</td>
<td>0.6528</td>
</tr>
<tr>
<td>Median maximum block (dermatome)</td>
<td>T3 (T2–T8)</td>
<td>T4 (T2–T8)</td>
<td>T4 (T2–T10)</td>
<td>0.502</td>
<td>0.0796</td>
</tr>
<tr>
<td>Time to maximum sensory block (min)</td>
<td>25 (10–30)</td>
<td>25 (10–30)</td>
<td>20 (2–30)</td>
<td>0.86</td>
<td>0.0771</td>
</tr>
<tr>
<td>Duration at T10 (min)</td>
<td>129 (58–178)</td>
<td>131 (50–205)</td>
<td>84 (45–145)</td>
<td>0.86</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Sensory regression (min)</td>
<td>270 (210–450)</td>
<td>255 (180–360)</td>
<td>210 (180–330)</td>
<td>0.44</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Grade 3 motor block (%)</td>
<td>18 (90%)</td>
<td>19 (95%)</td>
<td>12 (63%)</td>
<td>0.7436</td>
<td>0.0053*</td>
</tr>
<tr>
<td>Time to maximum motor block (min)</td>
<td>5 (2–25)</td>
<td>5 (2–20)</td>
<td>10 (5–20)</td>
<td>0.1748</td>
<td>0.002*</td>
</tr>
<tr>
<td>Motor block regression (min)</td>
<td>180 (90–360)</td>
<td>180 (90–210)</td>
<td>90 (60–120)</td>
<td>0.0511</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Time to mobilization (min)</td>
<td>306 (243–364)</td>
<td>286 (201–389)</td>
<td>218 (164–340)</td>
<td>0.13</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Time to micturition (min)</td>
<td>369 (270–513) (n=14)</td>
<td>347 (225–433) (n=11)</td>
<td>311 (90–410) (n=12)</td>
<td>0.4128</td>
<td>0.962</td>
</tr>
</tbody>
</table>

**Discussion**

This prospective double-blind randomized study has shown that solutions of bupivacaine, levobupivacaine, and ropivacaine made hyperbaric relative to CSF by the addition of glucose, provide reliable and predictable spinal anaesthesia for various elective procedures. In addition, the study shows that although the blocks produced by bupivacaine and levobupivacaine are clinically indistinguishable, the block produced by ropivacaine is of shorter duration (when each of the drugs is administered at a dose of ‘15 mg’).

It is now well established that, compared with plain solutions, the use of hyperbaric local anaesthetic solutions results not only in a more predictable cephalad spread, but also increases the duration of the clinically useful block (given by duration at the T10 dermatome), and leads to a
more rapid regression of sensory block and recovery from motor block.\textsuperscript{4, 5} The concentration of glucose used (30 mg ml\textsuperscript{-1}) is slightly lower than is usual, but it was the easiest single concentration to achieve using readily available solutions, and provides a solution that is sufficiently hyperbaric for its purpose.

In this study, the rate of onset and extent of the sensory block to pinprick showed no statistically significant difference between the three agents with respect to the onset time to T10, maximum extent of cephalad spread, and the time to maximum spread. The factors which determine intrathecal spread of local anaesthetic agents have been investigated in numerous clinical studies, the results of which have been the subject of a recent review.\textsuperscript{12} Many of the factors have a relatively minor influence and manipulation of these is largely beyond the clinician’s control. However, the two main factors, the baricity of the injected solution and the patient’s position immediately after intrathecal injection, are amenable to alteration by the clinician. Given that there is little difference between the density of 5 mg ml\textsuperscript{-1} solutions of the three local anaesthetic agents (with glucose 30 mg ml\textsuperscript{-1} at 37°C; Table 1),\textsuperscript{13} and that a standardized protocol for positioning was used immediately after injection to standardize the effect of gravity on spread, it is not surprising that the observed pattern of onset of the sensory block was similar in all three groups. However, patients in the ropivacaine group experienced a less intense motor block with 63% of patients (12/19) achieving Bromage scores of 3, in contrast to the 90% and 95%, respectively, for bupivacaine and levobupivacaine.

The ropivacaine group also showed a more rapid recovery from both the sensory and motor blocks, compared with the
other two groups. This is a general finding in keeping with the results of other studies comparing ropivacaine with bupivacaine when solutions of equal dose and density are compared. McNamee and colleagues compared two groups receiving plain solutions of ropivacaine and bupivacaine at a dose of 17.5 mg in patients undergoing total hip arthroplasty. They observed a similar rate of onset and extent of sensory block and less intense motor block with ropivacaine. A more rapid recovery from the sensory and motor blocks was observed in the ropivacaine group. The more rapid recovery profile of ropivacaine has led some investigators to question the suitability of ropivacaine for use in spinal anaesthesia. Two earlier studies, one clinical and the other in volunteers, compared ropivacaine and bupivacaine and concluded that ropivacaine offers no clinical advantage compared with bupivacaine, primarily because of a shorter duration of action. One of these studies also reported a higher incidence of backache and concluded that the incidence of side-effects was greater, even though there was no statistically significant difference observed. In the present study, we found no difference between the three agents with respect to the incidence of side-effects.

The interpretation of the findings and conclusions of previous studies comparing ropivacaine, bupivacaine, and levobupivacaine is often complicated by the fact that different doses of the agents are compared in the same study. Many of the protocols for these studies appear to be designed with the assumption that ropivacaine is less potent than bupivacaine. The issue of potency is complex when considering a local anaesthetic block, since we must consider both the sensory and motor components of the block. It is also important to remember that the potency of a drug relates to the effect produced and not to the duration of that effect. The interpretation of the finding for intrathecal ropivacaine of a less intense motor block and a more rapid recovery of the sensory and motor functions has been the subject of some controversy. Some have argued that this is a specific drug effect of ropivacaine demonstrating an increased separation of the sensory and motor blocking effects by virtue of a lower lipid solubility, whereas others claim that the observed differences are merely due to reduced potency of ropivacaine compared with bupivacaine.

Kallio and colleagues in a randomized, double-blinded study compared plain solutions of ropivacaine 20 and 15 mg with plain bupivacaine 10 mg in 90 ambulatory patients. They found that ropivacaine 15 mg provided a faster recovery of motor block, but a similar duration of sensory block to bupivacaine 10 mg. This finding would appear to add weight to the argument for an increased motor/sensory difference with ropivacaine. At the doses used, similar extents and durations of sensory block were observed, but motor block was less intense and shorter duration with ropivacaine. If the differences in that study were due just to differences in potency, we would expect parallel differences in the motor and sensory components of the spinal block compared with bupivacaine.

Regardless of the exact explanation for the more rapid recovery profile of ropivacaine, this study provides further evidence that hyperbaric solutions of ropivacaine, administered in a dose of 15 mg, produce predictable and reliable spinal anaesthesia for a variety of surgical procedures of relatively short duration. One patient in the ropivacaine group required general anaesthesia due to inadequate spread (to L4). No motor block developed and the sensory block regressed rapidly, probably indicating a failure of delivery of the full dose into the subarachnoid space.

Mean height was greater in the ropivacaine group (mean 8 cm, sampling probability <0.05) than the bupivacaine group and may be due to a higher proportion of male patients in the ropivacaine group. This difference might relate to the slightly greater median cephalad spread (one dermatome) in the bupivacaine group, although this was not statistically significant. It might be expected that a fixed dose of local anaesthetic would spread further in shorter patients, but only one of many studies looking at this has shown more extensive spread in shorter patients. The main reason for this is that most of the variation in height between adult patients relates to differences in the length of the lower limb long bones, not the length of the vertebral column.

This study was not carried out exclusively in the day-case setting, but we believe that hyperbaric ropivacaine merits consideration for use in ambulatory surgery. The ideal agent for day-case anaesthesia is the one which when injected intrathecally would produce a rapid onset of a reliable block providing adequate surgical anaesthesia of appropriate duration and followed by a rapid regression of the motor and sensory blocks with minimal side-effects or residual effects. The standard agent for use in this setting has been lidocaine, but concerns persist regarding the incidence of TNS. Although not unheard of, the incidence of TNS is much lower with ropivacaine than lidocaine and thus it might warrant consideration as an agent for the day-case setting. A recent study investigating the mechanism of neural damage of intrathecally injected local anaesthetics in rabbits has reported that lidocaine and tetracaine were equally damaging and worse than bupivacaine, with ropivacaine being least toxic.

Two patients (one each from the ropivacaine and bupivacaine groups) complained of headache in the first 24 h after intrathecal injection. In both, the headache was mild,

### Table 4 Frequency of adverse events

<table>
<thead>
<tr>
<th>Adverse events, n (%)</th>
<th>Bupivacaine (n=20)</th>
<th>Levobupivacaine (n=20)</th>
<th>Ropivacaine (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>5 (25)</td>
<td>6 (30)</td>
<td>6 (32)</td>
</tr>
<tr>
<td>Mild localized back</td>
<td>2 (10)</td>
<td>3 (15)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (5)</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Transient neurological symptoms</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
frontal in distribution, of short duration (<24 h), unaffected by changes in posture, and not associated with other symptoms such as photophobia. The headache did not limit mobilization after operation. From this description, the headaches were not thought to be due to CSF leak as a result of dural puncture.

Most clinical studies comparing bupivacaine and levobupivacaine have found little difference between the drugs and have concluded that they have similar actions. Glaser and colleagues in a recent prospective randomized, double-blinded study compared plain solutions of 3.5 ml of 0.5% levobupivacaine and 3.5 ml of 0.5% bupivacaine in 80 patients undergoing elective hip replacements. They were unable to identify any clinical differences and concluded that levobupivacaine is an alternative to bupivacaine without offering any specific clinical advantage when used in spinal anaesthesia. Our findings are in keeping with these conclusions, although they are a little surprising. The drugs are marketed in the same nominal concentrations, but levobupivacaine was introduced after a change in the regulations regarding drug labelling so its solutions contain 12.6% more active drug than those of racemic bupivacaine. For completeness, we would mention that solutions of ropivacaine (which has a slightly lower molecular weight) contain, in molar terms, 4.5% more active drug than those of racemic bupivacaine.

In conclusion, hyperbaric ropivacaine produces a spinal block which has sensory block onset characteristics similar to equivalent doses of hyperbaric bupivacaine or levobupivacaine, but with a less intense motor block. Both the sensory and motor blocks are also subject to a more rapid recovery with ropivacaine compared with bupivacaine or levobupivacaine which are clinically indistinguishable. This suggests that ropivacaine may be suitable for short procedures where a rapid return of ambulatory function is desirable, such as in the day-case setting, where its recovery profile could confer a distinct clinical advantage.

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