Regional Anaesthesia

Randomized controlled trial of patient-controlled epidural analgesia after orthopaedic surgery with sufentanil and ropivacaine 0.165% or levobupivacaine 0.125%

I. Smet, E. Vlaminck and M. Vercauteren

Department of Anaesthesia, Algemeen Ziekenhuis Nikolaas, Sint Niklaas, Belgium. Department of Anaesthesia, University Hospital Antwerp, Wilrijkstraat 10, B-2650 Edegem, Belgium

*Corresponding author. E-mail: marcel.vercauteren@uza.be

Background. Ropivacaine, and to a lesser extent also levobupivacaine, is commonly used for postoperative epidural analgesia. Despite ED50 data suggesting a potency difference between these drugs, clinically they can be difficult to distinguish. As a consequence, it is unclear which concentration of each drug to use when comparing them for long-term analgesia.

Methods. One hundred patients undergoing total hip or knee replacement were selected to participate in a double-blind randomized study comparing ropivacaine 0.165% with levobupivacaine 0.125% to which was added sufentanil 1 μg ml⁻¹ for postoperative analgesia by the epidural route. Patient-controlled epidural analgesia (PCEA) was offered for 48 h. After the first 24 h, the basal infusion was omitted.

Results. Pain scores both at rest and on mobilization were similar between both groups. The volume of local anaesthetic solution consumed during the first 48 h after surgery was 25% higher in those patients receiving ropivacaine (P = 0.02). Patients receiving ropivacaine made a mean (SD) of 38.5 (16) PCEA demands in the first 48 h after surgery compared with 28 (13) in the levobupivacaine group (P = 0.04).

Conclusions. Both local anaesthetics provided effective postoperative analgesia but, even in a 25% weaker concentration, a small volume of levobupivacaine and opioid substance was consumed. These differences may be explained by a potency difference or by the duration of action of levobupivacaine.

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In many hospitals, racemic bupivacaine has been replaced to a large extent by ropivacaine and levobupivacaine for patient-controlled epidural analgesia (PCEA) as these are perceived to be safer drugs.

Levobupivacaine 0.125% provides satisfactory analgesia with both lumbar and thoracic epidural catheter placement. Selecting the optimal ropivacaine concentration is more difficult as its potency when compared with other drugs is still the subject of debate. Two studies performed in 1999 suggest that ropivacaine may be 40% less potent than bupivacaine whereas this difference is only 2% for levobupivacaine. Benhamou and colleagues found the ED50 value for ropivacaine to be 19% higher than for levobupivacaine, but this difference did not appear to be clinically significant. Camorcia and colleagues reported that ropivacaine and levobupivacaine were both less potent than bupivacaine, and ropivacaine appeared to be 20% less potent than levobupivacaine. In contrast, Polley and colleagues found a similar ED50 value for ropivacaine and levobupivacaine in parturients with cervical dilation of up to 7 cm, despite their having previously reported a 40% difference found between ropivacaine and bupivacaine.

Studies using the minimal local anaesthetic concentration (MLAC) design, which calculate the ED50 dose for
a predefined endpoint, suggest that ropivacaine and levobupivacaine have different potencies. Despite this, in most clinical randomized trials, aiming at administering effective doses for the majority of patients, it appeared difficult to find significant differences between the newer local anaesthetics and racemic bupivacaine.

As a consequence, it is extremely difficult when performing comparative studies to decide what concentrations of local anaesthetic to select and how to interpret the results.

In addition, although studies comparing local anaesthetic solutions given as a single bolus were unable to find differences in quality or duration of effect between different drugs, there is a lack of studies comparing ropivacaine and levobupivacaine over longer periods of time.

The available studies seem to suggest that there is a potency difference between ropivacaine and levobupivacaine, although it is probably <40% found in the initial studies of neuraxial blockade. The purpose of the present study was to determine whether there are differences in consumption, demand dosing, postoperative analgesic quality, or side-effects between ropivacaine and levobupivacaine when used more than 48 h in concentrations of comparable potency.

Methods

Patients undergoing primary total hip or knee replacement were enrolled into a randomized double-blind study. The protocol was approved by the hospital ethics committee and all patients gave written informed consent. Patients were randomized on the basis of a computer-generated table of random numbers generated using Arcus Quickstat version 1.

Exclusion criteria included: weight >100 kg, age >80 yr, any use of analgesics during the week preceding surgery, a contra-indication for neuraxial anaesthesia, or difficulty in understanding patient-controlled analgesia.

The patients received combined spinal–epidural anaesthesia. The spinal component consisted of 3 ml of hyperbaric bupivacaine 0.5% to which was added sufentanil 5 μg. If the spinal block proved insufficient for surgery, epidural lidocaine 2% supplements were allowed to a maximum of 10 ml, after which the patient underwent general anaesthesia and was excluded from the study. During surgery, patients were sedated with a target-controlled infusion of propofol (target concentration 1–2 μg ml⁻¹) so that they were asleep but arousable when spoken to. After operation, patients received a mixture of either ropivacaine 0.165% with sufentanil 1 μg ml⁻¹ or levobupivacaine 0.125% with sufentanil 1 μg ml⁻¹ depending on the group to which they had been randomized. The solutions were prepared in 400 ml bags and numbered by the hospital pharmacist to maintain clinician and patient blinding. Once the Bromage score had decreased to zero on the non-operated side and there was no evidence of residual sedation, a PCEA regimen was started. This delivered a 3 ml h⁻¹ basal infusion for the first 24 h with additional demand doses of 4 ml with a lockout time of 20 min. After the first 24 h, the basal infusion was stopped. Every 12 h, the following variables were recorded: heart rate, arterial pressure and ventilatory frequency, visual analogue scale (VAS) pain scores on a scale of 0–10 both at rest and on mobilization, volume of the test solution delivered, and the injection attempt (I/A) ratio recorded on the PCEA device. We also recorded evidence of side-effects, including vomiting, sedation on a five-point scale (none, slight, sleepy but eye opening to command, not reacting to voice, and unrousable) and motor block on the non-operated side using the Bromage score (0, no motor block; 1, unable to straight leg raise; 2, unable to knee flex; and 3, completely immobile).

If analgesia was insufficient after 1 h of maximal dosing from the PCEA device, patients were given i.v. acetaminophen 1000 mg and i.v. tramadol 100 mg. If this was insufficient, a non-steroidal anti-inflammatory drug was added. Patients requiring such rescue medication were not considered for the final evaluation.

All epidural catheters were removed 48 h after the start of the PCEA infusion. No other analgesic drugs were allowed within the protocol.

As it was assumed that because of the PCEA regimen, differences between pain scores would be minimal. The primary outcome measure was the volume of epidural solution consumed in each group. We calculated that to detect a 15% difference between the two groups, with a standard deviation of 60 ml for the volume of epidural solution consumed more than 48 h as found in our pre-study pilot data (unpublished), 35 subjects would be required in each group to obtain a study power of 0.8 with a P-value of 0.05. ANOVA for repeated measures was used to compare VAS pain scores, heart rate, and arterial pressure. Unpaired, two-tailed Student’s t-tests were used to compare the volumes of epidural solution consumed, injection/attempt (I/A) ratios, age, and weight. For non-parametric data, Fisher’s exact test was used. A P-value of <0.05 was considered to be significant.

Results

Of 117 consecutive patients approached, 100 were enrolled in the study. In the ropivacaine and levobupivacaine groups, 12 and 10 patients, respectively, were excluded from the analysis because of insufficient analgesia requiring rescue analgesia (six patients in the ropivacaine group vs one in the levobupivacaine group), pump malfunction, catheter disconnection, sensory block in the non-operated limb only, or removal from the study on the patient’s request. Thus, the ropivacaine group contained 38 patients.
whereas 40 patients were included in the levobupivacaine group (Fig. 1).

The study groups were comparable with respect to patient characteristics and type of surgery (Table 1).

After 48 h, the total volume of local anaesthetic and sufentanil solution consumed was higher in the ropivacaine group (Table 2). The ropivacaine group required a mean (SD) volume of 221 (64) ml compared with 178 (54) ml for the levobupivacaine group \((P=0.02)\). The mean (SD) dose of ropivacaine for the first 48 h after surgery was 463 (105) mg and was significantly greater than the dose of levobupivacaine, which was 222 (67) mg \((P=0.007)\). The number of PCA demands was greater in the ropivacaine group \((P=0.04)\). The \(I:A\) ratio between both groups did not differ. Pain scores at rest and on mobilization were similar with mean values at rest and remained below 1.5 in both groups. Upon mobilization, these mean values were <2.5 at all times which we considered to represent satisfactory pain management (Fig. 2).

The incidence of hypotension, defined as a decrease of at least 20% from baseline values at any time point and regardless of duration, was low and never exceeded an incidence of 20% (Table 3). Pruritus, mostly mild, was

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**Table 1** Patient characteristics. Data are mean (SD) or number of patients

<table>
<thead>
<tr>
<th></th>
<th>Ropivacaine ((n=38))</th>
<th>Levobupivacaine ((n=40))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>62</td>
<td>65</td>
</tr>
<tr>
<td>Range</td>
<td>(47–79)</td>
<td>(33–78)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72 (16)</td>
<td>75 (18)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164 (9)</td>
<td>166 (10)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>20/18</td>
<td>19/21</td>
</tr>
<tr>
<td>Hip/knee replacement</td>
<td>20/18</td>
<td>22/18</td>
</tr>
<tr>
<td>ASA I/II</td>
<td>23/15</td>
<td>26/14</td>
</tr>
</tbody>
</table>

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**Table 2** Pain management data. Data are mean (SD). PCEA, patient-controlled epidural analgesia

<table>
<thead>
<tr>
<th></th>
<th>Ropivacaine ((n=38))</th>
<th>Levobupivacaine ((n=40))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of local anaesthetic consumed during the first 24 h after surgery (ml)</td>
<td>141 (44)</td>
<td>113 (35)</td>
<td>0.1</td>
</tr>
<tr>
<td>Volume of local anaesthetic consumed during 48 h (ml)</td>
<td>221 (64)</td>
<td>178 (54)</td>
<td>0.02</td>
</tr>
<tr>
<td>Amount of drugs consumed during 48 h (mg)</td>
<td>364.6 (105)</td>
<td>222.5 (67)</td>
<td>0.007</td>
</tr>
<tr>
<td>PCEA device demands/48 h</td>
<td>38.5 (16)</td>
<td>28 (13)</td>
<td>0.04</td>
</tr>
<tr>
<td>PCEA device injection:attempt ratio</td>
<td>0.75 (0.2)</td>
<td>0.8 (0.2)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

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**Fig 1** Consort diagram of the study.

**Fig 2** VAS pain scores on mobilization. Scores are presented as means and standard deviations. There were no statically significant differences. T0 at the start of PCEA, T1 at 12 h, T2 at 24 h, T3 at 36 h, and T4 at 48 h.
reported by 13% and 10% of patients in the ropivacaine and levobupivacaine groups, respectively, as the incidences of motor block, sedation, and vomiting were very low.

The results did not differ when patients undergoing knee and hip surgery were analysed separately. No differences were found between the two groups when evaluating the first and second 24 h periods separately.

**Discussion**

The present study shows that even if the potency difference between ropivacaine and levobupivacaine is taken into account larger volumes of the former are required during a 48 h PCEA regimen. There were no differences in analgesic quality or side-effects. The 20% larger sufentanil dose administered in the ropivacaine group when compared with the levobupivacaine group did not result in more sedation or vomiting.

There is a lack of studies comparing ropivacaine and levobupivacaine for postoperative epidural analgesia. Casati and colleagues\(^1\) compared ropivacaine 0.2% with levobupivacaine 0.125% after orthopaedic surgery, but their observation period was only 12 h. They concluded that the quality of analgesia and the degree of motor impairment were similar for both newer local anaesthetics. Senard and colleagues\(^9\) did not find any difference between PCEA with ropivacaine 0.1% and levobupivacaine 0.1% (to which was added a morphine background infusion) over a 48 h period except that fewer patients in the ropivacaine group experienced motor weakness.

Several aspects of the study design require further discussion. A basal infusion was used for the first 24 h. This may have explained the 20% incidence of hypotension at 12 h, which reduced to 10–15% at 24 h and was not a problem during the second day. A background infusion is not useful for epidural opioids alone,\(^10\) but with combinations of local anaesthetics and opioids, the use of a basal infusion seems to be common practice, although there is a lack of studies demonstrating benefit from this. Most studies have been performed in labouring patients where a moderate basal rate seems to offer clinical benefits without increasing total drug consumption.\(^11\) In one postoperative epidural study, patients receiving a night-time basal infusion of a local anaesthetic–fentanyl mixture demanded fewer doses from the PCEA device (but still received a larger total dose of local anaesthetic) and had lower pain scores upon coughing than in patients without this nocturnal infusion.\(^12\) In the present study, demands for local anaesthetic were made less than once an hour, which seems acceptable. A need for frequent demands may affect sleep quality and patient satisfaction. We considered that a basal rate infusion could be beneficial during the first 24 h after surgery when patients were not yet unfamiliar with the PCEA pump. The occurrence of hypotension suggests that it may be worth reducing the infusion time or volume.

Secondly, several studies have found a 40% potency difference between ropivacaine and racemic bupivacaine, whereas the difference between the latter and levobupivacaine seems to be small.\(^3–5\) More recent studies have weakened the initially calculated potency difference to less than 40%. During early labour, the difference between epidural levobupivacaine and ropivacaine was found to be close to 20%.\(^6,7\)

Criticisms have been made of MLAC calculations based upon sequential up and down allocation. All these studies were done in labouring patients and the ED50 values obtained do not correspond with those observed in practice. Most labour studies comparing racemic bupivacaine and ropivacaine were unable to find any clinical difference when identical concentrations were used.\(^13–16\) However, these studies may be flawed. Labour requires only a short period of analgesia. In these studies, initial potent doses of fentanyl or sufentanil were added to the local anaesthetic solution, so masking any difference in potency. Although epidural studies have not shown evidence of a potency difference, studies of spinal anaesthesia suggest that a 50% higher dose of ropivacaine is required to provide similar anaesthetic quality and duration to racemic bupivacaine.\(^17–20\) It is not clear why potency would depend on the route of administration.

In the present study, the 25% difference in volume of solution consumed was not reflected in any other differences favouring levobupivacaine.

The mean dose total of ropivacaine was 60% greater than that of levobupivacaine.

The larger consumption of ropivacaine does not necessarily suggest that the potency difference between both newer local anaesthetics is even more than the 25% assumed in the present study design. A shorter duration of action of ropivacaine may have caused a requirement for additional demands, although it would be unwise to believe that a 50% larger dose can be entirely explained by a difference in duration of action. Slight differences of duration of action may only become obvious after longer periods of administration as in the present study.

Finally, the addition of an opiate may have affected local anaesthetic analgesic quality and duration. However, there is no evidence that opiate added to local anaesthetic solutions would alter potency differences between them.

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**Table 3 Side-effects. Data are expressed as number of patients (%). There were no statistically significant differences**

<table>
<thead>
<tr>
<th></th>
<th>Ropivacaine (n=38)</th>
<th>Levobupivacaine (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension at 12 h</td>
<td>7 (18)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>At 24 h</td>
<td>4 (10)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5 (13)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Motor block</td>
<td>1 (2.6)</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (2.6)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Sedation &gt;2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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In conclusion, the present study found that both local anaesthetics provide satisfactory analgesia in the concentrations used. Despite a 25% higher ropivacaine concentration, the volume consumed was higher during a 48 h period when compared with levobupivacaine. This suggests either a potency difference between both local anaesthetics of more than 25% or a different duration of action. Regardless of the exact explanation, using lower concentrations of ropivacaine may be unwise as it could mean that more PCEA demands are made which may increase the total opiate dose if its concentration is not changed to allow for this.

References