The Dose–Response of Caudal Ropivacaine in Children

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Background: Ropivacaine, a new local anesthetic, is less cardiotoxic in adults and is less likely to cause motor blockade than is bupivacaine. The authors evaluated the clinical effectiveness and hemodynamic effects of ropivacaine compared with bupivacaine and the pharmacokinetics of ropivacaine when given for caudal blocks in 56 children $\pm 1.7$ yr old (mean $\pm$ SD).

Methods: Patients scheduled for inguinal hernia repair were randomly given a caudal injection (0.75 ml/kg) of ropivacaine, 0.25% (R0.25 group); ropivacaine, 0.5% (R0.5 group); or bupivacaine, 0.25% (B0.25 group). Postoperative measurements included the duration of analgesia, which was our primary outcome variable, and hemodynamic and respiratory monitoring for 4 h in the recovery room. Thereafter, analgesic requirements for the following 24 h were assessed by an independent observer on the ward using an observational pain–discomfort scale, which gives a cumulative score from 5 to 15 to estimate the quality of analgesia by assessment of behavioral objective parameters. Plasma levels of ropivacaine were measured before the procedure was started and 5, 10, 15, 20, 25, 30, and 45 min and 1, 2, 4, 6, 8, and 24 h after caudal block.

Results: A significantly longer ($P < 0.0001$) duration of analgesia (median [range]) was observed in the R0.5 group (1,440 [355–1,440] min), whereas the R0.25 group (208 [175–340] min) and the B0.25 group (220 [100–390] min) were comparable. All groups showed a significant decrease in mean arterial blood pressure and heart rate from baseline values, but differences between groups were not observed.

Conclusion: Ropivacaine is well tolerated and provides effective analgesia when given for caudal blockade in small children for inguinal hernia repair. (Key words: Anesthetics; bupivacaine; caudal anesthesia; duration of analgesia; pain.)

CAUDAL analgesia, a relatively simple technique with a predictable level of blockade, provides excellent postoperative analgesia. It is the most popular regional anesthetic used in pediatric surgery for various surgical procedures, such as lower abdominal, urologic, and lower limb operations. This long-acting regional technique provides analgesia beyond the duration of surgery, with a smooth recovery period and good postoperative pain control, and therefore reduces analgesic requirements and facilitates early discharge.

Long-acting anesthetics, such as bupivacaine, have had a well-defined role in regional anesthesia and analgesia for many years. Since the report of several cases of systemic toxic reactions after accidental intravenous injection of bupivacaine, the need for an effective, long-acting local anesthetic with a high therapeutic ratio has prompted researchers to develop new local anesthetics. Ropivacaine, a new long-acting amide local anesthetic agent, with fewer toxic cardiac and central nervous system effects provides greater separation of sensory and motor effects. These properties suggest advantages compared with bupivacaine for regional anesthesia and postoperative analgesia. In children, only limited data regarding the effectiveness of ropivacaine, especially for caudal anesthesia, are available.

We designed a double-blind, dose-ranging study to evaluate the hemodynamic effects and analgesic effectiveness of ropivacaine compared with bupivacaine in pediatric caudal anesthesia.

Methods

After institutional approval from our ethics committee and written informed parental consent, we enrolled 57 children classified as American Society of Anesthesiolo-
gists physical status I or II who were 1.5–7 yr old in this prospective, randomized, and double-blinded study. Children were scheduled for inguinal hernia repair and randomized, using a systematic random-sample technique, to one of three treatment groups for caudal block, with all patients receiving 0.75 ml/kg of the local anesthetic. In the B0.25 group, bupivacaine, 0.25%, was given. In the R0.25 group, ropivacaine, 0.25%, was given; and in the R0.5 group, ropivacaine, 0.50%, was administered. Drugs were prepared by an independent anesthesiologist who was not involved in the study. Surgery was performed by applying the same surgical technique and patient treatment in all the children included in the study.

All children were premedicated with 0.5 mg/kg rectal midazolam (maximum dose, 15 mg) according to the standard guidelines of our pediatric anesthesia department. Anesthesia was induced with halothane. An intravenous line was then started. After intravenous injection of 3 mg/kg propofol, a laryngeal mask was positioned and Ringer’s lactate solution was infused at a rate of 10 ml · kg⁻¹ · h⁻¹. Thereafter, caudal blocks were performed using 22-gauge Quincke needles under aseptic conditions with the children in the lateral position. They were immediately turned supine after slow injection of the drug. Anesthesia was maintained with halothane, 0.5–1%, and nitrous oxide, 70%, in oxygen. Standard monitors were used.

Noninvasive mean arterial pressure, heart rate, and oxygen saturation were recorded 5 min before induction of anesthesia (baseline value, 30 min after rectal sedation), followed by measurements at 5-min intervals during the anesthesia. All children breathed spontaneously with manual assistance during the anesthetic and surgical procedure. Anesthetic agents were discontinued at the beginning of skin closure. After the patients were sufficiently awake, they were brought to the recovery room breathing room air. After arrival, mean arterial pressure, heart rate, and percutaneous oxygen saturation were documented every 15 min until 4 h after caudal block.

Intra- and postoperative decreases in mean arterial pressure and heart rate more than 30% from baseline values were defined as severe hypotension or bradycardia, respectively, and were treated by the rapid infusion of fluids or, if unsuccessful, the use of ephedrine (equivalent to ephedrine), in aliquots of 0.02 or 0.01 µg/kg atropine, as appropriate. Hypoxemia was defined as a decrease in oxygen saturation less than 93% requiring supplemental oxygen by mask.

Analgesic effectiveness was documented using an observational pain–discomfort scale (OPS) and by the duration of analgesia after caudal blockade, which was defined as the interval from caudal block until the first pain medication was given. The OPS assessed behavioral objective parameters (crying, facial expression, position of the torso, position of the legs, and motor restlessness). Each parameter scores 1–3 (none, moderate, severe) to give a cumulative score of 5–15 to estimate the quality of analgesia (5 = excellent, 15 = ineffective). If the OPS score, assigned by a study nurse, was more than 11 in two subsequent measurements or the patient had obvious signs of pain, 20 mg/kg paracetamol was administered in suppository form. These children subsequently were eliminated from further evaluation. After an observation period of 4 h in the recovery room, the patients were discharged to the ward. To achieve an observation period of 24 h, parents were instructed to apply the OPS and assess the children during the following 20 h after discharge from the recovery room and to give rectal paracetamol if necessary. The duration of postoperative analgesia was defined as the time between caudal drug injection and the first rectal paracetamol administration. If no rectal paracetamol was necessary within 24 h, the duration of analgesia was counted as 1.440 min. The times from caudal injection to first supported standing and first spontaneous voiding after anesthesia were also documented. During the entire study period, two observers blinded to the therapeutic intervention were responsible for the assessment, drug administration, and parental instruction. Each observer did complete assessments during the 4-h observation period of a single patient.

To measure total plasma concentrations of ropivacaine, peripheral blood samples were collected via the established intravenous access in 12 patients in the R0.25 and R0.5 groups. Blood samples were taken before starting the caudal block, 5, 10, 15, 20, 30, and 45 min and 1, 2, 4, 6, 8, and 24 h after injection of the local anesthetic. Three milliliters peripheral blood was collected by a blinded observer for each assay of total ropivacaine plasma concentration. To limit blood sampling in this pediatric study as much as possible, we did not differentiate protein-bound from the total ropivacaine plasma concentration, and measurements of α1-glycoproteins were not performed (8 ml/blood/assay). The samples were taken in heparin-prepared tubes, and plasma was separated by centrifugation at room temperature within 30 min of collection. The plasma samples were stored at −30°C until drug assay. The assay of
plasma ropivacaine was performed by gas chromatography. The concentration of ropivacaine was given in nanograms per milliliter.

All data are presented as the mean and SD, except the duration of analgesia, which is given as the median and range, because of censored data. Frequency distributions were calculated using chi-square analysis. One-way analysis of variance was used to compare differences between groups, with post hoc comparison using the Scheffé test. Two-way analysis of variance for repeated measurements was used to assess changes over the time within and between groups. Chi-square analysis was used to compare differences between proportions. The Kruskal–Wallis H test assessed differences of duration of analgesia between groups. \( P < 0.05 \) was considered significant.

Results

The study groups were comparable with respect to patient age, height, weight, sex, and surgical procedure characteristics (table 1). Of 57 children included in the study, 56 were finally evaluated. One child was excluded because the caudal block failed after subcutaneous misplacement of the local anesthetic. All patients underwent the same type of surgery (i.e., inguinal hernia repair) according to standardized surgical conditions.

The duration of analgesia was significantly longer in the R0.5 group than in the B0.25 and R0.25 groups (fig. 1; \( P < 0.0001 \)). No difference was observed between the B0.25 and the R0.25 groups. Within the 24-h observation period, fewer children required additional analgesia in the R0.5 group compared with the other groups (\( P < 0.001 \)). The OPS scores were similar for as long as 2 h after caudal block. The R0.5 group had significantly lower scores 3 and 4 h after caudal block (\( P < 0.01 \); data not shown).

The time to first voiding was longer in the R0.5 group than in the two other groups (\( P < 0.05 \); table 2). Similarly, the standing interval was significantly prolonged in the R0.5 group (\( P < 0.0001 \); table 2). One child of this group experienced postoperative motor block, evidenced by inability to stand free by order or support.

Hemodynamic evaluation revealed a significant decrease over time in all groups for heart rate (\( P < 0.001 \)).

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>B0.25</th>
<th>R0.25</th>
<th>R0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>17</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>4 ± 1.3</td>
<td>5 ± 2.1</td>
<td>4 ± 2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>97 ± 12</td>
<td>106 ± 14</td>
<td>103 ± 15</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>15 ± 4</td>
<td>16 ± 4</td>
<td>16 ± 5</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>29 ± 14</td>
<td>30 ± 8</td>
<td>36 ± 19</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

**Table 2. Time to First Observation of Standing and Voiding after Caudal Injection**

<table>
<thead>
<tr>
<th></th>
<th>B0.25</th>
<th>R0.25</th>
<th>R0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>17</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Standing (min)</td>
<td>253 ± 39</td>
<td>248 ± 30</td>
<td>362 ± 42</td>
</tr>
<tr>
<td>Voiding (min)</td>
<td>248 ± 75</td>
<td>243 ± 30</td>
<td>291 ± 75</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

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Fig. 1. The duration of analgesia for each patient during the 24-h observation period. Values are presented as the median and range. B0.25 = bupivacaine 0.25%, R0.25 = ropivacaine 0.25%, R0.5 = ropivacaine 0.5%. The R0.5 group was significantly different compared with the other groups. No other differences were significant.

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and mean blood pressure ($P < 0.001$), with no difference between groups (data not shown). No pharmacologic intervention was necessary in any patient.

Figure 2 shows the concentration-versus-time curves for the two concentrations of ropivacaine obtained by in vitro sampling in plasma single-dose administration.

Discussion

Our data indicate that ropivacaine is an effective local anesthetic for pediatric caudal block. Ropivacaine at a concentration of 0.25% proved to be as effective as bupivacaine, 0.25%, with comparable minimal side effects. Ropivacaine, 0.50%, was more effective in terms of the duration of analgesia but led to a longer standing interval, longer time until first voiding, and to motor block in one child.

Compared with bupivacaine, ropivacaine, a new amide local anesthetic, is associated with less cardiac toxicity and a greater separation of sensory and motor effects, making it particularly attractive for use in children. Compared with bupivacaine, many clinical
trials showed a significantly shorter duration of motor and sensory blockade in ropivacaine recipients.\textsuperscript{16-18}

However, limited data are available concerning the use of ropivacaine for caudal blocks in children.\textsuperscript{11,12} Both of these studies indicate that ropivacaine is a safe drug for caudal anesthesia. Concerning postoperative analgesia, these investigations had contradictory results. One study shows superior postoperative analgesia with ropivacaine,\textsuperscript{11} whereas the other study shows no significant difference between ropivacaine and bupivacaine in terms of the duration of analgesia.\textsuperscript{12} In one of these studies, a significantly higher degree of motor block was observed after bupivacaine administration for caudal block, whereas no difference was found in the second study.\textsuperscript{12}

In our study, ropivacaine and bupivacaine at concentrations of 0.25\% produced reliable analgesia in all children with virtually no complications in any patient, indicating that both drugs can be recommended for pediatric caudal block. However, the safety profile of ropivacaine in adults, and the similar analgesic potency in our study population, slightly favors ropivacaine because large volumes of local anesthetics must be given to achieve adequate blockade, and intravenous infusion can occur accidentally.

Especially in children, the intrinsic vasoconstrictive properties of ropivacaine\textsuperscript{19-21} would be of particular interest because vasoconstriction leads to prolonged analgesia in this population and might not require the concomitant use of adrenaline. Ropivacaine, 0.5\%, is more effective in terms of the duration of analgesia but is accompanied by more extensive side effects. The time until first voiding and the standing interval were significantly prolonged, and motor block occurred in one child.

In adults, ropivacaine showed a higher maximum tolerated total venous plasma concentration compared with bupivacaine. At total venous plasma levels of 2.2 \( \mu \)g/ml, no side effects were detected. At doses producing cardiovascular depression or neurologic symptoms, changes were less pronounced with ropivacaine compared with bupivacaine.\textsuperscript{7} No data are available for ropivacaine in children. For bupivacaine, a plasma concentration 2 to 3 \( \mu \)g/ml is believed to be the threshold for toxic neurologic effects in children.\textsuperscript{22,23} We did not exceed the plasma levels of local anesthetics just noted in either of our study groups. Furthermore, we remained well below those levels, and, therefore, we believe that ropivacaine given for pediatric caudal block is appropriate.

We also could argue that parental assessment of acute pediatric pain is less objective than the OPS ratings of nurses.\textsuperscript{24} Parental thresholds of reaction to their child’s pain may differ widely, and analgesic medication may be inadequate even when the parents recognize that their child is in pain.\textsuperscript{25} We tried to make parental pain control uniform by advising parents about the use of our OPS, but the protocol also allowed the parents to give additional analgesics (rectal paracetamol if necessary or when the OPS score was > 11). But OPS ratings were never less than 12 when parents believed that their children were in obvious pain. In this study, we used an intermediate dose of 0.75 ml local anesthetic/kg body weight, although higher doses up to 1.25 ml/kg body weight may be used.\textsuperscript{26} It remains to be determined whether larger volumes of ropivacaine significantly prolong the duration of analgesia without increasing the incidence of side effects.

However, this is the first report of the use of caudal ropivacaine in children at two different concentrations and measuring plasma ropivacaine levels. Ropivacaine, 0.25\%, proved to be as effective as bupivacaine, 0.25\%, in a dose of 0.75 ml/kg body weight. Because of its beneficial pharmacodynamic properties, ropivacaine is a reasonable alternative to bupivacaine.

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