

The Dose-Response Relationship for Clonidine Added to a Postoperative Continuous Epidural Infusion of Ropivacaine in Children

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Epidurally administered clonidine enhances the quality and duration of postoperative analgesia when it is used as an adjunct to local anesthetics in children. We investigated the dose-response relationship for epidural clonidine when added to a continuous postoperative epidural infusion of ropivacaine. By use of an observer-blinded design, 55 pediatric patients (1–4 yr old) were randomly given a postoperative epidural infusion of plain ropivacaine 0.1% 0.2 mg · kg⁻¹ · h⁻¹ (Group R), ropivacaine 0.08% 0.16 mg · kg⁻¹ · h⁻¹ plus clonidine 0.04 μg · kg⁻¹ · h⁻¹ (Group RC1), ropivacaine 0.08% 0.16 mg · kg⁻¹ · h⁻¹ plus clonidine 0.08 μg · kg⁻¹ · h⁻¹ (Group RC2), or ropivacaine 0.08% 0.16 mg · kg⁻¹ · h⁻¹ plus clonidine 0.12 μg · kg⁻¹ · h⁻¹

(Group RC3). A clear dose-response relationship could be identified for a continuous infusion of epidural clonidine, with clonidine dosages in the 0.08–0.12 μg · kg⁻¹ · h⁻¹ range providing improved postoperative analgesia (reduced Children's Hospital of Eastern Ontario pain score, increased time to first supplemental analgesic demand, and a reduced total number of doses of supplemental analgesics during the first 48 h after surgery). Analgesia was improved without any signs of increased sedation or other side effects. The adjunct use of epidural clonidine in the dosage range of 0.08–0.12 μg · kg⁻¹ · h⁻¹ appears effective and safe for use in children.

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Continuous postoperative epidural bupivacaine infusions have gained widespread acceptance as an effective method of achieving high-quality postoperative pain relief in both infants and children (1). However, despite pharmacokinetic studies of epidurally administered bupivacaine (2) and dosage recommendations based on a large observational study (3), systemic toxicity (e.g., seizures, hypotension, arrhythmia) has been reported after the use of bupivacaine (4).

A number of studies have reported the successful clinical use of ropivacaine, a new local anesthetic associated with less risk of systemic toxicity for epidural or caudal blockade in children (5–7). The pharmacokinetics of this compound in children are similar to those of adults (8,9). Adjuncts to local anesthetics,

such as opioids, clonidine, and ketamine, have been administered to further enhance the quality of epidural analgesia (10,11). In previous studies, improved quality, as well as increased duration, of analgesia has been reported when single-bolus injections of clonidine (2 μg/kg) were added to caudally or epidurally administered local anesthetics (12,13). However, the optimal adjunct dose of clonidine for continuous epidural administration in children has not previously been established.

The aim of this study was to identify the dose-response relationship and possible side effects of clonidine when added to a postoperative continuous epidural infusion of ropivacaine in children.

Methods

After obtaining ethics committee approval and written, informed parental consent, 60 boys (age 1–4 yr, ASA physical status I) scheduled to undergo inpatient hypospadias repair were included in a prospective,

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randomized, observer-blinded study. Exclusion criteria included commonly accepted contraindications to epidural blockade and a history of allergic reactions to local anesthetics.

All patients received premedication with oral diazepam 0.4 mg/kg. After application of standard monitoring, general anesthesia was induced by mask with halothane and maintained with isoflurane 0.8%–1% in an oxygen/air mixture (fraction of inspired oxygen = 0.5) throughout surgery. The airway was maintained with a laryngeal mask or an orotracheal tube of appropriate size. Neuromuscular block was accomplished with atracurium 0.5 mg/kg when tracheal intubation was performed. After the induction of anesthesia, patients were placed in the lateral position, and under sterile conditions, an epidural catheter was placed at a low lumbar interspace (L5-S1) by using a Tuohy 19-gauge needle. After adequate loss of resistance, the epidural catheter was advanced 3 cm into the epidural space. All blocks were performed by a senior pediatric anesthesiologist.

After the placement of the epidural catheter, the patients received increments of 0.2% ropivacaine for a total dose of 1.4 mg/kg while we watched for signs of toxicity (no test dose was used). The maximum volume injected was 20 mL. The adequacy of the block was tested by pinprick during light anesthesia, as previously described (14,15). Children identified as having an incomplete block were excluded from the study. Sixty minutes after the initial injection of ropivacaine 0.2%, a continuous infusion of plain ropivacaine 0.1% was started at a rate of $0.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ and was continued for the duration of the surgical procedure.

At the end of surgery, the children were extubated when awake and were transferred to the recovery area. The time from discontinuation of the volatile anesthetic to spontaneous eye opening was noted, and the degree of motor block at awakening was recorded according to a modified Bromage scale (see below). At this point, children were allocated, according to a computer-generated random list, to receive one of four different epidural infusions: plain ropivacaine 0.1% $0.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (Group R), ropivacaine 0.08% $0.16 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ plus clonidine $0.04 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ($1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) (Group RC1), ropivacaine 0.08% $0.16 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ plus clonidine $0.08 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ($2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) (Group RC2), and ropivacaine 0.08% $0.16 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ plus clonidine $0.12 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ($3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) (Group RC3); these were infused with an infusion pump (Cadd; Sims Deltec, St. Paul, MN). The infusions were prepared and connected by an operator who took no further part in the study. After a brief observation period in the recovery area, patients were then returned to their regular ward, and the epidural infusion was continued for 48 h.

During the postoperative 48-h period, heart rate, blood pressure, and respiratory rate were measured at arrival in the recovery room and then every 2 h (when patients were awake) by an automatic device. The quality of pain relief was assessed by the Children's Hospital of Eastern Ontario Pain Score (CHEOPS) (lowest score, 4, no pain; highest score, 13, severe pain) (16). The degree of motor block in the lower extremities was recorded with a modified Bromage scale (0 = no motor block; 1 = inability to raise extended legs; 2 = inability to flex knees; 3 = inability to flex ankle joints) (17), and the degree of sedation was assessed with a three-point sedation scale based on eye opening (0 = eyes open spontaneously; 1 = eyes open to speech; 2 = eyes open in response to physical stimulation) (18). Pain, motor function, and sedation were assessed once in the recovery room (Table 1) and every 4 h if the patient was awake. During the night (11:00 PM to 7:00 AM), evaluations were omitted at least once to allow patients to sleep undisturbed overnight. Additional pain assessments were performed if the child complained of pain. Each child was prescribed acetaminophen/codeine suppositories (200 mg/5 mg, Lonarid; Boehringer, Ingel, Italy) (19) to be given by the nurse if patients had CHEOPS scores >9 on two consecutive assessments 5 min apart. All the assessments of the variables studied were recorded by nurse observers unaware of the mixture used for epidural infusions. The time to first analgesic demand and the total number of postoperative analgesic requests during the 48-h period were noted.

Side effects in the form of sedation (see above), nausea and vomiting, and respiratory depression (<12 breaths/min) were registered, as were hemodynamic side effects, defined as hypotension (systolic arterial pressure <70 mm Hg) and bradycardia (heart rate <80 bpm).

Data are presented as means and SD for normally distributed data and as median and range for nonnormally distributed data. The Shapiro-Wilks test was used to assess whether data were normally distributed. If this test did not indicate normal distribution, nonparametric tests were used to assess differences among and within groups. Differences among groups for age, weight, height, and time to spontaneous eye opening at the end of procedure were assessed by the Kruskal-Wallis analysis of variance. Multiple comparisons were performed by Mann-Whitney *U*-tests with Bonferroni's correction. Kruskal-Wallis analysis of variance was performed to assess variations of blood pressure, heart rate, and CHEOPS scores. Sedation scores and motor block were compared with the Mann-Whitney *U*-test. For all statistical analyses, the significance level was 0.05 and the tests were two tailed.

Table 1. Patient Data

| Patient data | Group | | | | |
|---|----------|---------|---------|---------|----|
| | R | RC1 | RC2 | RC3 | |
| ASA physical status | 1 | 1 | 1 | 1 | NS |
| Age (mo) | 28 ± 12 | 31 ± 10 | 28 ± 14 | 32 ± 9 | NS |
| Weight (kg) | 13 ± 7 | 14 ± 5 | 13 ± 6 | 13 ± 5 | NS |
| Preoperative heart rate (bpm) | 105 ± 10 | 108 ± 6 | 109 ± 9 | 108 ± 5 | NS |
| Preoperative systolic NIBP (mm Hg) | 82 ± 6 | 80 ± 8 | 79 ± 8 | 81 ± 5 | NS |
| Time to eye opening after anesthesia (min) | 5 ± 2 | 5 ± 1 | 4 ± 1 | 5 ± 2 | NS |
| Postoperative heart rate (bpm), 0-48 h | 106 ± 6 | 106 ± 5 | 107 ± 6 | 107 ± 5 | NS |
| Postoperative systolic NIBP (mm Hg), 0-48 h | 92 ± 8 | 93 ± 7 | 89 ± 8 | 88 ± 7 | NS |

NIBP = noninvasive blood pressure; NS = not significant.
Data are displayed as mean ± sd.

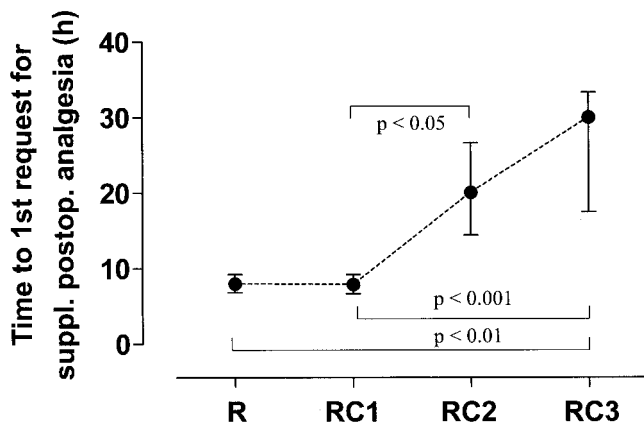


Figure 1. Time to first request for supplemental postoperative analgesia, displayed as median and 95% confidence interval. Group R versus Group RC3, $P < 0.01$; Group RC1 versus Group RC2, $P < 0.05$; and Group RC1 versus Group RC3, $P < 0.001$.

Results

Three subjects in Group R and two subjects in Group RC1 were excluded from the study because of inadequate epidural block or catheter dislocation, thus leaving 55 patients for final analysis. The four groups were similar with respect to age, weight, ASA physical status, baseline blood pressure and heart rate, and time to eye opening after anesthesia (Table 1). The children's cardiorespiratory status remained stable for the duration of the study (Table 1), and no adverse events were noted in any of the patient groups. All patients were assessed as pain free and without any signs of motor blockade during their stay in the recovery room. CHEOPS scores were lower in Group RC3 than RC2 than RC1 than R; the median time to the first administration of supplementary postoperative analgesia was 8.0 h in Group R, 8.0 h in Group RC1, 18 h in Group RC2, and 32 h in Group RC3 (Fig. 1). The median number of postoperative analgesic doses was 4.0 in Group R, 4.0 in Group RC1, 1.0 in Group RC2, and 1.0 in Group RC3 (Fig. 2). Sedation scores for the first 48

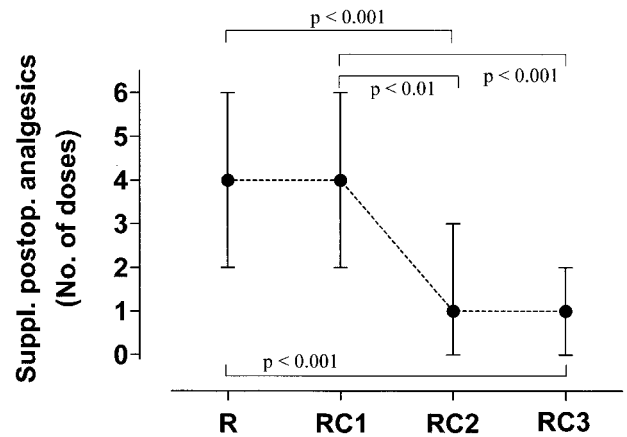


Figure 2. Total number of doses of supplemental postoperative analgesics, displayed as median and 95% confidence interval. Group R versus Group RC2, $P < 0.001$; Group R versus Group RC3, $P < 0.001$; Group RC1 versus Group RC2, $P < 0.01$; and Group RC1 versus Group RC3, $P < 0.001$.

postoperative hours are shown in Figure 3. No signs of motor block were observed in any of the patients during the observation period. All patients started oral intake 2 h after surgery. Four patients vomited after surgery: one in Group R, two in Group RC1, and one in Group RC3. For surgical reasons, all patients had either a transurethral catheter or a suprapubic catheter in place in the postoperative period. All epidural catheters were removed uneventfully 48 h after surgery.

Discussion

The main finding of this study was that adjunct doses of clonidine in excess of $0.04 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ are required to improve the analgesia of an epidural ropivacaine (0.08%) infusion after urogenital surgery in children. An adjunct clonidine dose of $0.08-0.12 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ seemed optimal because increasing sedation might be expected with a larger dose (20,21).

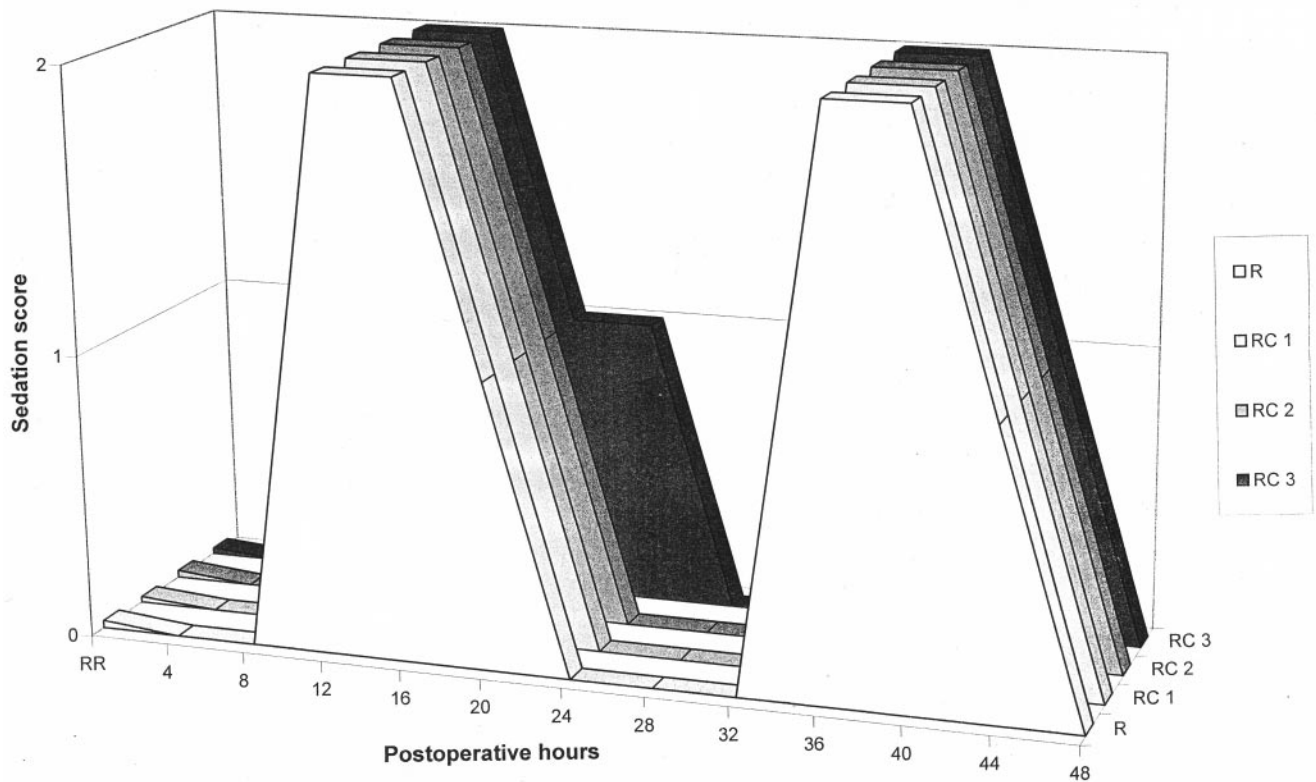


Figure 3. Sedation scores for the first 48 postoperative hours. No statistical difference was found among the different study groups. The two peaks in postoperative sedation coincide with the first and second postoperative night.

Several recent studies report ropivacaine to be a useful new addition to pediatric regional anesthesia (5-7). Despite the reduced tendency for motor blockade by ropivacaine compared with bupivacaine, the use of larger concentrations of ropivacaine caused undesired postoperative motor blockade in the lower extremities (22). To avoid unwanted motor blockade and also to reduce the risk of systemic toxicity, ropivacaine 0.1% has been used for postoperative analgesia in children. However, reducing the concentration to 0.1% does not provide clinically reliable postoperative analgesia (23). Use of clonidine as an adjunct to local anesthetics both enhances the quality of pain relief and substantially prolongs the duration of analgesia after caudal and epidural blockade in children (12-13). In previous studies, we have determined the pharmacokinetics of epidural clonidine 2 $\mu\text{g}/\text{kg}$ in children (24), and we have shown that a caudal bolus injection of ropivacaine 0.1% together with clonidine 2 $\mu\text{g}/\text{kg}$ results in better postoperative pain relief than plain ropivacaine 0.2% (25). Despite the well validated effect of clonidine as an adjunct to local anesthetics in pediatric caudal and epidural blockade, no previous data have been available regarding its dosage during continuous postoperative infusions.

Our prospective, observer-blinded, randomized controlled trial provides new information regarding the following three issues. First, our results support previous studies showing suboptimal postoperative analgesia associated with the use of plain ropivacaine 0.1% (23). Second, a clear dose-response for epidurally infused clonidine can be identified with respect to postoperative analgesia. An improved effect with clonidine was observed with respect to CHEOPS scoring and time to first supplemental analgesic request, as well as the total analgesic requirement during the first 48 postoperative hours with increasing doses of clonidine. A dose smaller than 0.08 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ was not associated with any measurable effect, whereas dosages $\geq 0.08 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ produced both clinically and statistically significant improvement in postoperative analgesia. Third, although a slight degree of clonidine-induced postoperative sedation might not be entirely undesirable in children, major sedation could, obviously, be undesirable. A slight trend toward increasing sedation was observed at the largest clonidine dosage in our study. This trend was not statistically significant, but this could potentially be explained by the limited number of patients included in the study. However, further increases in the clonidine dose might be associated with excess

sedation (20). Because a dosage of $0.12 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ was sufficient to provide excellent analgesia, larger doses may not be advisable as they could result in excessive sedation with no increase in analgesia. The previous reported safety of epidural clonidine administration in children (12-13) was further supported by our observations of cardiovascular stability (Table 1) and lack of any significant side effects. Thus, infusions of small concentrations of ropivacaine combined with clonidine are safe and can be used with routine clinical monitoring in healthy ASA physical status I children aged one to four years.

When interpreting the results regarding CHEOPS scores, it should be remembered that larger doses of clonidine produce sedation (20). Sedation is a major confounding factor with the CHEOPS scale (16). However, sedation scores were almost identical between the group not receiving clonidine (Group R) and the three different clonidine groups (Groups RC1, RC2, and RC3)(Fig. 1). The observed similar degree of sedation in all four groups makes any significant inference with CHEOPS scores less likely, in the authors' opinion.

We used a low lumbar epidural catheter technique instead of a caudal approach. The appropriateness of caudal catheters for prolonged postoperative use is a matter of discussion with different views. Despite the results published by Kost-Byerly et al. (26), some investigators still maintain that continuous caudal catheters are not appropriate because of the potential risk for bacterial contamination. Therefore, one could speculate that a low lumbar epidural block might not sufficiently block the sacral segments involved in hypospadias repair. If so, the clonidine groups could be at an advantage, because clonidine is thought to act via the dorsal horn, thus making these groups less sensitive to appropriate positioning of the catheter tip. However, adequate postoperative analgesia was present for eight hours in the group receiving ropivacaine only. The authors view this as evidence for appropriate blockade also of the sacral segments with the use of a low lumbar epidural block. This is consistent with our clinical experience and previous results reported from our group using lumbar epidural blocks for this type of surgery (27). However, as has been reported previously (23), an infusion of plain ropivacaine 0.1% is apparently not capable of providing reliable pain relief beyond eight postoperative hours.

In conclusion, epidural coinfusion of clonidine together with ropivacaine 0.08% improves postoperative analgesia compared with plain ropivacaine 0.1%. A clonidine dose of $0.08-0.12 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ appears optimal because smaller doses do not enhance ropivacaine analgesia.

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