Comparison of the effects of clonidine and ketamine added to ropivacaine on stress hormone levels and the duration of caudal analgesia

MERT AKBAS MD*, HALIDE AKBAS MD†, ARIF YEGIN MD*, NURSEL SAHIN MD* AND TULIN AYDOGU TITIZ MD*  
*Department of Anaesthesiology and †Central Laboratory, Akdeniz University Medical Faculty, Antalya, Turkey

Summary

Background: The purpose of this study was to compare the analgesic quality and duration of ropivacaine 0.2% with the addition of clonidine (1 μg·kg⁻¹) with that of ropivacaine 0.2% and the addition of ketamine (0.5 mg·kg⁻¹) to that of ropivacaine 0.2% and also compare the postoperative cortisol, insulin and glucose concentrations, sampled after induction and 1 h later following caudal administration in children.

Methods: According to the randomization, patients in the ropivacaine group (R; n = 25) received ropivacaine 0.2%, 0.75 ml·kg⁻¹; those in the clonidine group (RC; n = 25) received ropivacaine 0.2% 0.75 ml·kg⁻¹ plus clonidine 1 μg·kg⁻¹ and those in the ketamine/ropivacaine group (RK; n = 25) ropivacaine 0.2% 0.75 ml·kg⁻¹ plus ketamine 0.5 mg·kg⁻¹ (10 mg·ml⁻¹ concentration). Drugs were diluted in 0.9% saline (0.75 ml·kg⁻¹) and prepared by a staff anesthesiologist not otherwise involved in the study. In all groups, the duration of analgesia, analgesic requirements, sedation and insulin, glucose, cortisol concentrations were recorded and statistically compared.

Results: There were no significant differences among the three study groups with respect to age, weight or duration of surgery. Caudal administration of clonidine 1 μg·kg⁻¹ or ketamine 0.5 mg·kg⁻¹ induced a longer duration of analgesia (P < 0.05) compared with ropivacaine alone. Insulin levels were increased and cortisol reduced in all groups. Glucose concentration was increased in all groups and statistically significant (P < 0.05).

Conclusions: Addition of ketamine and clonidine to ropivacaine 0.2% 0.75 ml·kg⁻¹, when administered caudally in children, prolongs the duration of postoperative analgesia. The need for subsequent postoperative analgesic is also reduced. Caudal analgesia attenuates or allows partial changes to postoperative cortisol, insulin or blood glucose responses to surgery.

Keywords: caudal analgesia; clonidine; glucose; ketamine; stress hormones

Correspondence to: Mert Akbas MD, Department of Anaesthesiology, Akdeniz University Medical Faculty, 07070 Antalya, Turkey (email: akbasmert@akdeniz.edu.tr).
Introduction

Stress responses to surgical trauma and postoperative pain elicit diffuse changes in hormonal secretion such as cortisol and prolactin (1,2). Plasma cortisol and prolactin concentrations remain increased for several days postoperatively (3,4). Epidural anesthesia with local anesthetics has been shown to attenuate the hormonal responses to surgery in adults and children, and provides effective postoperative analgesia (5–7).

The sacral epidural approach is the most useful and popular pediatric regional block. It is mainly used as an adjunct to general anesthesia to provide a smooth recovery and good immediate postoperative ambulation is required. Ropivacaine has been used successfully for caudal epidural blockade (9,11). This means that it may be more suitable for day-case anesthesia when early ambulation is required. Ropivacaine has been used successfully for caudal epidural blockade (9,11).

Ketamine has also been demonstrated to improve analgesic efficacy when administered by the lumbar epidural route (12–14). Ketamine in combination with bupivacaine, has been shown to prolong the duration of postoperative analgesia when administered caudally in children undergoing orchidopexy (15) and inguinal herniotomy (16).

Clonidine is an α2-receptor agonist known to prolong postoperative pain relief and reduce the need for additional analgesic requirement (17–19) without significant hemodynamic or respiratory effects.

Thus, the aim of this study was to compare the analgesic quality and duration of ropivacaine 0.2% with the addition of clonidine (1 μg·kg⁻¹), and the addition of ketamine (0.5 mg·kg⁻¹) to that of ropivacaine 0.2% following caudal administration in children and also compare the postoperative cortisol, insulin and glucose concentrations sampled after induction and 1 h later following caudal administration.

Methods

After we obtained approval from the local ethics committee and informed parental consent, 75 patients (ASA physical status I–II, age 2–12 years) scheduled for inguinal hernia repair and circumcision were randomly allocated into three study groups. Children for whom there was contraindication to caudal block were excluded from the study. At the time of recruitment, parents were instructed in the use of the modified objective pain score (OPS) for assessment of postoperative pain and requirement for analgesia. This is an observational pain scoring system using five criteria: crying, agitation, movement, posture and localization of pain. Each criterion scores 0–2 to give a total score of 0–10 (20).

According to the randomization, patients in the ropivacaine group (R; n = 25) received ropivacaine 0.2% 0.75 ml·kg⁻¹; those in the clonidine group (RC; n = 25) received ropivacaine 0.2% 0.75 ml·kg⁻¹ plus clonidine 1 μg·kg⁻¹ and those in the ketamine group (RK; n = 25) received ropivacaine 0.2% 0.75 ml·kg⁻¹ plus ketamine 0.5 mg·kg⁻¹ (10 mg·ml⁻¹ concentration). Drugs were diluted in 0.9% saline (0.75 ml·kg⁻¹) and prepared by a staff anesthesiologist not otherwise involved in the study.

All children received 0.5 mg·kg⁻¹ intranasal midazolam 20 min before anesthetic induction. General anesthesia was induced with sevoflurane (8%) in oxygen-air and maintained with sevoflurane (1%) oxygen nitrous oxide via tracheal tube or laryngeal mask airway. After insertion of an IV access, 0.9% saline solution 10 ml·kg⁻¹ was started. After induction of anesthesia, initial blood samples were taken from a vein for glucose, cortisol and insulin concentrations. The caudal block was performed under aseptic conditions with a 22-gauge Quincke needle (B. Braun Melsungen, Germany) in the left lateral position. Immediately after the anesthetic was injected, the children were turned to a supine position.

Heart rate (HR), pulse oximetry (SpO₂), and systolic blood pressure (SBP) and diastolic blood pressure were obtained before and after injection of general anesthesia, after caudal injection and every 5 min thereafter, intraoperatively.

An intraoperative decrease in SBP or HR of more than 30% from preoperative values was defined as hypotension or bradycardia, respectively, and was treated with rapid infusion of fluids or with atropine 0.01 mg·kg⁻¹. Respiratory depression was defined as decrease in SpO₂ <95% requiring supplementary oxygen. An intraoperative increase in SBP or HR by >10% was defined as insufficient analgesia and was...
treated with fentanyl 1 μg·kg⁻¹. Anesthetic agents were discontinued at the completion of skin closure.

After surgery, patients were taken to a recovery room. Analgesia was assessed after 1 h by an observer who was unaware of the block used and the second blood samples for glucose, cortisol and insulin were obtained at the same time. The efficacy of postoperative analgesia was assessed by the Oucher Pain Scale (21). Scores greater than 60 were assessed as pain and this time was recorded and supplementary analgesic given in the ward or in the house by parents (paracetamol 15 mg·kg⁻¹ orally). A three-point sedation scale was used to assess the sedation after surgery (1, awake; 2, asleep but arousable by verbal contact; 3, asleep and not arousable by verbal contact). After discharge, parents were asked to assess the child regularly and to give analgesia if OPS was ≥4. Paracetamol 15 mg·kg⁻¹ was given orally every 4 h as required. Parents were contacted by telephone the day after the surgery to determine the requirement for analgesia after discharge from the hospital. The total requirement for analgesia in the first 24 h after operation was noted.

Lower limb blockade was assessed with a modified Bromage scale (0, no motor block, child moves limbs freely; 1, inability to raise legs; 2, inability to flex knees; 3, no movement possible in legs). During the first 24 h after operation, the following complications were observed: motor blockade of lower extremities, nausea and vomiting, disturbances of micturition and hallucination.

Endocrine measurement

Venous blood samples were centrifuged immediately and stored at −20°C until assayed. Serum cortisol and insulin concentrations were measured by electrochemiluminescence immunoassay (ECLIA) on an Elecsys E-170 analyser (Roche Diagnostic Systems, Basel, Switzerland). Serum glucose concentrations were determined by the glucose oxidase (GOD-PAP) method on a Modular P system (Roche Diagnostics Systems).

All values are expressed as mean ± sd. Data analysis was performed by factorial ANOVA with a Scheffe posthoc comparison to detect differences in demographics, time for surgery, Sedation scores, Oucher scores, OPS, stress hormone levels and duration of analgesia. ANOVA for repeated measurements was used to determine intergroup and intragroup differences in hemodynamic changes. Results were considered to be statistically significant at P < 0.05.

Results

There were no significant differences among the three study groups with respect to age, weight or duration of surgery (Table 1). Similarly, systolic blood pressure and heart rate values did not significantly differ among the groups (Figure 1).

Caudal administration of clonidine 1 μg·kg⁻¹ or ketamine 0.5 mg·kg⁻¹ induced a longer duration of analgesia (P < 0.05) compared with caudal ropivacaine alone (Table 2). None of the children required additional analgesics in the intraoperative period. However, within the 24-h postoperative study period, 16% of children in the RK and RC groups required additional analgesics and 24% in group R (Table 2).

No statistically significant differences were observed among the three groups with the SpO₂ value. No episode of SpO₂ <95% was detected. Bradycardia was observed only in one child in groups R and RC. Nausea was observed in three children in group R, five in group RC, seven in Table 1

<table>
<thead>
<tr>
<th>Group data for groups R, RK and RC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group R (n = 25)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
</tr>
</tbody>
</table>

NS, not significant. Values are expressed as mean ± sd.

Figure 1

Systolic blood pressure (SBP) and heart rate (HR) changes. (no significant differences).
group RK. Vomiting was observed in three children in group R, three in group RC, six in group RK. There were no incidents of hypotension or hallucinations in any of the children after caudal injection.

There were no sedation score differences between group R and RK, but sedation scores were higher in group RC for the first 1-h period after the operation than the other groups and was statistically significant \( (P < 0.05) \) (Table 3).

There were no statistically significant differences among the groups with respect to Oucher’s Pain Scale and modified OPS. No motor blockade was observed in any of the groups. In addition, we observed no adverse central nervous system effects, and none of the patients developed short-term neurological impairment or deficit during the 6-week follow-up period.

Plasma cortisol, insulin and glucose concentrations are shown in Table 4. Insulin was increased only in group R \( (P < 0.05) \). Cortisol concentration was reduced only in group RK \( (P < 0.05) \). Glucose concentration was increased in all groups \( (P < 0.05) \).

### Discussion

Lower abdominal and genitourinary operations are generally associated with severe postoperative pain which in turn may lead to agitation and restlessness. This stimulus increases stress hormone levels (22–24). Therefore, we also compared the insulin and blood glucose concentrations together with cortisol concentration between the groups during the post-induction and early postoperative period.

Murat et al. showed that epidural anesthesia reduced the cortisol response to surgery (25). Nakamura and Takasaki measured cortisol concentrations in children who received caudal anesthesia or general anesthesia before, during and after lower abdominal surgery. They showed that caudal analgesia suppressed the cortisol responses during and after surgery (26). Salerno et al. have also shown that epidural anesthesia suppressed the postoperative cortisol response to surgery in infants under 1 year of age (27). Our results 1 h after surgery were similar to these studies. Cortisol concentration was reduced only in group RK \( (P < 0.05) \).

### Table 2
Postoperative analgesic requirements of the patients

<table>
<thead>
<tr>
<th></th>
<th>Group R ((n = 25))</th>
<th>Group RK ((n = 25))</th>
<th>Group RC ((n = 25))</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of analgesic requirement</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Time to first analgesic requirement (h)</td>
<td>4 ± 3.23</td>
<td>10 ± 4.32</td>
<td>14 ± 3.1</td>
<td>&lt;0.05*</td>
</tr>
</tbody>
</table>

NS, not significant.

*Group R vs groups RK and RC.

### Table 3
Sedation states of the patients \( (n) \)

<table>
<thead>
<tr>
<th>Time</th>
<th>Sedation score</th>
<th>Group R ((n = 25))</th>
<th>Group RK ((n = 25))</th>
<th>Group RC ((n = 25))</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>–</td>
<td>0.043*</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>9</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>18</td>
<td>14</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>1</td>
<td>11</td>
<td>7</td>
<td>1</td>
<td>0.03*</td>
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<tr>
<td></td>
<td>2</td>
<td>8</td>
<td>16</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>1</td>
<td>17</td>
<td>17</td>
<td>2</td>
<td>&lt;0.001*</td>
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<td>7</td>
<td>8</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1</td>
<td>–</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>1</td>
<td>22</td>
<td>23</td>
<td>9</td>
<td>&lt;0.001*</td>
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<td></td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>15</td>
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</tr>
<tr>
<td></td>
<td>3</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>180 min</td>
<td>1</td>
<td>24</td>
<td>25</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>–</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

NS, not significant.

*Group RC vs groups R and RK.

### Table 4
Preoperative and postoperative changes for insulin, cortisol and glucose

<table>
<thead>
<tr>
<th></th>
<th>Insulin ((\mu U/ml^{-1}))</th>
<th>Cortisol ((\mu g/dl^{-1}))</th>
<th>Glucose ((mg/dl^{-1}))</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.8 ± 2.4</td>
<td>6.9 ± 6.5</td>
<td>16.8 ± 7.1</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6.9 ± 6.5</td>
<td>16.2 ± 8.2</td>
<td>96.4 ± 38.2</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>0</td>
<td>3.7 ± 3.2</td>
<td>5.2 ± 4.3</td>
<td>13.9 ± 6.5</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5.2 ± 4.3</td>
<td>10.6 ± 7.4</td>
<td>92.9 ± 22.7</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>0</td>
<td>6.8 ± 8.8</td>
<td>7.7 ± 8.1</td>
<td>17.6 ± 7.5</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7.7 ± 8.1</td>
<td>17.4 ± 9.5</td>
<td>85.3 ± 7.9</td>
<td>&lt;0.05*</td>
</tr>
</tbody>
</table>

Values are significant at \( P < 0.05 \).

Values are given as mean ± sd.

0, induction; 1, 1 h after induction.

*0 vs 1 for insulin and glucose; ’0 vs 1 for cortisol and glucose; *0 vs 1 for glucose.
After induction of anesthesia, insulin concentrations began to fall. As surgery proceeded there is reduction of insulin secretion and hyperglycemic responses develop. During the perioperative period, there is a reduction of insulin response at a cellular level, known as insulin resistance (28). We found only one study of insulin concentrations in children with caudal anesthesia: Tuncer et al. assessed the effects of caudal block on plasma cortisol, prolactin, insulin and glucose concentrations during and after surgery. Mean insulin concentrations were lower in the caudal group than the control group (29). In our study insulin was increased only in group R (P < 0.05). But in our opinion more studies should be performed to explain this.

Because of the endocrine response to surgery, anabolic hormone secretion increases and catabolic hormone secretions reduce. With the increase of cortisol and catecholamine levels, glucose production begins to increase because of hepatic glycogenolysis and gluconeogenesis. The mechanism which contributes to the glucose homeostasis is ineffective during the perioperative period. Thus, with the help of insulin resistance hyperglycemia is produced (28,30). Tuncer et al. measured glucose concentrations who received caudal anesthesia or general anesthesia. They showed that glucose concentrations increased in both group, however glucose levels were lower in the caudal group than in the control group. In our study, 1 h after surgery, glucose concentrations increased in all groups and was statistically significant compared with preoperative levels but increases were less in groups RK and RC than in group R.

Several authors reported that caudal block provided lower pain scores and analgesic requirements in the first 4–8 h postoperatively (31–33). We have shown that ketamine enhanced postoperative analgesia by 10 ± 4.3 h. This finding supports the study performed by Lee and Sanders (34). Our study has also shown a significant decrease in the need for subsequent postoperative analgesic requirements when caudal ketamine is used than with ropivacaine alone.

Clonidine has previously been shown to enhance the duration and quality of analgesia of local anesthetics in pediatric regional anesthesia (17–19), and in our study by adding clonidine to ropivacaine more effective postoperative analgesia was provided compared with ropivacaine and ropivacaine/ketamine. We have shown that clonidine enhanced postoperative analgesia by 14 ± 3.1 h. Our study has also shown a significant decrease in the need for subsequent postoperative analgesic requirements than in the caudal ropivacaine group.

Additional postoperative sedation did not occur with caudal ketamine. The sedation scores were the same for groups R and RK. Patients receiving ropivacaine/clonidine combination seemed more sedated and had higher sedation scores in the early postoperative period (1 h after discharge), and this was clinically and statistically significant (P < 0.05) compared with the other groups, although it might also be the result of the residual effect of anesthetic gases.

No patients in the ketamine/ropivacaine group had emergence delirium, hallucinations or nightmares. These complications of caudal ketamine have been reported when higher doses (0.5–1 mg kg⁻¹) have been used, but not with 0.5 mg kg⁻¹ (35).

The duration of motor block, measured by the time to spontaneous leg movement, was the same for all groups. Caudal ropivacaine at a concentration of 0.2% did not cause motor blockade in any patient by the time of recovery room discharge (30 min after surgery). Hospital discharge was not delayed in any patient because of motor block. Previous studies have demonstrated prolonged motor block when caudal bupivacaine 0.25% is used in children (15,16), so the results of our study suggest that the use of ropivacaine 0.2% is preferable for caudal epidural use in children even with the addition of ketamine or clonidine.

As spinal control of bladder function resides in the sacral roots S2, 3, 4, caudal anesthesia may result in disturbances of micturition. Payne et al. observed 34% incidence of urinary incontinence in children receiving caudal anesthesia (36). However, the reported incidence of urinary incontinence is very low (16). In our study, we did not observe any complications of micturition.

In conclusion, the addition of ketamine 0.5 mg kg⁻¹ and clonidine 1 µg kg⁻¹ to ropivacaine 0.2% 0.75 ml kg⁻¹, when administered caudally in children, prolongs the duration of postoperative analgesia. The need for subsequent postoperative analgesic is also reduced. Addition of clonidine makes children more sedated than ketamine and the result of this study indicate that caudal analgesia...
may relatively attenuate or make partial changes to the postoperative cortisol, insulin and blood glucose responses to surgery.

Acknowledgement

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References


9 Da Conceicao MJ, Coelho L, Khalil M. Ropivacaine 0.25% compared with bupivacaine 0.25% by the caudal route. Paediatr Anaesth 1999; 9: 229–233.

10 Da Conceicao MJ, Coelho L. Caudal anaesthesia with 0.375% ropivacaine or 0.375% bupivacaine in paediatric patients Br J Anaesth 1998; 80: 507–508.


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