Analgesic effectiveness of caudal levobupivacaine and ketamine

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Background. Ketamine is used increasingly in paediatric anaesthetic practice to prolong the action of a caudal block. This study was designed to determine if adding S(+) -ketamine 0.5 mg kg⁻¹ allows a lower concentration of levobupivacaine to be used for caudal anaesthesia without loss of clinical effectiveness.

Methods. One hundred and sixty-four children (ASA I or II) aged 3 months–6 yr were randomly allocated to receive 1 ml kg⁻¹ of levobupivacaine 0.15% with 0.5 mg kg⁻¹ S(+) -ketamine (Group 1), levobupivacaine 0.175% with 0.5 mg kg⁻¹ S(+) -ketamine (Group 2), or levobupivacaine 0.2% (Group 3) by the caudal route. Pain, motor block, sedation, and requirement for postoperative analgesia were assessed up to 6 h after operation.

Results. There was no significant difference between the groups in effectiveness at first surgical incision. Significantly lower analgesic requirements were reported in Group 2 compared with Group 3 at wakeup, 180 and 360 min after operation. Time to first rescue analgesia was longer in Group 2 compared with Group 1 or 3. Kaplan–Meier survival analysis of analgesia free time demonstrated a significant advantage of Group 2 over Groups 1 and 3 (log rank P=0.05). The incidence of postoperative motor block was not significantly different between the groups. No excess sedation or dysphoric reactions were observed in the ketamine groups.

Conclusions. The addition of 0.5 mg kg⁻¹ S(+) -ketamine to levobupivacaine 0.175% for caudal analgesia for lower abdominal and urological surgery is significantly more effective in providing postoperative analgesia than levobupivacaine 0.15% with 0.5 mg kg⁻¹ S(+) -ketamine or levobupivacaine 0.2%.

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A survey of paediatric anaesthetists in 2002 reported that more than 50% of anaesthetists used an adjuvant drug when performing caudal analgesia with the most commonly used being ketamine, clonidine, fentanyl, and diamorphine.¹ Ketamine has been shown to have a synergistic effect with caudal local anaesthetics.² Ketamine local anaesthetics combinations have been demonstrated to speed the onset of analgesia, prolong the duration of caudal analgesia, and reduce the incidence of ineffective analgesia.³–⁵ Epidural ketamine has allowed lower concentrations of bupivacaine and ropivacaine to be used and as a result, the incidence of postoperative motor block has been lower.³

S(+) -ketamine 0.5 mg kg⁻¹ added to 0.20–0.25% of bupivacaine or ropivacaine for caudal anaesthesia is highly effective in improving the quality and duration of the analgesia in children.¹⁵ Levobupivacaine has been demonstrated to be an extremely effective agent for caudal analgesia,⁶–⁸ but its use in combination with ketamine has not previously been reported. We conducted this double-blind randomized controlled trial to determine if ketamine added to lower concentrations of levobupivacaine is as
effective as levobupivacaine 0.2% alone for caudal anaesthesia in children.

Methods

After approval from the Hospital Research Ethics Committee, informed written consent was obtained from the parents of 180 children. Patients undergoing elective lower abdominal or urological procedures of anticipated duration <120 min who were between 3 months and 6 yr of age, with ASA score I–III, and weighing <20 kg were enrolled.

Anaesthetic technique

All children were fasted and received oral or rectal premedication with midazolam 0.5 mg kg\(^{-1}\) 30–45 min before surgery. I.V. anaesthesia was induced with propofol 2–4 mg kg\(^{-1}\) adjusted) in 50% oxygen–air mixture administered by laryngeal mask airway or endotracheal tube without neuromuscular blocking agents. Ventilation was not controlled until after the first skin incision and assessment of ventilatory response to the stimuli had been made. Ventilation was then controlled or assisted in order to obtain an end-tidal carbon dioxide \(\left(\frac{\text{CO}_2}{\text{air}}\right)\) ≤45 mm Hg. After induction of anaesthesia, patients were placed in the lateral decubitus position and a consultant anaesthetist performed a caudal block using a 22 G i.v. cannula. The children were randomized in double-blind fashion into three separate groups. The first group received 1 ml kg\(^{-1}\) of levobupivacaine 0.15% (Chirocaina®, Abbott, Latina, Italy) and preservative-free S(+)k etamine 0.05% (Ketanest S®, Pfizer, Germany). The second group received 1 ml kg\(^{-1}\) of levobupivacaine 0.175% (1.75 mg kg\(^{-1}\)) and ketamine 0.05% (0.5 mg kg\(^{-1}\)). The third group received 1 ml kg\(^{-1}\) of levobupivacaine 0.2% (2 mg kg\(^{-1}\)) without ketamine. The randomization sequence was computer generated and the drugs were prepared in a double-blinded manner.

Non-invasive blood pressure (BP), heart rate (HR), respiratory rate (RR), oxygen saturation, and end-tidal CO\(_2\) were monitored continuously. Three minutes after local anaesthetic injection, a mechanical stimulus was applied at the surgical dermatome or at the immediate superior dermatome with a modified Allis clamp (m 30–132–15, Martin®, Tuttlingen, Germany) for the evaluation of block onset. Patients were stimulated every 3 min after the caudal block until block effectiveness or a maximum of 15 min after caudal injection (five stimuli). Any related movement or significant change in the HR or RR resulted in the discontinuation of the stimulus. Analgesic onset time was defined as the time in minutes between local anaesthetic injection and the absence of gross movement or significant (>20%) change in HR, BP, or RR on application of the clamp. A physiological response or movement at 15 min was considered as prolonged local anaesthetic onset. Data from patients who responded with movements or physiological changes to the fifth stimulus but did not respond to first surgical stimulus were assigned an onset time equivalent to the time between caudal block and surgical incision.

Caudal block efficacy during surgery was defined as the absence of gross movements or significant (>20%) change in BP, HR, or RR associated with surgical stimulation. In the event of gross movements or significant physiological changes after incision or during surgery, children were treated with an i.v. bolus of fentanyl 2 μg kg\(^{-1}\).

The primary endpoint of the study was the quality of postoperative pain control. This was defined by the number of children requiring rescue analgesia because of a Children and Infants Postoperative Pain Scale (CHIPS) Scale >4 during the first 6 h after caudal block. Postoperative pain was evaluated using the CHIPS medieval (Table 1). In cases where the CHIPS scale was four points, children received either rectal codeine 0.5–1 mg kg\(^{-1}\) plus acetaminophen 10–15 mg kg\(^{-1}\), i.v. morphine 0.05–0.1 mg kg\(^{-1}\), or i.v. ketorolac 1 mg kg\(^{-1}\). In the postoperative recovery ward, pain intensity, emergence agitation, and Aldrete scores were recorded every 10 min until an Aldrete score of 8 was achieved. The postoperative behaviour of the children was evaluated using a four-point scale. These were: (1) calm child: does not need any kind of intervention; (2) consolable child: requires only physical contact with the parents; (3) agitated child: a screaming and crying child; and (4) aggressive child: must be physically restrained in order to avoid harming himself. We defined postoperative agitation as a score of three or four points. We did not perform structured neurobehavioural testing and documentation of odd behaviour on awakening was recorded on an observational basis.

The incidence of residual motor blockade was considered a secondary outcome measure and was evaluated using a modified Bromage scale. A score of 0 was

<table>
<thead>
<tr>
<th>Item</th>
<th>Structure</th>
<th>Points</th>
</tr>
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<tbody>
<tr>
<td>Crying</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Moaning</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Screaming</td>
<td>2</td>
</tr>
<tr>
<td>Facial expression</td>
<td>Relaxed/smiling</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Wry mouth</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Grimace (mouth and eyes)</td>
<td>2</td>
</tr>
<tr>
<td>Posture of the trunk</td>
<td>Neutral</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Variable</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Rear up</td>
<td>2</td>
</tr>
<tr>
<td>Posture of the legs</td>
<td>Neutral, relaxed</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Kicking about</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Tightened legs</td>
<td>2</td>
</tr>
<tr>
<td>Motor restlessness</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Restless</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 1 Children and Infants Postoperative Pain Scale. In the postoperative period, scores between 0 and 3 indicate mild or no pain, scores 4 and above indicate analgesic requirements with increasing urgency as scores increase.
assigned if no motor block was present. A score of 1 indicated an inability to stand unassisted, 2 indicated ability to flex the ankle but not the knee, and 3 indicated complete motor block in a fully awake child. Significant residual motor blockade was defined as a motor block score equal to or greater than 1 point after awakening and 180 min after the last dose of local anaesthetic. In the event of an asymmetric block, the highest numerical value was recorded.

An anaesthetist not primarily responsible for the conduct of the anaesthetic carried out preoperative evaluation and data collection. This anaesthetist obtained informed consent, confirmed validity of the inclusion criteria, and allocated the patients using computer-generated random number sequence to the study groups. In the event of an emergency related or possibly related to the study or study drugs, the pharmacist was authorized to disclose the contents of the syringe to the consultant anaesthetist. The study blinding was broken before statistical analysis.

Statistical analysis

The initial sample size estimation was performed based on a number of assumptions from prior studies of caudal anaesthesia in children. Assuming an incidence pain after surgery of 0.5, a two-sided type I error of 0.05, a power of 0.80, and an effect size of 0.50, more than 55 in each group were required to find a significant difference in the number of children requiring rescue analgesia in the first hours after surgery.

Quantitative data are presented as mean, standard deviation or range, and qualitative data as frequency and 95% confidence interval (95% CI). ANOVA or Kruskal–Wallis test was used for analysis of differences in age, weight, sex, block effectiveness during operation, residual motor blockade, postoperative agitation, and number of patients requiring analgesics after operation. Type of surgery, ASA physical status, block effectiveness during operation, residual motor blockade, postoperative agitation, and number of patients requiring analgesics after operation were analysed with χ² or Fisher’s exact test. Pain and sedation scores (at various times) and frequency of rescue analgesia were compared using Mann–Whitney U-tests. Significance was defined as P<0.05. All statistical comparisons were accomplished with Epi Info, version 2005 [EpiInfo 3.2.2, Center for Disease Control and Prevention (CDC), Atlanta, GA, USA].

The incidence and time to first rescue analgesia were analysed using Kaplan–Meier survival analysis with comparison between the groups using the log-rank test. Survival data were defined as time from caudal anaesthesia to the requirement of first rescue analgesia. Patients who did not require rescue analgesia during the 6 h of observation were considered ‘censored’. The Mantel-Cox (log-rank) test was used to perform intergroup comparisons.

### Results

One hundred and eighty children were included in the study, 164 were analysed as per protocol and 16 children were excluded. Fourteen patients did not receive the drug under study (seven in Group 2, four in Group 1, and three in Group 3). One child in Group 3 underwent local and peripheral block because of technical difficulties with the epidural block. One patient in Group 2 was lost to follow-up.

The clinical characteristics of the children are shown in Table 2. There were no significant differences in age, weight, gender, type of surgery, surgery time, end-tidal sevoflurane concentration during surgery, time to awakening, or postoperative agitation.

Analgesic onset time measured with a mechanical stimulus was not significantly different between the three groups. Median analgesic onset was 6 (IQR 6–9) min in Groups 1 and 2, and 9 (IQR 6–9) min in Group 3. Analgesic onset exceeding 15 min (manifesting as movements or physiological changes to the fifth mechanical stimulus) was present in seven children in Group 2 compared with two children in each of the other groups (χ² P=0.06). There were no significant haemodynamic changes after caudal boluses and during surgery for any agent.

There were no significant differences between the groups in the proportion of children with effective epidural block at the first surgical incision (χ² P=0.13). Adequate analgesia on first incision was demonstrated in 56 patients (95% CI 85–99%) in Groups 1 and 3 and 50 children (95% CI 87–99%) in Group 2. Two children (95% CI 0–13) in Group 2 received an extra dose of i.v. fentanyl after incision (χ² P=0.73).

CHIPPSS scores at wakeup were significantly different between Group 2 and Group 3 at wakeup (Wilcoxon rank sum P=0.05) but at no other time up to 360 min (Fig. 1). There were no significant differences between Group 1 and Group 3 (P=0.38) or Group 1 and Group 2 (P=0.44) at any time. The contribution of sedation induced by systemic absorption of caudal ketamine to lower CHIPPSS

### Table 2 Patients’ clinical characteristics. Data are mean (range), mean (SD), or number of children for sex and type of surgery

<table>
<thead>
<tr>
<th></th>
<th>Levobupivacaine 0.15% + Ketamine (n=56)</th>
<th>Levobupivacaine 0.175% + Ketamine (n=52)</th>
<th>Levobupivacaine 0.20% (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>3 (0.25–5.7)</td>
<td>3 (0.8–5.0)</td>
<td>3 (0.5–4.6)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>14 (3)</td>
<td>13 (2)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>4/52</td>
<td>6/46</td>
<td>9/47</td>
</tr>
<tr>
<td>Inguinal hernia</td>
<td>32</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Orchidopexy</td>
<td>16</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Surgery time (min)</td>
<td>37 (23)</td>
<td>36 (20)</td>
<td>33 (21)</td>
</tr>
<tr>
<td>Wakeup time (min)</td>
<td>21 (10)</td>
<td>20 (10)</td>
<td>18 (8)</td>
</tr>
</tbody>
</table>
scores could not be determined, but sedation was not a feature in either of the caudal ketamine groups. Wakeup times were not significantly different between the groups (21 min Group 1, 20 min Group 2, and 18 min Group 3). Hallucinations, nightmares, odd behaviour or unexplained distress, excessive agitation, or restlessness was not reported in any child.

Ninety children (95% CI 47–63%) received rescue analgesia after surgery. In children with a CHIPPS score >4, the median time (inter-quartile range) to first analgesic requirement was 145.5 (90–235) min for Group 1, 167.5 (87–214) min for Group 2, and 94.5 (68–180) min for Group 3. There was no difference in median analgesic times between Group 1 and Group 2 (Kruskal–Wallis $P=0.66$), Group 1 and Group 3 (Kruskal–Wallis $P=0.12$) nor Groups 2 and 3 (Kruskal–Wallis $P=0.08$). Twenty-two children in Group 2 received analgesia because of CHIPPS >4 points compared with 38 children in Group 1 and 30 patients in Group 3 ($P=0.03$ for $\chi^2$). Differences in analgesic requirements were significant at wakeup ($\chi^2 P=0.05$), 180 min ($\chi^2 P=0.04$), and 360 ($\chi^2 P=0.03$) min after caudal block. Mantel-Cox (log-rank) analysis (Fig. 2) to compare the rate of requirement for postoperative analgesia demonstrated that Group 1 (levoketamine 0.15%) was significantly different ($P=0.05$) to Group 2 (levoketamine 0.175%) but not Group 3 (levoketamine 0.2%) ($P=0.24$). There was no significant difference between Group 2 and Group 3 ($P=0.15$). No additional analgesia in the 6 h postoperative observation period was demonstrated in 32% of patients in Group 1, 57% of Group 2, and 46% of Group 3.

The incidence of residual motor block on awakening was not statistically different between the groups (Fig. 3) on awakening ($\chi^2 P=0.8$) or 3 h after caudal block injection ($\chi^2 P=0.6$). Postoperative nausea and vomiting (PONV) occurred in five patients, one each in Groups 2 and 3 and three in Group 1. Postoperative agitation was present in 10 patients in Group 1, 11 in Group 2, and 14 in Group 3.

**Discussion**

The key finding of this study is that the addition of 0.5 mg kg$^{-1}$ of preservative-free $S(+)$-ketamine to caudal levobupivacaine 0.175% significantly decreases the need for rescue analgesia in the immediate postoperative period. When $S(+)$-ketamine 0.5 mg kg$^{-1}$ is added to 0.15% caudal levobupivacaine, the quality of postoperative analgesia is equivalent to that produced with caudal 0.2% levobupivacaine alone. This is consistent with previous reports of caudal ketamine in association with bupivacaine and ropivacaine for intra- and postoperative analgesia. Ketamine local anaesthetics combinations have been shown to speed the onset of analgesia, prolong the duration of caudal analgesia, and reduce the incidence of ineffective analgesia compared with local anaesthetics alone. Most studies use the duration of postoperative analgesia or the time to first analgesic request to determine the effect of ketamine on local anaesthetic effectiveness. When racemic ketamine 0.25 mg kg$^{-1}$ is added to bupivacaine or ropivacaine for caudal anaesthesia, the duration of postoperative analgesia...
analgesia after orchidopexy than either clonidine 0.25 mg kg\(^{-1}\) or bupivacaine 0.25% produces a longer median duration of analgesia. Using S(+-)ketamine 0.5 mg kg\(^{-1}\) produces the same duration of analgesia as studies using S(+)ketamine 0.5 mg ml\(^{-1}\), despite a four-fold potency difference. One conclusion is that there is a ceiling effect on the concentration of ketamine and another is that the concentration of local anaesthetic is much more critical to the effect than the ketamine dose. Other advantages of S(+)ketamine include fewer psychomotor side-effects, less salivation, and shorter recovery time compared with the racemic mixture. A number of studies have examined the effect of a combination of caudal S(+)ketamine and local anaesthetics on perioperative analgesia. Marhofer and colleagues\(^{19-21}\) reported that caudal S(+)ketamine 1 mg kg\(^{-1}\) provided equipotent intra- and postoperative analgesia compared with 0.75 ml kg\(^{-1}\) of bupivacaine 0.25% with 1:200 000 adrenaline but 0.5 mg kg\(^{-1}\) provided sufficient analgesia only during the intraoperative period. De Negri and colleagues\(^{19}\) found that the addition of S(+)ketamine 0.5 mg kg\(^{-1}\) to ropivacaine 0.2% for lower abdominal surgery resulted in an improvement in postoperative analgesia compared with ropivacaine alone.

Using neuraxial analgesics other than local anaesthetics may confer distinct advantages such as avoiding motor blockade and the serious complications associated with inadvertent intravascular injection of the local anaesthetic solution. Inadvertent intravascular injection of ketamine will not result in significant complications, as the caudal dose is lower than the i.v. dose. Ketamine, however, has a relatively short duration of action when used alone. A combination of caudal ketamine and clonidine\(^{22,23}\) or tramadol is effective but associated with unacceptable sedation or significant PONV.\(^{24,25}\)

In our study, caudal ketamine 0.5 mg kg\(^{-1}\) did not increase the incidence of emergence agitation, PONV, or residual motor blockade. Side-effects of ketamine such as delirium, hallucinations, or nightmares can occur with caudal ketamine at doses of 0.5–1 mg kg\(^{-1}\)\(^{11,26}\) but have not been reported at doses of 0.25 mg kg\(^{-1}\).\(^{18,26}\)

Toxic reactions after prolonged neuraxial exposure to racemic ketamine formulations with preservatives (benzethonium chloride or chlorbutanol) have been reported in animal species. Spinal neurotoxicity after continuous intrathecal racemic ketamine infused over 3 weeks for terminal cancer-related pain has been reported. Controversy exists about the risk–benefit ratio of neuraxial ketamine. As a result, only preservative-free S(+)ketamine should be used for neuraxial anaesthesia. The risk of spinal toxicity, however, is greatest in prolonged subdural administration.
for cancer pain. Physiological NMDA receptor activity is necessary for cell survival and cerebral function and prolonged NMDA receptor blockade by ketamine results in apoptosis of central neurons of immature rat brain.\(^{30}\) As yet, no permanent neurological injury has resulted from single-shot caudal ketamine use but caution is warranted.

In conclusion, the addition of 0.5 mg kg\(^{-1}\) of S(\(+\))-ketamine to caudal levobupivacaine 0.175% significantly decreases the need for rescue analgesia in children undergoing abdominal and urological surgery compared with levobupivacaine 0.2%. The effect of ketamine added to levobupivacaine 0.15% is as effective as levobupivacaine 0.2% alone. Preservative-free S(\(+\))-ketamine may be used by the caudal route as a local anaesthetic sparing agent allowing lower concentrations of levobupivacaine to be used. To determine if the effect of ketamine is synergistic or purely additive would require isobolographic analysis.

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**References**

1 Sanders JC. Paediatric regional anaesthesia, a survey of practice in the United Kingdom. Br J Anaesth 2002; 89: 707–10
6 Locatelli B, Ingelmo P, Sonzogni V, et al. Randomized double blind phase III, controlled trial comparing levobupivacaine 0.25%, ropivacaine 0.25% and bupivacaine 0.25% by the caudal route in children. Br J Anaesth 2005; 94: 366–71
7 Ingelmo P, Locatelli B, Sonzogni V, et al. Caudal 0.2% ropivacaine is less effective during surgery than 0.2% levobupivacaine and 0.2% bupivacaine: a double blind randomized controlled trial. Paediatr Anaesth 2006; 16: 955–61
27 Vranken J, Troost D, deHaan P, et al. Severe toxic damage to the rabbit spinal cord after intrathecal administration of preservative free S(\(+\))-ketamine. Anesthesiology 2006; 105: 813–8