Randomized controlled trial comparing morphine or clonidine with bupivacaine for caudal analgesia in children undergoing upper abdominal surgery

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Key points

- The use of clonidine or morphine to prolong analgesia provided by caudal bupivacaine was compared in children undergoing upper abdominal surgery.
- Clonidine increased the duration of analgesia and sedation with fewer side-effects compared with morphine.
- Clonidine was a safe and effective supplement to caudal bupivacaine analgesia for upper abdominal surgery.

Background. Various additives have been used to increase the duration of analgesia provided by bupivacaine administered by single-shot caudal injection in children.

Methods. A prospective, randomized, double-blind controlled study in 50 ASA I–II children (34 boys and 16 girls) aged 1–6 yr undergoing upper abdominal surgery was conducted. Patients were divided into two groups to receive either morphine 30 $\mu$g kg$^{-1}$ (MB) or clonidine 2 $\mu$g kg$^{-1}$ (CB) in bupivacaine 0.2% (1.25 ml kg$^{-1}$) for caudal analgesia. The duration of analgesia (FLACC scale) and sedation and side-effects such as vomiting, itching, respiratory depression, hypotension, and bradycardia were observed.

Results. The mean duration of analgesia was 16.5 (3.6) h in the CB group compared with 10.2 (2.3) h ($P$<0.01) in the MB group. Subjects who received clonidine (CB) were sedated for longer [7.1 (0.8) h] compared with the MB group [3.8 (0.7) h; $P$<0.01]. Vomiting was observed in 4% and 12% of subjects in the CB and MB groups, respectively. Sixteen per cent of subjects reported itching in the MB group ($P$¼0.03), and none in the CB group. No hypotension, bradycardia, or respiratory depression was observed in any subjects.

Conclusions. Caudal clonidine 2 $\mu$g kg$^{-1}$ in bupivacaine 0.2% provides a longer duration of analgesia and sedation compared with caudal morphine 30 $\mu$g kg$^{-1}$ in bupivacaine 0.2% without significant side-effects in children undergoing upper abdominal surgery.

Keywords: anaesthetic technique, caudal; anaesthetics, morphine, clonidine, bupivacaine; side-effects

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Caudal epidural block is one of the most common regional anaesthetic techniques used in children. The main disadvantage of caudal anaesthesia is the relatively short duration of action, even with the use of long-acting local anaesthetics such as bupivacaine. There is a concern regarding the use of caudal catheters to administer repeated doses or infusions of local anaesthetic due to the risk of infection. To improve the duration of action and quality of analgesia of a single-shot caudal block with bupivacaine, various additives have been used, for example, opioids, neostigmine, and clonidine, with their associated side-effects.1 2

Although addition of caudal opioids has been shown to provide sustained analgesia, their use can result in troublesome side-effects, including the potentially serious risk of respiratory depression.3 During the last decade, the use of clonidine has become increasingly popular in paediatric anaesthesia, particularly when administered caudally with a local anaesthetic.4 The majority of studies of single-dose caudal clonidine in children have involved lower abdominal,5 urogenital, or lower extremity surgery.6 7 No study has prospectively compared the addition of clonidine or morphine with bupivacaine administered as a single-dose caudal block for upper abdominal procedures such as exploratory laparotomy. We therefore designed this prospective, randomized, double-blind study to compare the duration of postoperative analgesia, sedation, and side-effects, if any, of single-dose caudal clonidine or morphine combined with bupivacaine, in paediatric patients undergoing upper abdominal surgery.

Methods

The study was conducted at Kalawati Saran Children’s Hospital from June 2008 to February 2009. After institutional review board approval, 50 ASA I–II children of either sex aged 1–6 yr undergoing upper abdominal surgery under
general anaesthesia with tracheal intubation were recruited for the study after a written informed consent by the parents/guardian. Exclusion criteria included a history of developmental delay or mental retardation, which could make observational pain intensity assessment outside the norm; a known or suspected coagulopathy; a known allergy to any of the study drugs; or abnormalities of the sacrum and any signs of infection at the site of the proposed caudal block. The children were randomized in a double-blind fashion to receive either a single-caudal dose of clonidine combined with bupivacaine (CB group) or morphine combined with bupivacaine (MB group). The randomization was performed en bloc in a 1:1 ratio according to a computer-generated list using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) and delivered in sealed, opaque, sequentially numbered envelopes by an anaesthesiology resident.

Patients were kept fasting as per the ASA guidelines (clear liquids, 2 h; breast milk, 4 h; infant formula, non-human milk, and light meal, 6 h). General anaesthesia was induced with either sevoflurane in oxygen or thiopental 5–7 mg kg\(^{-1}\) (depending on the presence of i.v. cannula), and the trachea was intubated with an appropriate sized tracheal tube facilitated with rocuronium 0.9 mg kg\(^{-1}\). Anaesthesia was maintained with sevoflurane in nitrous oxide and oxygen and fentanyl 2 \(\mu\)g kg\(^{-1}\) i.v. After tracheal intubation, patients were placed in the lateral decubitus position, and a single-dose caudal block was performed by a consultant anaesthetist under all aseptic precautions using a 23 G needle. The placement of the needle was confirmed by the characteristic ‘pop’ of the penetration of the sacrococcygeal ligament followed by the ‘whoosh’ test\(^{6}\) with 0.5 ml of air as per our institutional practice. After negative aspiration for blood and cerebrospinal fluid, the patients in Group CB received clonidine 2 \(\mu\)g kg\(^{-1}\) in 1.25 ml kg\(^{-1}\) of bupivacaine 0.2%, whereas those in Group MB received morphine 30 \(\mu\)g kg\(^{-1}\) in 1.25 ml kg\(^{-1}\) of bupivacaine 0.2% (total bupivacaine did not exceed 2.5 mg kg\(^{-1}\)). The total volume of injectate was 1.25 ml kg\(^{-1}\).

Concentration of sevoflurane was adjusted based on intraoperative haemodynamics to maintain an end-tidal concentration of 1.5–2%. All patients had a urethral Foley catheter inserted before the incision. The lactated Ringer’s solution was used as the maintenance fluid and intraoperative losses were adequately replaced. Heart rate, non-invasive arterial pressure, and peripheral oxygen saturation (\(S_{\text{PO}}\)) were recorded after induction of anaesthesia and every 5 min thereafter intraoperatively. Electrocardiogram, end-tidal carbon dioxide, and sevoflurane concentration were monitored continuously throughout the procedure. An intraoperative increase in baseline arterial pressure or heart rate of \(\geq 20\%\) was defined as insufficient analgesia and was treated with additional doses of fentanyl (1 \(\mu\)g kg\(^{-1}\)). Ondansetron i.v. 0.08 mg kg\(^{-1}\) was administered before reversal with glycopyrrolate and neostigmine. The patients, after extubation of the trachea, were shifted to post-anaesthesia care unit (PACU) when they were capable of maintaining a patent airway, for observation. In the PACU, heart rate, \(S_{\text{PO}}\) (using pulse oximeter), and ventilatory frequency were monitored continuously, and data were recorded every 15 min until the child was awake and cooperative. All health-care personnel providing direct patient care, the patients, and their parents or guardians were blinded as to the caudal medications administered.

Using the FLACC pain scale with its 0–10 score range,\(^9\) each patient’s pain intensity was assessed by a resident doctor (blinded to the treatment) upon arrival in the PACU. The sedation score was assessed on a four-point scale (1, alert and aware; 2, asleep, arousable by verbal contact; 3, asleep, arousable by physical contact; and 4, asleep, not arousable). The pain and sedation scores were observed every hour. A note was made for the presence of other side-effects such as vomiting, itching, bradycardia (heart rate \(\leq 60\) beats min\(^{-1}\)), hypotension (<20% of baseline), and respiratory depression (defined as \(S_{\text{PO}}<95%\) requiring supplemental oxygen). Urinary retention was not assessed, as all the children already had a urinary catheter in situ. The total duration of surgery was also noted. The duration of sedation was defined as the time between administering the drug and reaching a sedation score \(\leq 2\). The patients were then shifted from the PACU to the ward. The duration of postoperative analgesia was defined as the time between administering the drug and an FLACC score \(\geq 4\). At this point, fentanyl 1 \(\mu\)g kg\(^{-1}\) was given i.v. as a rescue analgesic with concomitant administration of acetaminophen suppository 40 mg kg\(^{-1}\).

**Statistical analysis**

A commercial software package (Medcalc software version 9.2.1.0, Mariakerke, Belgium) was used. The primary endpoint of the study was the time to FLACC score \(\geq 4\) after the administration of the study drug. Before the study, the number of subjects required in each group was determined using a power calculation with data obtained from a pilot study. The expected mean duration of analgesia for the clonidine and morphine groups was 14.2 (4.1) and 10.9 (3.7) h, respectively. This indicated that a sample size of 24 subjects would be required in each group in order to detect a difference of 4 h in the duration of analgesia between the groups with \(\alpha=0.05\) and \(\beta=0.2\) with an effect size of 0.84. We therefore recruited 25 subjects in each group. Data are presented as mean or median with range or standard deviation (sd) as appropriate.

The two-sample (unpaired) t-test was used to compare patient characteristics and the duration of analgesia and sedation between the two groups. The categorical data such as sex and incidence of side-effects were analysed by the Mann–Whitney U-test. A P-value of \(<0.05\) was considered to be statistically significant. A post hoc power analysis was performed at the completion of the study using GPOWER (version 3.1.2, Franz Faul, Universitat Kiel, Germany; www.psycho.uni-duesseldorf.de/aap/projects/gpower).
Results

We enrolled 50 ASA I–II subjects (34 boys and 16 girls) aged 1–6 yr undergoing elective upper abdominal surgery for this prospective, randomized, double-blind trial. Subject characteristics are described in Table 1. All caudal blocks were regarded as clinically successful. None of the subjects required additional fentanyl doses intraoperatively.

The total duration of analgesia (for FLACC score ≥4) was 16.5 (3.6) h in the CB group when compared with 10.2 (2.3) h in the MB group (P<0.01). The post hoc calculated power of the study was found to be 0.99. Subjects in Group CB remained sedated for a longer period [7.1 (0.8) h] when compared with those in Group MB [3.8 (0.7) h; P<0.01]. Vomiting was observed in 4% (1) and 12% (3) of subjects in Groups CB and MB, respectively. Sixteen per cent (4) of subjects reported itching in the MB group (P=0.03), whereas none did so in the CB group. No incidents of hypotension or bradycardia were observed. The $S_{pO2}$ did not decline below 95% in any of the subjects in the PACU (Table 2).

Discussion

The main findings of our study were that the addition of clonidine 2 μg kg$^{-1}$ to bupivacaine administered caudally provided an increase in sedation and duration of postoperative analgesia compared with the addition of morphine 30 μg kg$^{-1}$ to bupivacaine.

Caudal block is a remarkably versatile technique frequently used for providing regional anaesthesia for abdominal and lower limb surgery. Additive drugs are frequently combined with the local anaesthetic to extend the duration of postoperative analgesia. Over the last decade, there has been a 58% increase in the use of caudal additives with clonidine (42%) and ketamine (38%) being the most commonly used drugs. However, the use of opioids as additives has decreased from 36% to 18%. This could be both due to a higher incidence of unwanted effects (nausea, vomiting, pruritis, and urinary retention) with their use and due to the greater efficacy of ketamine and clonidine.

The analgesic action of intrathecal or epidural clonidine results from direct stimulation of pre- and post-synaptic $\alpha_2$-adrenoceptors in the dorsal horn grey matter of the spinal cord, thereby inhibiting the release of nociceptive neurotransmitters. Sedation after epidural clonidine results from activation of $\alpha_2$-adrenoceptors in the locus coeruleus, an important modulator of vigilance. This suppresses the spontaneous firing rate of the nucleus, thereby resulting in increased activity of inhibitory interneurones such as $\gamma$-aminobutyric acid-ergic pathways to produce central nervous system depression. Clonidine has been shown to produce analgesia without causing significant respiratory depression after systemic, epidural, or spinal administration. Although epidural clonidine also causes
hypotension, bradycardia, and sedation in higher doses, serious adverse effects are uncommon in the dose range normally used in children (1–2 μg kg⁻¹).¹⁶–²⁰

A number of papers on the use of caudal clonidine have been published over the past 10 yr focusing primarily on the quality of analgesia obtained with local anaesthetics.¹⁷–²⁰ The results of these studies vary widely. The duration of analgesia achieved has been reported to vary between 5.8 and 16.5 h, for which there are a variety of reasons. The majority of studies used non-standardized surgery and non-standardized anaesthetic techniques both within- and between-treatment groups. Moreover, differences in the dose of clonidine and the local anaesthetic agents used, concomitant use of premedication, indications for rescue analgesia, type of drugs used for rescue analgesia, and different methods of assessment of pain and statistical analysis could account for this variability.³

Most of these studies on caudal clonidine have evaluated its role as an additive for infra-umbilical surgeries, but no studies are available for upper abdominal surgery. These studies have consistently shown caudal clonidine to increase the duration of postoperative analgesia (Table 3).¹⁶–²⁰ There is a suggestion, however, that prolongation of analgesia by clonidine is dependent on the concentration of bupivacaine administered. In fact, three studies have shown that there is no benefit of adding clonidine to bupivacaine 0.125%.²² ²⁵ ²⁶ Hansen and colleagues²⁷ have further suggested that clonidine has its primary action not on the spinal cord but its role as an additive for infra-umbilical surgeries, but no studies are available for upper abdominal surgery. These studies have consistently shown caudal clonidine to increase the duration of postoperative analgesia (Table 3).¹⁶–²⁰ There is a suggestion, however, that prolongation of analgesia by clonidine is dependent on the concentration of bupivacaine administered. In fact, three studies have shown that there is no benefit of adding clonidine to bupivacaine 0.125%.²² ²⁵ ²⁶ Hansen and colleagues²⁷ have further suggested that clonidine has its primary action not on the spinal cord but mainly due to systemic absorption. Thus, the action of clonidine might depend on the concentration and volume of bupivacaine administered caudally.

Luz and colleagues²² showed that the mean duration of analgesia achieved in children undergoing orchidopexy, hernia repair, or circumcision was comparable whether caudal clonidine 1 μg kg⁻¹ or morphine 30 μg kg⁻¹ was added to bupivacaine 0.18%, 1.5 ml kg⁻¹: 6.3 (so 3.3) vs 7.1 (3.4) h (P=0.43) for the clonidine and morphine groups, respectively. Vetter and colleagues²⁸ reported caudal morphine produced more sustained initial analgesia than did caudal clonidine (P=0.02); no difference was observed in pain scores, total morphine use, time to first oral intake, or discharge home. However, less postoperative nausea and vomiting (P=0.01) and pruritus (P=0.007) with caudal clonidine (2 μg kg⁻¹) than with caudal hydromorphone or caudal morphine (50 μg kg⁻¹) was observed. They did not identify

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**Table 1** Subject characteristics. CB, clonidine–bupivacaine group; MB, morphine–bupivacaine group

<table>
<thead>
<tr>
<th></th>
<th>Group CB (n = 25)</th>
<th>Group MB (n = 25)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>2.9 (1–6)</td>
<td>2.8 (1.5–6)</td>
<td>0.81</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>11.3 (3.10)</td>
<td>11.8 (2.18)</td>
<td>0.58</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (72%)</td>
<td>16 (64%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Female</td>
<td>7 (28%)</td>
<td>9 (36%)</td>
<td></td>
</tr>
<tr>
<td>Duration of surgery (h)</td>
<td>2.2 (1.22)</td>
<td>2.0 (1.01)</td>
<td>0.64</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>16 (64%)</td>
<td>18 (72%)</td>
<td>0.291</td>
</tr>
<tr>
<td>Resection</td>
<td>8 (32%)</td>
<td>5 (20%)</td>
<td></td>
</tr>
<tr>
<td>Hepaticoanastomosis</td>
<td>1 (4%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
<tr>
<td>Fentanyl administered</td>
<td>2 μg kg⁻¹</td>
<td>(in both groups)</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2** Comparison of caudal clonidine–bupivacaine and morphine–bupivacaine. CB, clonidine–bupivacaine group; MB, morphine–bupivacaine group

<table>
<thead>
<tr>
<th></th>
<th>Group CB (n = 25)</th>
<th>Group MB (n = 25)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of analgesia (h)</td>
<td>16.5 (3.6)</td>
<td>10.2 (2.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Duration of sedation (h)</td>
<td>7.1 (0.8)</td>
<td>3.8 (0.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (4%)</td>
<td>3 (12%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Itching</td>
<td>0</td>
<td>4 (16%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(SpO₂ &lt; 95%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Table 3** Duration of analgesia with caudal clonidine in the published literature

<table>
<thead>
<tr>
<th>References</th>
<th>Authors</th>
<th>Surgery</th>
<th>Clonidine (μg kg⁻¹)</th>
<th>Bupivacaine</th>
<th>Duration of analgesia (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Jamali and colleagues</td>
<td>Subumbilical and urologic</td>
<td>1</td>
<td>0.25%, 1 ml kg⁻¹</td>
<td>16.5 (9.5)</td>
</tr>
<tr>
<td>17</td>
<td>Lee and Rubin</td>
<td>Orthopaedic</td>
<td>1</td>
<td>0.25%, 1 ml kg⁻¹</td>
<td>9.8 (2.1)</td>
</tr>
<tr>
<td>18</td>
<td>Klimscha and colleagues</td>
<td>Herniotomy</td>
<td>1</td>
<td>0.25%, 0.75 ml kg⁻¹</td>
<td>6.0 (4.5–6.0)</td>
</tr>
<tr>
<td>19</td>
<td>Cook and colleagues</td>
<td>Orchidopexy</td>
<td>2</td>
<td>0.25%, 1 ml kg⁻¹</td>
<td>5.8</td>
</tr>
<tr>
<td>22</td>
<td>Luz and colleagues</td>
<td>Herniotomy, orchidopexy, circumcision</td>
<td>1</td>
<td>0.18%, 1.5 ml kg⁻¹</td>
<td>6.3 (3.3)</td>
</tr>
<tr>
<td>24</td>
<td>El-Hennawy and colleagues</td>
<td>Lower abdominal surgeries</td>
<td>2</td>
<td>0.25%, 1 ml kg⁻¹</td>
<td>12 (9)</td>
</tr>
</tbody>
</table>
any postoperative respiratory depression, excessive sedation, hypotension, or bradycardia. In fact, we could find no study using single-shot caudal block for upper abdominal surgery and also none that compares morphine with clonidine for the same. A dose of 30 μg kg⁻¹ of caudal morphine was chosen by us as it is probably the minimum dose that can effectively prolong the duration of analgesia without producing significant side-effects.⁷⁸

The main limitation of our study was that we did not observe the relative potency of the analgesic effect of the two drugs as the equipotent doses of morphine and clonidine are not available in the published literature. The motor effect prolongation, if any, of bupivacaine administered caudally was also not studied.

Nurse-controlled analgesia is generally the preferred modality for providing parenteral analgesics in small children undergoing upper abdominal surgery. However, single-shot caudal clonidine 2 μg kg⁻¹ in bupivacaine 0.2% provides a longer duration of analgesia and sedation compared with caudal morphine 30 μg kg⁻¹ in bupivacaine 0.2% without significant side-effects in children undergoing upper abdominal surgery.

**Conflict of interest**

None declared.

**References**

15. Eyres RL, Chalkiadis G, Taylor R. Efficacy and safety of levobupivacaine as caudal anaesthesia in paediatric surgery. *Inter Monitor Reg Anaesth* 1999; 11: 31A