Caudal bupivacaine supplemented with caudal or intravenous clonidine in children undergoing hypospadias repair: a double-blind study

T. G. Hansen¹*, S. W. Henneberg², S. Walther-Larsen², J. Lund¹ and M. Hansen¹

¹Department of Anaesthesia and Intensive Care, Odense University Hospital, DK-5000 Odense C, Denmark.
²Department of Anaesthesia, The Juliane Marie Centre, Copenhagen University Hospital Rigshospitalet, DK-2100 Copenhagen, Denmark

*Corresponding author. E-mail: tomghansen@dadlnet.dk

Background. Clonidine is used increasingly in paediatric anaesthetic practice to prolong the duration of action of caudal block with a local anaesthetic agent. Which route of administration of clonidine is the most beneficial remains unknown. We compared the effects of caudal and i.v. clonidine on postoperative analgesia produced by caudal bupivacaine after hypospadias repair.

Methods. Forty-six children (ASA I or II) aged 24–104 months received standardized premedication with midazolam, a general anaesthetic and a caudal block with bupivacaine 0.25%, 0.5 ml kg⁻¹. The children were randomized in a double-blind fashion to two groups: the i.v. group received clonidine 2 µg kg⁻¹ i.v. and simultaneously the same volume of saline caudally. The caudal group received clonidine 2 µg kg⁻¹ caudally and a similar volume of saline i.v. After surgery, all children received acetaminophen 20 mg kg⁻¹ rectally or orally 6-hourly and were given a patient-controlled or nurse-controlled analgesia (PCA/NCA) pump with i.v. morphine (bolus of 25 µg kg⁻¹ and an 8-min lockout period with no background infusion). Monitoring of scores for pain, sedation, motor block, and postoperative nausea and vomiting was performed by nurses blinded to the study allocations. Time to first activation of the PCA/NCA pump and 0–24 h and 24–48 h morphine consumption were also recorded.

Results. Forty-four children completed the study. Age, weight and duration of anaesthesia and surgery were similar in the two groups. The median (range) time to first activation of the PCA/NCA pump was similar in the two groups: 425 (150–1440) min in the i.v. group and 450 (130–1440) min in the caudal group. The number of children not requiring postoperative morphine was four and seven respectively. Morphine consumption during 0–24 h and 24–48 h was similar between groups.

Conclusions. The analgesic effect of clonidine 2 µg kg⁻¹ as an adjunct to caudal block with bupivacaine 0.25%, 0.5 ml kg⁻¹ is similar whether administered i.v. or caudally.


Keywords: anaesthetic techniques, caudal epidural block; anaesthetic techniques, i.v.; anaesthetics local, bupivacaine; children; receptors, alpha₂-receptor agonists; sympathetic nervous system, clonidine

Accepted for publication: September 30, 2003

Caudal epidural block is one of the most common regional anaesthetic techniques used in children. It is generally considered a simple and safe procedure and its main disadvantage is its relatively short duration of action, even with the use of long-acting local anaesthetic agents such as bupivacaine.¹ In order to improve the duration of action and quality of analgesia of a caudal block with bupivacaine, various drugs have been used, e.g. opioids, epinephrine, midazolam, neostigmine, ketamine and clonidine.² ⁵ All these agents have potential side-effects.
Since the discovery that epidural clonidine, an α2 receptor agonist, produces analgesia, the drug has been used increasingly in anaesthetic practice. During the last decade the use of clonidine has become increasingly popular in paediatric anaesthesia, particularly when administered caudally with a local anaesthetic agent. Clonidine has been shown to produce analgesia without causing significant respiratory depression after systemic, epidural or spinal administration. Although epidural clonidine may also cause 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).

The α2 receptor is also the binding site for the adrenergic neurotransmitter norepinephrine. There is some evidence to suggest that clonidine’s analgesic effects are more pronounced after neuroaxial administration. However, α2 receptors are widely distributed throughout the central nervous system, with three isoreceptors (α2A, α2B, α2C) recognized so far. The α2 receptors are located primarily on afferent terminals centrally and peripherally, but they are also found in the superficial laminae of the spinal cord and within several brainstem nuclei known to be involved in analgesia. Animal studies have demonstrated analgesic action at all three sites, but so far their relative clinical importance is controversial and subject to ongoing debate.

We therefore designed a randomized, double-blind, controlled paediatric study. The aim was to compare the effects of clonidine administered either i.v. or caudally on postoperative analgesia produced by caudal bupivacaine.

Materials and methods

The study was approved by the scientific committees of Vejle and Funen Counties and for Copenhagen and Frederiksborg, and by the Danish Medicines Agency (Lægemedicinstyrelsen). Written informed parental consent was obtained for each child. Forty-six boys, ASA status I or II, aged 2–8 yr, scheduled to undergo elective in-patient hypospadias repair were recruited for the study from two Danish centres.

Exclusion criteria were any contraindication to a caudal block or the study medication. Children who had received any analgesic drugs within the past 24 h were not included. After inclusion, the children were randomized in double-blind fashion to receive clonidine 2 μg kg⁻¹ (Catapressan® 150 μg ml⁻¹; Boehringer-Ingelheim, Frankfurt, Germany) either caudally or i.v. as an adjunct to caudal bupivacaine 0.25%, 0.5 ml kg⁻¹. The randomization was performed en bloc according to a computer-generated list and delivered in sealed, opaque, sequentially numbered envelopes.

Anaesthetic technique

All children had Emla® applied to the dorsum of both hands 1 h before surgery. Twenty minutes before surgery they received midazolam 0.5–0.75 mg kg⁻¹ orally (standard formulation mixed with sweet fruit syrup) or rectally (standard formulation). General anaesthesia was induced with either sevoflurane 8% in oxygen 100% via a facemask or propofol 3–5 mg kg⁻¹ i.v. After induction, an i.v. catheter was sited and an infusion of normal saline 5–10 ml kg⁻¹ h⁻¹ was commenced. Anaesthesia was maintained with oxygen 40% in nitrous oxide, isoflurane 0.5–1.0% and fentanyl 2 μg kg⁻¹ i.v. All patients maintained spontaneous breathing via a laryngeal mask airway (LMA™) of an appropriate size.

A nurse not otherwise involved in the study prepared the study medication. One millilitre of clonidine (150 μg ml⁻¹) was diluted with 9 ml of normal saline in a 10-ml syringe. For each child, two syringes were prepared: one syringe contained the diluted clonidine (15 μg ml⁻¹) to give a dose of 2 μg kg⁻¹ (a total volume of 0.13 ml kg⁻¹), and the other contained the same volume of normal saline.

The caudal block was performed with the child positioned in the left lateral position by a consultant anaesthetist using an aseptic technique and a 23-gauge needle. After negative aspiration of blood and cerebrospinal fluid, bupivacaine 0.25%, 0.5 ml kg⁻¹ was injected caudally together with either the study medication or normal saline. Simultaneously, the content of the second syringe, containing the same volume of either study medication or saline, was administered i.v. The anaesthetist and all nursing staff involved in the care of the child during the study period were blinded to the contents of the two syringes with the study medication.

Heart rate, non-invasive blood pressure and peripheral oxygen saturation (SpO₂) were recorded after induction of anaesthesia and every 5 min thereafter intraoperatively. End-tidal carbon dioxide and isoflurane were monitored continuously after placement of the LMA and throughout the procedure. An intraoperative decrease in arterial pressure or heart rate of >15% from preoperative values was defined as hypotension or bradycardia respectively, and was treated with rapid infusion of normal saline 10–20 ml kg⁻¹ or i.v. atropine 10 μg kg⁻¹. Respiratory depression was defined as a decrease in SpO₂ of <95% requiring supplementary oxygen. An intraoperative increase in baseline arterial pressure or heart rate of >10% was defined as insufficient analgesia and was treated with additional doses of fentanyl 1 μg kg⁻¹ as needed.

After surgery, the children were transferred to the recovery room when they were sufficiently awake and capable of maintaining a free airway. In the recovery room, the children were given patient-controlled or nurse-controlled analgesia (PCA/NCA) using a Pharmacia-Deltac pump (Astra Tech, Copenhagen, Denmark). The children received morphine 25 μg kg⁻¹ i.v. as a bolus on demand with a lockout interval of 8 min and no background infusion. At the time of inclusion, all children and their parents were told the principles of PCA/NCA. Additionally, all children received regular acetaminophen 20 mg kg⁻¹ every 6 h rectally or orally.

224
In recovery, heart rate, $S_O_2$, and respiratory rate were monitored every 15 min until the child was awake and cooperative. During the study period, pain, sedation, motor block and postoperative nausea and vomiting were recorded by experienced paediatric nurses blinded to the treatment groups every 3 h after surgery using a scale of 0–3: 1 = no pain, 2 = minor pain, 3 = moderate pain, and 4 = severe pain; sedation score (0 = alert and aware, 1 = asleep, arousable by verbal contact, 2 = asleep, arousable by physical contact, and 3 = asleep, not arousable, and it was noted whether the child was in normal sleep, recorded as X); postoperative nausea and vomiting (PONV) score (0 = no PONV, 1 = PONV that disappeared spontaneously with no need for intervention, 2 = PONV that disappeared after medical treatment, and 3 = PONV that did not disappear despite medical treatment); motor block score (0 = spontaneous movements of hips, knees and ankles, 1 = movements of knees and ankles but no movements of hips, 2 = only movements of ankles, and 3 = no movements of lower limbs). Urinary retention was not assessed, as all children had a urinary catheter sited by the surgeon. The indication for administering the first morphine dose and subsequent doses was a pain score $\geq$ 1. On the postoperative ward, the children were under constant supervision by experienced paediatric nurses, and hence any pain experienced by children using NCA was treated if and when it occurred (and similarly for children receiving PCA).

The duration of postoperative analgesia was defined as the time between administering the study drug (caudally or i.v.) and the first activation of the PCA/NCA pump with i.v. morphine. In addition, the number of morphine doses administered during the first 0–24 h and subsequent 24–48 h was noted in all the children.

**Statistical analysis**

Data are presented as mean or median with range or 95% confidence interval (CI) as appropriate. The primary endpoint of the study was time to first activation of the PCA pump. Before the study, the number of patients required in each group was determined using a power calculation with data obtained from previous studies. A pre-study power analysis indicated that a sample size of 18 would be required in each group in order to detect a 40% difference between the groups with $\alpha = 0.05$ and $\beta = 0.2$ and a standard deviation of 40% in this population.

Statistical comparison was performed using GraphPad InStat and Prism version 3.00 for Windows (GraphPad Software, San Diego, CA, USA; www.graphpad.com). The two-sample (unpaired) $t$-test was used to compare patient characteristics and the number of morphine doses administered between the two groups. The Mann–Whitney $U$-test was used to compare the time to first morphine dose between the two groups. In order to perform this analysis without disregarding patients who did not request any morphine, we arbitrarily set the time to first morphine request as $t = 24$ h (1440 min) and subsequently calculated median values for both groups. Fisher’s exact test was used to compare the number of patients in each group who did not require any morphine during the entire postoperative period and the distribution of children on PCA/NCA between the two groups. The overall global analgesic efficacies in the two groups were evaluated using the Kaplan–Meier survival curve method followed by the log rank test. The end-point for this analysis was the time to first activation of the PCA/NCA pump. A $P$ value of less than 0.05 was considered statistically significant.

### Results

Forty-six boys were included in the study. One child was excluded because, in addition to a hypospadias repair, he also had a left-sided orchidopexy repair performed; a second child was excluded because, after anaesthetic induction and after the caudal block had been performed, the surgeon decided that the child did not need the operation after all.

The physical characteristics of the remaining 44 children are shown in Table 1. Age, weight and duration of anaesthesia and surgery were similar between the i.v. and caudal groups. The distribution of children on PCA/NCA was 13/10 in the i.v. group and 12/9 in the caudal group ($P = 1.0$). All caudal blocks were regarded as clinically successful. None of the children required additional fentanyl doses intraoperatively. No incidents of hypotension, bradycardia or bradypnoea were seen in any of the children studied and no episodes of $S_O_2 < 95\%$ were recorded.

The median (range) time to first activation of the PCA/NCA pump was similar in the two groups [425 (150–1440) min in the i.v. group and 450 (130–1440) min in the caudal group; $P = 0.66$], as was the number of patients who did not use any morphine at all during the study period. In addition, the numbers of morphine doses during the first 0–24 h and subsequent 24–48 h were statistically similar between groups (Table 2). Using a log rank test (the Mantel–Haenszel test), we compared the percentage of patients who did not use any morphine over time in each group. There was no difference between the two groups ($P = 0.45$) (Fig. 1). Pain scores were similar and mainly $\leq 1$ in both groups, as were sedation scores. No motor block was observed in either of the two groups on awakening or during the 48-h study period. Two patients from the i.v. group and one patient

<table>
<thead>
<tr>
<th>Table 1 Physical characteristics of the children studied. Data are mean (95% CI). No significant differences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous group (n=23)</strong></td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Age (months)</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
</tr>
</tbody>
</table>

*CI*: confidence interval.
Table 2 Postoperative morphine consumption for the two groups of children undergoing hypospadias repair. Time to first morphine dose is given as median (range). The number of morphine doses is mean (95% CI). The number of patients who did not require morphine are also given. No statistically significant differences were found between the two groups for any of the measured variables.

<table>
<thead>
<tr>
<th></th>
<th>Intravenous group (n=23)</th>
<th>Caudal group (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first morphine dose (min)</td>
<td>425 (150–1440)</td>
<td>450 (130–1440)</td>
</tr>
<tr>
<td>No. of patients not requiring morphine</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>No. of morphine doses (0–24 h)</td>
<td>4.5 (2.8–6.2)</td>
<td>3.1 (1.4–4.8)</td>
</tr>
<tr>
<td>No. of morphine doses (24–48 h)</td>
<td>2.4 (1.0–3.9)</td>
<td>1.7 (0.3–3.0)</td>
</tr>
</tbody>
</table>

Discussion

The key finding of the present study is that the analgesic efficacy of clonidine 2 mg kg\(^{-1}\) as an additive to caudal block with bupivacaine 0.25%, 0.5 ml kg\(^{-1}\) in children undergoing hypospadias repair is unaffected by whether clonidine is administered i.v. or by the caudal route. Our study also confirmed previous studies showing that supplementing a caudal block from bupivacaine with clonidine 2 mg kg\(^{-1}\) results in a mean time of 6–7 h to requesting systemic analgesics.\(^2\) \(^8\) \(^12\) \(^13\)

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.\(^8\) \(^12\) \(^13\) 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 is a variety of causes. 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 may all account for this variability. In most of the previous studies, rescue analgesia was provided with acetaminophen, and consequently the duration of the caudal block was defined as the time between performing the block and subsequent administration of the first acetaminophen dose. However, as acetaminophen is only a mild analgesic, its use is justifiable only as the primary analgesic agent in the treatment of pain after minor surgery. The prolonged time to onset of action of a dose of acetaminophen (especially after rectal administration) suggests that acetaminophen should not be used in these circumstances.\(^16\) \(^17\) The interpretation of the results of previous studies is therefore difficult.

We used a standardized anaesthetic technique and a standardized surgical procedure, i.e. hypospadias repair. All children in our study received premedication with midazolam, and after surgery all children received regular acetaminophen in addition to on-demand i.v. morphine via PCA/NCA. PCA has been used extensively as a research tool in clinical pharmacological studies involving analgesics in both adults and children.\(^18\) \(^19\) The overall quality of analgesia obtained in this study was thus based on the morphine consumption pattern via the PCA/NCA.

It is tempting to interpret the results of this study as if the primary site of action of clonidine were outside the spinal cord, not least because \(\alpha_2\) adrenoceptors are found throughout the body. Clonidine is a highly lipophilic drug, and thus will be absorbed and reach the systemic circulation fairly quickly irrespective of the site of administration.\(^20\) \(^22\) It has certainly been shown that oral as well as intrathecal administration of clonidine prolongs the duration of action of intrathecal block with local anaesthetics.\(^23\) Additionally, i.m. clonidine has been shown to be as effective as epidural administration for postoperative analgesia.\(^24\) Though, as previously mentioned, several paediatric studies involving caudal use of clonidine together with local anaesthetics have indicated a spinal mechanism of action.\(^2\) \(^8\) \(^12\) \(^13\) there is also evidence for extraspinal effects of clonidine. Co-administration of clonidine with local anaesthetics has been shown to improve the quality of peripheral nerve blocks.\(^25\) \(^27\) Therefore, the exact mechanisms responsible for the analgesic action of clonidine administered intrathecally or systemically remain to be clarified.

If we had included more patients in our study, it is possible that we would have found a statistically significant difference between the two groups. However, in our opinion such a difference would be of minor clinical relevance.

The volume (0.5 ml kg\(^{-1}\)) of bupivacaine 0.25% used in our study differs from that used in many studies (1 ml kg\(^{-1}\)),
and this may have influenced the duration of action of the caudal blocks. The caudal blocks would not have had to recede by many dermatomes before the children experienced pain. However, we used the volume of local anaesthetic agent that has been recommended for years by Armitage to cover sacral dermatomes, and there is no evidence that a larger volume of the same concentration of a local anaesthetic increases the duration of a caudal block. More importantly, however, it is possible that the relatively small volume of bupivacaine used in our study was insufficient to transport the clonidine to the spinal cord, leaving only direct action on the nerve routes in the caudal area as the mechanism of action. Additionally, it has been shown that sacral nerve roots are more difficult to penetrate than lumbar nerves, and thus the analgesic action of clonidine at this site may be minimal.

In conclusion, within the context of the present study, using i.v. or caudal clonidine (2 μg kg⁻¹) as an additive to caudal block with bupivacaine 0.25%, 0.5 ml kg⁻¹ in children undergoing hypospadias repair results in comparable analgesia. Further studies are required to elucidate the exact mechanisms of analgesia from clonidine when administered together with local anaesthetic agent.

References

7 Ho D, Keneally JP. Analgesia following paediatric day-surgical orchidopexy and herniomy. Paediatr Anaesth 2000; 10: 627–31
13 Eisenach J, Detweiler D, Hood D. Hemodynamic and analgesic actions of epidurally administered clonidine. Anesthesiology 1993; 78: 277–87
18 Singelyn FJ, Gouverneur JM, Robert A. A minimum dose of clonidine added to mepivacaine prolongs the duration of anesthesia and analgesia after axillary brachial plexus block. Anesth Analg 1996; 83: 1046–50