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ORIGINAL ARTICLE

Caudal bupivacaine supplemented with morphine or clonidine, or supplemented with morphine plus clonidine in children undergoing infra-umbilical urological and genital procedures: a prospective, randomized and double-blind study

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Abstract
Purpose We aimed to evaluate postoperative analgesia of morphine, or clonidine, or morphine plus clonidine, added to caudal bupivacaine in children undergoing infra-umbilical urological and genital procedures.
Methods Eighty patients aged 1–10 years were prospectively enrolled. After the induction of general anesthesia, the patients were randomized to four caudal anesthesia groups: Group B (1.0 mL/kg of bupivacaine 0.166% with epinephrine 1:600,000); Group BM (1.0 mL/kg of bupivacaine 0.166% with epinephrine 1:600,000 plus morphine 20 μg/kg); Group BC (bupivacaine 0.166% with epinephrine 1:600,000 plus clonidine 1.0 μg/kg), and Group BMC (bupivacaine 0.166% with epinephrine 1:600,000 plus morphine 20 μg/kg and clonidine 1.0 μg/kg). Duration of surgery, emergence time, postoperative pain score measured by the face, legs, activity, cry, consolability (FLACC) scale, postoperative analgesia time, and overall use of rescue analgesics were recorded.
Results The FLACC pain score (6, 12, and 24 h after the surgery) and the number of patients requiring analgesics during the first 24 h of the postoperative period were higher in Groups B and BC than in Groups BM and BMC ($p < 0.05$). The incidence of pruritus and urinary retention was comparable between the groups ($p > 0.05$). However, the incidence of postoperative nausea and vomiting (PONV) was higher in Groups BM (35%) and BMC (25%) than in Groups B (5%) and BC (5%) ($p < 0.05$).
Conclusion To conclude, we showed that 20 μg/kg of morphine added to caudal bupivacaine 0.166% plus epinephrine 1:600,000 decreased the use of analgesics in the postoperative period, although it was associated with an increased incidence of PONV. However, the addition of clonidine (1.0 μg/kg) to caudal bupivacaine provided no additional clinical benefit over bupivacaine alone.

Keywords Caudal anesthesia · Children · Clonidine · Morphine

Introduction

Caudal block is commonly used as a pediatric analgesic technique for surgery [1]. The ideal concentration of caudal bupivacaine to provide adequate analgesia is between 0.125 and 0.175% [2, 3]. Morphine [4–9] and clonidine [10–17] have been added to local anesthetics in an attempt to improve the duration and quality of caudal block analgesia. Unfortunately, these agents have potential side effects that can limit their use [11, 14, 18, 19]. The incidence of adverse effects is usually dose-dependent; therefore, it would be appropriate to use the lowest effective dose of these adjuncts.

The association of drugs with different mechanisms and sites of action could improve pain relief; however, no data have been reported on the effects of the addition of low doses of morphine and clonidine to a low concentration of bupivacaine for caudal anesthesia in children. Therefore,

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the main outcome of this prospective, randomized, double-blind study was to evaluate the analgesic profile (pain score, duration of analgesia, and overall use of analgesics) of single-dose caudal morphine (20 μg/kg) and/or clonidine (1 μg/kg), combined with bupivacaine 0.166% with epinephrine (1:600,000) in a volume of 1 mL per kilogram, in pediatric patients undergoing infra-umbilical urological and genital procedures. Secondary outcomes were the side effects and safety profiles of the addition of these agents to bupivacaine.

Methods

Patients and study design

After obtaining institutional review board approval and written parental informed consent, we enrolled 80 children, aged 1–10 years, American Society of Anesthesiologists (ASA) physical status I or II, who were scheduled to undergo infra-umbilical urological and genital procedures. Patients were excluded if they had any neurologic disability, history of epilepsy, if they were taking any central nervous system medication, or if there was any contraindication to caudal epidural anesthesia.

Patients were randomized by computer-assisted, randomized treatment assignments in sequentially ordered and sealed envelopes. The treatment groups were: Group B, in which patients received 1.0 mL/kg of bupivacaine 0.166% with epinephrine 1:600,000; Group BM, in which patients received 1.0 mL/kg of bupivacaine 0.166% with epinephrine 1:600,000 plus morphine 20 μg/kg; Group BC, in which patients received bupivacaine 1.0 mL/kg of 0.166% with epinephrine 1:600,000 plus clonidine 1.0 μg/kg; and Group BMC, in which patients received 1.0 mL/kg of bupivacaine 0.166% with epinephrine 1:600,000 plus morphine 20 μg/kg and clonidine 1.0 μg/kg. Sterile syringes containing the test solutions were prepared by one of the investigators who was not involved in administering the caudal anesthesia. Bupivacaine 0.166% with epinephrine 1:600,000 was obtained by diluting bupivacaine 0.5% with epinephrine 1:200,000 at a ratio of 1:3 with normal saline. The subjects and their parents or guardians were blinded to the caudal medication administered.

Caudal block

No sedative premedication was given. The patients were monitored with electrocardiogram, non-invasive blood pressure, pulse oximetry, temperature, capnography, end-tidal anesthetic concentration, and a bispectral (BIS) monitor. Anesthesia was induced by mask inhalation of sevoflurane 8% in 50% N_2O/50% O_2, and atracurium 0.5 mg/kg was administered to facilitate endotracheal intubation. The child was then turned to the left lateral position, and caudal blockade was performed using a 22-gauge intravenous catheter with an inner needle inserted through the sacrococcygeal ligament into the caudal space. The needle was removed, and the catheter was advanced 0.5–1 cm. After negative aspiration for blood or cerebrospinal fluid the study solution was administered over 1 min. Anesthesia was maintained using controlled ventilation with isoflurane in 50% N_2O/50% O_2. The inhaled concentration of isoflurane was adjusted to maintain hemodynamic stability, which was defined as a change in systolic blood pressure and heart rate of no more than 20% of baseline parameters [20]. The operation was performed without using i.v. fentanyl, and no other opioids or sedative drugs were given intraoperatively. Mean arterial pressure (MAP), heart rate (HR), and maintenance end-tidal isoflurane concentration were registered every 15 min. At the end of surgery, anesthesia was discontinued and the neuromuscular block was reversed with neostigmine (0.04 mg/kg) and atropine (0.02 mg/kg). The patient was extubated based on clinical criteria. The patient was then transported to the post-anesthetic care unit (PACU).

Data collection procedure

Demographic data such as gender, age, ASA physical status, and weight were noted. Duration of surgery and emergence time (the time from the end of surgery to first spontaneous eye opening) was also recorded. The pain score of the patients was evaluated with the pediatric observational face, legs, activity, cry, consolability (FLACC) scale (0–10 score range) [21] at 1, 3, 6, 9, 12, and 24 h after the end of the surgery. The intensity of pain was classified as none or mild ($\leq$4), moderate (5–7), and severe ($\geq$8). Similarly to other authors, we routinely start analgesic treatment with weak analgesics and reserve opioids for more intense pain [22, 23]. Metamizol is an analgesic drug used in some countries for the treatment of postoperative pain in children [22] and it is also our routine to use it as the first analgesic rescue agent. If necessary, we also use other analgesic drugs (nonsteroidal anti-inflammatory drugs [NSAIDs] and opioids). Thus, in the present study, postoperative pain was treated firstly with metamizol, followed by ibuprofen or morphine according to the intensity of the pain. If the patient presented with pain between the recorded intervals of FLACC, another evaluation was done in order to determine the intensity of the pain and the type of analgesic to use. The postoperative analgesia time (time from the caudal anesthesia to the first use of analgesics) and the number of doses of rescue analgesics (metamizol, ibuprofen, or morphine) in the postoperative period (24 h) were recorded. MAP, respiratory rate, and HR were monitored every hour during the first 6 h and then every 3 h in

the 24-h postoperative period. Postoperative nausea and vomiting (PONV) was assessed in the same periods as those used for pain assessment. Rescue treatment of PONV was done with ondansetron (0.15 mg/kg) given at intervals of 4 h. Side effects such as urinary retention and pruritus were also noted. A research nurse blinded to the treatment groups performed all follow-up data collection.

Statistical analysis

Based on a previous study [14], a power analysis suggested that a minimum of 18 patients would be necessary in each group to detect a 50% difference in the number of patients receiving postoperative analgesics between Group B and the other treatment groups (Group BM, Group BC, and Group BMC) with a power of 90% and an error of 0.05. Therefore, we decided to enroll 20 patients in each group. Data were analyzed using one-way analysis of variance (ANOVA), the Kruskal–Wallis test, Mann–Whitney *U*-test, χ^2 test, or Fisher's exact test, when appropriate. The Kolmogorov–Smirnov test was used to test for normality of distribution. A p value of <0.05 was considered as the minimum level of statistical significance.

Results

Eighty-four patients were assessed for eligibility. Four patients were excluded according to the exclusion criteria. Complete study data were collected for the 80 initially enrolled patients. There were no complications (such as epidural bleeding, infection, or difficulty of accessing the caudal space) during administration of the caudal block. There were no differences between the groups in age, gender, weight, ASA physical status, duration of surgery, and emergence time (Table 1). The groups were similar regarding the operation type (Table 2). No analgesic drugs were given to any patient during anesthesia. There were no statistically significant differences in MAP, HR, and end-tidal concentration of isoflurane changes with time in any group compared with baseline values (data not shown).

The median FLACC score was higher in Groups B and BC than in Groups BM and BMC from 6 to 24 h after the end of surgery ($p = 0.001$) (Table 3). No patients in Groups BM and BMC had moderate or severe pain. One patient in Group BC had moderate pain at 6 h. One patient in Group B and one in Group BC had moderate pain at 12 h. One patient in Group BC had severe pain at 12 h. Two patients in Group B had moderate pain at 24 h. One patient in Group B and one in Group BC had severe pain at 24 h. While the time to first rescue analgesia did not differ between the groups (Table 1), the number of patients requiring rescue analgesics was higher in Group B and Group BC than in Groups BM and BMC during the first 24 h of the postoperative period ($p = 0.018$ BM vs. B; $p = 0.008$ BM vs. BC; $p = 0.046$ BMC vs. B; $p = 0.022$ BMC vs. BC) (Table 4). The number of rescue doses of metamizol was higher in the groups without morphine

Table 1 Demographic data and surgical data ($N = 80$)

Variable	Group B ($N = 20$)	Group BM ($N = 20$)	Group BC ($N = 20$)	Group BMC ($N = 20$)	p
Age (months)	50.0 ± 25.0	57.3 ± 30.9	56.8 ± 32.2	77.8. ± 33.5	0.062[a]
Weight (kg)	18.3 ± 7.1	21.6 ± 11.2	17.9 ± 7.4	23.5 ± 8.0	0.198[a]
Gender					
Male	17 (85%)	15 (75%)	17 (85%)	18 (90%)	0.626[b]
Female	3 (15%)	5 (25%)	3 (15%)	2 (10%)	
ASA physical status					
I	16 (80%)	17 (85%)	12 (60%)	16 (80%)	0.253[b]
II	4 (20%)	3 (15%)	8 (40%)	4 (20%)	
Duration of surgery (min)	96.4 ± 48.1	80.3 ± 29.2	108.1 ± 57.1	89.3 ± 46.1	0.534[c]
Emergence time (min)	12 (5–18)	10 (7–30)	10 (2–28)	11 (4–20)	0.633[d]
Postoperative analgesia time (min)	360 (60–540)	360 (360–540)	360 (120–540)	540 (320–720)	0.345[d]

Values are means (SD), medians (ranges), or numbers (%)

Group B (1.0 mL/kg of bupivacaine 0.166% with epinephrine 1:600,000), *Group BM* (1.0 mL/kg of bupivacaine 0.166% with epinephrine 1:600,000 plus morphine 20 μg/kg), *Group BC* (bupivacaine 0.166% with epinephrine 1:600,000 plus clonidine 1.0 μg/kg), *Group BMC* (bupivacaine 0.166% with epinephrine 1:600,000 plus morphine 20 μg/kg and clonidine 1.0 μg/kg, *ASA* American Society of Anesthesiologists

[a] One-way analysis of variance (ANOVA)

[b] χ^2 test

[c] Mann–Whitney *U*-test

[d] Kruskal–Wallis test

Table 2 Type of surgery ($N = 80$)

Variable	Group B ($N = 20$)	Group BM ($N = 20$)	Group BC ($N = 20$)	Group BMC ($N = 20$)
Operation type				
Infraumbilical or inguinotomy	9	11	9	7
Genital or perineal	11	9	11	13

Fisher's exact test: $p = 0.752$ BM versus B; $p = 0.752$ BM versus BC; $p = 0.340$ BM versus BMC; $p = 1.000$ BC versus B; $p = 0.747$ BC versus BMC; $p = 0.747$ BMC versus B

Table 3 Postoperative face, legs, activity, cry, consolability (FLACC) pain scores

Time (h)	Group B ($N = 20$)	Group BM ($N = 20$)	Group BC ($N = 20$)	Group BMC ($N = 20$)
1[a]	2 (0–4)	2 (0–4)	1.5 (0–4)	1 (0–3)
3[a]	2 (1–3)	1 (0–2)	2 (0–3)	2 (0–5)
6[b]	3 (2–4)	1 (0–2)	3 (2–5)	1 (0–3)
12[b]	3 (2–5)	1 (0–3)	4 (2–8)	1 (0–2)
24[b]	3.5 (2–8)	1 (1–3)	3 (1–8)	2 (1–3)

Values are medians (ranges)

[a] Kruskal–Wallis test, $p > 0.05$

[b] Kruskal–Wallis test, $p < 0.0001$

Table 4 Patients requiring rescue and number of rescue doses stratified by analgesic

	Group B ($N = 20$)	Group BM ($N = 20$)	Group BC ($N = 20$)	Group BMC ($N = 20$)
Patients requiring rescue[a]	10 (50%)	3 (25%)	11 (55%)	4 (20%)
Rescue doses by analgesic				
Metamizol[b]	10 (50%)	3 (25%)	11 (55%)	4 (20%)
Ibuprofen[c]	3 (15%)	0 (0%)	1 (5%)	1 (5%)
Morphine[d]	0 (0%)	0 (0%)	1 (5%)	1 (5%)

Values are *n* (%)

[a] χ^2 test, $p = 0.018$ BM versus B; $p = 0.008$ BM versus BC; $p = 0.046$ BMC versus B; $p = 0.022$ BMC versus BC; $p = 0.751$ B versus BC; $p = 0.677$ BM versus BMC

[b] χ^2 test, $p = 0.018$ BM versus B; $p = 0.008$ BM versus BC; $p = 0.046$ BMC versus B; $p = 0.022$ BMC versus BC

[c] χ^2 test, $p = 0.255$

[d] χ^2 test, $p = 0.561$

during the first 24 h of the postoperative period ($p = 0.002$ BM/BMC vs. B/BC; Fisher's exact test) (Table 4). In contrast, there was no difference between the groups regarding the number of doses of ibuprofen and morphine (Table 4).

Table 5 Postoperative side effects

Variable	Group B ($N = 20$)	Group BM ($N = 20$)	Group BC ($N = 20$)	Group BMC ($N = 20$)
Urinary retention[a]	0 (0%)	2 (10%)	0 (0%)	2 (10%)
Pruritus[b]	0 (0%)	2 (10%)	0 (0%)	0 (0%)
PONV[c]	1 (5%)	7 (35%)	1 (5%)	5 (25%)

Values are *n* (%)

PONV postoperative nausea and vomiting

[a] Fisher's exact test, $p = 0.487$ BM or BMC versus B or BC

[b] Fisher's exact test, $p = 0.487$ BM versus B, BC, or BMC

[c] Fisher's exact test, $p = 0.021$ BM versus B; $p = 0.021$ BM versus BC; $p = 0.090$ BMC versus B; $p = 0.090$ BMC versus BC

The incidence of pruritus and urinary retention was comparable between the groups (Table 5). However, the number of patients with PONV was higher in the morphine groups (BM/BMC) than in the groups without morphine (B/BC) ($p = 0.006$; Fisher's exact test) (Table 5). All the episodes of vomiting were considered mild and were treated with one dose of ondansetron (0.15 mg/kg). No episode of clinically significant postoperative respiratory depression, hypotension, or bradycardia was identified.

Discussion

Our study found that the addition of morphine to a solution of bupivacaine 0.166% and epinephrine 1:600,000 in caudal blockade decreased the use of analgesics in the postoperative period of infra-umbilical urological and genital procedures, although this addition was associated with an increase in the incidence of PONV. In addition, the FLACC pain score was lower in the morphine group compared with the groups receiving caudal bupivacaine and bupivacaine plus clonidine. The addition of clonidine to caudal bupivacaine provided no additional clinical benefit over bupivacaine alone.

Ansermino et al. [24] performed a systematic meta-analysis of 12 randomized control trials comparing the use of local anesthetic with the use of clonidine combined with local anesthetic for caudal blockade in children. Eight of these trials showed an increase in the duration of analgesia with the addition of clonidine. Although we did not show an increase in the duration of analgesia (time to first use of analgesics) in the presence of either morphine or clonidine, the duration of analgesia observed with all our groups, including the bupivacaine group, was similar to that in other studies (3–10 h) [6, 12, 14–16]. It has been shown that the use of different concentrations of clonidine (1–5 μg/kg) provided variable increases in the analgesic duration of caudal anesthesia [11–14, 25]; these differing effects on the

analgesic duration may have been due to differences in the premedication and volatile anesthetics used, types of surgery, indications for rescue analgesia, methods of assessing pain, and methods of statistical analysis [3].

A previous study showed that 61% of children who received clonidine (1 μg/kg) added to 0.18% bupivacaine, and 50% of children who received morphine (30 μg/kg) did not require supplementary systemic analgesics after orchidopexy, hernia repair, or circumcision [15]. It was demonstrated that a significantly larger percentage of pediatric patients undergoing ureteral reimplantation who received caudal clonidine (2 μg/kg) in 0.2% ropivacaine required IV morphine in the PACU compared with the percentage of patients who had received morphine (50 μg/kg), combined with 0.2% ropivacaine [26]. Another study showed that forty-seven percent of children who had received a single dose of epidural morphine (60 μg/kg) for major orthopedic, thoracic, genitourinary, or abdominal surgical procedures required no parenteral analgesic for 12 h after receiving this agent at this dose [27].

Our results are similar to those in a previous study that found that clonidine (2 μg/kg) did not significantly modify the time to first rescue analgesic or decrease the overall need for rescue analgesics in children who received 0.125% bupivacaine with epinephrine 1:200,000 for caudal analgesia [23]. Another study showed that the use of clonidine (1.0 μg/kg) in a caudal block provided no additional clinical benefit over bupivacaine alone regarding the pain score and the requirement for analgesics in the postoperative period [28]. Clonidine (1.0 and 2 μg/kg) added to low-volume caudal bupivacaine (0.5 mL/kg) also has limited clinical benefit for children undergoing circumcision [29]. Similar results were obtained with the addition of 2 μg/kg of clonidine to bupivacaine 0.125% in pediatric caudal blockade [30].

Several explanations have been proposed for the differences in outcomes between the studies that showed no effect [23, 28–30] and those that showed that clonidine prolonged the duration or improved the quality of caudal analgesia with bupivacaine [10–17]. One hypothesis for the lack of effect of clonidine is that it was owing to the low volume of the caudal solution used (0.5 mL/kg) [28, 29]. Another hypothesis is that clonidine may be effective only when combined with concentrations of bupivacaine greater than 0.125% [29, 30]. Finally, another possible explanation for the lack of effect of clonidine is the addition of epinephrine. Epinephrine and clonidine, respectively, decrease the rate of systemic absorption of local anesthetics and potentiate the analgesia of local anesthetics. Thus, when both agents are used together, any additional effect of clonidine on analgesia could be masked by the presence of epinephrine [3]. Although we did not observe a delay in the time to first rescue analgesic in the presence of morphine, a lower number of patients in the morphine group used analgesics in the postoperative period. In addition, we observed that the FLACC pain score was lower in the B and BC groups than in the BM and BMC groups at 6, 12, and 24 h after the surgery (Table 3).

The caudal analgesic mechanisms of action of clonidine and morphine are distinct. The analgesic effect of morphine is attributable to a local action on opioid receptors at the spinal cord level [3]. The analgesic activity of clonidine results from the direct stimulation of pre- and postsynaptic α2-adrenoceptors in the substantia gelatinosa of the dorsal horn of the spinal cord, thereby inhibiting the release of nociceptive neurotransmitters [3]. Thus, we would expect a synergistic effect when both agents are used together. However, we did not find a synergistic effect of clonidine and morphine on analgesia.

We observed no significant changes in hemodynamic parameters in any of our study groups, with these findings being similar to the observations of others [10–13, 15]. The incidence of PONV in our morphine groups (BM and BMC, around 25–35%) was higher than that in the groups without morphine (B and BC), a finding that was also similar to findings in a previous study using 50 μg/kg of morphine [7]. In our practice, we routinely use ondansetron as a prophylactic antiemetic agent after epidural morphine. However, in the present study we did not use any prophylactic antiemetic therapy, to better reflect the differing risk of PONV among the groups. In addition, the presence of vomiting did not delay the introduction of oral feeding in our patients. Two patients in Group BM and two in Group BMC had urinary retention that was detected clinically (e.g., by pain or incomplete voiding). The urinary retention was managed with simple interventions such as mobilization, providing privacy, or applying a warm bag over the suprapubic region. Finally, two patients in Group BM had pruritus that did not require anti-pruritic treatment.

The most serious complication associated with the use of caudal morphine is respiratory depression, but the overall risk in children is unknown [3]. The incidence differs between different studies, but seems to depend on the dose used and the age of the patient. In fact, most cases of respiratory depression occurred in infants less than 3 months old and with doses of caudal morphine ranging from 40 to 70 μg/kg [3]. Although we have no evidence of respiratory depression, the present study was not powered to detect it and therefore the safety of caudal analgesia with morphine remains to be determined. We did not assess sedation, which is a common side effect of clonidine and morphine. However, in the present study, the use of clonidine or morphine did not lengthen the emergence time, suggesting that the doses used likely did not increase sedation. Indeed, other studies also support the assumption that, once the patients were awake, no further differences in sedation were observed between different groups of agents used in the caudal blocks [10, 12, 14].

As far as we know, is not clear whether the benefits observed with opioids justify the potential risks. In fact, the use of caudal epidural opioids in children has been questioned because of side effects, patient discomfort, delay of patient discharge, and marginal efficacy [31]. Thus, we think that the addition of morphine in caudal anesthesia does not seem to be justified for minor surgery that can be performed as day-case surgery, because pain control for these procedures can be achieved with the use of non-opioid agents. Probably, the use of morphine as a caudal additive might be reserved for those procedures that require postoperative analgesia with intravenous opioids.

In conclusion, we showed that morphine 20 μg per kilogram decreased the use of analgesics during the first 24 h following infra-umbilical urological and genital procedures. However, the trade-off was an increased incidence of postoperative nausea and vomiting (PONV). We do not know if the prophylactic administration of ondansetron and/or dexamethasone would have reduced the incidence of vomiting to a more acceptable level therefore providing both prolonged analgesia and an acceptable incidence of PONV.

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