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SCIENTIFIC ARTICLE

Combination of clonidine–bupivacaine in caudal epidural anesthesia for hypospadias surgery in children: prospective, randomized, blind study☆

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Post-operative pain;
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Abstract
Background and objectives: The combination of clonidine with local anesthetic administered for epidural anesthesia via caudal route seems to improve the quality of postoperative analgesia, but with conflicting results. This study compared the postoperative analgesia of three different doses of clonidine combined with bupivacaine in caudal epidural anesthesia in children undergoing hypospadias repair.
Methods: Eighty children aged 1–10 years, candidates for surgical repair of hypospadias, were randomly divided into four groups of 20 patients to receive general anesthesia combined with caudal epidural anesthesia with bupivacaine 0.165% alone or in combination with 1, 2 or 3 $\mu g.kg^{-1}$ of clonidine. The primary outcome was morphine consumption in the first 24 h postoperatively. Mean arterial pressure, heart rate, end-tidal concentration of sevoflurane, time to awakening, pain severity (FLACC scale), level of sedation (RAMSAY), duration of analgesia, and occurrence of adverse effects were also compared.
Results: Intraoperatively, there was no difference between groups regarding mean arterial pressure, heart rate, end-tidal concentration of sevoflurane, and time to awakening. Postoperative morphine consumption and pain severity were similar between groups, but the group receiving clonidine (3 $\mu g.kg^{-1}$) had lower heart rate and higher sedation level than the group receiving bupivacaine alone.

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Conclusions: The combination of clonidine at doses of 1, 2 or 3 μg.kg^{-1} with bupivacaine 0.16% via caudal epidural route did not alter the consumption of morphine in the early postoperative period of children undergoing hypospadias repair.

PALAVRAS-CHAVE
Dor pós-operatória;
Anestesia peridural caudal;
Analgesia;
Bupivacaína;
Clonidina

Associação clonidina-bupivacaína na anestesia peridural caudal para cirurgia de hipospádia em crianças: estudo prospectivo, randomizado, encoberto

Resumo
Justificativa e objetivos: A associação de clonidina ao anestésico local administrado por via peridural caudal parece melhorar a qualidade da analgesia pós-operatória, mas com resultados conflitantes. Este estudo comparou a analgesia pós-operatória de três diferentes doses de clonidina associada à bupivacaína na anestesia peridural caudal em crianças submetidas à correção de hipospádia.
Método: Oitenta crianças entre um e dez anos, candidatas à correção cirúrgica de hipospádia, foram divididas, aleatoriamente, em quatro grupos de 20 pacientes para receber anestesia geral associada à anestesia peridural caudal com bupivacaína 0,166% isolada ou associada a 1, 2 ou 3 μg.kg^{-1} de clonidina. Como desfecho principal avaliou-se o consumo de morfina nas primeiras 24 horas de pós-operatório. Compararam-se também pressão arterial média, frequência cardíaca, concentração expirada de sevoflurano, tempo de despertar da anestesia, intensidade da dor pela escala FLACC, nível de sedação (Ramsay), tempo de duração da analgesia e ocorrência de efeitos adversos.
Resultados: No transoperatório, não houve diferença entre os grupos quanto à pressão arterial média, frequência cardíaca, concentração expirada de sevoflurano e ao tempo de despertar. No pós-operatório, o consumo de morfina e a intensidade da dor foram similares entre os grupos, mas o grupo que recebeu 3 μg.kg^{-1} de clonidina apresentou menor frequência cardíaca e maior sedação do que o grupo que recebeu somente bupivacaína.
Conclusões: A associação de clonidina nas doses de 1, 2 ou 3 μg.kg^{-1} à bupivacaína 0,166% por via peridural caudal não alterou o consumo de morfina no pós-operatório imediato de crianças submetidas à correção de hipospádia.

Introduction

Postoperative pain management is of fundamental importance to reduce the organic, functional and psychological damages originated by the algic process.[1] As a strategy for postoperative pain prophylaxis in children, caudal epidural anesthesia stands out for its technical ease and favorable risk-benefit ratio.[2] Bupivacaine is a local anesthetic traditionally used via caudal epidural route at concentrations of 0.125%–0.175%[3]; as it promotes short duration analgesia limited to approximately six hours.[2] Therefore, the association of other drugs, mechanisms, and different sites of action is evaluated in an attempt to improve the quality and duration of analgesia promoted by bupivacaine. However, there are controversies about the actual benefits of such combinations in terms of analgesic efficacy and incidence of undesirable effects.

Among the caudal–epidural adjuvant drugs, opioids appear to prolong the duration of analgesia, but their use is limited by adverse effects such as nausea, vomiting, pruritus, and urinary retention.[4,5] On the other hand, caudal–epidural clonidine has been investigated in different combinations and dosages, without relevant adverse effects, but with variable efficacy. Thus, controversy persists about its safer and more effective dose.[6] The aim of this study was to evaluate the analgesic efficacy and side effects of caudal epidural anesthesia with 0.116% bupivacaine alone or in combination with three different doses of clonidine in children undergoing surgical repair of hypospadias. The primary outcome was morphine consumption in the first 24 postoperative hours in the different groups studied.

Methods

The present study was previously registered on ClinicalTrials.gov (NCT02769390). After approval by the institutional Ethics Committee and obtaining written informed consent from parents or guardians, 80 boys with ages between 1 and 10 years and who were candidates for surgical repair of hypospadias were included in the study. Exclusion criteria

were children with neurological disorders, coagulation disorders, puncture site infection, anatomical changes of the spine, or those with a physical status classification of III or more, according to the American Society of Anesthesiologists (ASA).[7]

The patients were randomized into four groups to receive different caudal epidural anesthetic solutions: Group B: 0.166% bupivacaine; Group BC1: 0.166% bupivacaine combined with clonidine (1 $\mu g.kg^{-1}$); Group BC2: 0.166% bupivacaine combined with clonidine (2 $\mu g.kg^{-1}$); Group BC3: 0.166% bupivacaine combined with clonidine (3 $\mu g.kg^{-1}$).

No patient received preanesthetic medication and all underwent general anesthesia prior to caudal epidural anesthesia. After monitoring with cardioscopy, non-invasive blood pressure, pulse oximetry, capnography, temperature, and the registering of baseline values, sevoflurane administration was started at 8% concentration and reduced to 5%. Venous puncture was performed when there was no spontaneous movement, presence of regular breathing and eyeball centralization. A laryngeal mask (LM) was then placed in patients with airway hyperreactivity, or orotracheal tube (OTT) in the remaining patients. Intubated patients received cisatracurium four minutes earlier at a dose of 0.1 $mg.kg^{-1}$. General anesthesia was maintained with sevoflurane, whose inspiratory concentration was adjusted to maintain hemodynamic stability, defined as change in mean arterial pressure (MAP) and heart rate (HR) up to 20% of baseline values, which were used in a previous study.[4]

After controlled mechanical ventilation, caudal epidural anesthesia was performed by the same anesthesiologist in all patients. A second anesthesiologist, who did not follow the patients' subsequent evolution, drew the groups and prepared the anesthetic solution under sterile conditions. To obtain the 0.166% bupivacaine concentration, one part of 0.5% bupivacaine was diluted in two parts of double-distilled water. After skin asepsis, the sacral hiatus was located, having as landmark the posterior superior iliac spines and the spinal processes of the sacral vertebrae. The puncture was performed with a 22 G Tuohy needle and the correct positioning was checked using the loss of resistance technique. After negative aspiration for blood or cerebrospinal fluid, 1 $mL.kg^{-1}$ of the standardized solution (within 20 mL maximum) was slowly injected, according to the group. As established in a previous study, we considered as failure of caudal epidural anesthesia an increase in MAP and/or HR over 20% of baseline values or the occurrence of motor reaction to the surgical incision, which was authorized 20 min (min) after the caudal puncture.[4] In the event of failure, intravenous fentanyl (2 $\mu g.kg^{-1}$) was given, and the patient was excluded from the study. Intraoperatively, the values of MAP, HR, and end-tidal sevoflurane concentration were recorded every 5 min. At the end of surgery, the duration of anesthesia was recorded, defined as the time from induction of general anesthesia to removal of the ventilation device; the duration of surgery was defined as the time from the surgical incision until the end of the dressing; and the awakening time defined as the time elapsed between the discontinuation of sevoflurane and removal of the ventilation device. All patients received intravenous dexamethasone (0.15 $mg.kg^{-1}$) and ondansetron (0.15 $mg.kg^{-1}$) during anesthetic induction. No intravenous opioids were given intraoperatively. Postoperative data collection was performed by one of the three pediatric resident physicians of the institution, previously trained in the application of the pain and sedation scales, who previously had a high degree of agreement in the evaluation of patients in the service. In addition, the assessors were blinded to the drug used in caudal epidural anesthesia. In the first 12 h, MAP and HR were recorded (in addition to the intensity of sedation and pain) every hour until the 6th hour and at the 8th, 10th and 12th hours. To measure MAP, either during anesthesia or postoperatively, a digital device with pediatric cuffs was used. To assess sedation, the Ramsay scale was used.[8] Sedation intensity was classified as mild (Ramsay 1–2), moderate (Ramsay 3–4), or intense (Ramsay 5–6). The FLACC scale[9] was used for pain assessment with scores for no pain (0–2 points), mild pain (3–4 points), moderate pain (5–7 points), or severe pain (8–10 points). In addition to the scheduled measurement times up to the 12th hour, pain was also assessed within the first 24 h at every time that analgesics were requested by the patient or his caregiver. The investigators also recorded the duration of analgesia, defined as the time elapsed between the end of surgery and the first rescue dose of morphine, in addition to the occurrence of adverse defects. Rescue analgesia was performed with venous morphine at a dose of 20 $\mu g.kg^{-1}$ for mild pain, 30 $\mu g.kg^{-1}$ for moderate pain, and 50 $\mu g.kg^{-1}$ for severe pain. In case of persistent pain, these same doses were repeated at 15-min intervals until the elimination of pain. Morphine doses, as well as the intervals and total consumption in the first 24 h, as well as the occurrence of adverse effects (vomiting, tremors, and dry mouth) were recorded.

Considering the consumption of morphine in the first 24 postoperative hours as the primary endpoint, the sample was calculated based on a pilot study that included the first seven patients in the group receiving bupivacaine solution (Group B) compared with the first seven patients in the group receiving the combination of bupivacaine and 1 $\mu g.kg^{-1}$ clonidine (Group BC1). Based on the observed standard deviation (10.71 $\mu g.kg^{-1}.day^{-1}$) and considering the difference to be detected of 11 $\mu g.kg^{-1}.day^{-1}$, a two-tailed hypothesis, with a test power of 90% and a level of significance of 5% provided the number of 20 patients in each group.

In the statistical analysis, the Shapiro–Wilk test was used to evaluate data for normality. The chi-square test (χ^2) was used to compare ASA physical status, adverse effects, and number of morphine doses between groups. The Jonckheere-Terpstra test was used to compare weight, pain and sedation scores, total morphine dose and analgesia time. Analysis of variance was used to compare age, duration of surgery, duration of anesthesia, time to awakening, sevoflurane concentration, HR and MAP. Multiple comparisons were performed using the Bonferroni procedure. A p-value <0.05 was considered statistically significant. Data analysis was performed using the Statistical Package for Social Science (SPSS) version 18.0.

Results

From February 2014 to October 2015, 88 patients who met the inclusion criteria were recruited. Out of this total, eight

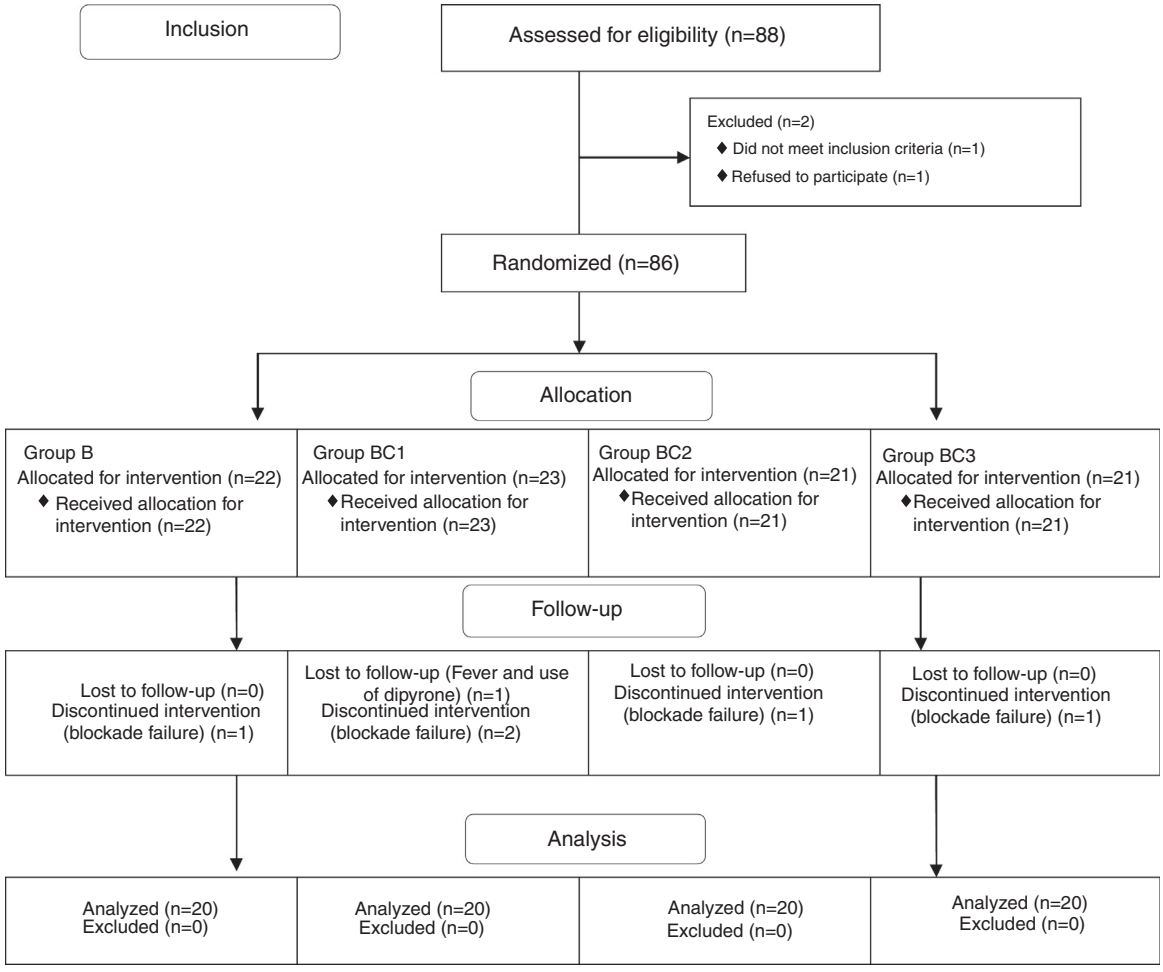

Figure 1 Flowchart for selection of study participants.

were excluded, five (5.7%) of whom due to blockade failure (Fig. 1).

The final analysis included 80 patients, 20 in each group. The groups were similar regarding age, weight, and physical status according to ASA classification (Table 1).

In the intraoperative period, HR was 98.66 ± 13.99 bpm (mean ± SD), while the median MAP was 56.68 mmHg (45.5 ± 81.6 mmHg). The overall mean of end-tidal sevoflurane concentration was 2.74 ± 0.37%. The duration of surgery was 33.9 ± 12.47 min (mean ± SD), while the duration of anesthesia was 67.30 ± 15.03 min (mean ± SD), and the time to awakening was 13.88 ± 3.88 min (mean ± SD). None of these variables presented a statistically significant difference between the groups. Likewise, there was no difference between groups regarding the use of laryngeal mask and orotracheal intubation: Group B (LM = 2; OTT = 18); Group BC1 (LM = 4; OTT = 16); Group BC2 (LM = 3; OTT = 17); Group BC3 (LM = 4; OTT = 16) ($p > 0.05$).

In the postoperative period, MAP did not differ between groups at any of the assessment times, while HR was lower in the Group BC3 compared to Group B in the second and the sixth hour ($p < 0.05$) (Table 2).

Pain assessment using FLACC scale was similar between the groups ($p > 0.05$). Sedation assessment using Ramsay scale presented a statistically significant difference in the frequency of patients who had different levels of sedation. This difference was seen between groups B and BC3 on the fourth, fifth, and sixth postoperative hours, in which the Group BC3 scored higher than Group B ($p < 0.05$) (Table 3).

Thirty patients (37.5%) did not use rescue analgesics in the first 24 h postoperative – seven children in Group B (35%), eight in Group BC1 Group (40%), seven in Group BC2 (35%), and eight in Group BC3 (40%) – and therefore had an analgesic time of more than 24 h. Among children who used analgesic ($n = 50$), the analgesia time ranged from 90 ± 1.162 min, with no statistically significant difference between groups (Table 4).

There were no reports of vomiting or tremors, whereas dry mouth was observed in four (20%) patients of Group BC2 and two (10%) patients of Group BC3, with no significant statistical difference ($p > 0.05$).

Discussion

As the main result of the present study, there was no reduction in morphine consumption when the three doses of clonidine (1, 2 or 3 $\mu g.kg^{-1}$) were combined with the administration of 0.165% bupivacaine. Several authors obtained

Table 1 Comparison of age, weight, and physical status of the four groups of children undergoing caudal epidural anesthesia with different anesthetic solutions.

	Groups				
	B ($n=20$)	BC1 ($n=20$)	BC2 ($n=20$)	BC3 ($n=20$)	p-Value
Age (years)	5.70 ± 1.92	5.10 ± 2.07	5.40 ± 2.64	4.65 ± 2.39	0.511
Weight (kg)	21.9 ± 7.65	18.85 ± 9.42	22.05 ± 9.42	20.30 ± 7.82	0.760
ASA 1/ASA 2	16/4	13/7	14/6	17/3	0.646

Age and weight presented as mean ± SD.
ASA, classification of physical state according to the American Society of Anesthesiologists, presented as *n*.

Table 2 Postoperative comparison of the heart rate of 80 children undergoing hypospadias correction under general anesthesia combined with caudal epidural anesthesia with bupivacaine alone or in combination with clonidine.

Hour	Group B ($n=20$)	Group BC1 ($n=20$)	Group BC2 ($n=20$)	Group BC3 ($n=20$)
1st	99.65 ± 21.15	97.30 ± 22.57	90.60 ± 20.84	89.50 ± 21.81
2nd	106.90 ± 19.81[a]	98.65 ± 22.91	93.05 ± 20.48	87.15 ± 18.96[a]
3rd	103.85 ± 19.80	108.50 ± 25.40	100.85 ± 20.13	97.00 ± 15.12
4th	102.60 ± 17.04	107.50 ± 22.01	102.50 ± 17.64	95.15 ± 14.36
5th	106.55 ± 17.63	102.25 ± 21.59	97.90 ± 21.59	95.45 ± 17.17
6th	106.95 ± 19.46[a]	102.95 ± 21.85	100.65 ± 15.41	90.80 ± 13.62[a]
8th	101.25 ± 16.37	99.70 ± 19.45	100.90 ± 15.80	98.40 ± 13.62
10th	98.05 ± 12.64	97.75 ± 16.31	96.80 ± 16.50	94.55 ± 10.41
12th	96.85 ± 10.68	95.25 ± 18.74	96.80 ± 17.57	92.35 ± 10.52

B, bupivacaine; BC1, bupivacaine + clonidine 1 $\mu g.kg^{-1}$; BC2, bupivacaine + clonidine 2 $\mu g.kg^{-1}$; BC3, bupivacaine + clonidine 3 $\mu g.kg^{-1}$.
Heart rate presented as beats per minute.
Data presented as mean ± standard deviation.
[a] $p < 0.05$ comparison of B vs. BC3 using Bonferroni test after Anova (in the 2nd hour $p = 0.024$ and in the 6th hour $p = 0.046$).

controversial results using the bupivacaine-clonidine combination, at doses similar to those of the present study. Most of the studies included only small surgeries and minor pain stimuli, even performed on an outpatient basis. The use of local anesthetic adjuvants in caudal epidural anesthesia is a common practice, and clonidine stands out for its safety and low incidence of adverse effects. However, the actual efficacy of clonidine when associated with long-term local anesthetics, as well as the most adequate and safe dose, remains a topic of wide discussion.

The available studies show a great heterogeneity of the method, with emphasis on the type and concentration of local anesthetic, volume of anesthetic solution, association with vasopressor, intensity of pain relief, venous administration of opioid analgesics intraoperatively, type of analgesic used in rescue analgesia, and different scores used for pain assessment. A meta-analysis assessing the benefits of caudal epidural clonidine in studies published from 1966 to 2011 concluded that this drug possibly improves the duration and quality of analgesia, but the biases of the studies analyzed have greatly limited this conclusion.[6] Thus, as a way to improve the reliability of results, the present study sought to reduce some of these confounding factors. As such, we opted to perform a single surgical procedure known to be painful,[10] in addition to the use of the FLACC scale, which is appropriate for postoperative pain assessment in the evaluated group.[9] Although the airway access was through a laryngeal mask or tracheal tube, which was also seen in another study,[11] no analgesic or opioid was used intraoperatively, regardless of airway management. Similarly to another study,[4] bupivacaine was chosen at a concentration of 0.166%, since studies suggest its ideal concentration for caudal epidural use is 0.125 to 0.175% as compared to the preparation at 0.25% that provides similar analgesia with less motor blockade.[2]

Morphine was selected for rescue analgesia; it was given on demand and after previous pain evaluation to allow adequate control and facilitate consumption calculation. However, considering its emetic effect, we opted for dual prophylaxis for nausea and vomiting, despite the possibility of a prolonged caudal epidural anesthesia with dexamethasone.[12] The use of this drug in all patients, however, reduces possible interferences in the comparison between groups. In addition, we did not use fixed-time analgesic regimens, as well as the combination of analgesics from other classes, such as dipyrone, paracetamol, and other non-steroidal anti-inflammatory drugs, or the combination of opioids such as tramadol and codeine.

Among the previous studies addressing the use of caudal epidural clonidine, several infraumbilical surgeries were studied, with a predominance of herniorraphies, and the authors observed that 0.25% bupivacaine (1 $mL.kg^{-1}$) promotes less effective analgesia than its combination with clonidine (1 $\mu g.kg^{-1}$).[11] In addition of including surgeries less painful than hypospadias, the duration of analgesia was established based on the FLACC score (≥4 points) unlike the

Table 3 Frequency of patients with different intensities of sedation assessed using Ramsay scale in the postoperative period in the four groups of children undergoing caudal epidural anesthesia with different anesthetic solutions.

Times	Sedation intensity	Groups (*n*)				Total (*n*)	*p*
		B	BC1	BC2	BC3		
1st hour	Mild	14	13	13	11	51	0.066
	Moderate	5	6	7	9	27	
	Deep	1	1	0	0	2	
2nd hour	Mild	0	1	0	0	1	0.071
	Moderate	17	14	13	16	60	
	Deep	3	5	7	4	19	
3rd hour	Mild	16	15	16	16	65	0.083
	Moderate	2	5	4	4	15	
	Deep	0	0	0	0	0	
4th hour	Mild	18	15	16	15	64	0.042
	Moderate	2	5	4	4	15	
	Deep	0	0	0	1	1	
5th hour	Mild	19	17	17	12	65	0.030
	Moderate	1	3	3	8	15	
	Deep	0	0	0	0	0	
6th hour	Mild	20	19	15	17	71	0.016
	Moderate	0	1	5	3	9	
	Deep	0	0	0	0	0	
8th hour	Mild	20	19	17	18	74	0.051
	Moderate	0	1	3	2	6	
	Deep	0	0	0	0	0	
10th hour	Mild	19	15	18	19	71	0.111
	Moderate	1	5	2	1	9	
	Deep	0	0	0	0	0	
12th hour	Mild	19	17	11	11	58	0.05
	Moderate	1	3	9	9	22	
	Deep	0	0	0	0	0	

B, bupivacaine; BC1, bupivacaine + clonidine 1 $\mu g.kg^{-1}$; BC2, bupivacaine + clonidine 2 $\mu g.kg^{-1}$; BC3, bupivacaine + clonidine 3 $\mu g.kg^{-1}$. Sedation intensity was classified as mild (0–2 points on Ramsay scale), moderate (3–4 points on Ramsay scale) or deep (5–6 points on Ramsay scale).

Table 4 Frequency of patients receiving morphine, dose of morphine used and time of postoperative analgesia in children undergoing caudal epidural anesthesia with three different doses of clonidine.

	B (*n* = 20)	BC1 (*n* = 20)	BC2 (*n* = 20)	BC3 (*n* = 20)	*p*
n (%)	13 (65%)	12 (60%)	13 (65%)	12 (60%)	–
Dose[a]	50 (20–140)	45 (20–80)	40 (20–120)	45 (20–140)	0.332
Time[b]	345 (90–757)	424 (136–702)	411 (125–1162)	307 (226–1109)	0.877

Dose and time presented as median (minimum–maximum).
B, bupivacaine; BC1, bupivacaine + clonidine 1 $\mu g.kg^{-1}$; BC2, bupivacaine + clonidine 2 $\mu g.kg^{-1}$; BC3, bupivacaine + clonidine 3 $\mu g.kg^{-1}$.
[a] Morphine dose in $\mu g.kg^{-1}$ in 24 h.
[b] Analgesia time in minutes.

present study in which the cut-off point for analgesia was a FLACC score = 3, which established mild pain and demanded medication.[11]

Only three publications compared different doses of clonidine via caudal route, as in the present study. The first one compared the combination of clonidine 1 and 2 $\mu g.kg^{-1}$ with 0.25% bupivacaine in children undergoing inguinal hernia repair and observed that clonidine prolonged the duration of caudal epidural anesthesia compared to bupivacaine alone. There was no difference between groups receiving 1 and 2 $\mu g.kg^{-1}$ of clonidine.[13] The second study compared three doses of clonidine combined with 0.125% bupivacaine (1, 1.5, and 2 $\mu g.kg^{-1}$) in children undergoing inguinal herniorrhaphy and concluded that clonidine, mainly at 2 $\mu g.kg^{-1}$, prolonged the duration of the blockade.[14] The third study compared doses of 1 and 2 $\mu g.kg^{-1}$ of clonidine combined with 0.25% bupivacaine in circumcision surgeries and failed to demonstrate benefit.[15] It should be highlighted that in the two studies performing inguinal hernia surgical repair there was a consensus in the results, unlike the one

performing penile surgery or even other studies that, indifferently, investigated penile or non-penile surgeries.[11,16] Therefore, we can infer that the comparison of different types of surgery may be the most relevant factor in the justification of controversies. The tested dose of clonidine was ineffective in suppressing pain in more painful surgeries, unlike in less painful procedures.[13,14]

There are two specific studies of caudal epidural clonidine for surgical repair of hypospadias. The first one compared caudal epidural anesthesia with 0.25% bupivacaine alone or combined with clonidine at a dose of 1 $\mu g.kg^{-1}$ and found comparable analgesia,[17] which corroborates the findings of the present study. The second study evaluated caudal epidural anesthesia with 0.25% bupivacaine combined with clonidine at the dose of 2 $\mu g.kg^{-1}$ via caudal epidural route, while in the comparative group, caudal epidural anesthesia was administered with 0.25% bupivacaine and clonidine (2 $\mu g.kg^{-1}$) was given orally. The results showed comparable analgesia between venous and caudal epidural administration of clonidine.[18] Although the methodological difference of the latter makes comparison difficult, this finding raises the discussion about the local or systemic effect of clonidine and opens space for future research on mechanisms of clonidine and other α_2 adrenergic agonists and the most indicated and safe route for its administration.

Because central nervous system actions and sedative effects, there is some concern that clonidine may promote excessive sedation postoperatively or prolong the emergence from anesthesia. The results of the present study demonstrated that the addition of clonidine to bupivacaine did not prolong the average awakening time of patients, which was 13.8 min, similarly to another study in which clonidine did not prolong the average awakening time, which was 12.4 min in anesthesia for urogenital surgeries.[4] However, another study has shown that clonidine (1 $\mu g.kg^{-1}$) prolonged the awakening time.[19] More investigations are needed to better elucidate this issue. Regarding postoperative sedation, the results presented here showed more intense sedation in the group receiving the highest dose of clonidine (3 $\mu g.kg^{-1}$) compared to the group not receiving this adjuvant. This occurrence was limited to the sixth postoperative hour, which amounts to the eight hours of the drug action when we added the duration of surgery. Likewise, it was observed that the HR was lower in the group receiving the highest dose of clonidine, reiterating the known sympatholytic effects of the drug. However, no patient had excessive sedation leading to any other complications, as well as no significant hemodynamic repercussions. These findings reinforce previous knowledge about the safety of caudal epidural clonidine at the doses used in the present study.

Finally, some authors have questioned whether caudal epidural anesthesia would be associated with an increased risk of postoperative surgical complications in hypospadias surgical repair. Among these, we highlight a recent study that retrospectively evaluated a series of 395 hypospadias repair in which caudal epidural anesthesia (58%) or penile blockade (42%) was performed. The authors demonstrated that urethrocutaneous fistula or glandular dehiscence occurred in 22 patients (5.6%) and that caudal epidural anesthesia was related to a 13-fold increase in the occurrence of such complications. However, other risk factors identified were all of a surgical nature: proximal hypospadia, prolonged surgery, and shorter surgery time.[20] At the heart of this controversial discussion are the facts that caudal epidural anesthesia is more frequently used in the more complex hypospadias and it is not known whether such complications would be directly related to this anesthetic technique or to surgical factors. In view of the well-known benefits of this technique, new controlled studies are necessary before the current practice is modified. It is worth noting that in the present study 37.5% of the patients did not use morphine or any other analgesic in the postoperative period, which reinforced the advantages of caudal epidural anesthesia to control the postoperative pain in this painful surgery.

The present study has some limitations. Although we have standardized a single type of surgery, the diversity of surgical techniques for hypospadias repair and the ability of different surgeons may have interfered in the intensity of the pain resulting from the procedure. In addition, the broad age range of patients and the assessment of pain by three professionals may have influenced the results. However, the examiners were previously trained and presented a high degree of agreement in the assessments prior to the present study.

Conclusion

The findings of the present study demonstrated that clonidine at a dose of up to 3 $\mu g.kg^{-1}$ did not improve the analgesic quality of epidural caudal anesthesia with 0.165% bupivacaine. It was also found that clonidine at a dose of 3 $\mu g.kg^{-1}$ resulted in a higher degree of sedation and reduction in postoperative HR limited to the first hours, but without other clinical repercussions.

Conflicts of interest

The authors declare no conflicts of interest.

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