Original Article

A double-blinded randomized control trial to compare the duration of analgesia using morphine, clonidine, or dexmedetomidine as adjuvants to ropivacaine in caudal anesthesia in children undergoing infraumbilical surgeries

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Abstract

Background and Aims: Adjuvants added to the caudal block prolong the duration of analgesia. In a developing country with economic constraints, the choice of an adjuvant will be the medication with a longer duration of analgesia, a favorable side-effect profile, and the least expensive option. We wished to study the duration of postoperative analgesia afforded by three adjuvants: morphine, clonidine, and dexmedetomidine, at doses wherein minimal or nil adverse effects would be attributed to the adjuvant. The primary objective of the current study is to compare the duration of postoperative analgesia with morphine, clonidine, or dexmedetomidine as adjuvants to 0.2% ropivacaine in a for caudal block, in children undergoing elective abdominal, urogenital, and lower limb surgeries. The secondary objectives are (a) to study the total analgesic requirement during the first 24 hours after surgery and (b) to compare the incidence of complications among the three groups.

Material and Methods: Sixty-three children aged 1–6 years, belonging to American Society of Anesthesia (ASA) physical status I, II, and scheduled to undergo elective infraumbilical surgeries, were enrolled in the study. The children were randomly assigned to one of three groups: Group D received a caudal block with dexmedetomidine 1 μg/kg, Group M received morphine 30 μg/kg, and Group C received clonidine 1.5 μg/kg. All groups also received 0.2% ropivacaine (1–1.25 ml/kg) as part of the caudal block. The duration of analgesia, total analgesic requirements during the first 24 hours after the surgery, and the incidence of complications in the three groups were monitored by a pain nurse who was blinded to the study allocation.

Results: The three groups were comparable with respect to age, sex, weight, and duration of surgery. The median time taken for the first rescue analgesic in the dexmedetomidine group was 380 minutes, in the clonidine group was 360 minutes, and in the morphine group was 405 minutes. Though the morphine group had a longer duration of analgesia, it was not statistically significant ($P = 0.843$). The total perioperative opioids used and side effects were similar among the three groups. There were no episodes of intraoperative bradycardia noted in Groups D, M, and C. However, one patient in Group D required treatment for bradycardia in the postanesthesia care unit. In terms of intraoperative hypotension, 10 patients (43.5%) in Group D, 5 patients (27.8%) in Group C, and 5 patients (22.7%) in Group M required treatment, but this difference was not statistically significant ($P = 0.299$). There was no significant difference observed in the time to awakening after the anesthesia among the three groups. Postoperative nausea and vomiting were noted in five patients (21.7%) in Group D, one patient (5.6%) in Group C, and four patients (18.2%) in Group M ($P = 0.382$). One patient in Group M had a sedation score of 5 and required 4 hours of supplemental oxygen via face mask in the ward. Additionally, one patient in Group D reported numbness in both

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feet lasting 12 hours with spontaneous resolution. While a significant number of patients in all three study groups experienced urinary retention, no patient reported pruritus in the ward.
Conclusion: Caudal administration of morphine, dexmedetomidine, and clonidine in children undergoing infraumbilical surgery resulted in an equivalent duration of analgesia.

Keywords: Analgesia, clonidine, developing country, dexmedetomidine, morphine, ropivacaine

Introduction

Caudal epidural analgesia is the commonest regional block performed in pediatric anesthesia. Various adjuvants have been added to single-shot caudal blocks to extend the analgesic duration and improve the quality of analgesia afforded by the local anesthetics: opioids, adrenaline, ketamine, neostigmine, midazolam, clonidine, and dexmedetomidine, to name a few.[1] The use of additives is often associated with troublesome adverse effects, such as pruritus, vomiting, urinary retention and respiratory depression with opioids,[2] prolonged postoperative sedation with dexmedetomidine and midazolam,[3,4] hypotension, bradycardia, and respiratory depression with clonidine.[5] In general, the higher the dose of the additive used, the longer the duration of analgesia noted. However, the drawback of using a higher dose is a higher incidence of side effects. In our institute, we use clonidine as an adjuvant to ropivacaine for caudal anesthesia. We would like to compare clonidine with morphine and dexmedetomidine in terms of providing a longer duration of postoperative analgesia and the incidence of side effects. Our hypothesis is that caudal morphine and dexmedetomidine cause prolonged duration of analgesia as compared to clonidine since individual studies have shown a longer duration of analgesia with morphine and dexmedetomidine.[6,7] So, the primary objective of the current study is to compare the duration of postoperative analgesia with morphine, clonidine, or dexmedetomidine as adjuvants to 0.2% ropivacaine in a caudal block in children undergoing elective abdominal, urogenital, and lower limb surgeries. The secondary objectives are: (a) to study the total analgesic requirement during the first 24 hours after surgery and (b) to compare the incidence of complications such as hypotension, bradycardia, respiratory depression, pruritus, and excessive sedation.

Material and Methods

This prospective, randomized double-blinded study was conducted at a tertiary-level teaching hospital in southern India between May and October 2020. The study was accepted by the hospital's Institutional Review Board and Ethics Committee and was registered with the Clinical Trial Registry of India (CTRI/2020/07/026481). Written informed consent was obtained from the parents/guardians of all trial participants. Children aged 1–6 years with American Society of Anesthesiology (ASA) physical status I and II, who were scheduled to undergo elective lower abdominal, urogenital, perianal, or lower limb surgery were enrolled in the study. Children with a history of developmental delay, diagnosed intellectual disability, suspected coagulopathy, prior allergy to local anesthetics or study drugs, local infection at the site of the caudal block, emergency surgery, or with a preoperative Glasgow Coma Scale score less than 15, were excluded. The participants were randomized using a computer-generated list in a double-blinded manner to receive a single-shot caudal block with either dexmedetomidine (Group D), morphine (Group M), or clonidine (Group C), along with 0.2% ropivacaine.

Permuted computer-generated block randomization with the blocks in the ratio 2:4:6 was used. The generated random numbers were kept in sealed, opaque, and sequentially numbered envelopes. Patients and their guardians were not aware of the study drug assigned. The study drugs were prepared by an anesthesiologist in the operating theater who was not involved in the research after the patient was assigned to a study group. The Acute Pain Services (APS) nurses who assessed the patients for 24 hours postoperatively were also blinded to the group allocation.

Participants were fasted according to the ASA guidelines. The general anesthetic protocol was standardized for the purpose of the study. All patients were induced in the presence of their parent/guardian with incremental concentrations of sevoflurane in oxygen after which an intravenous cannula was secured. Approximately 1–2 μg/kg of fentanyl and 0.5 μg/kg of atracurium were administered intravenously to facilitate endotracheal intubation. After tracheal intubation, the child was carefully placed in the lateral decubitus position for a single-dose caudal block. The caudal anesthetic was performed with strict aseptic precautions using 0.2% ropivacaine (1–1.25 ml/kg) along with the study drug. The doses of the study drugs used in the caudal block were as follows: morphine, 30 μg/kg; clonidine, 1.5 μg/kg; and dexmedetomidine, 1 μg/kg. All components were diluted with normal saline and mixed in with the calculated volume of ropivacaine.

The patients were maintained with isoflurane in a 50% air–oxygen mixture to achieve a minimum alveolar concentration

of 0.8. Heart rate, oxygen saturation electrocardiogram, noninvasive blood pressure, oral temperature, and end-tidal carbon dioxide were monitored every 5 minutes after induction till the end of the surgery. Intravenous paracetamol 15 mg/kg was administered to all patients after induction and every 6 hours thereafter in the postoperative period for the first 48 hours after surgery. Fluid therapy was standardized during surgery with Ringer's lactate solution 6–10 ml/kg/hour. An intraoperative increase in the heart rate or blood pressure of >10% from the baseline was treated as inadequate analgesia with incremental doses of fentanyl or morphine. Intraoperative hypotension (blood pressure drop of >20% from the baseline) and bradycardia (heart rate <60 beats per minute) requiring treatment were noted intraoperatively and postoperatively for the first 24 hours. Intraoperative bradycardia was treated with IV atropine 0.02 mg/kg. Hypotension was initially managed by volume replacement with Ringer's lactate and then by boluses of ephedrine 0.06 mg/kg. The time to emergence from anesthesia (from discontinuation of isoflurane till eye-opening to verbal command) was noted in all three groups of patients. Postoperative pain was assessed using the FLACC scale and sedation with the Ramsay Sedation Scale in the postanaesthesia care unit (PACU) and for 24 hours postoperatively in the ward, in addition to the patient's heart rate, oxygen, and respiratory rate. These were noted every 15 minutes for two hours in the PACU, and hourly for the first four hours in the ward, and four-hourly thereafter for 24 hours. Observations in the ward were recorded by a team of APS nurses assigned to the pediatric postoperative ward. All doctors and nurses involved in direct patient care, the patients, and their parents/guardians were blinded as to which study drug was administered in the caudal block.

The duration of analgesia was defined as the time from administering the caudal block till the time of the first rescue analgesic in the PACU or ward. In the PACU or ward, rescue analgesia was administered with intravenous fentanyl 1 μg/kg, or intravenous morphine 0.1 mg/kg when the pain score was >3. One of the secondary outcomes, which comprised the total amount of intraoperative and postoperative opioids in the first 24 hours, was calculated in terms of morphine milligrams equivalent in the three groups. Furthermore, patients were also observed for side effects such as bradycardia (heart rate <60 per minute), hypotension (blood pressure <20% from the baseline), bradypnea (respiratory rate <12) desaturation (defined as peripheral oxygen saturation of 94% or less, requiring supplemental oxygen), pruritus, sedation (Ramsay sedation score >5), and urinary retention in children who did not have a urethral catheter *in situ*.

The standard of care in our institution is to use clonidine as an adjuvant. Literature[1] has reported the duration of analgesia to be 7 hours for clonidine administered with a local anesthesia. Based on this, we assume a minimum of 2 hours increase in duration of analgesia for the other two drugs compared to clonidine. Considering a difference of 2 hours with a standard deviation (SD) of 1.5 units, error of 2.5%, and power of 90%, we require a sample of 16 in each arm. To account for dropouts, we recruited 63 patients (21 in each arm).

Data were summarized using mean ± SD or median (range) for continuous variables and frequency, along with percentages for categorical variables. The difference in duration of analgesia compared to the standard (clonidine group) was calculated with a 95% confidence interval. Categorical data were expressed as frequency along with percentage. The normally distributed outcomes were compared using Analysis of variance (ANOVA), whereas the skewed data were compared using Kruskal–Wallis test. The postoperative analgesia duration was analyzed with Kaplan–Meier analysis and log-rank test were used to compare the duration among the three groups. The median duration with 95% confidence interval (CI) was presented. All analysis were done using STATA IC/16.0.

Results

During the study period 63 ASA I, II children, aged 1–6 years and undergoing elective infraumbilical surgeries were enrolled. The CONSORT statement for our study is given in Figure 1. The demographic characteristics of our study population are listed in Table 1. The three groups were comparable with respect to sex, weight, and duration of surgery. All the caudal blocks were regarded as clinically successful. There was no statistically significant difference among the three groups in the duration of analgesia, or in the total opioids used intraoperatively and postoperatively [Figure 2 and Table 2]. The total duration of analgesia was longer in the morphine arm as compared to the other two groups, but it was not statistically significant as calculated by the log-rank test ($P = 0.8$). On comparing the number of patients in each arm with inadequate analgesia (pain score >3) at different time points, there were marginally more numbers in Group D as compared to other groups [Table 3], which was not statistically significant. From the 10th hour onwards, Group D had a greater number of children who had high pain scores as compared to the morphine or clonidine group. On comparison between the three groups, though clinically longer, it was not statistically significant except in the 18th hour. There were no episodes of intraoperative bradycardia noted in Groups D, M, and C; one patient in Group D required treatment for bradycardia in the PACU, while no patients recorded bradycardia in the ward in the three groups. Ten (43.5%) patients in Group D,

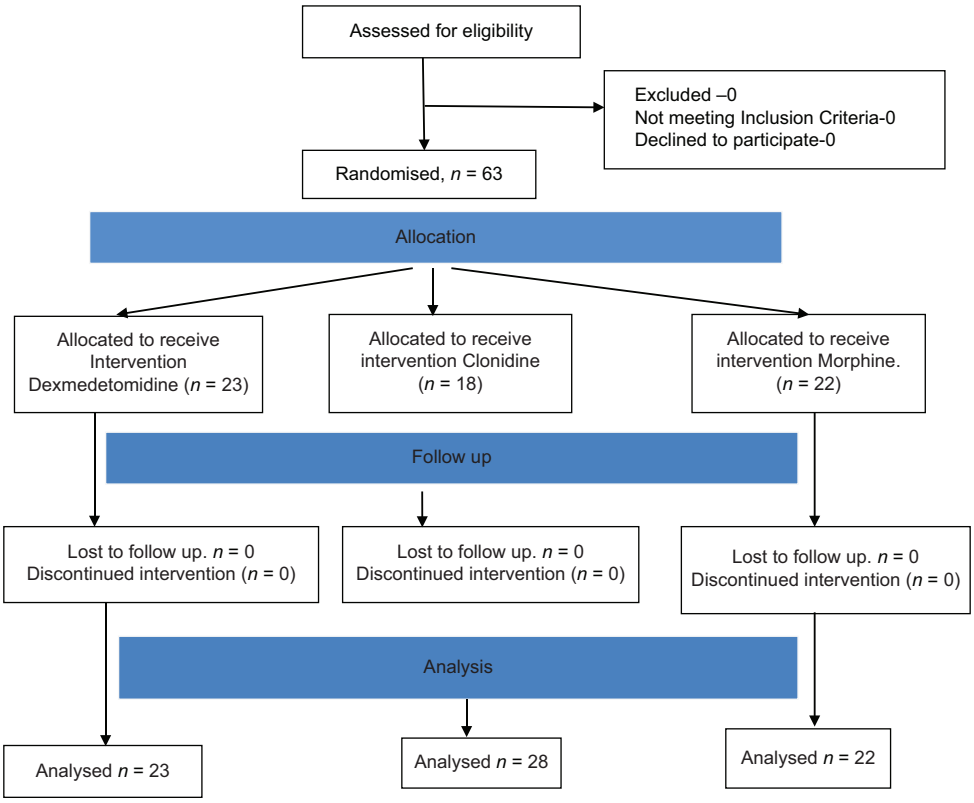

Figure 1: Consort statement for the study

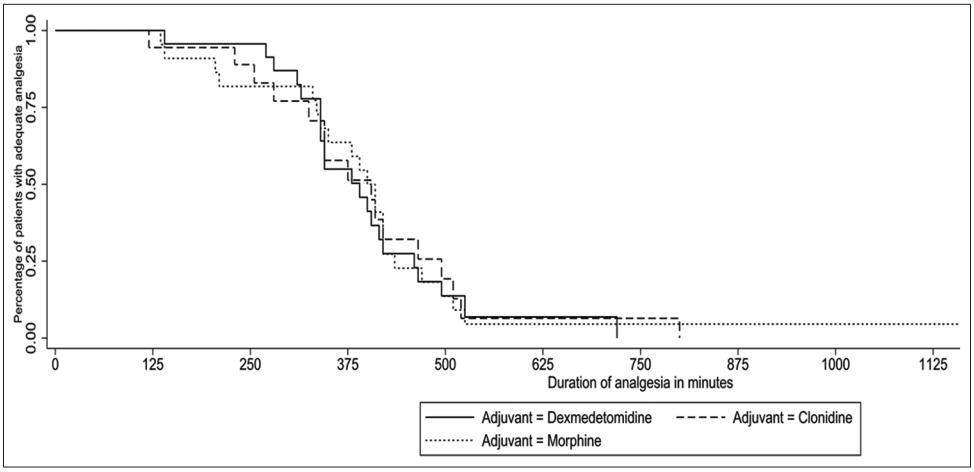

Figure 2: Primary outcome expressed as Kaplan–Meier analysis curve for comparison of the duration of postoperative analgesia among the three study drugs. *X*-axis denotes the percentage of patients with adequate analgesia. *Y*-axis represents duration of analgesia in minutes

five (27.8%) in Group C, and five (22.7%) in Group M had intraoperative hypotension requiring treatment, though this was not statistically significant while comparing the incidence between all three groups ($P = 0.3$). There was no significant difference in the time to awakening after the anesthesia in the three groups. Postoperative nausea and vomiting were noted in five patients (21.7%) in Group D, one (5.6%) in Group C, and four (18.2%) in Group M ($P = 0.4$). One patient in Group M had a sedation score of 5 and required 4 hours of supplemental oxygen via face mask in the ward. One patient in Group D reported numbness in both feet lasting 12 hours with spontaneous resolution. A significant number of patients, in all three study groups, had urinary retention but no patient reported pruritus in the ward [Table 4].

Discussion

The salient findings of our double-blinded, randomized,

Table 1: Demographic characteristics of the study population

Parameter	Group D (*n*=23)	Group C (*n*=18)	Group M (*n*=22)	*P*
Age (years)	3.00 (2.00, 4.00)	1.95 (1.00, 3.00)	3.00 (2.00, 5.00)	0.05
Weight (kilograms)	13.48 (4.47)	12.26 (3.80)	13.48 (3.67)	0.56
Sex				0.60
Male	18 (78.30%)	16 (88.90)	17 (77.30)	
Female	5 (21.70)	2 (11.10)	5 (22.70)	
Type of Surgery				
Bowel surgery	6 (26.09)	2 (11.11)	5 (22.73)	
Orthopedic surgery	4 (17.39)	5 (27.78)	3 (13.64)	
Urogenital surgery	13 (56.52)	11 (61.11)	14 (63.64)	
Surgery Duration (minutes)	110.00 (55.00, 140.00)	122.50 (90.00, 170.00)	90.00 (60.00, 150.00)	0.47
Blood loss (milliliters)	25.00 (10.00, 50.00)	27.50 (20.00, 50.00)	25.00 (10.00, 50.00)	0.96
Time to wakefulness (minutes)	25 (15.00,35.00)	17.50 (15.00,25.00)	17.50 (10.00,25.00)	0.30

Data are presented as presented as median and interquartile range (IQR) or n (%). Parameters such as age, duration of surgery, blood loss, time to wakefulness has been represented by median (IQR); parameters such as weight, sex, and type of surgery have been represented by n (%)

Table 2: Perioperative analgesic requirements in all three groups

	Group D	Group C	Group M	*P*
Intraoperative fentanyl requirement in mcg/kg	2.14	2.30	2.50	0.74
Total opioid requirement (as morphine equivalents, mg/kg) in 24 h	3.2	3.45	3.0	0.95
Number of patients requiring the PACU rescue analgesic	2 (8.69)	1 (5.55)	4 (18.18)	0.40

Fentanyl requirement represented as mcg/kg and total morphine requirement as mg/kg. The number of patients requiring rescue represented as n (%)

Table 3: Number of patients who have pain score >3 at different time intervals postoperative ward. Data are given as *n* (percentage)

Time interval	Group D (*n*=23)	Group C (*n*=18)	Group M (*n*=22)	*P*
At arrival	2 (8)	2 (11)	0 (0)	0.38
1 hr	3 (13)	1 (5)	0 (0)	0.19
2 hr	2 (8)	2 (11)	3 (13)	0.89
6 hr	2 (8)	1 (5)	0 (0)	0.50
10 hr	8 (34)	1 (5)	3 (13)	0.06
14 hr	6 (26)	5 (27)	5 (22)	0.93
18 hr	9 (39)	1 (5)	3 (13)	0.02
24 hr	9 (39)	5 (27)	5 (22)	0.47

controlled three-armed study were that, there was no significant difference in the duration of analgesia when dexmedetomidine or clonidine or morphine was added to 0.2% ropivacaine in the single-shot caudal anesthesia for infraumbilical surgeries. The total dose of intra- and postoperative opioids, the number of children with effective analgesia at various time points, and the incidence of side effects in the postoperative period also remained the same between all three groups.

Several studies[2,3,6,8,9] over the past decade have compared various adjuvants to local anesthetics in the caudal blocks with respect to the quality of the block, duration of analgesia afforded, and side effects noted. A few three-armed studies enumerated in the discussion below, compared plain local anesthetic with two other arms using two different adjuvants. However, there has been no prior literature comparing dexmedetomidine, morphine, and clonidine in a three-armed randomized controlled study involving children aged 1–6 years for infraumbilical surgeries.

We have recorded a median duration of analgesia of 380 (315–460) minutes with dexmedetomidine. Studies, where dexmedetomidine was used as an adjuvant,[10-14] show a widely varied duration of analgesia compared to our study. A double-blinded randomized controlled trial involving 100 children by Goyal and colleagues reported 588 (±54) minutes with 1 μg/kg of dexmedetomidine added to 0.25% bupivacaine.[7] A median duration of 870 minutes was noted by Anand and colleagues when they used 2 μg/kg of dexmedetomidine with 0.2% ropivacaine in 60 children scheduled for lower abdominal surgery.[3] With respect to the former study, we opine that the decreased duration of analgesia in our study could be due to the shorter duration of action of ropivacaine. The prolonged duration of analgesia reported in the latter study may be attributed to the higher dose of adjuvant used as compared with our study.

While we recorded a median duration of analgesia with clonidine 2 μg/kg as 360 (280–465) minutes, varied durations have been reported by other authors: 990 min with 2 μg/kg added to 0.2% bupivacaine by Singh and colleagues,[8] 417 minutes with clonidine 2 μg/kg added to 0.125% bupivacaine by Lak and colleagues,[1] and 590.25 minutes with clonidine 1 μg/kg added to 0.25% bupivacaine as reported by Manickam and colleagues.[15] The different doses of clonidine used in these studies and the diverse local anesthetic vehicles used at dissimilar concentrations may contribute to the diverse results in this regard.

Table 4: Incidence of intraoperative and postoperative complications in three groups

Complications	Group D (*n*=23)	Group C (*n*=18)	Group M (*n*=22)	*P*
Intraoperative				
Bradycardia	0	0	0	-
Hypotension	10	5	5	0.32
Desaturation	0	0	0	-
PACU				
Bradycardia	1	0	0	-
Bradypnea	0	0	0	-
Desaturation	0	0	0	-
Hypotension	1	1	2	-
WARD				
Bradycardia	0	0	0	-
Hypotension	0	0	0	-
Desaturation	0	0	0	-
Bradypnea	0	0	0	-
Supplemental O_2	0	0	1	-
Motor weakness	1	0	0	-
Pruritus	0	0	0	-
Nausea, vomiting	5	1	4	0.35
Urinary retention	8 (6)	5	10 (6)	0.54
Sedation	0	0	1	-

Caudal morphine at a dose of 30 μg/kg provided analgesia for 405 (335–435) minutes. Krane[6] studied three doses of caudal morphine added to 1% lidocaine in 32 children and noted a mean duration of analgesia of 600 min with 30 μg/kg, 624 minutes with 67 μg/kg, and 804 minutes with 100 μg/kg morphine. Thus, the children who received 30 μg/kg of caudal morphine had a longer duration of analgesia compared to our study population. A recent study done by Sailo using 15 μg/kg of morphine with ropivacaine 0.2% has demonstrated duration of analgesia to be 438 minutes. This is similar to the range of analgesia obtained in our study population.[16]

One of the significant concerns regarding the use of an opioid additive is respiratory depression in the postoperative period. In our study, we did not find any patient belonging to the morphine group developed respiratory depression at the dose of 30 μg/kg. Similarly, the incidence of postoperative nausea and vomiting (PONV) and urinary retention was comparable between all three groups and not specific to morphine. Only one patient in the morphine group had a sedation score of 5 in the ward and required oxygen supplementation by face mask for 4 hours. There was no incidence of pruritus in the morphine group as compared to the incidence reported in previous studies.[8] Thus, it appears that at the doses used in our study and in contemporary literature, there is no significant incidence of serious adverse effects with all the three adjuvants we have used.[17,18]

One of the limitations of this study is that we included all infraumbilical surgeries. The analgesic requirements for various surgical procedures (orthopedic, genitourinary, etc.) might be different, which needs to be considered while interpreting the duration of analgesia and immediate postoperative analgesic requirements. Conducting a similar study among children for infraumbilical orthopedic and infraumbilical abdominal surgeries may provide a more accurate result in the future.

In a developing country, cost plays a vital role in rendering healthcare. The cost of additives and local anesthetics should be considered while choosing the analgesic regime. Adjuvants that provide comparable duration of analgesia with minimal side effects and are least expensive should be used for the benefit of the patient. Our study has demonstrated that clonidine, morphine, and dexmedetomidine provide similar duration of analgesia with no difference in the side-effect profile. Given the higher cost of dexmedetomidine, caudal morphine and clonidine incontestably offer a budgetary advantage in developing countries.

Conclusion

Caudal morphine, dexmedetomidine, and clonidine added to 0.2% ropivacaine provide an equivalent duration of analgesia and side-effect profile in children undergoing infraumbilical surgery.

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Conflicts of interest
There are no conflicts of interest.

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