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Randomized Trial

Efficacy and Safety of Dexmedetomidine Added to Caudal Bupivacaine in Pediatric Major Abdominal Cancer Surgery

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Background: Caudal analgesia has been prolonged by the addition of various adjuvants. Dexmedetomidine is a highly selective α2agonist with sedative and analgesic properties.

Objective: To investigate the effect of addition of dexmedetomidine to 0.25% bupivacaine for caudal analgesia in children undergoing major abdominal cancer surgery.

Study Design: A randomized double-blind trial.

Setting: Academic medical center.

Methods: Forty pediatric patients, aged 3 – 12 years, weighting 10 – 40 kg, and of American Society of Anesthesiologists (ASA) physical status I and II scheduled for major abdominal cancer surgeries under general anesthesia combined with caudal analgesia were enrolled. They were randomly allocated into 2 groups: Group I (BD): (n = 20) received 1 mL/kg bupivacaine 0.25% with dexmedetomidine 1 µg/kg and group II (B): (n = 20) received 1 mL/kg bupivacaine 0.25%. Heart rate (HR), mean arterial pressure (MAP), and oxygen saturation (SPO2) were recorded for 120 minutes. Pain was assessed immediately postoperative and at hours 2, 4, 6, 12, 18, and 24 of postoperative period by Face, Legs, Activity, Cry and Consolability (FLACC) score. Time to first request for analgesia and total analgesic consumption [Intravenous acetaminophen 15mg/kg (perfalgan, Squibb)] in the first 24 hours were recorded. The level of sedation was recorded using Ramsay's sedation scale. Adverse effects were recorded and treated.

Results: There was significant reduction in FLACC score in group BD at 2, 4, 6, and 12 hours postoperatively compared to group B. At the eighteenth and twenty-fourth hour there was no significant difference. Time of the first rescue analgesic requirement was significantly prolonged in group BD compared to group B. The mean total consumption of rescue analgesia in the 24 hours of the postoperative period was significantly decreased in group BD (405.00 ± 215.03) mg when compared with group B (810.35 ± 200.93) mg.

Limitations: This study is limited by its small sample size.

Conclusion: Addition of dexmedetomidine (1 µg/kg) to caudal bupivacaine 0.25% (1 mL/kg) in pediatric major abdominal cancer surgeries achieved significant postoperative pain relief for up to 19 hours, with less use of postoperative analgesics, and prolonged duration of arousable sedation. Hemodynamic changes were statistically significant, yet of no clinical significance.

Key words: Dexmedetomidine, caudal block, pediatric cancer surgery

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Caudal epidural analgesia has become one of the most popular and commonly performed regional blocks in pediatric anesthesia after its first description by Campbell in 1933 (1). It is a reliable and safe technique that can be used with general anesthesia for intra- and postoperative analgesia in patients undergoing abdominal and lower-limb surgery. The main disadvantage of caudal analgesia is

the short duration of action after a single injection (2).

Prolongation of caudal analgesia using a single-shot technique has been achieved by the addition of various adjuvants, such as epinephrine, opioids, ketamine, and α2 agonists (3). Clonidine is an α2-receptor agonist successfully used as an adjuvant in caudal regional anesthesia to reduce the need for additional pain treatment without significant hemodynamic or respiratory effects. Adjunct clonidine in the dose range of 1 – 2 µg/kg doubles the duration of analgesia compared with plain local anesthetics (4).

Dexmedetomidine is a highly selective α2agonist with sedative and analgesic properties. It has an α2/α1 selectivity ratio of 1600:1, which is 8 times more potent than clonidine (200:1) (5). Intrathecal dexmedetomidine was reported to produce analgesia in experimental animals (6), prolong the duration of spinal bupivacaine (7), and potentiate the effect of spinal morphine in cancer pain in humans (8). Our study aimed to investigate the effect of dexmedetomidine added to bupivacaine local anesthetic for caudal analgesia in children undergoing major abdominal cancer surgery.

Methods

After obtaining approval of the local ethics committee of the South Egypt Cancer Institute, Assiut University, Assiut, Egypt, and parental written informed consent, the study was conducted on 40 pediatric patients, aged 3 – 12 years, weighting between 10 – 40 kg, and of American Society of Anestheiologists (ASA) physical status I and II scheduled for major abdominal cancer surgeries, expected to last more than 90 minutes under general anesthesia combined with caudal analgesia. Children with sacral bone abnormalities, spina bifida, coagulopathy, mental delay or retardation, known allergy to the study drugs, and local infection at the site of injection were excluded from the study.

This was a randomized double-blinded prospective study. Randomized sampling was done by the lottery method. The patients and their parents or guardians and the anesthesiologist who administered the drugs were blinded to the study drugs. The drugs were prepared by pharmacy staff not participating in the study.

Patients were fasted for 4 hours and premedicated with oral midazolam 0.5 mg/kg one hour prior to induction of anesthesia. After applying standard monitors, general anesthesia was induced with inhalation of sevoflurane 8% in oxygen via face mask. An intravenous cannula was placed and fluid therapy was standardized during and after surgery. During surgery, children received lactated Ringer's solution 6 mL/kg/h, whereas dextrose 50 mg/mL in NaCl 4.5 mg/mL was infused at 4mL/kg/h in the postoperative period. A neuromuscular blocker (atracurium besylate 0.5 mg/kg) was used to facilitate endotracheal intubation. After securing the tube in place the patients were placed in the lateral decubitus position and a single dose caudal block was performed using a 23g needle and standard loss of resistance technique.

The children were randomly allocated into 2 groups:

Group I (BD): (n = 20) received 1 mL/kg bupivacaine 0.25% with dexmedetomidine 1 µg/kg (precedex 100 µg/mL; Hospira, Inc., Lake Forest, IL USA) in 1 mL normal saline.

Group II (B): (n = 20) received 1 mL/kg bupivacaine 0.25% with 1 mL normal saline. Maximum volume was 30 mL for both groups. A urinary catheter was placed in all patients.

Anesthesia was maintained with sevoflurane in oxygen with a maintenance dose of atracurium besylate (0.15 mg/kg) and controlled mechanical ventilation.
The inhaled concentration of sevoflurane was adjusted to achieve hemodynamic changes < 30% of the baseline values. No other narcotics, analgesics, or sedatives were administered intra-operatively. Standard monitoring was used during anesthesia and surgery. Heart rate (HR), mean arterial pressure (MAP), and oxygen saturation (SPO_2) were recorded for 120 minutes. The occurrence of intra-operative hypotension (hypotension was defined as systolic arterial pressure < 70 plus twice the age in years and associated with altered peripheral perfusion) requiring a fluid bolus and bradycardia (bradycardia was defined as HR below 60 beats/min) requiring atropine were recorded. Failure of caudal block was defined as any increase in HR or MAP more than 20% of the pre-incision values. In our study we encountered 4 failed caudal blocks that were eliminated from the study.

At the end of surgery, the residual neuromuscular blocking was reversed using a mixture of atropine (0.02 mg/kg) and neostigmine (0.05 mg/kg).

After extubation the patients were transferred to the postanesthesia care unit (PACU) and were monitored for vital signs (heart rate, noninvasive blood pressure, and saturation of peripheral oxygen). The Face, Legs, Activity, Cry, Consolability (FLACC) pain score (9) with its 0 – 10 score range was used to assess pain immediately postoperative and at hours 2, 4, 6, 12, 18, and 24 of the postoperative period. Intravenous acetaminophen 15

mg/kg (perfalgan, Squibb) was given when the FLACC score was ≥ 4. The time to first request for analgesia and the total analgesic consumption (acetaminophen) in the first 24 hours were recorded.

The level of sedation was recorded using Ramsay's sedation scale (10), Table 1. Postoperative adverse effects such as nausea, vomiting, hypotension, bradycardia, and respiratory depression (respiratory depression was defined as decreased SPO2 of less than 95%) were recorded and treated.

Statistical Analysis

Sample size estimation was based upon a mean difference in time to first analgesia of 9.0 hours with an expected background standard deviation of 2.0, an alpha error not exceeding 0.05, and power of the test of 90% was at least 4 per group. We intended to recruit at least 20 per group to account for random errors and additional comparisons. Analysis was performed using SPSS version 17 (Chicago, USA). Data was presented as mean ± SD, median and range, numbers, and percentages. Fisher Exact was used for testing proportion independence. Repeated measures ANOVA was used to test the change of different parameters having normal distribution over time in both study groups (time effect) and also to test the difference between group B and BD over time (group interaction). Bonferroni test was used for multiple pairwise comparisons. For FLACC and sedation score Friedman test was used to show effect of time in each study group. Pairwise comparisons were done using Wileoxan rank test with Bonferonni adjustment for number of comparisons. Less than or equal to 0.05 was considered significant.

Results

There were no significant differences among groups in demographic data, clinical characteristics, and duration of surgery (> 0.05), Table 2.

The time of the first rescue analgesic requirement was significantly prolonged in group BD in comparison to group B. Also the mean total consumption of intravenous acetaminophen rescue analgesia in the 24 hour postoperative study period was significantly decreased in group BD (405.00 ± 215.03) when compared with group B (810.35 ± 200.93), Table 3.

Though the pain score (FLACC) was lower in group BD from the immediate postoperative period to 12 hours after surgery than in group B, the results of the

Table 1. *Ramsay sedation score (10).*

Score	Description
1	Anxious and agitated or restless or both.
2	Co-operative, oriented, and calm.
3	Responsive to commands only.
4	Exhibiting brisk response to light glabellar tap or loud auditory stimulus.
5	Exhibiting a sluggish response to light glabellar tap or loud auditory stimulus.
6	Unresponsive.

Table 2. *Demographic data and duration of surgery.*

	Group BD N = 20	Group B N = 20	*P*-value
Age: years	3.65 ± 1.68	3.60 ± 1.68	0.902
Weight: Kg	14.20 ± 3.53	14.23 ± 3.72	0.935
Male/female	9/11	12/8	NS
Duration of surgery: Minutes	116.25 ± 14.41	116.25 ± 13.17	0.946
Diagnosis:			
Neuroblastoma	8 (40.0%)	9 (45.0%)	
sacrococcygeal teratoma	3 (15.0%)	3 (15.0%)	1.000
Wilms' tumor	9 (45.0%)	8 (40.0%)	

Data are expressed as mean ± SD and number (%).

Table 3. *Time to first analgesic request and acetaminophen consumption in the first 24 hours of postoperative period.*

	Group BD	Group B	*P*-value
	Mean ± SD	Mean ± SD	
Time to first analgesia (hours)	19.20 ± 4.61	6.60 ± 3.44	< 0.0001*
Total dose of analgesic (mg)	405.00 ± 215.03	810.35 ± 200.93	< 0.0001*

* *P* value is significant ≤ 0.05

Friedman test indicated that there was a statistically significant increase in FLACC in both study groups from the immediate postoperative period to 24 hours after surgery. Inspection of the median values shows that pain scores start to increase significantly after 2 hours of surgery in group B and only after 4 hours in Group BD (using post-hoc multiple comparisons with a Bonnferoni adjusted alpha value). After 18 hours of surgery both groups have more or less the same pain score, Fig 1.

Though sedation score starts to decrease significantly in both study groups in the second hour after surgery, group BD has significantly higher sedation scores starting immediately after surgery and up to 4 hours postoperative than group B. From the sixth hour up to 24 hours both groups have more or less same sedation score, Fig 2.

Regarding hemodynamic variables (MAP and heart rate) measured during the intra-operative period, MAP showed a significant drop in both study groups (*P* value for time effect < 0.001) but it was more evident in group BD (*P* value for group interaction < 0.001). Pairwise comparisons show that MAP became stable 15 minutes after starting surgery in group B but continued to decrease up to 30 minutes during the intra-operative period in group BD. In both groups it started to rise again after one hour of surgery. Though the drop in MAP was statistically significant, it was of no clinical significance, Fig. 3.

The heart rate dropped significantly in both study groups from the preoperative time to 15 minutes after starting surgery in group B and to 30 minutes in group BD (*P* value for time < 0.001) then started to rise again with no difference between groups (*P* value for group interaction = 0.24), Fig 4.

During the postoperative period, Pairwise comparisons of changes in MAP in both study groups showed that group BD did not experience significant changes in MAP in postoperative period as compared to an oscillation of significant drop and increase in the group B (*P* value for interaction = 0.006), Fig. 5.

HR in group B increased significantly after 6 hours

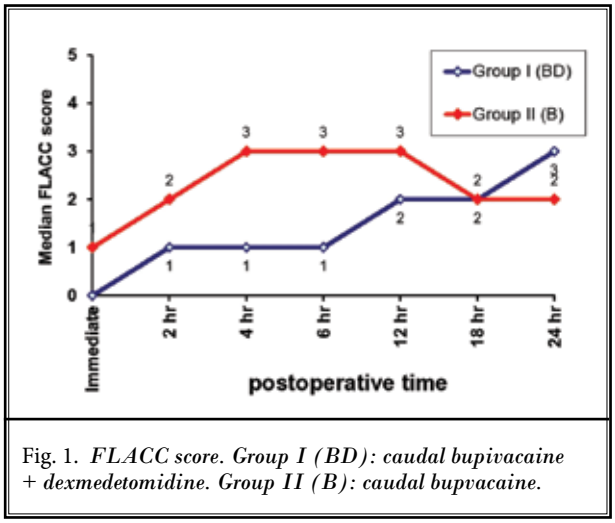

Fig. 1. *FLACC score. Group I (BD): caudal bupivacaine + dexmedetomidine. Group II (B): caudal bupvacaine.*

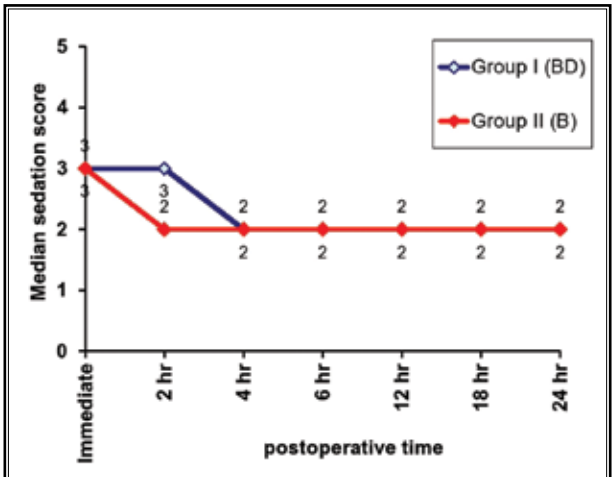

Fig. 2. *Sedation score. Group I (BD): caudal bupivacaine + dexmedetomidine. Group II (B): caudal bupvacaine.*

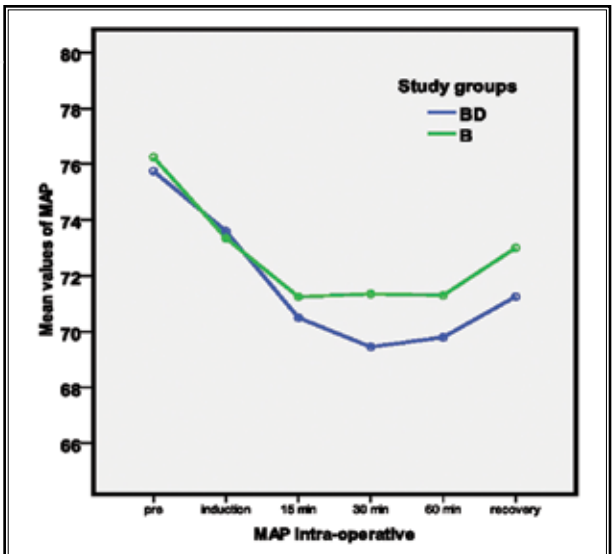

Fig 3. *Intra-operative mean arterial blood pressure (MAP) changes. Group BD: caudal bupivacaine + dexmedetomidine. Group B: caudal bupvacaine.*

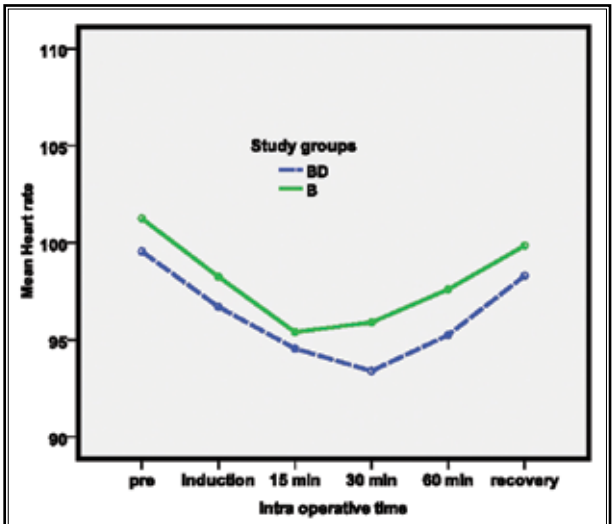

Fig 4. *Intra-operative heart rate (HR) changes. Group BD: caudal bupivacaine + dexmedetomidine. Group B: caudal bupvacaine.*

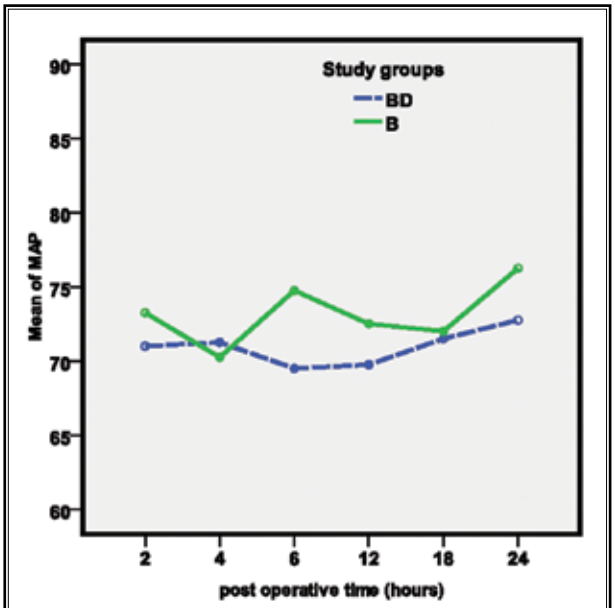

Fig 5. *Post-operative mean arterial blood pressure (MAP) changes. Group BD: caudal bupivacaine + dexmedetomidine. Group B: caudal bupvacaine.*

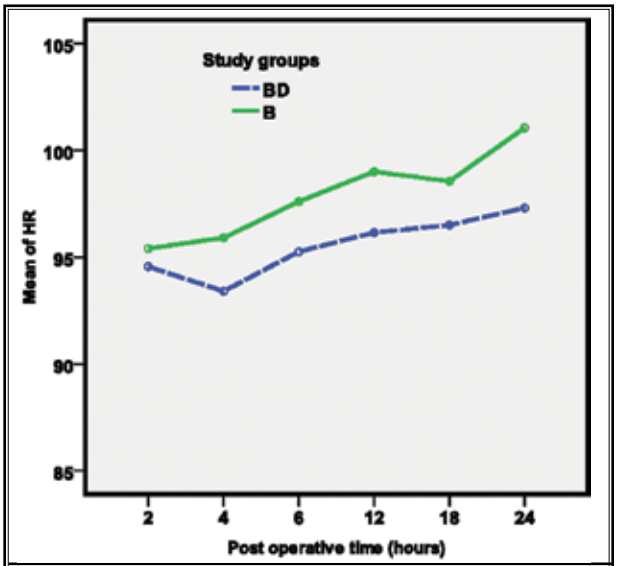

Fig. 6. *Post-operative heart rate (HR) changes. Group BD: caudal bupivacaine + dexmedetomidine. Group B: caudal bupivacaine.*

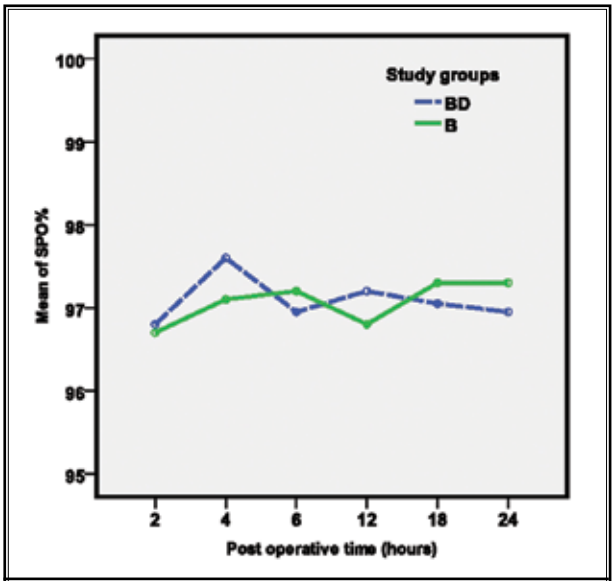

Fig 7. *Post-operative arterial oxygen saturation (SPO2) changes. Group BD: caudal bupivacaine + dexmedetomidine. Group B: caudal bupivacaine.*

postoperatively and continued to increase up to 24 hours in comparison to group BD which showed a non-significant drop then increased gradually to become significantly higher only in the twenty-fourth hour after surgery, P for time effect < 0.001. There was no interaction between the 2 groups, $P = 0.15$, Fig. 6.

SPO2 during the postoperative period showed a significant increase after 2 hours of surgery followed by a significant drop after 4 hours with no significant change afterwards in group BD. In group B SPO2 level was maintained stable up to 24 hourspostoperative

with no group interaction, $P = 0.10$, Fig. 7.

There were no recorded cases of postoperative nausea and vomiting (PONV) in both groups.

Discussion

This is the first study to compare the effect of dexmedetomidine on the duration of caudal bupivacaine block in pediatric cancer patients. The main findings of our study were that the addition of dexmedetomidine 1 µg/kg to bupivacaine 0.25% administered caudally in pediatric abdominal cancer surgery provided a significant increase in the duration of postoperative analgesia (19.20 ± 4.61) hours, reduced the postoperative rescue analgesic consumption, and prolonged the time of the first rescue analgesic request when compared with caudally administered bupivacaine alone in the first 24 hours of the postoperative period. Although most of our surgical procedures were upper abdominal operations associated with large skin incisions and extensive tissue dissection and resection, results of our study conducted on pediatric cancer patients didn't show much difference from other studies on pediatric non-cancer patients.

Animal studies conducted in rats, rabbits, dogs, and sheep have used intrathecal dexmedetomidine at a dose range of 2.5 – 100 µg without any neurological deficits (11-14). Fukushima et al (15) administered 2 µg/kg dexmedetomidine epidurally for postoperative analgesia in humans without any reports of neurological deficits. Maroof et al (16) used dexmedetomidine epidurally at approximately 1.5 µg/kg to decrease the incidence of postoperative shivering without any reports of neurological deficit. Also, studies in children indicated that neuraxial administration of dexmedetomidine at no more than 2 µg/kg and a concentration of no more than 2 µg/ml does not cause neurotoxicity (17,18).

Dexmedetomidine like clonidine (19,20) enhances the effects of local anesthetics without increasing the incidence of side effects (21). Dexmedetomidine is a highly selective α2 adrenoceptor agonist. The mechanism of action of dexmedetomidine differs from clonidine as it possesses a selective α2 adrenoceptor agonist, especially for the 2A subtype of this receptor, which causes it to be a much more effective sedative and analgesic agent than clonidine without undesirable cardiovascular effects from α1 receptor activation (22).

The mechanisms of the analgesic action of α2-agonists have not been fully elucidated. The activation of inwardly rectifying G1-protein-gated potassium channels results in membrane hyperpolarization decreasing the firing rate of excitable cells in the central nervous system (CNS). This is considered a significant mechanism of inhibitory neuronal action of α2-adrenoceptor agonists (23). Another prominent physiologic action ascribed to α2-adrenoceptors is their reduction of calcium conductance into the cell, thus inhibiting neurotransmitter release. These 2 mechanisms represent 2 very different ways of affecting analgesia: in the first, the nerve is prevented from ever firing, and in the second, it cannot propagate its signal to its neighbor (23). Administration of an α2-agonist via an intrathecal or epidural route provides an analgesic effect in postoperative pain without severe sedation. This effect is due to the sparing of supraspinal CNS sites from excessive drug exposure, resulting in robust analgesia without heavy sedation (24).

Also in our study there was a significant reduction in the FLACC score in group BD at 2, 4, 6, and 12 hours postoperatively in comparison with group B. Our results regarding postoperative pain relief are in agreement with El-Hennawy et al (17). When dexmedetomidine and clonidine were administered, both in a dose of 2 µg/kg as adjuvant with 0.25% bupivacaine caudally, they found that the duration of analgesia was significantly prolonged in the group receiving the bupivacaine–dexmedetomidine mixture (analgesia time was 16 hours) over the group receiving bupivacaine alone (analgesia time was 5 hours).

Neogi et al (25) compared clonidine 1 µg/kg and dexmedetomidine 1 µg/kg as adjuncts to ropivacaine 0.25% for caudal analgesia in pediatric patients and concluded that addition of both clonidine and dexmedetomidine with ropivacaine administered caudally significantly increased the duration of analgesia. The mean duration of analgesia was 6.32 ± 0.46 hours in the ropivacaine group, 13.17 ± 0.68 hours in the clonidine group, and 15.26 ± 0.86 hours in the dexmedetomidine group. Also the FLACC score was significantly reduced in the dexmedetomidine with ropivacine group. Saadawy et al (18) have demonstrated that the addition of dexmedetomidine 1 µg/kg tobupivacaine 2.5 mg/mL (1 mL/kg) significantly improved the efficacy of caudal analgesia with less use of postoperative analgesics.

As regards hemodynamics, there was a statistically significant difference in the group that received the bupivacaine–dexmedetomidine mixture when compared with the group that received bupivacaine alone, yet it was of no clinical significance. Although bradycardia and hypotension are considered to be the most promi-

nent adverse effects of α2-adrenoreceptor agonists, these side effects appear to be less pronounced in children than in adults. Dexmedetomidine has a favorable safety profile and stable hemodynamics, which are in concordance with the reports published by several other authors (10,17,20,21,26-30).

Xiang et al (31) have also demonstrated that supplementation of caudal bupivacaine with dexmedetomidine (1 µg/kg) reduced the hemodynamic response to hernial sac traction in children undergoing inguinal hernia repair.

The antihypertensive effect of dexmedetomidine results from stimulation of α2 inhibitory neurones in the medullary vasomotor center (nucleus reticularis lateralis) of the brainstem, which leads to a reduction in norepinephrine release and sympathetic nerve outflow from the CNS to the peripheral tissues. Moreover, epidurally administered dexmedetomidine decreases the electrical activity of preganglionic sympathetic nerves. Bradycardia is caused by an increase in vagal tone resulting from central stimulation of parasympathetic outflow, as well as a reduced sympathetic drive (32).

Dexmedetomidine has unique sedative properties caused by hyperpolarization of excitable cells in the locus coeruleus (33). It produces a unique form of sedation, in which patients become responsive as well as calm and cooperative when aroused, and then back to sleep when not stimulated. Confusion, cited as a common problem for other traditional sedatives, has not been described for dexmedetomidine as it does not depend primarily on activation of the γ-aminobutyric acid system (34).

In the current study the duration of sedation was prolonged and there were significantly higher sedation scores in group BD in comparison with group B. However, there were no cases of deep sedation and the prolonged sedative effect of dexmedetomidine was easily reversed with verbal or physical stimuli. In a study by Saadawy et al (18), patients were also able to achieve appropriate sedation (maintaining responsiveness and co-operation), and anxiolysis, with minimal hemodynamic and respiratory depression.

No respiratory depression was reported in our study, and none of the children had an SPO2 value of $<$ 95%. This confirms results from previous studies that α2 agonists have no clinical respiratory effects (10).

Conclusion

The addition of dexmedetomidine (1 µg/kg) to caudal bupivacaine 0.25% (1 mL/kg) in pediatric major abdominal cancer surgeries achieved significant postoperative pain relief up to 19 hours, eliminating the need for postoperative opioids and prolonged duration of arousable sedation. Though hemodynamic changes were statistically significant, they were of no clinical significance. No side effects were recorded.

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