Original Article

Intraperitoneal dexmedetomidine as an adjuvant to bupivacaine for postoperative pain management in children undergoing laparoscopic appendectomy: A prospective randomized trial

ABSTRACT

Background and Aims: Intraperitoneal local anesthetic is an effective analgesic approach in laparoscopic appendectomy in adults. The aim of the study was to compare the postoperative pain when intraperitoneal bupivacaine is administered alone versus the addition of dexmedetomidine to it in children undergoing a laparoscopic appendectomy.

Methods: In this prospective randomized trial, 52 children were randomly allocated to Group B who received intraperitoneal bupivacaine 0.25% (2 mg/kg) or Group BD who received intraperitoneal bupivacaine 0.25% (2 mg/kg) plus dexmedetomidine (1 mcg/kg) for postoperative analgesia in children undergoing laparoscopic appendectomy. Postoperative pethidine consumption at day 1 was recorded and considered the primary outcome of the study. Patients were evaluated for pain scores at 0, 2, 4, 6, 12, and 24 h, time to first request of pethidine, sedation scores at 0, 2, 4, and 6 h, length of hospital stay, and parents' satisfaction. Chi-square, Fisher's exact, Student's *t*-test, and Mann–Whitney U-tests were used for analysis.

Results: Postoperative visual analog scale scores were lower in Group BD at 2, 4, and 6 h (mean = 3, 3, 3, respectively) compared with Group B (mean = 4, 5, 4, respectively) ($P < 0.05$). Patients in Group BD had more sedation scores at 0, 2, and 4 h ($P < 0.05$), longer time to first rescue analgesia ($P = 0.03$), lesser rescue analgesic consumption ($P = 0.02$), shorter length of hospital stay ($P = 0.02$), and higher parents' satisfaction ($P = 0.01$).

Conclusion: Adding dexmedetomidine to intraperitoneal bupivacaine provides adequate postoperative analgesia in children undergoing laparoscopic appendectomy.

Keywords: Bupivacaine; children; dexmedetomidine; laparoscopic appendectomy; postoperative pain

Introduction

Appendectomy is routinely performed through the less-painful laparoscopic approach. A Cochrane review concluded that pain was reduced after laparoscopic versus open appendectomy in both children and adults.[1] However, substantial postoperative pain was common among children undergoing laparoscopic appendectomy.[2]

Intraperitoneal local anesthetic (IPLA) appears promising in pediatric surgery although the high absorptive capacity of the peritoneum and high peritoneal surface area in children. Hence, the delivery of an effective dose without toxicity in children could be challenging.[3]

Access this article online	
Website: www.saudija.org	Quick Response Code
DOI: 10.4103/sja.SJA_760_17	

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How to cite this article: Elnabtity AM, Ibrahim M. Intraperitoneal dexmedetomidine as an adjuvant to bupivacaine for postoperative pain management in children undergoing laparoscopic appendectomy: A prospective randomized trial. Saudi J Anaesth 2018;12:399-405.

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Hamill *et al.* investigated the efficacy of intraperitoneal bupivacaine on pain after acute laparoscopic appendectomy in children. They found no clinical benefit because of the limited dose of local anesthetic available in children.[4]

Dexmedetomidine (alpha-2 adrenergic agonists) has become one of the frequently used drugs in anesthesia as it has been reported to provide analgesia, anxiolysis, and an anesthetic-sparing action with minimal respiratory depression plus its sedative effect that mimics natural sleep.[5]

Intraperitoneal instillation of dexmedetomidine with bupivacaine reduces the pain after elective laparoscopic cholecystectomy in adults as compared to that with bupivacaine alone or with tramadol. In addition, the postoperative requirement for rescue analgesia is reduced.[6]

We hypothesized that adding dexmedetomidine to IPLA will reduce postoperative pain, decrease opiate requirements, and decrease length of hospital stay in children undergoing laparoscopic appendectomy.

Methods

After approval of the hospital's "Research and Ethics Committee," a prospective randomized, double-blinded trial was performed at our institute (from June 2016 to March 2017). This study was registered in the US National Institutes of Health, ClinicalTrials.gov (trial registry number: NCT03067740). A written informed consent for participation in the trial was obtained from parents or the legal guardians of the children. Fifty-two children of the American Society of Anesthesiologists physical status I or II, aged 8–14 years, of both genders, with a suspected acute appendicitis scheduled for laparoscopic appendectomy, were included in this study.

Exclusion criteria were the diagnosis of developmental delay, attention deficit disorder, chronic pain, psychiatric illness, and those allergic to any of the medications used in the study.

Patients were randomized into Group B and Group BD with a 1:1 allocation ratio. The allocated intervention was written on a slip of paper, placed in sealed serially numbered and opaque envelopes. The envelopes were serially opened, and the allocated intervention was implemented. Patients allocated to Group B (bupivacaine; $n = 26$) received bupivacaine 0.25% (Bucaine® 0.25%, Hikma Pharmaceutical, Amman, Jordan) intraperitoneally at a dose of 2 mg/kg followed by 5 ml of normal saline. In Group BD (bupivacaine + dexmedetomidine; $n = 26$), bupivacaine 0.25% (2 mg/kg) was instilled intraperitoneally followed by dexmedetomidine 1 mcg/kg diluted in 5 ml of normal saline.

All investigators, parents, and patients were blind to which method was being used.

All patients were transferred to the operating room without premedication. On arrival to operating room, a 22-gauge intravenous (IV) cannula was inserted and 20 ml/kg/h crystalloid was dripped intraoperatively. The patients and their parents were instructed on the use of the 10-cm visual analog scale (VAS), with scores ranging from 0 (no pain) to 10 (worst pain imaginable). Baseline measurements of heart rate (HR), systolic blood pressure (SBP), temperature (°C), respiratory rate (RR), and room air oxygen saturation (SpO_2) were obtained using a patient monitoring system.

All children received premedication with midazolam 0.05 mg/kg intravenously. Preoxygenation with 100% oxygen was done for 3 min. General anesthesia was induced with IV propofol 2 mg/kg, rocuronium 0.6 mg/kg, and fentanyl 2 mcg/kg. Bag-mask ventilation was applied until the patients become fully relaxed. Endotracheal intubation was performed; tube size was calculated according to the formula: (|age in years + 16|/4).[7] Anesthesia was maintained with a sevoflurane 2% with oxygen-air mixture which is adjusted to maintain SpO_2 >97%. Minute ventilation was adjusted to maintain the end-tidal CO_2 in the range of 34–38 mmHg.[6] Patients in both groups received IV paracetamol 15 mg/kg after establishment of the endotracheal intubation. Intermittent boluses of fentanyl 0.5 mcg/kg were used to achieve adequate depth of anesthesia.

In both groups, laparoscopic surgery was performed according to the standard surgical protocol. Infiltration of port sites was done with 4-ml lignocaine 1% at a maximum dose of 3 mg/kg. A standardized surgery involved 3 ports, a 5 or 10 mm umbilical Hasson cannula and 3- or 5-mm left iliac fossa and suprapubic ports. Pneumoperitoneum was achieved using nonhumidified and nonheated CO_2, with intra-abdominal pressure maintained at around 10–12 mmHg.

At the end of surgery, the allocated intervention was implemented in both groups.

Reversal of the muscle relaxant was done using neostigmine (0.05–0.07 mg/kg) and atropine (0.02 mg/kg). Patients were then transferred to the postanesthesia care unit (PACU) where monitoring of vital signs was carried out.

In the postoperative period, assessment was made for pain on awakening in PACU (time of PACU admission = "0" time)

and at 2, 4, 6, 12, and 24 h. Abdominal and/or shoulder pain was assessed on the 10-cm VAS. Sedation was assessed at 0, 2, 4, and 6 h using the Ramsay sedation scale as follows: 1: Anxious or agitated, 2: Cooperative, oriented, and tranquil, 3: Responds to commands only, 4: Brisk response to light glabellar tap or to verbal stimulus, 5: Sluggish response to light glabellar tap or to verbal stimulus, and 6: no response to stimulus.

Postoperative analgesic regimen included regular IV paracetamol (15 mg/kg) every 8 h, and rescue analgesia with IV pethidine 1 mg/kg[8] was administered whenever VAS ≥4, maximum 4 doses in the first 24 h. Postoperative nausea and vomiting were recorded and treated with IV ondansetron (0.15 mg/kg).

The time to the first administration of pethidine (started from tracheal extubation) and its total postoperative consumption was recorded. Duration of surgery and PACU stay were also noted.

Side effects of drugs under the study were assessed and recorded by the ward nurses and managed by on-duty ward physician for 24 h postoperatively. Oxygen desaturation was considered when SpO_2 dropped below 93% and managed by oxygen face mask 6 L/min. A drop in HR by 20% or more of the baseline was regarded as bradycardia and managed by IV atropine 0.02 mg/kg whereas HR >20% of the baseline was regarded as tachycardia. A drop in SBP by 20% or more of the baseline was regarded as hypotension and managed by IV crystalloids while a SB*P* value higher than the baseline by 20% was regarded as hypertension. Tachycardia and hypertension were managed by incremental doses of fentanyl 0.5 mcg/kg. Other possible complications were recorded and managed accordingly.

Before discharge to home, length of stay in the hospital was recorded and parent's satisfaction was assessed using the 7-point Likert scale[9] as follows: 1: Extremely dissatisfied, 2: Dissatisfied, 3: Somewhat dissatisfied, 4: Undecided, 5: Somewhat satisfied, 6: Satisfied, and 7: Extremely satisfied.

Postoperative 24 h pethidine consumption was recorded and considered as the primary outcome of the study while the other observed parameters were considered as the secondary outcomes.

To calculate the sample size, the postoperative opioid consumption at day 1 in a pilot study on 14 patients was taken into account. With a confidence interval of 95% and a power of 80%, we needed 23 patients in each group. Considering an anticipated drop out of 10%, 60 patients were asked to participate in the study.

Data are presented as a mean ± standard deviation, median, number, and proportion, as appropriate. $P < 0.05$ indicated statistical significance.

Statistical analysis was performed using SPSS program version 19 (Armonk, IBM Corp., NY, USA) and EP16 program for Microsoft Office Excel Software (Microsoft Excel, Redmond, Washington: Microsoft 2007, Computer software). Student's *t*-test, Chi-square test, Mann–Whitney U-test, and Fisher's exact test were used for statistical analysis, as appropriate.

Results

Out of 56 consecutive patients scheduled for the emergency laparoscopic appendectomy during the study period, 4 patients were excluded (two patients were excluded from each group). Hence, 52 patients were enrolled in the study (26 in each group) and considered for analysis [Figure 1].

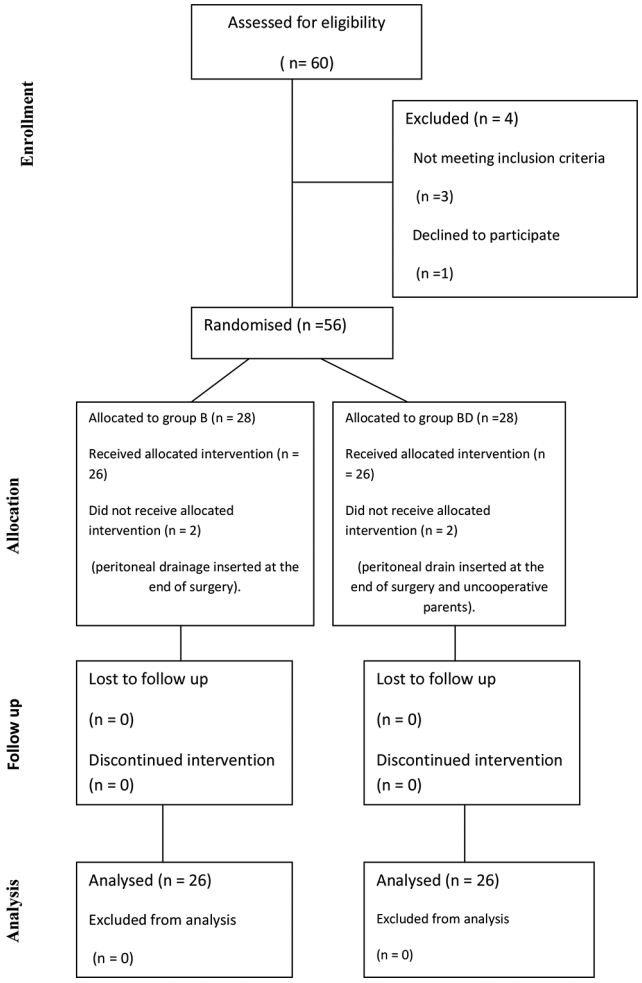

Figure 1: CONSORT flow diagram

Baseline characteristics of patients included in the study are shown in Table 1. There were no statistically significant differences between groups regarding mean values of baseline vital signs and intraoperative surgical findings [Table 1].

There were no statistically significant differences between groups regarding mean duration of surgery, intraoperative fentanyl consumption, and time of PACU stay [Table 2].

Patients in Group BD had a significantly longer time to first analgesia request ($P = 0.03$), lesser rescue analgesic consumption in the first 24 h ($P = 0.02$), shorter length of hospital stay ($P = 0.02$), and higher parents' satisfaction scores ($P = 0.01$) [Table 2]. In addition, Group BD patients had significantly lower median VAS scores of postoperative abdominal and/or shoulder pain at 2, 4, and 6 h, median (range) = 3 (1–5), 3 (1–7), and 3 (1–8), respectively, as opposed to bupivacaine group, median (range) = 4 (1–7), 5 (1–7), and 4 (2-7), respectively (P = 0.04, 0.02, and 0.03, respectively) [Figure 2].

Sedation scores were significantly higher in Group BD at 0 time, 2 h, and 4 h after the procedure ($P = 0.002$, 0.002, and 0.03, respectively) in comparison to Group B [Table 3].

Reported perioperative side effects include bradycardia (11.5% in BD vs. 0% in B), nausea (11.5% in BD vs. 19.2% in B), vomiting (7.6%in BD vs. 11.5% in B), dizziness (7.6% in BD

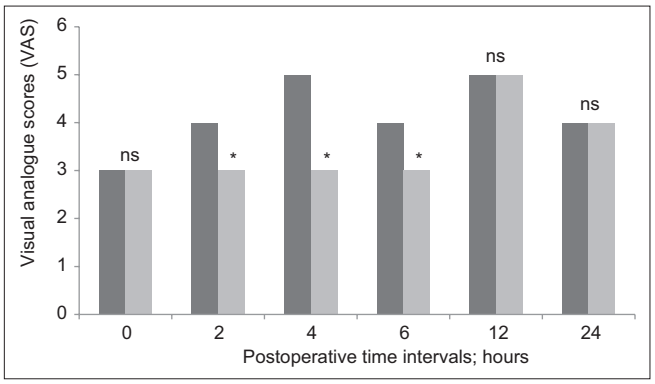

Figure 2: The median values of visual analog scale scores for postoperative abdominal and/or shoulder pain at different time intervals

Table 1: Patient characteristics, baseline vital signs, and intraoperative surgical findings

Patient characteristics	Bupivacaine group ($n=26$)	Bupivacaine-dexmedetomidine group ($n=26$)	*P*
Age (years)	10.75 (1.84)	11.53 (1.75)	0.11
Weight (kg)	31.36 (5.4)	29.55 (4.82)	0.24
Gender (male/female)	16/10	14/12	0.57
ASA (I/II)	22/4	19/7	0.3
Baseline vital signs			
Temperature (°C)	37.31 (0.54)	37.36 (0.51)	0.73
HR (beats/min)	87.16 (10)	85.15 (9.25)	0.36
SBP (mmHg)	115.34 (5.27)	116.73 (3.2)	0.72
RR (breaths/min)	17.69 (2.26)	17.76 (2.04)	0.89
Intraoperative surgical find			
Acute catarrhal appendicitis	17 (65.3)	15 (57.6)	0.5
Presence of pus	8 (30.7)	10 (38.4)	
Perforated appendix	0	1 (3.8)	
Normal appendix	1 (3.8)	0	

Values are presented as mean±SD or *n* (%). No statistical difference was reported between groups. ASA: American Society of Anesthesiologists; HR: Heart rate; SBP: Systolic blood pressure; RR: Respiratory rate; SD: Standard deviation

Table 2: Intra- and postoperative variables ;duration of surgery; min, intraoperative consumed fentanyl; mcg, time of postanesthesia care unit stay; min, time to first rescue analgesia; h, length of hospital stay; days, postoperative rescue pethidine consumed; mg, and parents' satisfaction score

Postoperative variables	Bupivacaine group ($n=26$)	Bupivacaine-dexmedetomidine group ($n=26$)	*P*
Duration of surgery (min)	52.11 (8.42)	50.38 (10.19)	0.53
Intraoperative fentanyl (mcg)	92.5 (16.2)	86.5 (17.32	0.34
Time of PACU stay (min)	36.3 (7.26)	38.26 (6.32)	0.36
Time to first rescue analgesia (h)	4.26 (1.35)	5.1 (1.47)	0.03*
Length of hospital stay (days)	3.61 (0.85)	2.92 (0.97)	0.02*
Rescue pethidine consumed in 24 h (mg)	35 (20-65)	25 (10-55)	0.02*
Satisfaction scores (%)			
Score 5	9 (34.6)	1 (3.8)	0.01*
Score 6	12 (46.1)	14 (53.8)	
Score 7	5 (19.2)	11 (42.3)	

*$P<0.05$: Statistical significance. Values are presented as mean±SD, median (range), or *n* (%). PACU: Postanesthesia care unit; SD: Standard deviation

Table 3: Ramsay sedation score in postanesthesia care unit (0 time), at 2, 4, 6h postoperatively

Time (h)	RSS	Bupivacaine group ($n=26$)	Bupivacaine-dexmedetomidine group ($n=26$)	*P*
0	1	5 (19.2)	0	0.002*
	2	10 (38.4)	5 (19.2)	
	3	6 (23)	3 (11.5)	
	4	5 (19.2)	13 (50)	
	5	0	5 (19.2)	
2	1	6 (23)	2 (7.6)	0.002*
	2	15 (57.6)	10 (38.4)	
	3	5 (19.2)	3 (11.5)	
	4	5 (19.2)	11 (42.3)	
4	1	7 (26.9)	3 (11.5)	0.03*
	2	16 (61.5)	11 (42.3)	
	3	3 (11.5)	8 (30.7)	
	4	0	4 (15.3)	
6	1	8 (30.7)	6 (23)	0.05
	2	14 (53.8)	13 (50)	
	3	4 (15.3)	7 (26.9)	

*$P<0.05$: Statistical significance. Values are presented as *n* (%). RSS: Ramsay Sedation Score

vs. 3.8% in B), and headache (3.8% in both groups). All are without significant differences between groups. There were no reported cases of hypotension, hypoxia, or signs of local anesthetic toxicity in both groups.

Discussion

In the present study, we noted that intraperitoneal administration of dexmedetomidine (1 mcg/kg) in combination with bupivacaine 0.25% (2 mg/kg), as compared to bupivacaine 0.25% (2 mg/kg) alone, in children undergoing laparoscopic appendectomy, was associated with reduced postoperative pain, increased time to first rescue analgesia, and reduced requirements for rescue pethidine postoperatively. Dexmedetomidine offered also a shorter postoperative length of hospital stay with no significant side effects and better overall parents' satisfaction.

IPLA have been used in adults following many laparoscopic surgeries. It could be considered a viable option for early postoperative period to reduce pain scores and decrease the postoperative analgesic requirements after laparoscopic general surgical procedures,[10,11] open hysterectomy,[12] and laparoscopic gynecological procedures.[13]

IPLA exhibits an analgesic effect by blocking free afferent nerve endings in the peritoneum. The systemic absorption of local anesthetics through the peritoneal surface, which could be detected in the serum circulation 2 min after bolus instillation into the peritoneum, may also play a part in the analgesic effect by attenuating nociception.[14]

Many trials have reported IPLA as an effective analgesic approach in laparoscopic appendectomy in adults.[15-17] The results obtained in these trials were attributed to the anti-inflammatory action of amide local anesthetics which antagonize the action of prostaglandins in the inflammatory area, inhibit leukocyte migration and metabolism, and inhibit lysosomal enzyme release in case of peritonitis.[18]

Many trials have reported dexmedetomidine as an adjuvant to IPLA in laparoscopic surgeries to improve postoperative pain scores, prolong the time to the first request of analgesia, and decrease the postoperative analgesic consumption.[6,19]

Dexmedetomidine has been shown to reduce pro-inflammatory cytokine levels in experimental sepsis[20] and postoperative patients.[21] The anti-inflammatory action of dexmedetomidine was attributed to modulation of cytokine during the stress response, which may also be stimulated through α2-adrenoceptors; inhibition of apoptosis; central sympatholytic effects, including stimulation of cholinergic anti-inflammatory pathways; and antinociceptive action involving interactions between pain and immune factors (pro-inflammatory cytokines).[22-24] Furthermore, perineural administration of dexmedetomidine causes local analgesia by enhancement of the hyperpolarization-activated cation current, which prevents the nerve from returning to resting membrane potential for subsequent firing.[25]

Intraperitoneal bupivacaine was compared to normal saline as a control in children undergoing laparoscopic appendectomy for postoperative pain control. There was no significant difference in overall pain scores, in the right iliac fossa or suprapubic pain scores, opioid use, recovery parameters, or complications. These results were attributed to the acidic environment caused by inflammatory reactions that

could reduce the efficacy of local anesthetics, the relatively low dose and volume of bupivacaine used and the entirely nonbalanced groups with a trend to the more perforated appendix in the intervention arm.[4] These results are not coinciding with the results obtained by the current study as we added dexmedetomidine (1 mcg/kg) as an adjuvant to intraperitoneal bupivacaine. The anti-inflammatory analgesic properties of dexmedetomidine probably compensated for the limited dose and volume of the local anesthetic used in pediatric patients and increased the potency of bupivacaine which could have otherwise been decreased by the inflamed acidic tissues.

IPLA was studied in 30 children undergoing different laparoscopic procedures including appendectomy. It reduced visceral pain scores at 3, 6, and 12 h and shoulder pain scores at 6 and 12 h postoperatively.[26] The authors did not perform subgroup analysis of patients undergoing appendectomies, which can explain their results agreeing with ours, although they did not add any adjuvants to the local anesthetic. IPLA was also studied in 41 patients (aged 1–23 years) who had undergone robotic-assisted pyeloplasty. A total of 22 patients received aerosolized bupivacaine (30 ml) sprayed onto the peritoneum, either at the beginning or the end of surgery and 19 patients did not receive IPLA. Postoperative opioid consumption was lower in the "spray-at-the-beginning" group, and hospital stay was shorter in both intervention groups compared with controls.[27] Despite dissimilarities between their study and ours, regarding types of surgeries and patients' ages, their results agree with ours.

Bupivacaine sprayed onto the peritoneum through an atomizer was compared to the same dose nebulized intraperitoneally with insufflation gas over 15–30 min, in children undergoing robotic-assisted laparoscopic urologic surgery. The authors noted reduced opioid requirements in both intervention groups in comparison to historical controls.[28]

Instillation of intraperitoneal levobupivacaine in children undergoing laparoscopic surgery for undescended testes or cholecystectomy was evaluated. The authors reported lower pain scores and opioid consumption in the first 6 h after surgery.[29]

Our results are similar to these two studies although the authors did not include laparoscopic appendectomy and did not add any adjuvants to local anesthetics used in their studies.

Limitations of the present study include not measuring the plasma levels of bupivacaine and dexmedetomidine after administration. However, we did not exceed the maximum dose allowed and no cases of toxicity were reported in the study. In addition, the immediate preoperative explanation of VAS is less appropriate and may lead to inadequate understanding about the scale. It is preferred to explain VAS before sending the patient to the operating room.

Conclusion

Adding dexmedetomidine to intraperitoneal bupivacaine in children undergoing laparoscopic appendectomy reduced postoperative pain and postoperative analgesic requirements and increased the time to first analgesic request. Dexmedetomidine offered not only a shorter postoperative hospital stay without significant side effects but also better overall parents' satisfaction.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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