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Original Research Article

Analgesic Effect of Intrathecal Fentanyl vs Dexmedetomidine as Adjuvants to Bupivacaine Following Abdominal Surgery for Cancer in Children, a Randomized Trial

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Abstract

Background. Intrathecal fentanyl in spinal anesthesia improves intra- and postoperative analgesia. Dexmedetomidine is a fascinating adjuvant with regards to neuraxial anesthesia in children experiencing surgery for abdominal malignancy. **Patients and Methods.** After endorsement by the institutional reviewing board (IRB) and guardians' written informed consent, this research was carried out on 60 pediatric malignancy patients scheduled for major abdominal surgery. Children were randomly distributed into three groups (20 patients each): Group C: given 2 mL of bupivacaine 0.5% (0.4 mg/kg) intrathecally, injected gradually over 20 seconds. Group F: the same as group C, plus fentanyl 0.2 μg/kg. Group D: the same as group C, plus dexmedetomidine 0.2 μg/kg. Pain at zero, two, four, six, 12, 18, and 24 hours postoperatively was evaluated by Face, Legs, Activity, Crying, and Consolability (FLACC) score. First analgesic request and postoperative unfavorable effects were recorded for 24 hours postoperatively. **Results.** A significant decrease was recognized in the mean FLACC score in groups D and F at six, eight, and 12 hours postoperatively, in contrast to group C ($P \leq 0.05$). First analgesic request was significantly prolonged in group D (7.67 $\pm$ 0.57 hours), in contrast to groups F and C (5.40 $\pm$ 1.09 hours and 4.23 $\pm$ 3.27 hours, respectively, $P < 0.04$). Paracetamol utilization was significantly decreased in group D (316.67 $\pm$ 28.86 mg), in contrast to group C (391.00 $\pm$ 52.00 mg, $P < 0.03$), without a significant difference between group F (354.44 $\pm$ 46.67 mg) and groups D and C ($P > 0.05$). **Conclusions.** Adding dexmedetomidine and fentanyl to intrathecal bupivacaine improved postoperative analgesia following abdominal surgery for cancer in children, with better overall analgesia of dexmedetomidine compared with fentanyl.

Key Words: Intrathecal; Fentanyl; Dexmedetomidine; Bupivacaine; Pediatric Major Abdominal Cancer Surgery

Introduction

Spinal anesthesia for newborn children's surgery was first focused on by Master H. Tyrrell Dim, who stressed its significant future position for medical procedures in pediatrics [1].

In spite of being proposed for pediatric thoracic surgeries in 1933, it was later deserted because of the progress in general anesthesia [2].

Since 1984, and after re-presentation of spinal anesthesia into current practice [3], it has been utilized either

alone for surgical procedures in the lower portion of the body [4] or used complementarily for general anesthesia in babies [5].

Intrathecal fentanyl improves analgesia both intra- and postoperatively [6] and improves the biological parameters of psychological reaction to surgery [7]. It is broadly utilized as an adjuvant for spinal anesthesia in grown-ups, but not in pediatric patients. Its impact on the duration of spinal anesthesia was examined in inguinal herniorrhaphy in newborn children by Batra et al. [8]. Untoward cts, such as nausea, vomiting, or respiratory depression, are not uncommon [9].

Dexmedetomidine is a highly selective α2-adrenergic receptor (α2-AR) agonist. Intravenous dexmedetomidine shows a synergistic impact with local anesthesia, upgrading postoperative pain control [10]. Neuraxial dexmedetomidine causes antinociception by deactivating spinal microglia and astrocytes, diminishing the noxious stimuli–evoked liberation of nociceptive substances and further intruding on the spinal neuron–glia cross-talk and controlling nociceptive transmission under chronic painful conditions [11]. Along these lines, it diminishes both intra- and postoperative anesthetic utilization and prolongs the postoperative pain-free period [10].

The ordinarily utilized dose of 5 μg of intrathecal dexmedetomidine has been considered the dose that is comparable to clonidine 1:10 through intrathecal injection. Higher doses of 15–20 μg of intrathecal dexmedetomidine have been utilized as an adjuvant, creating a discussion about the dose of intrathecal dexmedetomidine [12]. In this examination, we chose a dose of 0.2 μg/kg of intrathecal dexmedetomidine for our pediatric patients. This portion would be practically similar to the commonly utilized dose of 5 μg.

We planned this research to compare the analgesic effect of intrathecal fentanyl and dexmedetomidine as adjuvants to bupivacaine in pediatric patients experiencing surgery for abdominal malignancy.

Methods

This randomized double-blinded prospective study was approved by the local morals advisory group of the South Egypt Cancer Institute, Assiut University, Assiut, Egypt. It was registered at www.clinicaltrials.gov (identifier: NCT 02861716) before enrollment of the first patient, and written informed consent was collected from all patients' parents. We enrolled 60 pediatric patients at age three to 12 years, weight 10–30 kg, American Society of Anesthesiologists class I–II who were scheduled for major surgery for abdominal malignancy expected to last >90 minutes under general anesthesia combined with intrathecal anesthesia.

Children with spina bifida, sacral bone variations, hypersensitivity to drugs, coagulopathy, and local infection at the injection site were excluded from the study.

Standard monitoring included pulse oximetry, noninvasive arterial blood pressure, and electrocardiography. Premedication included diazepam 0.01 mg/kg and ondansetron 0.1 mg/kg. General anesthesia was delivered with sevoflurane 8% in oxygen. At that point, an intravenous cannula was introduced. Standard fluid infusion was started during and after the medical procedure. Endotracheal intubation was assisted by neuromuscular bar (atracurium besylate 0.5 mg/kg).

Patients were put in the lateral decubitus position after securing the endotracheal tube in place to perform intrathecal injection utilizing a 25-gauge needle (Braun®, Germany) and utilizing the cerebrospinal fluid free-flow technique.

Opaque sealed envelopes containing a Personal computer-produced randomization sequence were applied. Patients were arbitrarily randomized into three groups. Patients and their parents were blinded to the gathering task. The envelopes were sequentially numbered and dispersed on the day of the medical procedure before acceptance of general sedation. Each group included 20 patients:

1. Group C: children got 0.4 mg/kg of intrathecal bupivacaine 0.5%, injected gradually for more than 20 seconds.
2. Group F: children got 0.4 mg/kg of intrathecal bupivacaine 0.5% in addition to fentanyl 0.2 μg/kg, injected gradually for more than 20 seconds.
3. Group D: children got 0.4 mg/kg of intrathecal bupivacaine 0.5% in addition to dexmedetomidine 0.2 μg/kg, injected gradually for more than 20 seconds.

The anesthetist who gave the research drugs and the attending anesthetist were blinded to the substance in the sterile syringes containing the medications.

Anesthesia and muscle relaxation were continued with sevoflurane in a 50% oxygen-air admixture, and atracurium besylate (0.15 mg/kg) was repeated after fixed periods. Patients were mechanically ventilated in a volume-controlled mode with ventilation parameters that kept end tidal CO2 at 35–45 mmHg. The inhaled concentration of sevoflurane was tuned to avoid hemodynamic changes >30% of their particular baselines. No other narcotics, analgesics, or sedatives were administered intra-operatively. Children received lactated ringer's solution 6 mL/kg/h intraoperatively and dextrose 50 mg/mL in NaCl 4.5 mg/mL at a rate of 4 mL/kg/h postoperatively.

Heart rate, noninvasive arterial blood pressure (mean, systolic, and diastolic), and peripheral arterial oxygen saturation were recorded at baseline and every 10 minutes intra-operatively until the end of the medical procedure. Intra-operative hypotension requiring a fluid bolus and bradycardia requiring atropine were recorded.

Toward the end of the operative procedure, the remaining neuromuscular block was reversed utilizing atropine (0.02 mg/kg) and neostigmine (0.05 mg/kg).

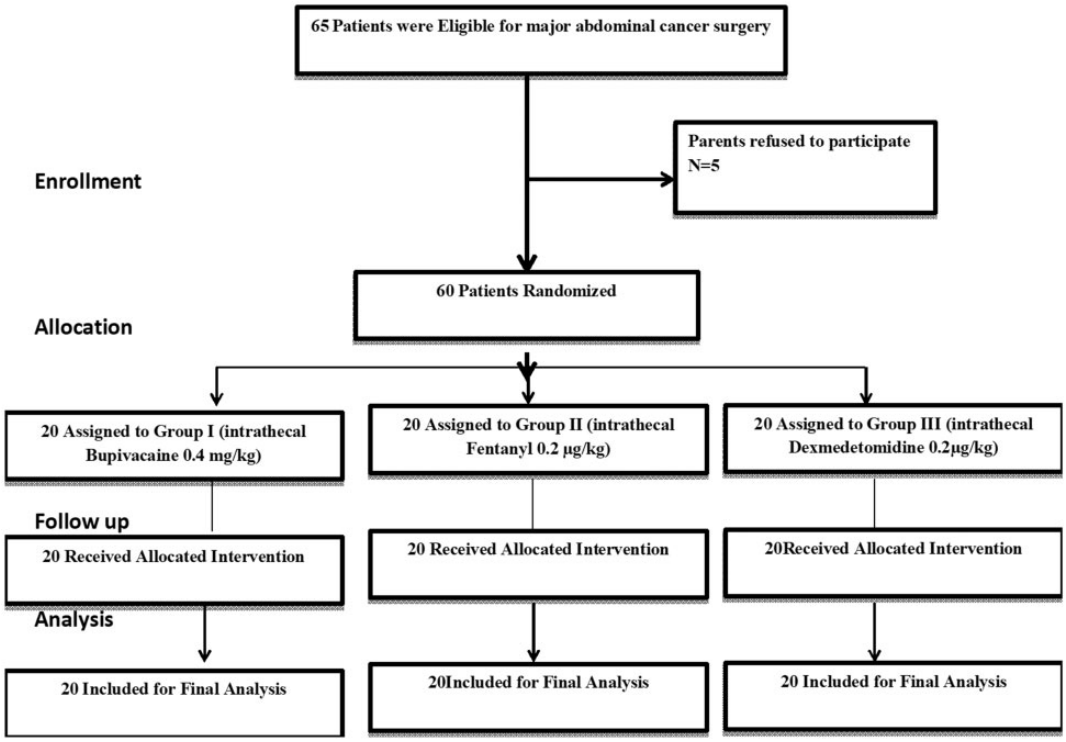

Figure 1. Flow diagram of the study recruitment.

After extubation, patients were moved to the pediatric intensive care unit (PICU) and were observed by a physician blinded to group assignment for vital signs (heart rate, noninvasive arterial blood pressure, oxygen saturation, and respiratory rate) immediately postoperation (zero hours) and at two, four, six, eight, 12, 18, and 24 hours postoperation. The Face, Legs, Activity, Crying, and Consolability (FLACC) pain score (0–10 score range [13]) was used to measure pain immediately postoperation and at two, four, six, 12, 18, and 24 hours postoperation. The time to first request for analgesia (intravenous paracetamol 20 mg/kg [Perfalgan]) was recorded when the FLACC score was $\geq$4, with a maximum of four doses per day, and total paracetamol consumption was recorded in the 24 hours postoperation. The degree of sedation was measured utilizing the Ramsey sedation scale at the same time points as the FLACC scale.

Postoperative unfavorable effects, including nausea, vomiting, pruritus, hypotension, bradycardia, arrhythmia, and respiratory depression (respiratory depression was characterized as diminished SpO2 of <95% or respiratory rate <10/min), were recorded and dealt with appropriately.

Statistical Analysis

Our primary end point was change in FLACC scores in the study groups. Secondary end points were the time to first analgesic request, total analgesic consumption postoperatively, and incidence of perioperative side effects. Sample size calculation showed that 17 patients in each group were required to detect a difference in the mean FLACC score as small as 1.5 times its standard deviation with a power of 90% and a significance level (P value) of 0.05. We enrolled 20 patients per group to compensate for possible dropouts.

SPSS, version 20, was used for data entry and analysis. Data were presented as number, percentage, and mean ± SD. The chi-square test was used to compare between qualitative variables. The Mann-Whitney test was used to compare quantitative variables between the studied groups. The Wilcoxon signed-rank test was used to compare between two time-points within the same group. P values <0.05 were considered statistically significant.

Results

Sixty patients finished the study, and they were divided into groups, with 20 in each group (Figure 1). There were no significant differences between the three groups in demographic data (Table 1).

Patients in group D showed significantly lower mean Systolic blood pressure (SBP) at 10, 20, 30, 90, and 120 minutes intra-operatively, in contrast to both groups C and F ($P < 0.05$) (Figure 2). Also, there was a significant decrease in mean diastolic blood pressure in group D at 30 and 60 minutes intra-operatively contrasted with group C and at 90 and 120 minutes compared with groups C and F ($P < 0.05$) (Figure 3). No significant difference was found between groups with regards to intraoperative mean heart rate values ($P < 0.05$) (Figure 4).

Table 1. Demographic data in the three studied groups

Item	Group C (N = 20)	Group F (N = 20)	Group D (N = 20)	*P* Value
Age, y				
Mean ± SD	7.05 ± 2.92	6.80 ± 2.68	7.62 ± 2.98	0.650n.s.
(min–max)	(2.0–12.0)	(2.0–11.0)	(2.5–12.0)	
Sex				
Male, No. (%)	10 (50)	9 (45)	11 (55)	0.819n.s.
Female, No. (%)	10 (50)	11 (55)	9 (45)	
Weight				
Mean ± SD	18.95 ± 5.68	18.61 ± 5.59	19.48 ± 5.86	0.890n.s.
(min–max)	(10.0–28.0)	(10.0–28.0)	(9.6–29.0)	

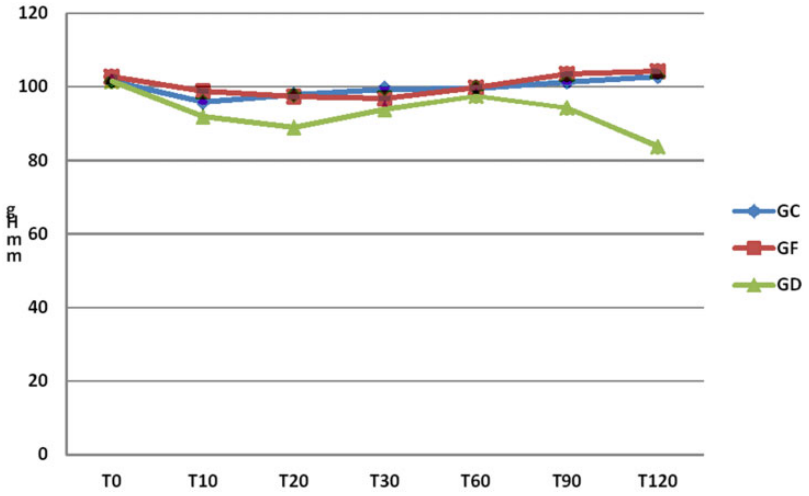

Figure 2. Mean intra-operative systolic blood pressure in the three studied groups.

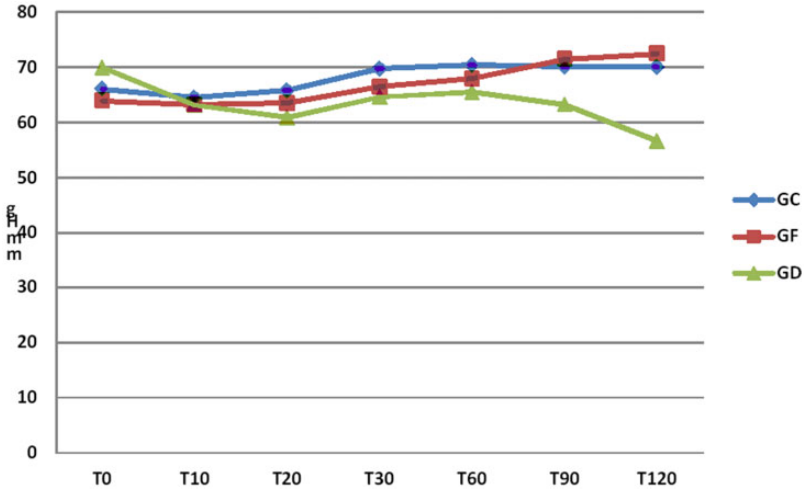

Figure 3. Mean intra-operative diastolic blood pressure in the three studied groups.

There was no significant difference between the three groups in mean postoperative SBP, Diastolic blood pressure, heart rate, or sedation score ($P < 0.05$).

There was a significant decrease in mean FLACC score in groups D and F at six, eight, and 12 hours postoperatively compared with group C ($P \leq 0.05$) (Figure 5). Time to the first request of rescue analgesia was significantly longer in group D (7.67 ± 0.57 hours) compared with groups F and C (5.40 ± 1.09 hours and 4.23 ± 3.27 hours, respectively, $P < 0.04$) (Table 2).

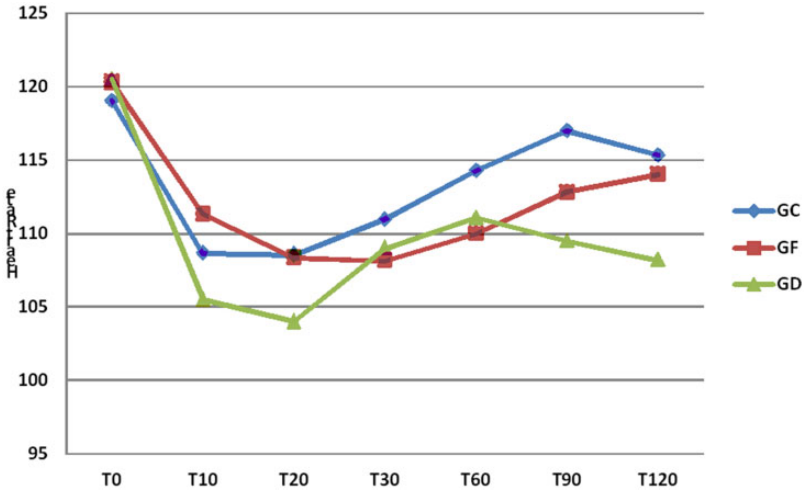

Figure 4. Mean intra-operative heart rate in the three studied groups.

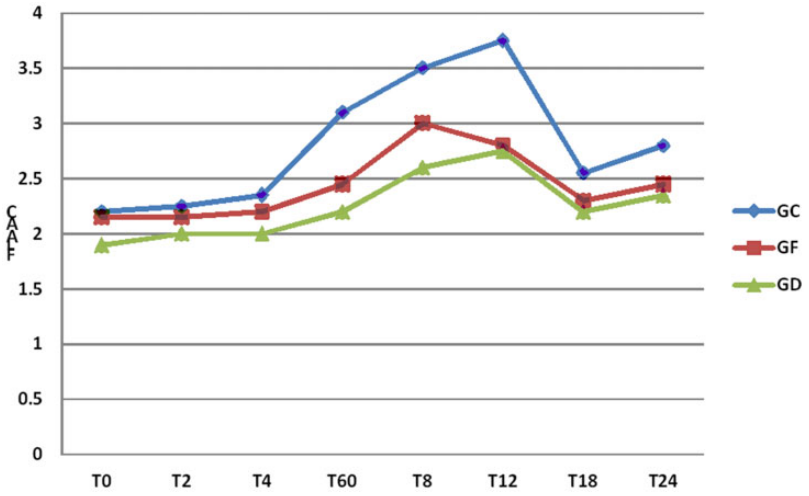

Figure 5. Mean postoperative Face, Legs, Activity, Cry, Consolability (FLACC) scale in the three studied groups.

Postoperative total paracetamol utilization was significantly diminished in group D (316.67 ± 28.86 mg), in contrast to group C (391.00 ± 52.00 mg) and group F (354.44 ± 46.67 mg, $P < 0.03$) (Table 2). All children in group C received rescue analgesia during the study period (20 patients = 100%), while only nine (45%) and three (15%) patients received rescue analgesia in groups F and D, respectively (Table 2).

No significant difference was observed in the incidence of postoperative unfavorable effects among groups ($P < 0.05$) (Figure 6).

Discussion

In this research, we studied the postoperative pain-relieving effect of intrathecal fentanyl (0.2 μg/kg) and dexmedetomidine (0.2 μg/kg) as adjuvants to bupivacaine in pediatric patients experiencing surgery for abdominal malignancy. FLACC scores markedly decreased in the fentanyl and dexmedetomidine groups compared with the control group. First request of rescue analgesia was delayed in group D in comparison with the other two groups. Total postoperative paracetamol utilization was diminished in group D, in contrast to group C, whereas comparing group F and the other two groups yielded insignificant differences.

Intrathecal narcotics can be utilized securely for anesthesia during major surgical procedures [14], and several scientists researched the use of neuro-axial morphine in major pediatric surgical procedures [15,16]. Intrathecal narcotics adequately diminish visceral pain and improve the intraoperative and early postoperative quality of the subarachnoid block [17, 18]. Intrathecal (IT) fentanyl reduces pain by direct contact with the substantia

Table 2. Time to first request for paracetamol and total cumulative dose

Item	Group C (N = 20)	Group F (N = 20)	Group D (N = 20)	*P* Value
1. Total dose	391.00 ± 52.00	354.44 ± 46.67	316.67 ± 28.86	<0.03*
2. First request	(N = 20)	(N = 9)	(N = 3)	<0.04*
3. Number of patients who requested analgesia	4.23 ± 3.27	5.40 ± 1.09	7.67 ± 0.57	
	(N = 20)	(N = 9)	(N = 3)	

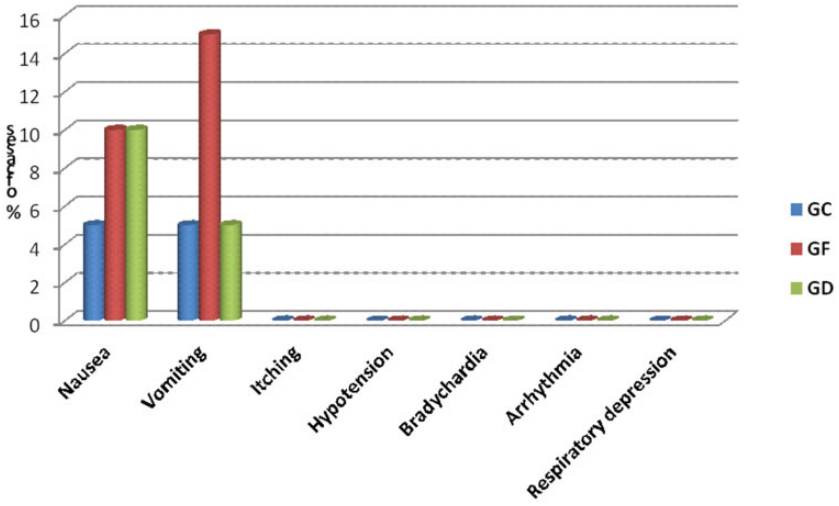

Figure 6. Postoperative side effects in the three studied groups.

gelatinosa of the spinal cord and blocking fibers conveying nociceptive impulses both pre- and postsynaptically with cephalad spread of sensorial block [17, 18]. The clinical impact is because of the absorption of the narcotic across lipid membranes into the cord (with consequent faster onset of lipophilic fentanyl in contrast to morphine). Due to this lipophilicity, there is a little cephalad spread with fentanyl in contrast to morphine.

Dexmedetomidine is an α2-adrenergic receptor agonist that can prolong the duration of analgesia of local anesthetics in spinal, paravertebral, and transversus abdominis blocks [19–21].

This impact results from nearby vasoconstriction, which results in increase in potassium conductance in Aδ and C fibers, entering the central nervous system either through systemic absorption or by dissemination into the cerebrospinal fluid and reaching α2 receptors in the superficial laminae of the spinal cord and brainstem or indirectly provoking spinal cholinergic neurons [22–25]. The pain-relieving impact of dexmedetomidine is due to suppression of C-fiber transmitters and Substance P and hyperpolarizing postsynaptic dorsal horn neurons [26], and this pain-relieving impact is connected to their proclivity to couple to the spinal α2 adrenergic receptors [27].

It has been demonstrated that combination of general anesthesia with caudal or epidural dexmedetomidine potentiates the administered neuraxial local anesthetics, diminishes the intraoperative consumption of anesthetics, reduces intraoperative awareness, improves intraoperative oxygenation, and increases postoperative analgesia [22, 23, 28].

Guevara-López et al. [29] found that ceaseless intrathecal administration of clonidine did not result in histological neurotoxicity. Also, single-dose intrathecal administration of clonidine (3, 12.5, or 25 μg/kg during 14 successive days or 70 μg/kg during 4.5 successive days) did not cause histopathological changes related to neurotoxicity [30, 31]. Işgüzar et al. concluded that intrathecal infusions of dexmedetomidine at a dose of 10 μg^{-1} created analgesia with no histopathological indication of injury in the spinal cord [32].

Intrathecal infusions of dexmedetomidine at low doses (0.75 and 1.50 μg/kg) are neurologically safe [33]; moreover, in vitro tests demonstrated that dexmedetomidine prevents neurotoxicity created by local anesthetics when joined with them [34].

We found that both intrathecal fentanyl and dexmedetomidine when added to bupivacaine decreased the FLACC score in the initial 24 hours postoperation. Dexmedetomidine had a better effect in terms of postponing the time to first analgesic request and diminishing the dose of rescue analgesia, in contrast to fentanyl. This finding is in accordance with those of the meta-analysis

by Sun et al. [35] looking at the impacts of dexmedetomidine and fentanyl as adjuvants to local anesthetics in spinal anesthesia, in which they found that dexmedetomidine has a markedly longer pain-free period and fewer postoperative analgesic demands.

Mahendru et al. [36] looked at the intrathecal administration of fentanyl, clonidine, and dexmedetomidine in lower limb surgical procedures and found that there was a marked reduction in rescue analgesic utilization with dexmedetomidine, in contrast to clonidine and fentanyl, which enforces the analgesic effect of dexmedetomidine as an intrathecal adjuvant. Likewise, including dexmedetomidine or fentanyl as an intrathecal adjuvant significantly improved pain-relieving capability [37]. Al-Mustafa et al. [38] and Eid et al. [12] revealed a dose-dependent prolongation of motor and sensory block with diminished analgesic demands with intrathecal dexmedetomidine (5, 10, and 15 μg).

In our study, intraoperative hemodynamics were only decreased in the dexmedetomidine group, in contrast to the fentanyl and control groups; this conflicts with the findings of Mahendru et al., who found no difference in mean arterial pressure (MAP) or heart rate (HR) within the studied groups (which included IT fentanyl, clonidine, and dexmedetomidine) during the intra- and postoperative periods [36]. This might be due to the difference in the types of patients and surgical procedures (adults experiencing lower limb surgical procedures vs pediatric patients with major abdominal surgical procedures), with progressively fragile patients and more noteworthy fluid shifts expected in our study, which may have resulted in hemodynamic changes.

A meta-analysis [35] has additionally concurred with our outcomes in regards to symptoms (nausea, vomiting, sedation, or respiratory depression), where no critical difference was found, aside from significantly higher rates of pruritus with intrathecal fentanyl. Mahendru et al. [36] also reported a higher rate of pruritus with intrathecal fentanyl, compared with dexmedetomidine, yet it was of no statistical significance.

This study has a few limitations: first, the small sample size. Further studies with larger sample sizes are needed to better assess the safety of the adjuvants we used. In addition, we did not confine our cases to a solitary type of surgical procedure, which would have been more homogenous; rather, we contemplated pediatric major abdominal surgical procedures for malignancy. Moreover, we did not measure exhaled anesthetic concentration, which would have been very informative with regards to the intraoperative effects of these adjuvants. Finally, studying various dosages of each medication would have given an increasingly complete picture for better correlation.

In conclusion, adding both dexmedetomidine and fentanyl to intrathecal bupivacaine in pediatric major abdominal cancer surgery decreased postoperative pain, postoperative analgesic utilization, and prolonged time to first analgesic demand, with better analgesia of dexmedetomidine compared with fentanyl.

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