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Safety and Efficacy of Intrathecal Morphine in Children Undergoing Surgery for Abdominal Neuroblastoma. Dose Finding, Randomized, Clinical Study

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Abstract

Background: Pediatric patients have remained undertreated for postoperative pain because of the difficulty of pain assessment and apprehension. Intrathecal opioids—including morphine—have become a popular method for providing post-operative analgesia in children. **Objectives:** To compare different doses of morphine via intrathecal route (2 μg/kg, 5 μg/kg, and 10 μg/kg) for post-operative analgesia in pediatric patients following for abdominal neuroblastoma surgery. **Methods:** This randomized, double-blinded, study was approved by local ethics committee of South Egypt Cancer Institute, Assiut University, Assiut—Egypt, and registered at https://www.clinicaltrials.gov/ at no.: "NCT03158584". Forty-five patients scheduled for surgical excision of abdominal neuroblastoma were divided into 3 groups (15 patients each); group (I): received intrathecal morphine 2 μg/kg added to normal saline (3 mL volume). Group (II): received intrathecal morphine 5 μg/kg. Group (III): received intrathecal morphine 10 μg/kg. Intra-, and post-operative hemodynamics, FLACC score, time to first request of rescue analgesia, total analgesic consumption, and side effects were recorded for 24 hours. **Results:** there was a significant reduction in FLACC score in groups II and III starting immediately till 24 hours postoperatively compared to group I ($P < 0.05$). None of the patients in groups II and III ($n = 15$ each), while all the patients in group I ($n = 15$) required postoperative rescue analgesia. In group (I), time to first request of rescue analgesia, cumulative perfalgan, and fentanyl consumptions were 5.47 ± 1.60 hours, 613 ± 182.92 mg, and 10.37 ± 3.78 μg respectively. There was no significant difference among groups regarding postoperative sedation ($P > 0.05$). No significant difference was observed between groups in side effects.

Conclusions: 5 μg/kg of IT morphine achieved a reasonable balance between postoperative analgesia, and the incidence of side effects in pediatric patients following major abdominal cancer surgeries.

Keywords

Morphine, Intrathecal Route, Abdominal Neuroblastoma, FLACC Score, Acute Pain

1. Background and Objectives

Postoperative pain management in pediatric and children has developed rapidly. However, postoperative pain in children remained undertreated due to the difficulty of pain assessment, apprehension regarding cardio-respiratory depression, etc… [1].

Opioid drugs play the most important role in the treatment of acute postoperative pain. Although many physicians are cautious regarding the risk of respiratory depression associated with morphine administration, acute pain counteracts the respiratory depression induced by opioids [2].

Opioids can be administered orally, IV, in the epidural space or intrathecally (IT) [3]. The choice of the route of administration of opioids is based on the anesthesiologists' preferences, the anticipated degree of postoperative pain for the type of operation, and the duration of the hospital stay.

The first use of intrathecal morphine for postoperative pain control in children was reported by Jones *et al.* in 1984 [4]. Later on, intrathecal opioids have become increasingly a popular method for providing post-operative analgesia in children. Several randomized trials have shown that children who received intrathecal morphine intra-operatively had reduced pain and opioid requirements in the postoperative period [4] [5].

It has been used as an analgesic adjuvant during cardiac [6] [7], orthopedic [8] [9] and urological surgeries in children [10] frontal encephalocele repairs, [11] and in the long-term management of cancer pain [12]. IT morphine doses in these studies were in the range of 10 - 30 mcg/kg, and clinically significant side effects were reported.

In this study, we aim to compare different low doses of intrathecal morphine (2 μg/kg, 5 μg/kg, 10 μg/kg) for post-operative pain relief in pediatric patients undergoing surgical removal of abdominal neuroblastoma.

2. Methods

After obtaining approval of the local ethics committee of South Egypt Cancer Institute, Assiut University, Assiut-Egypt, and parental written informed consent, this randomized double-blinded clinical study was registered at https://www.clinicaltrials.gov/ at no.: "NCT 03158584". All cases fulfilling the after coming inclusion and exclusion criteria presented to our cancer institute in

the time period (18 months) were included in this study. It included pediatric patients aged 2 - 6 years, weighting 10 - 30 kg, and of American Society of Anesthesiologists (ASA) physical status I - II, scheduled for surgerical excision of abdominal neuroblasoma under general anesthesia combined with intrathecal morphine. Children with sacral bone abnormalities, spina-bifida, bleeding diathesis, local infection at the vicinity of injection site, mental delay or retardation, and known allergy to any of the study drugs were excluded from the study.

After applying standard monitoring probes (oxygen saturation [SpO_2], non-invasive blood pressure [NIBP], electrocardiograph [ECG], and end-tidal carbon dioxide [$ETCO_2$]) general anesthesia was induced with inhalation of sevoflurane 8% in oxygen via face mask. An intravenous line was placed and fluid therapy was standardized during and after surgery. All patients received an I.V. dose of fentanyl of 10 μg/kg. During surgery, children received lactated ringer's solution 6 mL/kg/hr. whereas dextrose 50 mg/mL in Nacl 4.5 mg/mL was infused at 4 mL/kg/hr in the postoperative period. Atracurrium 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 and a single dose of intrathecal morphine was given (at L4-5/L5-S1 space) using a 25 g needle (Braun®, Germany) and free flow of CSF technique.

The children were randomly assigned using an online research randomizer (http://www.randomizer.org) into one of three groups (15 patients each) [13]:

Group (I): children received intrathecal morphine 2 μg/kg added to normal saline (3 mL volume).

Group (II): children received intrathecal morphine 5 μg/kg added to normal saline (3 mL volume).

Group (III): children received intrathecal morphine 10 μg/kg added to normal saline (3 mL volume).

Attendant anesthetist who gave intrathecal injections was blinded to the injectate administered. 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 within a range of <30% of the baseline values. No other narcotics, analgesics or sedatives were administrated intra-operatively.

Heart rate (HR), non-invasive blood pressure (mean, systolic, and diastolic), oxygen saturation (SpO_2) were recorded intra-operatively for 120 minutes. The occurrence of intra-operative hypotension (defined as systolic arterial pressure < 70 plus twice the age in years and associated with altered peripheral perfusion) requiring a fluid bolus, and bradycardia (defined as HR less than 60 beats/minute) requiring atropine were recorded.

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

After extubation, patients were transmitted to the post-anesthesia care unit (PACU), and were followed up for changes in the vital signs (HR, NIBP, SpO_2, and respiratory rate), immediately postoperatively (0 hour) and at 2, 4, 6, 12, 18

and 24 hours of the postoperative period.

The face, Legs, Activity, Crying, and Consolability (FLACC) pain score (Table 1) with its 0 - 10 score range was used to assess pain immediately (0 hour) and at 2, 4, 6, 12, 18, 24 hours postoperatively. Time to first request of rescue analgesia (Intravenous acetaminophen 15 mg/kg (perfalgan®) which was given when the FLACC score ≥ 4) was recorded. Also I.V. fentanyl 0.5 μg/kg was used on demand and the total acetaminophen/fentanyl consumption was recorded in the 24 hours postoperatively. The level of sedation was recorded using Ramsey sedation scale (Table 2). Postoperative adverse effects such as nausea, vomiting, pruritus, hypotension, bradycardia and respiratory depression (respiratory depression was defined as decreased SpO_2 of less than 95%) were recorded and treated.

Intra and post-operative follow up of patients was done by blinded observers to patients' group assignment.

3. Statistical Analysis

Data entry and analysis were done using SPSS version 20® (Statistical Package for Social Science). Data were presented as number, percentage, mean ± standard deviation. Chi-square test was used to compare between qualitative variables. Mann-Whitney test was used to compare quantitative variables between the studied groups. Wilcoxon Signed Rank test was done to compare every two times in the same group.

Table 1. FLACC score.

Criteria	Score 0	Score 1	Score 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting, back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams, sobs, frequent complaints
Controllability	Content, relaxed	Reassured by touching, hugging or being talked to, distractible	Difficult to console or comfort

Table 2. Ramsay sedation scale.

1	Patient is anxious and agitated or restless, or both
2	Patient is co-operative, oriented, and tranquil
3	Patient responds to commands only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response

4. Results

Among the 50 patients who were screened for eligibility, 45 patients were finally analyzed and were equally distributed in the three studied groups (n = 15) (Figure 1).

There was no significant difference among the groups as regards demographic data (sex, age and weight) and duration of both anesthesia and surgery (P > 0.05) (Table 3).

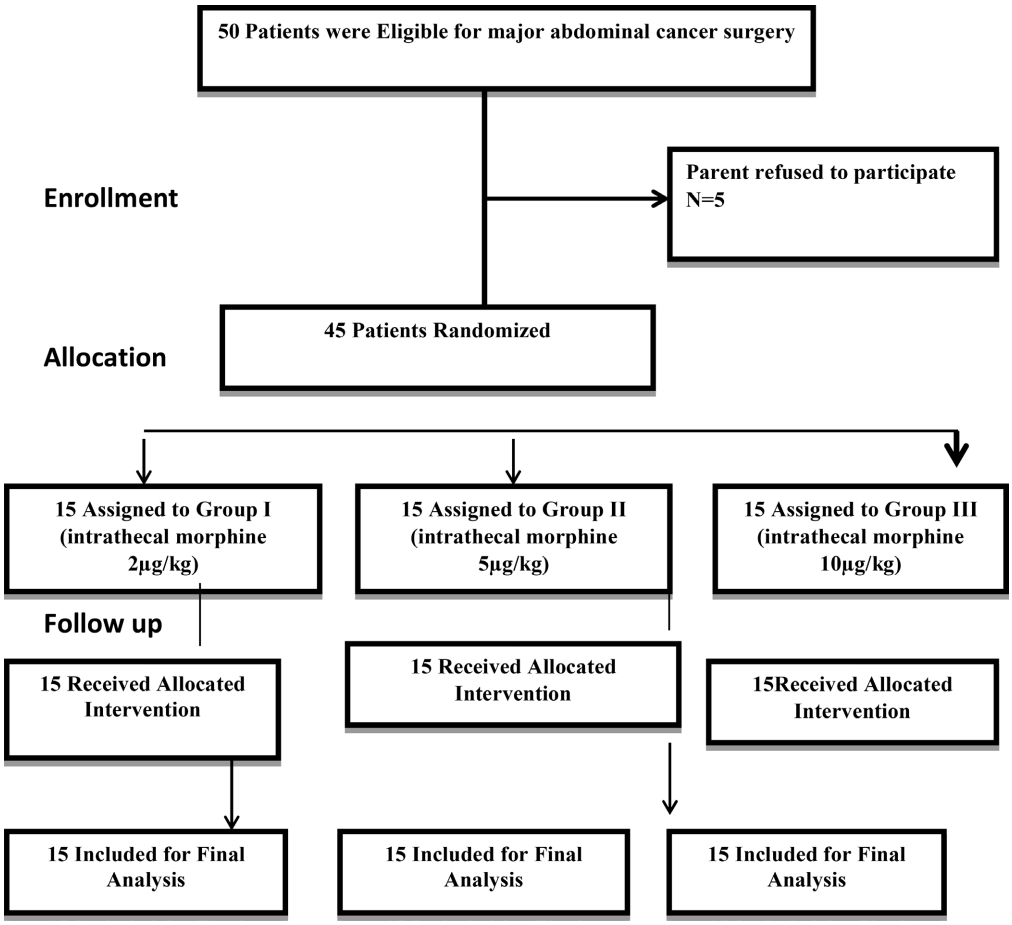

Figure 1. Flow chart of cases through the study.

Table 3. Demographic and clinical data of the study groups.

		Group 1 Mean ± SD	Group 2 Mean ± SD	Group 3 Mean ± SD	P-value
Sex	Male	8 (53.33%)	6 (40%)	7 (46.67%)	0.765
	Female	7 (46.67%)	9 (60%)	8 (53.33%)	
Age (yrs.)		6.47 ± 2.2	6 ± 2.07	6.93 ± 2.02	0.482
Weight (kg)		19.33 ± 3.98	18.47 ± 3.4	19.73 ± 3.45	0.622
Duration of anesthesia (hrs.)		2.77 ± 0.45	2.72 ± 0.48	2.68 ± 0.48	0.887
Duration of surgery (hrs.)		2.55 ± 0.39	2.52 ± 0.41	2.5 ± 0.38	0.939

There was a significant reduction in mean FLACC score in groups II and III starting immediately postoperative till 24 hours postoperative compared to group I ($P < 0.05$) (Figure 2). No patient in group II and group III required rescue analgesia in the first postoperative 24 hours. In group I, all patients (n = 15) required postoperative rescue analgesia. In the group I, the time to first request of rescue analgesia was 5.47 ± 1.60 hours, cumulative postoperative perfalgan and fentanyl consumption were, 613 ± 182.92 mg, and 10.37 ± 3.78 μg, respectively. There was no significant difference among groups regarding postoperative Ramsey sedation score ($P > 0.05$), (Figure 3). Also there were no significant

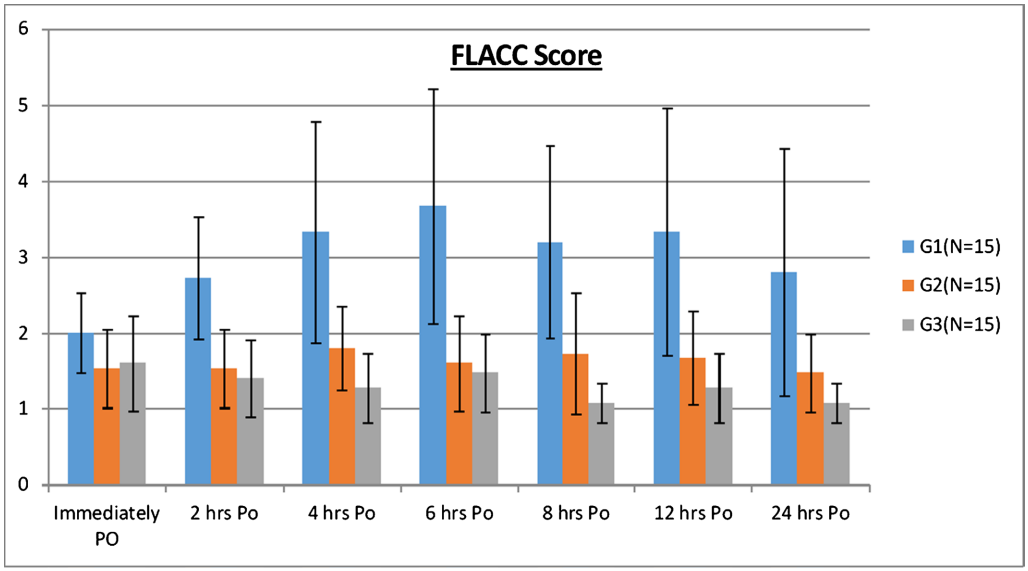

Figure 2. Changes of FLACC score in the three groups.

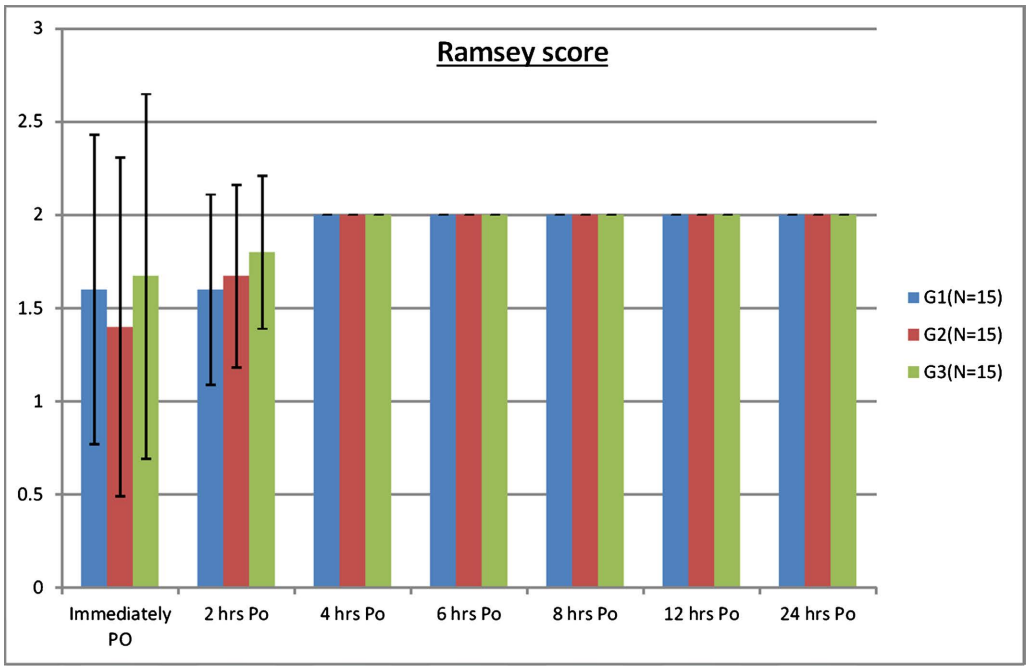

Figure 3. Changes in Ramsy sedation score in the three groups.

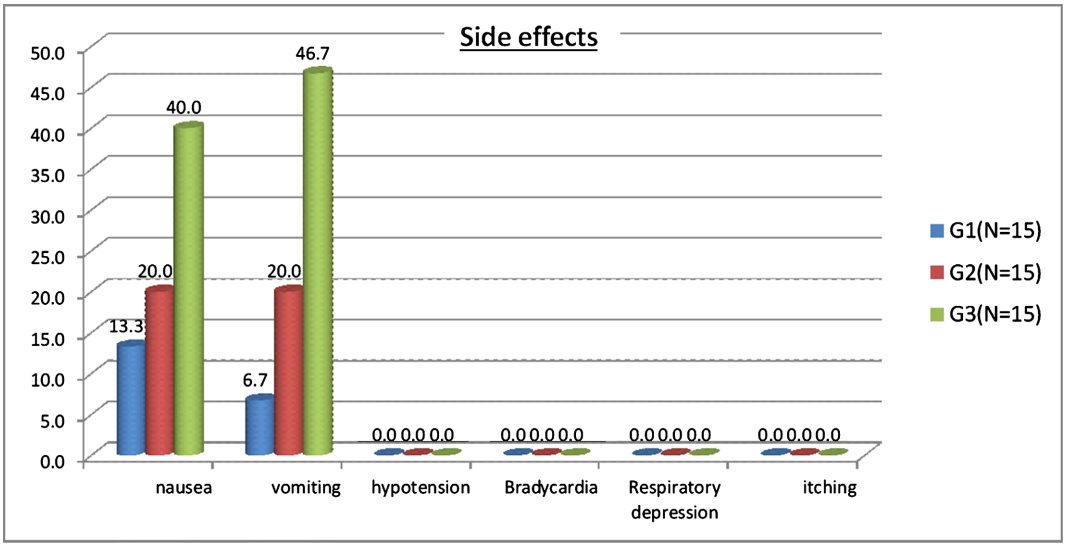

Figure 4. Incidence of side effects in the three groups.

differences between groups in the intra-operative and postoperative hemodynamics including HR, SBP and DBP.

The overall incidence of postoperative nausea and vomiting among groups was: for nausea 2 patients [13.3%] in group I versus 3 patients [20%] in group II and 6 patients [40%] in group III (P = 0.202), while for vomiting it was 1 patient [6.7%] in group I versus 3 patients [20%] in group II and 7 patients [46.7%] in group III (P = 0.004) (**Figure 4**).

No patients experienced pruritus, respiratory depression, sedation, bradycardia or hypotension (**Figure 4**).

5. Discussion

In the current study, we compared different doses of IT morphine (2, 5, and 10 μg/kg) for postoperative analgesia in pediatric patients who underwent surgical excision of abdominal neuroblastoma. It was obvious that IT morphine, especially at doses of 5, and 10 μg/kg, had an efficient analgesic effect as all the patients who received these doses had continuous pain relief that lasted for 24 hours postoperatively, without the need for rescue analgesia and without significant side effects.

We have chosen the intrathecal route for many reasons; first, the technique is easy and second the injection of local anaesthetics plus morphine into free flowing cerebro-spinal fluid (CSF) is indicative of correct position with no contact with nerve roots. This is not the case with lumbar or thoracic epidural approach. Caudal administration has been shown to be easy and safe. However, absence of end point such as free flow of CSF as associated with caudal anesthesia, immediate assurance of correct placement cannot be happened [14].

Previously, several studies evaluated the use of IT opioids in the pediatric population, Gall *et al.* [5], assessed both the analgesic effect and complications of intrathecal morphine using doses (20 and 30 μg/kg) after Spinal Fusion. Al-

though a long-lasting analgesia was observed (more than 22 hours in 60% of the studied patients) and nine of the 56 patients experienced significant respiratory depression requiring naloxone. Moreover, IT morphine was used for postoperative analgesia in spine and cardiothoracic surgical procedures at doses from 10 - 30 μg/kg [15] [16] [17] [18].

It is reported that IT morphine, although very effective with respect to postoperative analgesia, can cause severe side effects, and it is better to be avoided. The incidence of pruritus, emesis, and respiratory depression is dose-dependent and with a reported incidence varying from 60% to 80% for emetic symptoms [19], 20% - 100% for pruritus [20], and 0.36% for respiratory depression [21].

Depending on the type of pain elicited by the surgical procedure, the optimal intrathecal morphine dosage for postoperative pain control is different for each type of surgery [22].

In a study by Ganesh and colleagues [3], and after using a dose of IT morphine of 4 - 5 μg/kg in surgical pediatric patients, they found a low incidence of side effects and concluded that IT morphine at this dose can provide an effective and safe option for postoperative analgesia after various surgical procedures.

Gall and colleagues [23], comparing 2 and 5 μg/kg intrathecal morphine in 30 children undergoing scoliosis surgery, reported significantly lower median VAS scores compared to placebo, with significantly higher postoperative morphine consumption in the lower dosage group. Furtherly, Eschertzhuber and colleagues [24] compared low (5 μg/kg) versus high (15 μg/kg) doses of IT morphine in children undergoing spinal fusion, and concluded that, pain scales were reduced in both groups compared to control group, and despite lack of statistical significance, there was a trend towards lower consumption of postoperative I.V. opioids in the high dose group that lasted for 4 days.

In concordance with that, VAS score was below 3 all over the postoperative follow-up period, we found that rescue analgesia was only used by patients in group I that received the lowest IT morphine dose (2 μg/kg) of the three study groups, thus we limited the need to further use of opioids in the postoperative period, this is of special importance, putting in mind the experimental evidence that intrathecal and systemic opioids act synergistically [25]. Such interactions are so potent, especially when dealing with pediatric patients, that clinicians have advocated against their intentional use [26].

In our study, the incidence of postoperative nausea and vomiting (PONV) was related to the IT morphine dose used, it was highest among group III patients (nearly half of the patients developed PONV). Although this difference was not statistically significant, yet, it is of clinical importance.

In their work, Eschertzhuber and colleagues [24], in spite of medical prophylaxis, reported no statistical difference between high and low doses of IT morphine regarding PONV, yet incidence was still higher in high dose group. In a study by Apiliogullari and colleagues [4], there was no significant difference between those patients that received IT morphine (2 μg/kg) and control group regarding PONV, the use of propofol in the sedation of patients and the lower

dose of IT morphine might play a role in these results. In our anesthetic protocol, we didn't use propofol in the induction, which may explain the relatively high incidence of PONV in our cases. The anti-emetic effect of propofol might have modified this effect.

The most feared side effect of intrathecal morphine is respiratory depression; the reported incidence of respiratory depression in adult patients who received an intrathecal opiate is 0.36% [19]. High doses of opioids, concomitant use of any intravenous sedative, and general anesthesia increase the risk of respiratory depression.

In our study, there were no reported cases of respiratory depression. We avoided the use of any sedative drugs or I.V. anesthetics; this, besides the relatively smaller IT morphine doses compared to previous doses, could be responsible for the absence of respiratory depression in our cases.

As all our patients had urinary catheters inserted routinely after induction of general anesthesia, evaluation of the incidence of urinary retention was not possible.

We think that our work has a number of limitations; among which is the follow-up period of 24 hours, which could be extended for up to 48 or 72 hours in order to explore the ultimate duration of analgesia. The small sample size, although related to the nature of the disease, was not sufficient to powerfully investigate side effects. Finally, we recommend further research comparing the effect of combined IT and different I.V. anesthetic agents on the development of side effects.

6. Conclusion

5 μg/kg of IT morphine achieved a reasonable balance between postoperative analgesia and the incidence of side effects in pediatric patients following major abdominal cancer surgeries. We recommend further studies focused on postoperative pain management in children.

Data Availability

Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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