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ORIGINAL INVESTIGATION

# Efficacy of dexmedetomidine versus magnesium sulfate as an adjuvant to intraperitoneal bupivacaine in pediatric laparoscopic surgery: a randomized clinical trial

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**KEYWORDS**
Dexmedetomidine;
Magnesium sulfate;
Intraperitoneal analgesia;
Pediatric;
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## Abstract

*Background:* We evaluated the efficacy of dexmedetomidine versus magnesium sulfate as an adjuvant to intraperitoneal (IP) bupivacaine in pediatric laparoscopic inguinal herniorrhaphy.
*Methods:* Ninety-seven male children, ASA I–II, 1–6 years old, undergoing laparoscopic inguinal herniorrhaphy, were randomized to receive before peritoneal insufflation, IP 2 $mg.kg^{-1}$ bupivacaine 0.5% combined with either 1 $\mu g.kg^{-1}$ of dexmedetomidine (Group D), 30 $mg.kg^{-1}$ of magnesium sulfate (Group M), or normal saline (Group C). All tested drugs were diluted to the volume of 10 mL with normal saline. FLACC pain scores, need for rescue analgesics, time to flatus and first stool, emetic events, adverse effects, functional recovery, and parents' satisfaction were recorded for the first 48 h postoperatively.
*Results:* FLACC scores were significantly higher in Group C than in the other two groups at 6, 8, 12, 18, 24, and 48 hours after surgery with no differences between Groups D and M. Rescue analgesia was significantly higher in Group C with none of the children in Groups D and M requiring rescue analgesia ($p = 0.001$). Times to first flatus and stool, emetic events, and adverse effects did not differ among groups. Times to return to normal functional activity were comparable in all groups. Parents' satisfaction was greater in Groups D and M than in Group C ($p = 0.026$).
*Conclusion:* Dexmedetomidine and magnesium sulfate added to IP bupivacaine improved the analgesia afforded by bupivacaine in the first two postoperative days in children scheduled for laparoscopic herniorrhaphy.

Study conducted at the Faculty of Medicine, Assiut University, Egypt.

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## Introduction

Nowadays, in an era of minimally invasive surgery, pediatric laparoscopic inguinal hernia repair has become widely popular replacing the conventional open method and assuming an important place in pediatric surgery.[1]

Laparoscopic surgery has many advantages over open procedures, such as better cosmetics, shorter hospital stay, rapid recovery, and greater capability to visualize and repair a contralateral hernia.[1,2]

Pain after laparoscopy is less intense than after laparotomy, but laparoscopy is not pain free and analgesia after this type of surgery is inadequately studied.[3]

Diaphragmatic irritation with stretching of the peritoneum that accompanies gas insufflation may be the cause of diffuse abdominal pain. However, the exact mechanism of such pain remains uncertain.[4]

Intraperitoneal (IP) instillation/nebulization of local anesthetics has been used as a method for reducing postoperative pain and opioid use following laparoscopy through acting on visceral nociceptors of the peritoneum.[3]

Dexmedetomidine is a selective alpha-2 ($\alpha$2) adrenergic agonist known to have analgesic and sedative characteristics that can augment the duration of action of local anesthetics.[5] IP instillation of dexmedetomidine with bupivacaine reduced pain and rescue analgesia in children undergoing laparoscopic appendectomy.[6]

Magnesium sulfate ($MgSO_4$) also has been administered via different routes in anesthetic practice for relieving postoperative pain. Besides, it has been used to attenuate the adverse hemodynamic changes that occur with pneumoperitoneum and promote the quality of recovery.[7]

This study aimed to evaluate the efficacy of dexmedetomidine versus magnesium sulfate as an adjuvant to intraperitoneal bupivacaine in pediatric elective unilateral laparoscopic inguinal herniorrhaphy.

## Methods

This prospective, randomized, double-blinded, controlled clinical trial was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 2013. Ethical approval was provided by our Institutional Review Board on March 30, 2016 and the trial was registered at ClinicalTrials.gov. Written informed consent was taken from the parents or legal guardians of all participating children.

This study was done in the period from August 2016 to September 2019. Children aged 1 to 6 years scheduled for elective unilateral laparoscopic inguinal hernia repair were included in this study. Children were excluded if their physical status according to the American Society of Anesthesiologists (ASA) was III or higher (i.e., patients with severe cardiac, respiratory, hepatic, renal, or central nervous system impairment), were on magnesium therapy, received analgesics before surgery, or had an allergy to the study drugs.

The enrolled children were randomly assigned through a computer-generated random number table (www.random.org), by an anesthetist not involved in the study into three equal groups (n = 35).

Group D received 1 $\mu g.kg^{-1}$ of dexmedetomidine, Group M received 30 $mg.kg^{-1}$ of magnesium sulfate while Group C received normal saline. All the tested drugs were diluted to the volume of 10 mL using normal saline. Before peritoneal insufflation, 2 $mg.kg^{-1}$ bupivacaine 0.5% were instilled into the peritoneal cavity followed by the prepared diluted tested drug in a separate syringe.

On the day of surgery, the group into which children were allocated was revealed via a sealed envelope to an unblinded anesthetist who prepared and diluted the study drugs to a volume of 10 mL using normal saline in identical sterile syringes labeled with the randomly assigned numbers.

The surgeons, anesthesiologists, medical staff in the operating room, the children and their parents or guardians, Postanesthesia Care Unit (PACU) nurses, and ward nurses were blinded to the treatment group.

No premedication was used. A standardized anesthesia protocol was applied to all children. All children were connected to electrocardiography, noninvasive blood pressure, pulse oximetry, and thermometer for routine basic monitoring, and anesthesia was induced via a face mask using 8% sevoflurane in 100% oxygen. An intravenous cannula was inserted and an infusion of dextrose 5% in 0.45 NaCl was begun at 4–6 $mL.kg^{-1}.h^{-1}$. Anesthesia induction was completed with intravenous (IV) fentanyl 1 $\mu g.kg^{-1}$, propofol 2 $mg.kg^{-1}$, and cisatracurium 0.15 $mg.kg^{-1}$. After 3 minutes the trachea was intubated, and pressure-controlled ventilation was used to maintain the value of end-tidal $CO_2$ within a normal range (35–45 mmHg). Anesthesia was maintained with 2–3% sevoflurane in 100% oxygen, IV cisatracurium 0.03 $mg.kg^{-1}$, and IV fentanyl boluses 1–2 $\mu g.kg^{-1}$ were titrated to maintain the changes in heart rate and noninvasive mean arterial blood pressure within 20% of basal values.

All enrolled children received IV paracetamol 15 $mg.kg^{-1}$ before starting the surgery. The standardized prophylactic antiemetic was IV granisetron 40 $\mu g.kg^{-1}$.

In all groups, laparoscopic surgery was done according to the standard surgical protocol. After the primary trocar was placed through a periumbilical incision, intraperitoneal instillation of 2 $mg.kg^{-1}$ bupivacaine 0.5% followed by the diluted study drugs into the abdominal cavity was performed through the primary trocar outlet. Instillation was performed toward the undersurface of the diaphragm and the patients were shifted to the Trendelenburg position for 5 minutes before returning the operating table to the zero position. Then pneumoperitoneum was performed using non-humidified and non-heated $CO_2$, with the intra-abdominal pressure maintained around 10 mmHg, and a classical surgical technique was started.

After termination of the surgical procedure, the surgeon removed trocars, and $CO_2$ was cleared completely from the peritoneal cavity by manual compression of the abdomen. Sevoflurane was discontinued and residual muscle paralysis was reversed with 0.05 mg.kg$^{-1}$ neostigmine and 0.02 mg.kg$^{-1}$ atropine, and extubation of the trachea was done in the left lateral position with the head down.

In the PACU, all children were connected to standard monitoring. Modified Aldrete Score was evaluated every 5 minutes and when children achieved an Aldrete score of 9 or higher they were ready for discharge to the intermediate care unit.

## Data collection

Clinical data of participating children, surgery time, and anesthesia time were recorded.

Our primary outcome variable was the intensity of pain following surgery. It was assessed by parents or guardians of participants through the Face, Legs, Activity, Cry, and Consolability (FLACC, 0–10) pain score, where 0 = no pain and 10 = the worst possible pain[8], after explaining the aim and the way to use it to them.[9]

The evaluation of the FLACC scores began immediately after the children were admitted to the PACU ($T_0$) and then at 1 h ($T_1$), 2 h ($T_2$), 4 h ($T_4$), 6 h ($T_6$), 8 h ($T_8$), 12 h ($T_{12}$), 18 h ($T_{18}$), 24h ($T_{24}$), and 48 h ($T_{48}$) thereafter.

Paracetamol 15 mg.kg$^{-1}$ IV was given as a rescue analgesic when the FLACC pain score was > 3 and then every 6 h until the end of the study. Thirty minutes after the first paracetamol dose, if the FLACC score was still > 3, IV fentanyl 0.5 $\mu$g.kg$^{-1}$ was administered. Time to a first analgesic request and total dose of rescue analgesia in the first 48 hours was recorded.

The number of children who experienced an emetic episode (defined as a single vomit or retch, or any number of continuous vomits or retches separated by the absence of both vomiting and retching for at least 3 minutes)[9], times until first flatus and the first passage of stool during the first 48 h postoperative were recorded by child's parent or guardian.

The incidence of other adverse effects, including hypotension and bradycardia (defined by the reduction of more than 20% of the baseline mean arterial pressure or heart rate, respectively), respiratory depression, sedation, and urinary retention were controlled and recorded.

The degrees of children's functional limitation were evaluated by their parents (the secondary outcome variable) through the Functional Activity Score (FAS) whereas; (A = no limitation; B = mild limitation; and C = severe limitation)[10] at 6, 12, 18, 24, and 48 hours postoperative, until full functional recovery was achieved. The FAS measures the degree to which children return to their usual activities after surgery.[10]

Parents' satisfaction was assessed by the four-point Likert scale (1 = excellent; 2 = good; 3 = fair; and 4 = poor).

Children were hospitalized for follow-up for 48 h after surgery and were discharged from the hospital, when they were capable of drinking, urination, walking, and after recovery of bowel function.

## Sample size calculation and statistical analysis

Our primary outcome variable was the intensity of pain following surgery evaluated by the FLACC pain score. Sample size calculation was based on a previous study[9], with the assumption that there is a true difference of 2.0 in mean FLACC scores at 2 h after surgery among the groups. Assuming a standard deviation of 2.0, with a type I error of 0.05 and power of 90%. A sample size of 29 patients in each group was required. Hence, 35 children per group were then enrolled to compensate for possible protocol violations.

The Kolmogorov-Smirnov test was used for data normality.

Continuous variables were analyzed with analysis of variance (ANOVA) or the Mann-Whitney U-test as appropriate. The $\chi 2$ test or Fisher's exact test was applied for analyzing categorical variables as appropriate. All data are presented as mean (SD), or number (percentage) as appropriate. A $p$-value < 0.05 was considered as significant.

Statistical analyses were performed by computerized statistical software (SPSS, version 21; SPSS, Chicago, Ill).

# Results

One hundred and five patients were enrolled for eligibility, and eight patients were excluded from the study (Fig. 1). There were no significant differences among all groups regarding patients' characteristics and clinical data (Table 1).

The pain scores were comparable among the three studied groups in the first four hours after surgery ($p > 0.05$). However, they were significantly higher in Group C than in the other two groups later on ($p < 0.001$) (Fig. 2). No significant differences were found between both Groups D and M in mean FLACC scores throughout the study period ($p > 0.05$) (Fig. 2).

Time to first paracetamol dose was significantly earlier and the total dose of administered paracetamol was significantly higher in Group C with no children in Groups D and M requiring paracetamol administration. None of the children in all groups required intraoperative or postoperative fentanyl ($\mu$g) administration (Table 1).

The incidence of emetic episodes, time to first flatus (h), and time to first stool (h) after surgery were comparable in three studied groups as illustrated in Table 2.

No patient experienced bradycardia, hypotension, respiratory depression, sedation yielding to delayed hospital discharge, or urine retention needing urethral catheterization in three groups.

Children in Group C returned to full functional activity earlier during the first 6 h postoperative than Groups D and M. By the 12$^{th}$ postoperative hour, all children in Groups D and M had returned to normal activity with no residual functional limitation (Table 3).

The parents' satisfaction scores with analgesia were significantly higher in Groups D and M than in Group C, with no difference between Groups D and M ($p$ = 0.420) (Table 3).

All the children studied were successfully discharged home 48 h after the operation.

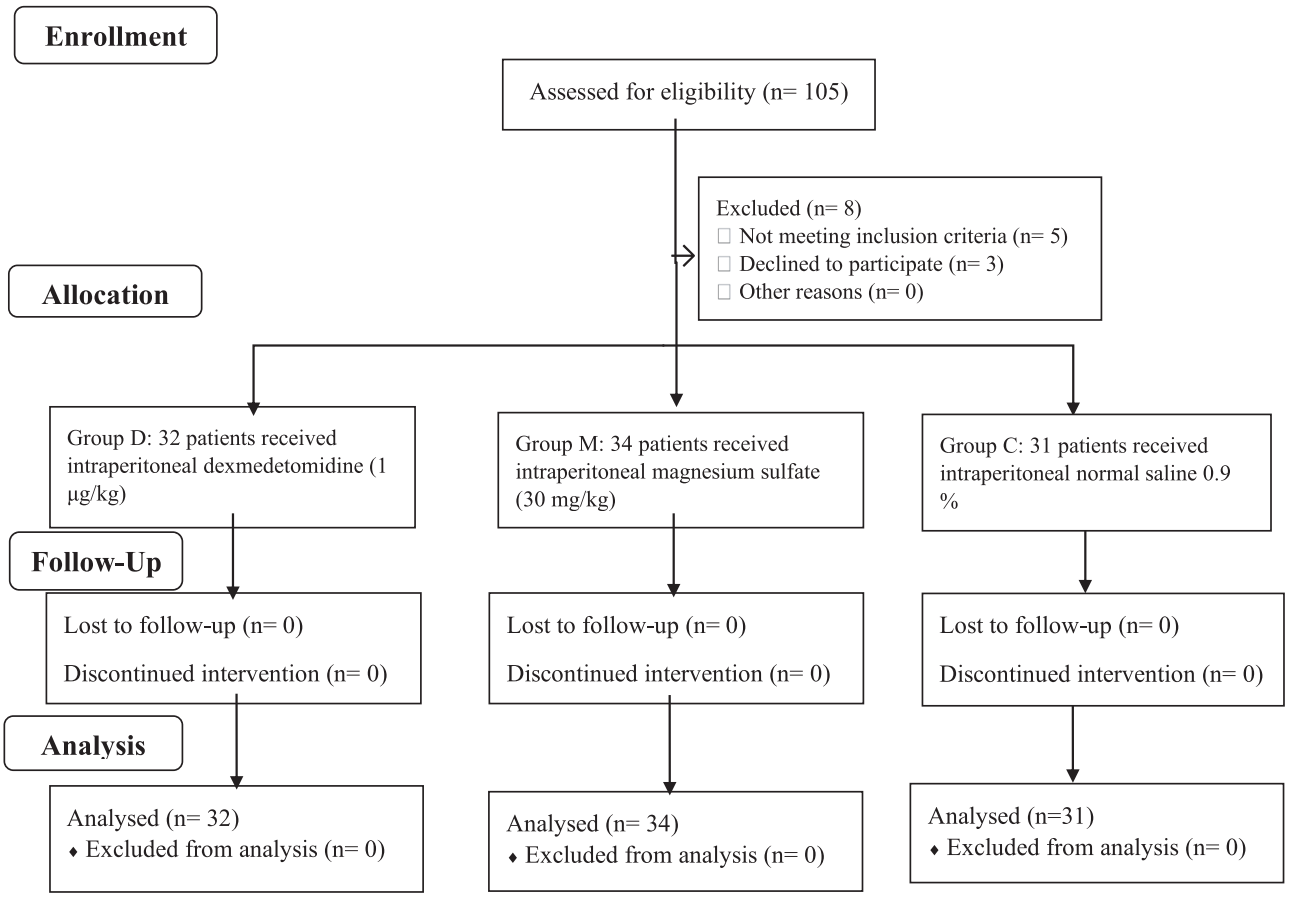


**Figure 1** CONSORT flow diagram of participants.

## Discussion

The present study demonstrated that the preemptive IP administration of bupivacaine 0.5% plus dexmedetomidine or magnesium sulfate in children scheduled for elective unilateral laparoscopic inguinal hernia repair provided greater analgesic efficacy compared to IP bupivacaine 0.5% alone with no differences in bowel function recovery and time to return to normal activity during the first 48 h postoperative.

Pediatric laparoscopic surgery has found increasing popularity all over the world as its use is safe even in neonates[4] and it allows rapid recovery[9] through effective, uncomplicated analgesia.[3]

**Table 1** Characteristics and clinical data of the three groups.

| | Group D (n = 32) | Group M (n = 34) | Group C (n = 31) | *p*-value |
|---|---|---|---|---|
| Age (years) | 3.9 (1.7) | 4.2 (1.4) | 3.8 (1.5) | 0.523 |
| Weight (kg) | 19.2 (5.5) | 16.9 (6.7) | 17.4 (6) | 0.283 |
| ASA class (I / II) | 20 (62.5)/ 12 (37.5) | 21 (61.8)/ 13 (38.2) | 22 (71)/ 9 (29) | 0.695 |
| Operation side (right/left) | 13 (40.6)/ 19 (59.4) | 15 (44.1)/ 19 (55.9) | 11 (35.5)/ 20 (64.5) | 0.776 |
| Duration of surgery (min) | 46.4 (8.9) | 42.7 (7.4) | 43.3 (7.1) | 0.115 |
| Duration of anesthesia (min) | 63.9 (7.6) | 65.1(6.3) | 62.5 (7) | 0.08 |
| Patients required intraoperative fentanyl ($\mu$g) | 0 (0) | 0 (0) | 0 (0) | – |
| Time to first paracetamol dose (h) | – | – | 8.97 (2.06) | <0.001 |
| Total dose of postoperative paracetamol consumption (mg) | 0 (0) | 0 (0) | 1850.81 (635.99) | <0.001 |
| Total dose of postoperative fentanyl consumption ($\mu$g) | 0 (0) | 0 (0) | 0 (0) | – |

Data are presented as mean (SD), or number of patients (%). A *p*-value < 0.05 was considered statistically significant. Group D, Dexmedetomidine group; Group M, Magnesium sulfate group; and Group C, Control group. ASA, American Society of Anesthesiologists.

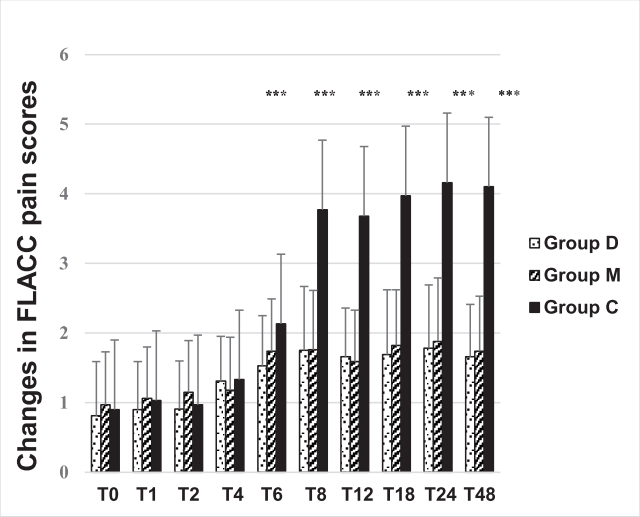


**Figure 2** Changes in FLACC pain scores in the three studied groups. Group D, Dexmedetomidine group; Group M, Magnesium sulfate group; and Group C, Control group. ***s indicates $p < 0.001$.

The exact mechanism of pain following laparoscopic surgery remains uncertain, and yet, rapid peritoneal distension, stretching of vessels and phrenic nerves, visceral handling, the existence of residual gas, and inflammatory biomarkers may be responsible for such pain.[4] Pain following laparoscopy is commonly presented by abdominal discomfort and shoulder tip pain in adults, while in pediatrics shoulder tip pain is less frequent.[1]

IP administration of local anesthetics and analgesics has been used recently to improve postoperative analgesia.[9] Tian et al. reported that IP ropivacaine is an effective method to control pain in toddlers undergoing laparoscopic herniorrhaphy.[9] Freilich et al. found that aerosolized bupivacaine given at the beginning of a robotic-assisted pyeloplasty surgery improved the quality of recovery.[11] Zanetta et al. reported that IP bupivacaine decreases opioid consumption after laparoscopic surgery in children.[12] Additionally, El Basha et al. found that IP levobupivacaine improved pain control after pediatric laparoscopic surgeries.[3]

Dexmedetomidine 1 $\mu g.kg^{-1}$ has been used recently intraperitoneally alone or combined with local anesthetics in adult laparoscopic surgeries because of its analgesic and sedative characters.[5,13,14]

Elnabtity and Ibrahim studied the effect of IP 1 $\mu g.kg^{-1}$ dexmedetomidine combined with 2 $mg.kg^{-1}$ bupivacaine 0.25% versus 2 $mg.kg^{-1}$ bupivacaine 0.25% alone at the end of the surgery, in children undergoing laparoscopic appendectomy. They reported reduced pain, opioid consumption, and hospital stay with no significant adverse events and with better overall parent satisfaction in the dexmedetomidine group.[6]

Dexmedetomidine induces analgesia by stimulation of 2A and 2C subtypes of $\alpha$2-adrenoceptors leading to the stimulation of descending medullispinal noradrenergic pathways or inhibition of the spinal sympathetic outflow at presynaptic ganglionic sites, reducing the release of C-fiber transmitters, and finally augmenting hyperpolarization of postsynaptic dorsal horn neurons.[15]

Magnesium sulfate ($MgSO_4$) has been used through several routes to provide analgesia[7,10] following laparoscopic surgeries.[16-18] It has been administered intraperitoneally combined with local anesthetics to reduce pain after laparoscopic cholecystectomy.[19] Actually, magnesium decreases calcium influx to cells, through non-competitive inhibition of the N-methyl-D-Aspartate (NMDA) receptors, which is vital in the neuronal signaling and pain processing in the central nervous system leading to inhibition of both somatic and visceral pain fibers.[20,21]

Further mechanisms of analgesia produced from IP instillation of local anesthetics and analgesics might be referred as blocking of peritoneal free afferent nerve endings plus the systemic absorption through the large peritoneal surface, as they could be detected in blood after 2 minutes from IP instillation.[6,9]

Nevertheless, the time of IP administration of the analgesic drug is still controversial. In our trial, we chose early IP administration although this analgesic technique was not used commonly in children[3] as some studies[22] reported that early IP administration of local anesthetics and analgesics at the beginning of laparoscopic surgery acts as preemptive analgesia, depressing central neural sensitization before the nociceptive stimulus triggers pain pathways allowing better postoperative analgesia compared with IP administration at the end of the surgery. However, those results were not corroborated by other studies.[23]

In the present study, children who had received preemptive IP dexmedetomidine and magnesium sulfate added to bupivacaine experienced prolonged pain free time with no need for rescue analgesics, without an increase in the incidence of adverse effects or delayed recovery from general anesthesia compared to those who received IP bupivacaine alone. We tried to keep the concentration of the IP administered local anesthetic the same in all patients by preparing it in a separate syringe and instilling it first in the peritoneal cavity before the tested drugs.

**Table 2** Postoperative emetic episodes and bowel function recovery time in the three studied groups.

| | Group D (n = 32) | Group M (n = 34) | Group C (n = 31) | *p*-value |
|---|---|---|---|---|
| Children with emetic episodes | 6 (18.8) | 7 (20.6) | 5 (16.1) | 0.898 |
| Time to first flatus (h) | 15.1 (1.3) | 15 (1) | 14.8 (1.3) | 0.715 |
| Time to first stool (h) | 20.3 (1.6) | 20.7 (1.7) | 20 (1.9) | 0.230 |

Data are presented as mean (SD) and number of patients (%). A *p*-value < 0.05 was considered statistically significant. Group D, dexmedetomidine group; Group M, magnesium sulfate group; and Group C, control group.

**Table 3** Functional activity scores of children and parent satisfaction.

| | Group D (n = 32) | Group M (n = 34) | Group C (n = 31) | *p*-value |
|---|---|---|---|---|
| Functional activity score at 6 h | | | | 0.084 |
| No limitation | 27 (84.4) | 30 (88.2) | 31 (100) | |
| Mild limitation | 5 (15.6) | 4 (11.8) | 0 (0) | |
| Severe limitation | 0 (0) | 0 (0) | 0 (0) | |
| Functional activity score at 12 h | | | | – |
| No limitation | 32 (100) | 34 (100) | 31 (100) | |
| Mild limitation | 0 (0) | 0 (0) | 0 (0) | |
| Severe limitation | 0 (0) | 0 (0) | 0 (0) | |
| Functional activity score at 18 h | | | | – |
| No limitation | 32 (100) | 34 (100) | 31 (100) | |
| Mild limitation | 0 (0) | 0 (0) | 0 (0) | |
| Severe limitation | 0 (0) | 0 (0) | 0 (0) | |
| Functional activity score at 24 h | | | | – |
| No limitation | 32(100) | 34 (100) | 31 (100) | |
| Mild limitation | 0 (0) | 0 (0) | 0 (0) | |
| Severe limitation | 0 (0) | 0 (0) | 0 (0) | |
| Functional activity score at 48 h | | | | – |
| No limitation | 32 (100) | 34 (100) | 31 (100) | |
| Mild limitation | 0 (0) | 0 (0) | 0 (0) | |
| Severe limitation | 0 (0) | 0 (0) | 0 (0) | |
| Parent satisfaction | | | | 0.026 |
| Excellent | 27 (84.4) | 26 (76.5) | 17(54.8) | |
| Good | 5 (15.6) | 8 (23.5) | 14 (45.2) | |
| Fair | 0 (0) | 0 (0) | 0 (0) | |
| Poor | 0 (0) | 0 (0) | 0 (0) | |

Data are expressed as number (%). A $p$-value $< 0.05$ was considered statistically significant. Group D, Dexmedetomidine group; Group M, Magnesium sulfate group; and Group C, Control group.

As a rule, effective postoperative analgesia is essential for good recovery after surgery.[24] Tian et al. found that IP ropivacaine could hasten bowel function recovery and reduce postoperative vomiting in toddlers in the same way as that intra and postoperative administration of epidural local anesthesia improves bowel function.[9] In the current study, children in three studied groups had comparable postoperative bowel recovery, emetic episodes, and usual activity recovery.

Wound cosmoses and time to return to full activity are additional parent and/or caregiver concerns. Gause et al. reported 2.5 days as the period until children return to full activity after unilateral laparoscopic inguinal hernia repair.[25] In our trial, the return to normal full activity was similar in all studied children. We believed that good effective analgesia in Group D and M with faster return to activity augments parent satisfaction with the used analgesic drugs.

This study was limited by the lack of sufficient data about the ideal effective dose of IP dexmedetomidine, and magnesium sulfate required for augmenting analgesia in children. Further studies are recommended to investigate different doses of both drugs whether given separately or combined to evaluate their optimal analgesic efficacy.

In conclusion, we have found that IP dexmedetomidine or magnesium sulfate added to bupivacaine before peritoneal insufflation could be an ideal safe effective way for pain control in children after laparoscopic inguinal herniorrhaphy with significant reduction of analgesic consumption, good recovery of gastrointestinal function, and with a faster return to normal usual activity. We suggest that dexmedetomidine given together with magnesium sulfate as an adjuvant to IP bupivacaine could be beneficial.

## Trial registration

ClinicalTrials.gov (NCT02820610).

## Institutional review board registration

IRB no: 17300153.

## Conflicts of interest

The authors declare no conflicts of interest. There were no fundings.

## CRediT authorship contribution statement

**Seham Mohamed Moeen:** Conceptualization, Methodology, Writing – original draft. **Ola Mahmoud Wahba:** Visualization, Formal analysis. **Ahmed Mohamed Mandour:**

Investigation, Data curation. **Noha Abdel Ghany:** Investigation, Data curation. **Mohamed AbdelKader Osman:** Conceptualization, Methodology, Investigation, Supervision. **Tarek Abdelazeem Sabra:** Methodology, Investigation. **Mohammed Hamada Takrouney:** Investigation, Data curation. **Ahmed Mohamed Moeen:** Conceptualization, Methodology, Supervision, Writing — original draft.

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