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The use of postoperative intravenous patient-controlled analgesia with low dose versus standard dose Morphine in children undergoing pelvic-abdominal exploration surgery

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Keywords

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Abstract:

Background: Patient-controlled analgesia is an effective method used to alleviate pain in children. Morphine is the standard opium-based analgesic used; however, its use is usually associated with adverse effects that may be severe. This study was carried out to evaluate the efficacy and safety of low-dose Morphine in controlling acute pain in children undergoing exploration surgery. **Methods:** This study was conducted at Beni-Suef University Hospital on 46 patients. The patients were divided randomly into two equal groups: The standard dose morphine group: Which received 0.05 mg morphine /kg/dose, and the low dose morphine group: Which received 0.01 mg morphine /kg/dose. During post-operative follow-up, the pain was assessed using VAS and VRS in addition to POSS sedation score and follow-up of adverse events. **Results:** There was no significant difference between the groups' mean VAS and VRS pain scores and their categories. However, the side

effects of Morphine, like PONV and respiratory depression, were significantly decreased in the low-dose morphine group. **Conclusions:** The present study shows that both the low dose and the standard dose of Morphine could effectively control the post-operative pain in patients-controlled analgesia of children undergoing pelvic-abdominal exploration surgeries with a lower incidence of postoperative complications in the low-dose morphine group.

1. Introduction:

Pediatricians, pediatric subspecialists, surgeons, and anesthesiologists have all taken an avid interest in the issue of perioperative pain management for children for quite some time. Our primary focus is on the perioperative period, during which we treat children and strive to do it ethically and professionally (1).

Adequate intra- and post-operative analgesia will alter the stress response and minimize morbidity and death. Recognizing, reducing, preventing, promptly bringing under control, and continuing even after the release from the hospital are some of the goals of the many distinct and varied practical techniques for post-operative pain management that have been developed and implemented in recent years. Post-operative pain treatment has been improved using various procedures and drugs supplied by different routes (2).

Opioid and non-opioid medications are the most prevalent forms of pharmacologic therapy after surgery. Opioid medications are effective, but their widespread use is limited by their substantial and undesirable side effects. Although respiratory depression brought on by opioids is potentially fatal and must be closely monitored, nausea, constipation or post-operative ileus, drowsiness, and itching are the most often reported side effects. Long-term usage is linked to tolerance and dependence, which may lead to addiction (3).

Since the 1970s, patient-controlled analgesia (PCA) has been used to treat a wide variety of pain, including both acute (such as post-operative or labor pain) and chronic (such as palliative care or cancer pain). By

letting the patient self-administer a predefined bolus dosage of medicine on-demand at the push of a button, PCA aims to effectively provide pain relief at a dose and schedule desired by the patient. Opioid boluses may be given alone or with a steady infusion through a specialized pump (4).

This study aimed to evaluate the efficacy and safety of low-dose Morphine in controlling acute pain in children undergoing exploration surgery.

2. Methods:

This randomized controlled trial study was conducted at Beni-Suef university hospital from October 2021 to March 2022. The study was performed on 46 patients ASA I & II of both sexes aged between 8 and 10 years, scheduled for exploration surgery under general anesthesia. Patients with a history of allergy to Morphine, mental disorders, or unsuitable for extubation were excluded from the study.

The patients were randomly assigned into one of two equal groups (23 patients each); Group A (control group): Receiving 0.05 mg morphine /kg, and Group B (low dose morphine group): Receiving 0.01 mg morphine /kg.

Anesthetic Technique:

For the anesthetic, we used the conventional procedure:

With venous access, children were given propofol (2.5-2.75 mg/kg) and fentanyl (2 microgram/kg) intravenously to produce general anesthesia. Induction with sevoflurane increasing concentration from 6 percent to 8 percent in 100 percent oxygen and muscle relaxant atracurium (0.5mg /kg) for elective procedures or suxamethonium (1mg /kg) in emergency surgeries for children for whom preoperative venous access was not possible.

Heart rate (HR), noninvasive blood pressure, oxygen saturation (SpO2), continuous electrocardiography, end-tidal carbon dioxide, and body temperature were all measured and recorded for each kid. After that, atracurium (0.1mg/k) is administered every 30 minutes to keep the patient under anesthesia. Sevoflurane (2% minimum alveolar concentration) and 100% air and oxygen are used for maintenance. At the end of the operation, the muscle relaxant effect of atracurium was reversed by using anti-choline esterase (neostigmine (0.07mg/kg) with atropine(0.02mg/kg). In group (A), a PCA pump with study solution is prepared by using (a 100 ml PCA pump where 6 mg

morphine is added to 100 ml normal saline 0.9%, then every 1 ml of the solution contains 60µg morphine) introduced to the patient post-operative upon arrival to PICU, while in group (B) a PCA with the Study solutions is prepared by using (a 100 ml PCA pump where a 1.2 mg morphine is added to 100 ml normal saline then every 1ml of solutions contains 12µg morphine) continuous infusion for 48 h post-operative.

Assessment parameters and follow-up:

The data recorded by anesthesia residents unaware of the study protocol included age in (years), weight(in kg), sex (Male /Female), ASA physical status (I/II), and the duration of surgery in (min). Postoperatively, heart rate (HR) (beat /min) and mean arterial blood pressure (MAP) in (mmHg) were recorded at 1, 2, 6, 12, 24, 36, and 48h.

Post-operative assessment of pain through (VAS) visual analog scale and (VRS) was done at rest and at movement also, at 1, 2, 6, 12, 24, 36, and 48h. Post-operative sedation assessment was assessed using the Pasero opioid-induced sedation scale **(5).**

After surgery, the patient's respiration rate was measured, and naloxone (0.1 mg/kg) was administered if it was fewer than 10 breaths per minute. Staff nurses collected yes/no data on post-operative nausea and vomiting (PONV), defined as the presence of nausea, itching, or vomiting at 1, 2, 6, 12, 24, 36, and 48 hours. Ondansetron was given if vomiting occurred at 0.2 mg/kg with a maximum single IV dose of 8 mg. The amount could be repeated after 4 hours if needed **(6).**

Data Analysis and Statistics:

Pearson's Chi-square test for independence of attributes/exact Fisher's test as applicable was used to compare groups based on categorical variables represented as numbers of patients or percentages of patients. After computing their means, medians, and standard deviations, we used the Mann-Whitney U-test to compare continuous variables across groups. The study was conducted using SPSS 20 (IBM). A significant level of P less than 0.05 was assumed to indicate a statistically significant result.

Ethical considerations:

The study was approved by the research ethics committee of the faculty of medicine of Beni-Suef University, number FNBSUREC/07092021/Mohamed. All data was anonymous, and the study was done according to the Helsinki standards.

3. Results:

This study was carried out at Beni-Suef university hospital on 46 patients of both sexes. Patients were randomly assigned into one of two equal groups (23 patients each), group (A), in which patients received the standard dose of Morphine, and group (B), in which patients received low-dose Morphine. All patients completed the study as shown by the flow diagram:

Flow Diagram:

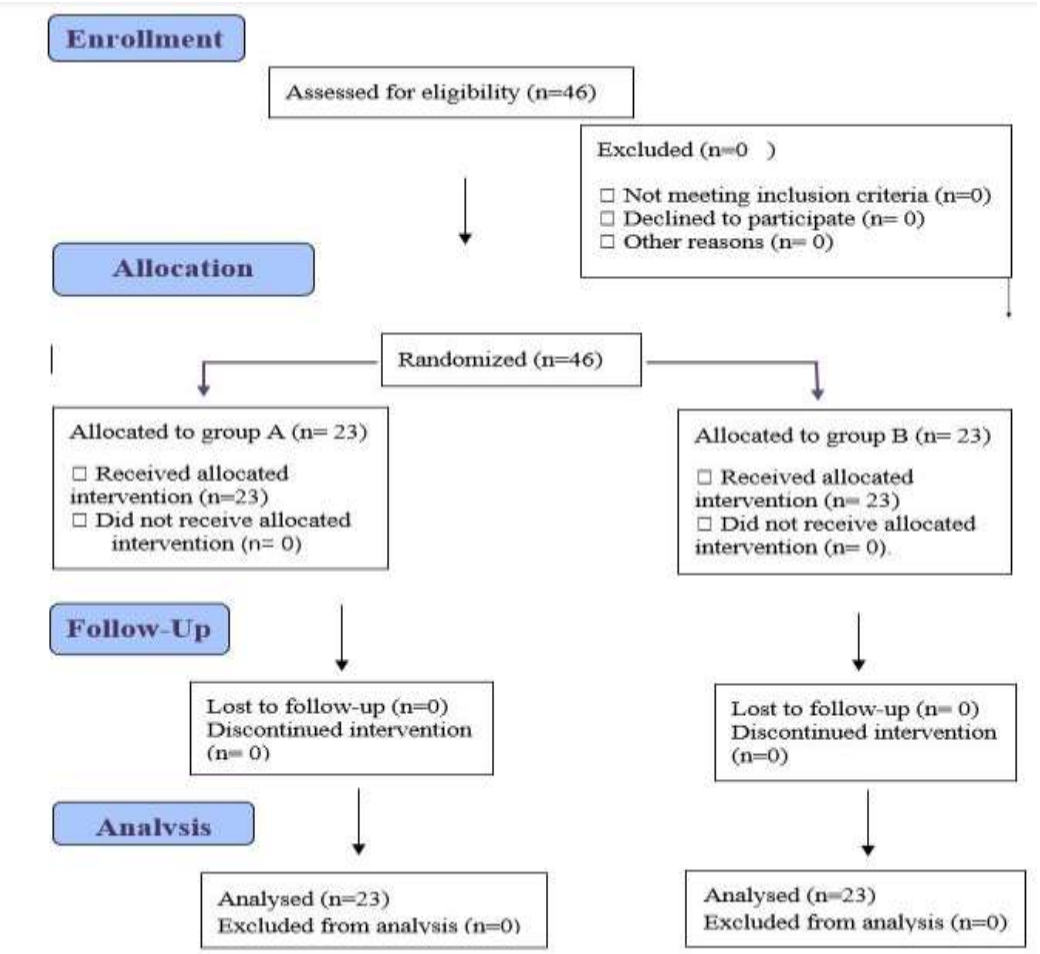

Table (1): Baseline characteristics of the studied patients.

Items	Standard dose group (no=23)	Low dose group (no=23)	P-value
Age in years (mean±SD)	8.8±0.8	9.1±0.8	0.180
Sex Male Female	 16(69.6%) 7(30.4%)	 13(56.5%) 10(43.5%)	0.359
Weight in kg	28.1±3.4	29.2±3.8	0.298
Duration of surgery in min	1.9±0.3	2±0.4	0.187
ASA physical status **I**	23(100%)	23(100%)	-----

This table showed no significant difference between the studied groups regarding the baseline characteristics (P-value >0.05).

Table (2): Comparison between the studied patients regarding the heart rate at different times.

Heart rate (beat /min) (mean±SD)	Standard dose group (no=23)	Low dose group (no=23)	P-value
1 hour	116±7	117±7	0.445
2 hours	112±7	113±6	0.670
6 hours	107±7	108±7	0.732
12 hours	103±7	103±6	0.765
24 hours	98±8	98±6	0.967
36 hours	94±8	94±6	0.888
48 hours	89±9	88±7	0.817
P-value within time in each group	<0.001*	<0.001*	

**P-value is significant*

This table showed no significant difference between the studied groups regarding the heart rate at 1, 2, 6, 12, 24, 36, and 48 hours post-operative (P-value >0.05). In both groups, the heart rate decreased significantly from 1 to 2, 2 to 6, 6 to 12, 12 to 24, 24 to 36, and 36 to 48 hours (P-value<0.001).

Table (3): Comparison between the studied patients regarding the mean arterial blood pressure at different times.

MAP (mmHg) (mean±SD)	Standard dose group (no=23)	Low dose group (no=23)	P-value
1 hour	103.6±3.1	104.7±2.4	0.194
2 hours	101.4±2.9	102.5±2.8	0.195
6 hours	97.9±3.1	99.6±2.7	0.065
12 hours	95.3±3.2	96.9±3.6	0.100
24 hours	93.1±3.3	94.3±3.3	0.239
36 hours	89.9±3.2	91.7±3.7	0.076
48 hours	88.4±4.4	89.4±3.4	0.440
P-value within time in each group	<0.001*	<0.001*	

**P-value is significant*

This table showed no significant difference between the studied groups regarding the mean arterial blood pressure at 1, 2, 6, 12, 24, 36, and 48 hours post-operative (P-value >0.05). The MAP decreased significantly in both groups from 1 to 2, 2 to 6, 6 to 12, 12 to 24, 24 to 36, and 36 to 48 hours (P-value<0.001).

Table (4): Comparison between the studied patients regarding the VAS score postoperatively and the need for an IV bolus of Morphine.

VAS (mean±SD)	Standard dose group (no=23)	Low dose group (no=23)	P-value
VAS at 1 hour	3.3±0.9	3.5±0.9	0.347
VAS 2 hours	2.8±0.9	2.7±0.8	0.730
VAS 6 rest	2.5±0.8	2.4±1	0.649
VAS 6 movement	4.1±1.2	4.3±1.3	0.566
VAS 12 rest	1.9±0.8	1.7±0.8	0.375
VAS 12 movement	3.1±1.1	3.2±1.3	0.903
VAS 24 rest	1.3±0.4	1.3±0.5	0.570
VAS 24 movement	2.3±1.1	2.1±1.1	0.689
VAS 36 rest	0.7±0.3	0.7±0.3	1.000
VAS 36 movement	1.6±0.7	1.4±0.7	0.420
VAS 48 rest	0.3±0.2	0.3±0.2	0.760
VAS 48 movement	0.9±0.6	1±0.5	0.626
Need for IV bolus of Morphine	3 (13.0%)	4 (17.4%)	0.681

This table showed no significant difference between the studied groups regarding the mean VAS at different times at rest and movement at different times (P-value>0.05). Also, there was no significant difference between both groups regarding the need for IV morphine bolus.

Table (5): Comparison between the studied patients regarding the POSS and VRS score postoperatively.

	Standard dose group (no=23)	**Low dose group (no=23)**	**P-value**
POSS	1.3±0.4	1.1±0.3	0.275
VRS	1.5±0.7	1.7±0.7	0.393

This table showed no significant difference between the studied groups regarding the mean POSS and VRS at different times at rest and movement (P-value>0.05).

Table (6): Comparison between the studied patients regarding post-operative nausea and vomiting at different times.

PONV	**Standard dose group (no=23)**	**Low dose group (no=23)**	**P-value**
1 hour	5(21.7%)	5(21.7%)	>0.999
2 hours	7(30.4%)	3(13.0%)	0.153
6 hours	8(34.8%)	2(8.7%)	0.032*
12 hours	9(39.1%)	3(13%)	0.044*
24 hours	8(34.8%)	2(8.7%)	0.032*
36 hours	5(21.7%)	0(0.0%)	0.049*
48 hours	1(4.3%)	1(4.3%)	>0.999

This table showed a significant difference between the studied groups regarding the occurrence of PONV (P-value <0.05) at 6,12,24, and 36 hours.

Table (7): Comparison between the studied patients regarding the occurrence of respiratory distress.

RD	**Standard dose group (no=23)**	**Low dose group (no=23)**	**P-value**
Post operative	7(30.4%)	1(4.3%)	0.047*

**P-value is significant*

This table showed that there was a significant difference between the studied groups regarding the occurrence of respiratory distress (P-value <0.05).

4. Discussion:

Patient satisfaction and good results can only be achieved via successful pain treatment. Exposure to pain for an extended period causes a physiological reaction, including changes in vital signs and the production of stress hormones, which slows the body's natural healing process and lowers the overall quality of life. Some people wrongly believe that newborns don't feel pain. In contrast, others think behavioral adjustments are the best way to deal with children's suffering. Managing children's pain is essential since it may affect their growth and development (7).

Epidural local anesthetics, intrathecal opioids, and systemic opioids via patient-controlled analgesia are only a few of the many analgesic procedures documented for use after surgery (PCA). Most postoperative analgesia procedures aim to lessen the patient's reliance on opioid pain relievers because of the risk of adverse effects such as nausea and vomiting, respiratory depression, and a slowed recovery of bowel function (8).

This study showed no significant difference between the groups regarding the mean VAS and VRS scores of pain and their categories. Also, the need for IV morphine bolus didn't differ significantly between both groups. These results indicate that both the low dose and the standard dose of Morphine had the same efficacy in controlling pain at different times of follow-up postoperatively.

The findings of this research are consistent with those of Goncharova et al. (2020), who compared the clinical efficacy and safety of tramadol with low-dose Morphine for treating pain syndromes in children who have had chemotherapy or a hematopoietic stem cell transplant. They discovered that the efficacy and the incidence of adverse effects were similar for patients treated with regular and low-dose Morphine (9).

In their study on multimodal pain management in pediatric spine deformity surgery, Shah et al. (2020) found that intravenous opioids were the primary medication for pain relief, and while there is no consensus on what dose of opioid is the optimum dose to control post-operative pain, managing pain while minimizing opioid administration is a ubiquitous goal to minimize adverse effects (10).

Similarly, Chertin et al. (2015) showed that even 0.01 mg/kg of Morphine may offer a tolerable degree of postoperative pain management in their research regarding the

low dosages of Morphine in children scheduled for kidney surgery (11).

On the other hand, **DiGiusto *et al.* (2014)** studied the efficacy of Morphine in patients-controlled analgesia in pediatrics. They reported that about (47.1%) were switched from Morphine to hydromorphone due to ineffective pain control and high rates of side effects (12).

ÖZALEVLI *et al.*, (2005) compared the efficacy of PCA with Morphine at a dose of 0.01 mg/kg to PCA with tramadol and recorded high pain scores in morphine groups with high rates for the demand of the rescue analgesia (13).

Also, the randomized study performed by **Doyle *et al.*, (1994)** comparing PCA morphine with doses of 0.01 and 0.02 mg/kg) in children, the lower dose was associated with higher pain scores (14).

The mean age of patients who received the standard dose of Morphine was 8.8±0.8 years, and most were male (69.6%). Also, patients who received low-dose morphine had an average age of 9.1±0.8 years, and most of them were males (56.5%). Their average weight was 28.1±3.4 kg for patients with a standard dose and 29.2±3.8 kg for patients with low dose morphine. All patients in both groups were ASA physical status I, and the mean duration of surgery was 1.9±0.3 hours in patients with standard dose and 2±0.4 in patients with low dose morphine. There was no significant difference between the studied groups regarding the baseline characteristics.

The study of **Ousley *et al.*, (2016)** about patient- controlled analgesia after appendicectomy in children showed that the mean age of patients was 12±3, and most were males (male/female) 308/233. Their average weight was 47±16 kg, and the mean surgery duration was 56±25 minutes. The longer duration time of our study may be due to the different types of abdominal surgery (15).

Also, the study of **Freedman-Weiss *et al.* (2020)** about opioid prescription after pediatric appendectomy showed that the mean age of patients was 12.1±4.1years and was primarily male (69.9%) (16).

Our study found that the heart rate and mean arterial blood pressure were within normal range in both groups. Higher values were immediate postoperatively and decreased significantly in each group with control of pain after the introduction of the PCA. Neither groups had significant differences regarding the heart rate and MAP.

Matching with our results was the study of **Karbasy *et al.* (2020)** about patient-controlled analgesia for abdominal surgery using Morphine or Morphine plus nitroglycerine. They reported that in the morphine group, the mean heart rate decreased significantly from 82.15 ± 15.02 beats/min immediately after surgery to 76.06 ± 9.91 beats/min after 24 hours. Also, the mean systolic blood pressure decreased significantly from 130.93 ± 18.16 mmHg immediately after surgery to 118.86 ± 20.19 mmHg after 24 hours, and the mean diastolic blood pressure decreased from 80.1 ± 12.45 immediately after surgery to 75 ± 10.66 mmHg after 24 hours (17).

Increased heart rate and blood pressure, tachypnea, and decreased oxygen saturation can be physiological indicators of pain **(18).** This could explain the results of our study in which the highest blood pressure and heart rate was within the 1st hour postoperatively, and with the introduction of Morphine using PCA, the pain was controlled, and the vital signs decreased gradually.

Post-operative assessment of sedation was performed using the POSS score. Our study found that both doses had a minimal sedation effect. The mean POSS scores were not significantly different between the studied groups.

Also, Donado et al. (2019) study about patient-controlled analgesia in a pediatric hospital between 2002 and 2016. They reported that there were 16,806 PCA administrations, and only Two patients were transferred to the ICU for PCA-related adverse effects like sedation, bradypnea, and desaturations (19).

There are three kinds of classical opioid receptors that opioid analgesics target: the mu, delta, and kappa receptors. This class of receptors is known as G-protein coupled receptors. Subsequent activation triggers a cascade of events within the cell, including suppressing adenylyl cyclase, attenuating voltage-gated Ca2+ channels, and activating K+ channels, all of which work together to reduce neuronal excitability by preventing the release of neurotransmitters at the synapse. Opioid-related adverse effects, such as drowsiness, nausea, vomiting, constipation, respiratory depression, tolerance, dependency, and abuse potential, are caused by receptor activation (20).

Regarding the post-operative side effects of Morphine, this study showed the highest rate of PONV in the standard dose group compared to the low dose group. There

was a significant difference between the studied groups regarding the occurrence of PONV at 6,12,24, and 36 hours. Higher rates were observed throughout all post-operative follow-up periods in the standard dose group. Regarding respiratory depression, higher rates were also observed in the standard dose group. There was a significant difference between the studied groups regarding the occurrence of respiratory distress.

The study of **Cohen *et al.* (2017)** about postoperative pain control in pediatric patients undergoing posterior spinal fusion showed that the use of Morphine was associated with nausea in (26%) of cases, emesis in (15%) and respiratory depression (15%) of cases (21).

Furthermore, Abou-Karam et al. (2015) found that the most common negative effects of morphine usage following pediatric surgery were sleepiness (18%), nausea and vomiting (9%), and constipation (17%), as reported by the legal guardians (15 percent) (22).

According to McNicol et al. (2015), the major side effect of PCA treatment is respiratory depression caused by opioids. A respiratory arrest may occur, despite the modest prevalence (2.3%) (23).

Post-operative nausea and vomiting are more common when opioids are used for pain management after surgery. This impact is dose-dependent and changes depending on the nature of the operation and the anesthetic used. Preventing opioid-related vomiting and nausea requires reducing the dosage of these drugs whenever feasible (1).

Research conducted by **Sadhasivam et al., 2015** on opioid-related side effects in pediatric surgical patients found that higher morphine dosages led to more respiratory depression (RD), postoperative nausea and vomiting (PONV), and more extended hospital stays as a result of these complications (24).

Unlike our results, the study of **Maxwell *et al.* (2005)** reported higher rates of side effects among the patients who received Morphine alone via the PCA at a dose of 0.01 mg/kg. The incidence and severity of pruritus were (77%), the severity of nausea and vomiting (70% and 35%) respectively (25).

Nausea and vomiting caused by opioids are common, especially at the start of treatment or after an increase in dose. Stimulation of the chemoreceptor trigger zone (CTZ), the vestibular apparatus (VA), and receptors in the gastrointestinal tract

have all been hypothesized to have a significant role. At the same time, the precise mechanisms remain unclear (20).

5. Conclusions:

The present study shows that both the low dose and the standard dose of Morphine could effectively control the post-operative pain in patients-controlled analgesia of children undergoing pelvic-abdominal exploration surgeries with a lower incidence of postoperative complications in the low dose morphine group.

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