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Role of adding dexmedetomidine, ketamine, and magnesium sulphate to caudal block as preemptive analgesia in hypospadias repair in pediatrics: A randomized double-blinded prospective trial

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ABSTRACT

Background: The caudal block (CB) is a quick, and safe approach for pediatric analgesia. Numerous adjuvants were added to extend the analgesia duration. Our trial aims to evaluate the significance of CB by adding dexmedetomidine, ketamine, and $MgSO_4$ to bupivacaine to provide postoperative analgesia in children undergoing hypospadias repair.

Methods: This randomized double-blinded study was performed on 75 male children undergoing hypospadias repair under CB. Patients were randomized into three equal groups. All received 0.5 ml/kg bupivacaine 0.25% caudally plus 1 ml volume containing either dexmedetomidine 1 µg/kg in Group D, 0.5 mg/kg ketamine in Group K or 50 mg of $MgSO_4$ in Group M.

Results: Time of first rescue analgesia was significantly delayed in group D (8.2 ± 3.45 h) than in group K (5.8 ± 2.85 h) and group M (3.7 ± 1.51 h) (*P* value = 0.007 vs. <0.001) and in group K than in group M (*P* value = 0.027). Heart rate and mean arterial blood pressure measurements after block and 60 min intraoperative reduced significantly in group D than in K and Group M. At 6 h and 12 h, FLACC scores were considerably lower with Group D compared to Group K, and Group M, and ketamine group compared to Group M at 4 h. The total amount of pethidine consumed 24 hours postoperatively was significantly lower in Group D than in Group K and Group M.

Conclusions: Dexmedetomidine as an additive to the CB significantly prolonged time to first analgesia required and decreased total rescue opioid consumption compared to ketamine and $MgSO_4$.

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1. Introduction

Hypospadias is a congenital anomaly characterized by the presence of urethral ventral meatus with an incidence of approximately 1 in 250 newborn males, which appears to be rising. It is classified into anterior and posterior [1].

Cases that are inaccurately diagnosed, inadequately treated, and insufficiently comprehended commonly complain of severe pain conditions. Poor management of childhood pain may have long-term adverse effects, such as neuro-endocrine damage, disrupted ingestion and sleep, and decreased pain threshold [2].

The caudal block (CB) is a quick, dependable, and safe approach for analgesia in pediatric patients when combined with general anesthesia intraoperatively or postoperatively [3]. It is the most used regional method in hypospadias surgery. CB results in a stress-free recovery with quicker ambulation, reduced chest infection risk, less painkiller use, and lower hospital stay [4].

Numerous adjuvants were added to bupivacaine, including opioids, ketamine, clonidine, $MgSO_4$, and dexmedetomidine, in the CB to increase the block quality and extend the analgesia duration [5,6].

Ketamine selectively antagonizes the receptor called ionotropic glutamate N-methyl D-aspartate (NMDA). Moreover, ketamine interacts directly with opioid receptors. Caudal ketamine is effective and safe for pediatric surgical procedures requiring prolonged postoperative analgesia [7,8].

Dexmedetomidine is an alpha 2-adrenergic receptor (2-AR) agonist, and the S-enantiomer of dextrorotatory medetomidine exerts its therapeutic properties by binding to G-protein-coupled 2-AR. It is utilized with local anesthesia in CBs during pediatric surgical procedures and gives a more extended period of analgesia without causing significant side effects [6,7].

Magnesium has antinociceptive and analgesic effects in humans. It might be regarded as a physiologic calcium antagonist due to its capacity

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to regulate calcium influx into the cell, which is the primary cause of these effects. NMDA antagonizes the central sensitization from nociceptive stimuli [9].

The role of magnesium sulfate as a sedative has been analyzed in several studies, and a significant reduction has been observed in midazolam consumption during the operation period of magnesium-treated individuals. However, these studies used magnesium sulfate through the intravenous route [10]. Caudal magnesium injection has analgesic effects on pediatric surgery patients [11].

So far, numerous studies have compared only two of dexmedetomidine, ketamine, and $MgSO_4$ [6,8,12]. However, the comparison between the three drugs has not been investigated. The current trial is designed to determine the effective role of dexmedetomidine, $MgSO_4$, and ketamine with CB as analgesics before the pediatric repair of hypospadias.

2. Materials and methods

The present randomized, double-blind study performed on 75 male children ages 1 to 7 years old, I and II classification of American Society of Anesthesiologists (ASA), underwent hypospadias repair at Kafrelsheikh University Hospital between May 2022 and October 2023.

The Approval code from the Ethical Committee was obtained from Kafr-Elsheikh University Hospitals (approval code: MKSU 51–2–16) and registration of clinicaltrials.gov (ID: NCT05837000) before starting the trial. Each parent (or guardian) gave written informed consent before enrolling in the trial.

Exclusion criteria: any child with a delay of development, psychological problems, and disease in the nervous and respiratory system or who was contraindicated for the CB including infection of block site, coagulopathies, or sacrum abnormalities.

2.1. Randomization and blindness

Cases were subjected to a comprehensive history gathering, physical evaluation, and regular biochemical tests. Randomization was accomplished using opaque, sealed envelopes, and a computer-generated number. The investigators and parent (or guardian) were blinded to the caudal injectate. The injectates were prepared by a pharmacist who did not participate in the study. All the syringes had the same appearance with the same volume to ensure blindness.

Before transferring to the operating room, children were randomized into three groups. All patients received 0.5 ml/kg bupivacaine 0.25% beside the additive drug diluted in 1 mL saline 0.9%. Group D patients were injected with dexmedetomidine of 1 µg/kg caudally, Group K patients were injected with ketamine of 0.5 mg/kg caudally, and group M patients were injected with magnesium of 50 mg caudally.

2.2. Intraoperative

The patients were attached to standard ASA monitoring upon entering the operation room, which comprised noninvasive arterial blood pressure (NIBP), electrocardiographic evaluation (ECG), temperature probe, pulse oximetry, and capnography.

Induction of anaesthesia was achieved with 100% Oxygen and sevoflurane 8% in spontaneous ventilation in oxygen. After the child lost consciousness, sevoflurane was decreased to 3–4% for several minutes to facilitate the insertion of an intravenous cannula.

A laryngeal mask airway (LMA) of the proper size was inserted. Then, sevoflurane concentration was reduced to 3% in 50% oxygen adequate to maintain spontaneous ventilation. The children were positioned in the lateral position so the caudal block could be performed.

2.3. Caudal block

The patient was placed in the lateral position. The sacral cornus and sacral hiatus were identified by touch. Following sterilization of the area, a 22-gauge needle was introduced into the skin at a 60-to-80-degree angle until it punctured the sacrococcygeal ligament (SCL), which was confirmed by a popping sensation. Subsequently, the needle angle was adjusted to 20 to 30 degrees, and the needle was advanced by 2 to 3 mm to penetrate the sacral canal. After confirming the absence of blood or cerebrospinal fluid through aspiration, the local anesthetic solution was slowly injected over the course of 1 minute, while closely monitoring hemodynamics and ECG readings.

The effect of the caudal block was tested after 15–20 min, and patients with a failed block were excluded (An increased heart rate (HR) of more than 20% from the basal HR of the child was considered as an inadequate caudal block), and 1 µg/kg fentanyl IV was injected.

During surgery, anesthesia was maintained by sevoflurane 2–2.5% in 50% oxygen with a fresh gas flow of 4–5 l/min; spontaneous ventilation was maintained. After surgery, the sevoflurane was discontinued, the LMA was removed, and 100% oxygen was continued through a face mask with the observation of possible early respiratory complications such as breath holding, airway obstruction, or laryngeal spasms. At modified Aldrete scale ≥9, cases were discharged to the post-anesthesia care unit (PACU). Mean arterial pressure (MAP) and HR changes were continuously assessed and recorded: preoperative, after block, and then every 20 minutes intraoperatively till the end of surgery.

2.4. Postoperative

The FLACC scale was used to assess postoperative pain; it spans from 0 to 10, where 0 indicates no discomfort and 10 indicates extreme pain imaginable [6]. Scores >4 suggest the need for analgesia. The patient was given 15 mg/kg of paracetamol by intravenous injection as standard analgesia. If the FLACC score remained at 4, pethidine 1 mg/kg was administered. The FLACC scale was evaluated after 30 minutes, 2, 4, 6, 12, 18, and 24 hours.

Time from the block to the time of the first pethidine injection (hours), which is the first required analgesia time, and the total amount consumed from pethidine (mg) in the first 24 h postoperative was noted.

Any adverse events were documented in PACU, including postoperative nausea and vomiting (PONV) (managed by ondansetron 0.1 mg/kg), hypotension (a decrease of 20% of the basal MAP and managed using IV fluid), and bradycardia (a reduction by 20% of the basal HR, which was adjusted with 0.01–0.02 mg/kg atropine through the intravenous route).

Our primary objective was the time of first rescue analgesia. The secondary outcomes were the total consumption of rescue analgesia, pain score, hemodynamics, and postoperative side effects.

2.5. Sample size calculation

3.1.9.2 version of G*Power computation (Universitat Kiel, Germany) was used in performing the sample size. According to prior research [7,8], the mean± SD of time to first analgesic request (the primary outcome) was 467 min with adding dexmedetomidine to caudal block and 385 min with ketamine and expected to be 321 min with $MgSO_4$ with a common SD of 152.5. The sample size was chosen using the following parameters: 0.391 effect size, 95% confidence limit, 80% research power, in a 1:1:1 group ratio, and adding three cases to each group to account for attrition. Thus, 25 individuals were recruited for each group.

3. Statistical analysis

Statistical analysis was performed using IBM's SPSS version 27 (Chicago, IL, USA). Data distribution normality was assessed using both histograms and Shapiro–Wilk test. Using the ANOVA (F) test, quantitative data were presented as the mean and standard deviation (SD) and analysed as the mean and SD, followed by post hoc comparisons using Tukey's test. For group comparisons, nonparametric quantitative data were presented as the median with interquartile range (IQR) and evaluated using the Kruskal–Wallis and Mann–Whitney tests. The Chi-square test was utilized to examine qualitative variables provided as percent and frequency. Statistical significance was deemed by a two-tailed P value ≤0.05.

4. Results

In the current study, 93 patients' eligibility was examined. Eleven patients did not match the criteria, and seven declined participations. Children remained were assigned to three groups randomly, and assigned children were monitored (Figure 1).

The three groups did not differ significantly in demographic information or surgical length (Table 1).

HR and MAP readings before and after surgery did not vary significantly among the three groups. HR and MAP measurements after block and 60 min intraoperative were decreased considerably in group D than K (P = 0.021 and 0.007 respectively) and were insignificantly different between group M and (group D and group K). At 20 min and 40 min, HR and MAP measurements were significantly decreased in group D than group K (P value = 0.014 and 0.001 respectively) and group M comparing to group K (P value = 0.027 and 0.017 respectively) and were insignificantly different between group D and group M (Figures 2–Figure 3).

The postoperative FLACC score measured at 30 minutes, 4, 18, and 24 hours did not differ significantly but differ significantly at 2, 6, and 12 hours among the three groups. FLACC score measurements had an insignificant alteration among both D and K groups at 4 h. Still, they were significantly lower in group D than group K at 6 h and 12 h (P = 0.006 and 0.008 respectively) and were significantly lower at 4 h, 6 h, and 12 h in group D than group M (P = 0.05) and was considerably lower at 4 h in group K than group M (P = 0.013) but had an insignificant difference between K and M groups at 6 h and 12 h (Table 2).

The time of first rescue analgesia median (IQR) was 8 (4–12) h in group D, 6 (4–8) h in the K ketamine group, and 4 (3–4) h in Group M. It was significantly delayed in group D than in group K and group M (P value = 0.027 vs. <0.001) and in group K than in group M (P value = 0.009).

In the first 24 hours following surgery, group D consumed median (IQR) was 40 (20–40) mg of pethidine, while groups K and M consumed 50 (40–60) mg and 60 (50–70) mg, respectively. After surgery, in the first 24 hours, a significant decrease in total pethidine intake was found in group D than in groups K and M (P = 0.023 vs. P = 0.001) and significantly lower with P = 0.024 in group K than in group M (Table 3).

The difference in PONV, hypotension, and bradycardia appeared insignificant among the three groups (Table 4).

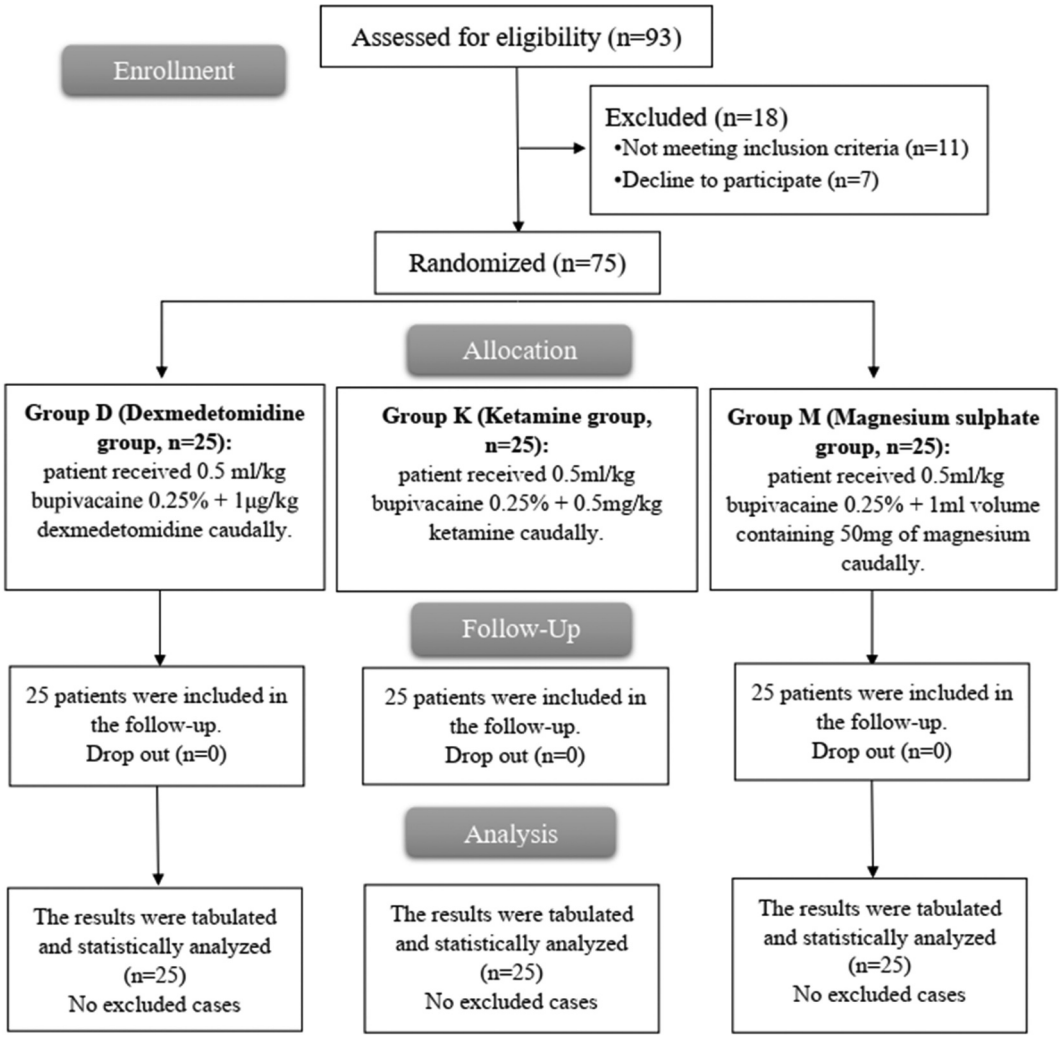

Figure 1. CONSORT flowchart of the enrolled patients.

Table 1. Demographics and duration of surgery among groups.

		Group D ($n = 25$)	Group K ($n = 25$)	Group M ($n = 25$)	P value
Age (years)		4.4 ± 1.85	4.6 ± 1.29	3.9 ± 1.45	0.205
Weight (kg)		18.4 ± 4.47	19.5 ± 2.47	17.7 ± 3.52	0.224
ASA	I	17 (68%)	15 (60%)	18 (72%)	0.657
physical state	II	8 (32%)	10 (40%)	7 (28%)	
Duration of surgery (min)		101.4 ± 13.66	104 ± 13.46	96.6 ± 11.88	0.133

Data are presented as mean ± SD or frequency (%), ASA: American Society of Anesthesiologists.

5. Discussion

Management of postoperative pain is a crucial aspect of pediatric anesthesiologists' practices. Various treatments and drugs to alleviate postoperative pain in pediatric patients are not devoid of severe adverse effects. In children, caudal epidural anesthesia is the most used regional technique for infraumbilical surgeries [7]. Adding various drugs to the CB, such as dexmedetomidine, $MgSO_4$, and ketamine, may demonstrate an analgesic effect and maximize the anesthetic impact of the caudal block.

Our finding found insignificant HR and MAP measurement differences between the three groups at the preoperative and the end of the surgery.

A significant decrease of HR and MAP measurements after block and 60 min intraoperative were detected in the Group D than in the Group K while at 20 min and 40 min were significantly decreased in the Group D compared to the Group K and Group M compared to ketamine group with insignificant difference between dexmedetomidine and Group M.

Significant effects of dexmedetomidine on HR and MAP may result from the activation of inhibitory neurons of α_2 in the medullary vasomotor center in the brainstem, resulting in a decrease in sympathetic outflow and turnover of norepinephrine [13].

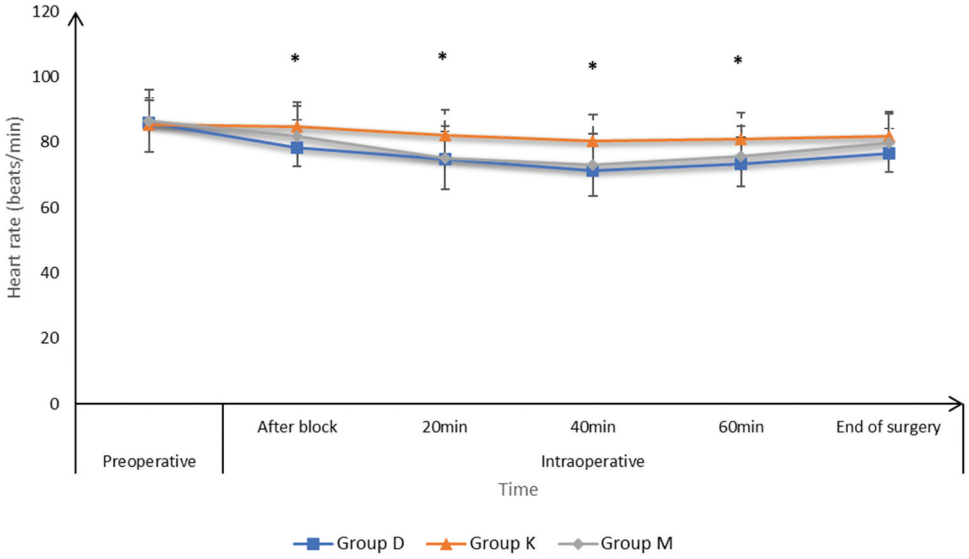

Figure 2. Heart rate (beats/min) of the studied groups.

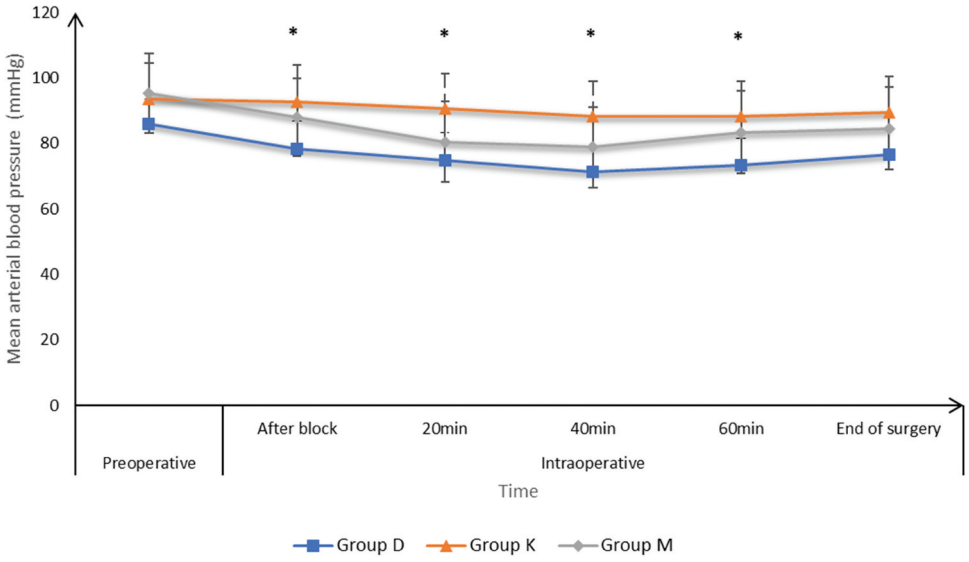

Figure 3. Mean arterial blood pressure (mmHg) of the studied groups.

Table 2. FLACC score of the studied groups.

	Group D ($n = 25$)	Group K ($n = 25$)	Group M ($n = 25$)	P value	Post hoc
30 min	0(0–1)	1(0–1)	0(0–1)	0.622	–
2 h	1(1–1)	1(1–2)	1(1–2)	0.482	–
4 h	1(1–4)	1(1–5)	3(2–5)	0.009	P1 = 0.719 P2 = 0.005 P3 = 0.013
6 h	2(1–2)	2(2–4)	3(2–5)	<0.001	P1 = 0.006 P2 < 0.001 P3 = 0.107
12 h	4(2–4)	4(2–6)	5(2–6)	<0.001	P1 = 0.008 P2 < 0.001 P3 = 0.081
18 h	2(1–4)	2(2–4)	2(2–4)	0.434	–
24 h	4(2–5)	4(2–5)	4(4–5)	0.085	–

The data is provided as the median (IQR), P1: *P* value between group D and K, P2: *P* value between group D and M, P3: *P* value between group K and M, FLACC: Face, Legs, Activity, Cry, and Consolability.

In line with our findings, Ali et al. [14] reported that the mean HR measurements insignificantly differ between groups M and D, with a decrease in group D compared to group M. MAP had no significant difference between the three study arms through intraoperative and postoperative periods.

Postoperative FLACC score measurements at 30 min, 2, 4, 6, 12, 18, and 24 insignificantly differed

Table 3. Time of first rescue analgesia and the total amount of pethidine in 1st 24 h postoperative among the studied groups.

	Group D ($n = 25$)	Group K ($n = 25$)	Group M ($n = 25$)	P value	Post hoc
Time of first rescue analgesia (h)	8 (4–12)	6 (4–8)	4 (3–4)	<0.001	P1 = 0.027 P2 < 0.001 P3 = 0.009
Total pethidine consumption in 1st 24 h postoperative (mg)	40 (20–40)	50 (40–60)	60 (50–70)	<0.001	P1 = 0.023 P2 < 0.001 P3 = 0.024

Data are presented as median (IQR). P1: *P* value between group D and K, P2: *P* value between group D and M, P3: *P* value between group K and M.

Table 4. Complications among the studied groups.

	Group D ($n = 25$)	Group K ($n = 25$)	Group M ($n = 25$)	P value
PONV	2 (8%)	6 (24%)	3 (12%)	0.250
Hypotension	4 (16%)	1 (4%)	2 (8%)	0.332
Bradycardia	2 (8%)	0 (0%)	1 (4%)	0.353

Data are provided as frequency (percent), PONV: Postoperative nausea and vomiting.

among the three groups. Similar to the Ali et al. study [14], who found that at the 12th and 24th hour postoperatively, all groups (D, M, and control) documented increased pain scores without statistically significant change among groups.

Also, in postoperative recordings from 12 to 24 h, there was no intergroup significant variance between D and K groups in FLACC between pediatrics who underwent congenital inguinal hernia repair in the Fahim and Menshawi study [6].

Our FLACC score data at 4 h, 6 h, and 12 h were significantly lower in group D than in group M.

On comparing the FLACC score between group D and group M in the Ali et al. study [14], it was lower in group D than group M without significant difference at 30 minutes, 1, 2, and 3 hours postoperatively. He was with our result at the 6th hour postoperatively. The difference is statistically significant since patients in group M achieved statistically higher FLACC scores than those in group D.

In this current study, FLACC scores were insignificantly different between the dexmedetomidine and ketamine groups at 4 h. They were significantly lower with patients taking dexmedetomidine than patients taking ketamine at 6 h and 12 h.

In a study by Fahim and Menshawi [6], FLACC scores decreased significantly with dexmedetomidine compared to ketamine at 8–12 hr postoperative, strengthening our previous finding.

There was a significant decrease at 4 h in group K than in group M, with insignificant variation between group K and group M at 6 h and 12 h in this trial.

In measuring postoperative pain by VAS in a study aimed to compare ketamine and $MgSO_4$ in pediatric surgeries, patients in Group K had significantly decreased VAS compared to Group M at 8 h and 12 h postoperatively, which differs from us in the significance [8]. Our different significant results at 4 h may be due to a higher dose of ketamine.

The time to first rescue analgesia was 8.2 ± 3.45 h in group D, 5.8 ± 2.85 h in group K, and 3.7 ± 1.51 h in group M. Time to first rescue was significantly delayed in group D than in group K and group M and was delayed considerably in group K than in group M.

A meta-analysis was conducted on 11 trials to assess the effectiveness of caudal dexmedetomidine in pediatric CB. They found that the time to first rescue pain was significantly longer in the group CA with the dexmedetomidine group. The duration of analgesia was 9.88 ± 0.90 h for the dexmedetomidine, comparable with our finding [15].

Different studies were in line with us, and dexmedetomidine had a significantly longer time to first postoperative analgesic than in ketamine [6]. Also, Ali and colleagues [14] found no significant variance between magnesium sulfate and dexmedetomidine regarding 1st analgesic requirement, with extended duration with dexmedetomidine than $MgSo_4$.

Farrag et al. supported our results and noted that caudal administration of 0.5 mg/kg ketamine significantly prolonged the postoperative analgesia duration by 8 h compared to $MgSO_4$ (up to 6.5 h).

According to the current results, complications, including bradycardia, PONV, and hypotension, were insignificantly different among the studied groups. Similarly, intergroup significant differences did not exist in the incidence of complications in Fahim and colleague's study [6].

Dexmedetomidine caused bradycardia in only one patient compared to no patients in the control group or with $MgSo_4$ in Ali et al. study [14]. However, of our patients, two had bradycardia in group D, but similarly, no patients in group M had bradycardia.

Although low dose of dexmedetomidine was used, it caused bradycardia because, it has direct effects on alpha-2 receptors located in the heart's conducting system. Stimulation of these receptors on cardiac tissue can directly slow down the heart's electrical

impulses and reduce heart rate. While $MgSO_4$ did not cause bradycardia because, it indirectly affects the heart by lowering blood pressure but does not directly impact cardiac receptors or the heart's electrical conduction system.

Moreover, Ali et al. [14] documented that one patient in group M developed vomiting compared to two patients in group D, while vomiting was absent in the control group.

Limitations: This study was conducted at a single center with a relatively small sample size. Also, we did not assess the sedation score.

6. Conclusions

The adjuvant effect of dexmedetomidine in the caudal block significantly prolonged the first analgesic required and lowered the total rescue pethidine consumption compared to ketamine and $MgSO_4$ in pediatric hypospadias repair. The number of patients in all three groups showed low complications with insignificant differences among the three medications.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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