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Efficacy of adding nalbuphine to caudal bupivacaine for postoperative analgesia in children undergoing hypospadias repair surgery. Randomized controlled trial

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ABSTRACT

Background: We hypothesized that adding nalbuphine to bupivacaine would prolong the duration of caudal epidural anaesthesia (CEA) in pediatric patients undergoing hypospadias repair surgery.

Methods: 60 children scheduled for elective hypospadias surgery under general anesthesia combined with CEA were divided into two equal groups: the control group received caudal bupivacaine 0.25% 1 ml/kg plus 2 ml normal saline. The Nalbuphine group received caudal bupivacaine 0.25% 1 ml/kg plus nalbuphine 0.1 mg/kg in 2 ml normal saline. Intraoperative and postoperative rescue analgesia was managed by giving intravenous paracetamol 15 mg/kg and/or 100mcg nalbuphine. The Face, Legs, Activity, Cry, Consolability (FLACC) pain scale, and the Richmond AgitationSedation Scale (RASS) score were measured. Pre-operative and post-operative blood samples were collected for a subgroup of patients for cortisol analysis.

Results: The duration of postoperative analgesia was significantly longer in the nalbuphine group ($p < 0.001$). The number of patients who needed postoperative supplemental analgesia was significantly lower in the nalbuphine group ($p < 0.001$). Total paracetamol consumption was significantly higher in the control group ($p < 0.001$). The FLACC and RASS were significantly lower in the nalbuphine group. Postoperative cortisol levels were lower in the nalbuphine group compared to the control group.

Conclusions: Adding caudal nalbuphine 0.1 mg/kg to bupivacaine 0.25% provides better postoperative pain control than bupivacaine alone in children undergoing hypospadias repair.

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1. Introduction

Pain is one of the most commonly misdiagnosed, undertreated, and poorly understood medical conditions, particularly in children [1]. Its management in pediatric patients is challenging due to the systemic side effects of opioids in this age group [2].

A common technique for inducing analgesia is a caudal block, which involves injecting local anesthetics into the epidural region through the sacral hiatus. The management of postoperative pain in children, especially those who had surgeries below the umbilicus, is preferred [3]. Because of its technical simplicity, high success rate (98%-100%), and ability to provide consistent analgesia, the caudal block is preferred over alternative therapies such as peripheral nerve blocks [4]. The essential benefit of a caudal block in paediatrics is that it reduces postoperative opioid demand, which worsens postoperative respiratory depression [4].

The CEA's brief postoperative analgesic period is its main drawback [5]. Recent years have seen a surge in the use of local anesthetics combined with adjuvants in the caudal block, including fentanyl, dexamethasone, neostigmine, ketamine, morphine, magnesium sulfate, clonidine, and dexmedetomidine [6]. These adjuvants will prolong analgesia, extending the time until the first analgesic is required, and decreasing the need for opioid administration [7].

Nalbuphine is a kappa-opioid receptor agonist and a partial mu-opioid receptor antagonist. It provides analgesia and sedation through its effects on kappa and mu-opioid receptors. Nalbuphine exhibits a ceiling effect, and incremental doses do not increase its analgesic effects [8]. The maximal analgesic effect dose is 0.3–0.4 mg/kg. It does not cause respiratory depression in children when administered at the prescribed levels. As a result, children can utilize it safely [9].

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We hypothesized that adding nalbuphine to bupivacaine would prolong the duration of caudal analgesia for acute postoperative pain management in children undergoing hypospadias repair surgery.

2. Patient and methods

Between March 2018 and September 2019, Assiut University Hospitals conducted a randomized, double-blind, placebo-controlled clinical trial. The study was carried out with the approval of Assiut University Hospitals' research ethics board (IRB number: 17100459) and with signed informed consent from each patient's legal guardian. The trial has been registered on ClinicalTrials.gov (NCT03476772). The study was carried out with the CONSORT principles and the Helsinki Declaration's criteria and revisions.

The study included 60 male children aged 2–10 years with American Society of Anesthesiologists (ASA) I physical status undergoing hypospadias repair surgery. We excluded patients with congenital anomalies in the lower spine, bleeding disorders, infection at the injection site, increased intracranial pressure, or guardian refusal.

2.1. Randomization and blinding

Patients were randomly allocated based on computer-generated codes into two groups:

The control group with 30 patients who received caudal block using only bupivacaine 0.25% 1 ml/kg plus 2 ml normal saline.

The nalbuphine group with 30 patients received caudal block using bupivacaine 0.25% 1 ml/kg plus nalbuphine 0.1 mg/kg in a 2 ml solution.

The total volume was similar in both groups to avoid bias.

Randomization was performed on the morning of surgery before the induction of GA. Randomization was concealed using opaque sealed envelopes with alphabetical codes. Patient identifications were affixed to opened envelopes and secured by a dedicated person unaware of the randomization procedures. Randomization procedures were performed by an anesthetist not involved in the present study. Anesthetist and Patient guardians were blinded to treatment assignments.

2.2. Anesthetic technique

All children fasted for at least six hours before surgery, with clear fluids allowed until two h before induction. Heart rate, non-invasive blood pressure, and oxygen saturation were monitored in the operating room. The anesthetic regimen was standardized. All participants were pre-oxygenated with 100% oxygen for 3 min via a facemask.

Both groups received 0.5 mg/kg of midazolam orally as a premedication half an hour before induction. Anesthesia induction was either achieved by incremental 1.5% doses of sevoflurane up to 7% in a 50% oxygen/air mixture without intravenous opioids or by intravenous fentanyl (2 µg/kg) and propofol (2.0–2.5 mg/kg). After induction and establishment of venous access, 0.5 mg/kg atracurium was given to facilitate endotracheal intubation; an endotracheal tube of appropriate size was inserted; and controlled ventilation was adjusted to maintain end arterial CO2 around 35 mmHg. Anesthesia was maintained with sevoflurane 2% in a 50% oxygen/air mixture.

A subgroup of patients (10 patients) was chosen randomly in each group for cortisol analysis. A 3 ml blood sample from the cortisol subgroup was collected immediately after induction. Samples were put in special chemistry gel tubes and delivered to the clinical pathology department for further analysis.

3. Caudal block

After anesthesia was administered and the patient was stabilized, he was placed in the left lateral decubitus position, the sacrococcygeal area was sterilized with povidone-iodine solution, and sterile wraps were applied. A 22-gauge hypodermic needle was used to locate the caudal epidural area. After aspiration without blood or CSF and confirmation of the caudal epidural space using the modified Swoosh test, the medication mixture was administered [10].

Adequate analgesia during surgery was defined by hemodynamic stability according to the absence of greater than 20% increases in heart rate or systolic blood pressure from baseline values obtained immediately before the first surgical incision. Patients with unsuccessful blocks were excluded from the study.

At the end of the operation, neostigmine 50 mcg/kg and atropine 15 mcg/kg were used to reverse the action of the muscle relaxant, and sevoflurane was discontinued. All patients were extubated and transported to the post-anaesthesia care unit. Participants were discharged from the PACU to a ward once the modified Aldrete score was nine or greater.

The same surgeon performed all procedures.

3.1. Assessment parameters

Age, weight, gender, ASA class, BMI, duration of surgery, and anesthesia were recorded. Noninvasive systolic and diastolic blood pressure (NIBP), mean blood pressure (MAP), heart rate (HR), and Spo2 were recorded at baseline (before block), immediately after block, after skin incision, at 5, 15, 20, 25, and 30 min, and the end of surgery. The same parameters were measured at 0, 15, 30, 45, and 60 min postoperatively,

on the PACU and at 2, 4, 6, 10, 15, 20, and 24 h postoperatively on the ward.

3.1.1. Assessments of postoperative pain

The Face, Legs, Activity, Cry, Consolability (FLACC) pain scale [11] at the time of admission to PACU; and at 30 min, 60 min, 90 min, 2, 4,6,8, 12, and 24 h after recovery from anesthesia to assess the need for rescue analgesia. The FLACC pain scale score ranges from 0 to 10, with zero meaning no pain and 10 meaning the worst pain.

Postoperative rescue analgesia included intravenous 15 mg/kg paracetamol as a bolus as required or whenever the FLACC score was ≥ 4 (if two assessments separated by a 5-minute wait produced a FLACC score of ≥ 4) over 24 h. If the scale persisted, more than 3, I.V. 0.1 mg/kg nalbuphine was given.

The time to first analgesic request and the duration of postoperative analgesia (time from the caudal block to the first use of analgesics). Total analgesic consumption in the first 24 h was recorded. The number of doses of rescue analgesics provided after surgery was also recorded. The number of patients who needed rescue analgesia and the total analgesic consumption during the first 24 h postoperatively were recorded.

3.1.2. Sedation and agitation assessment

Sedation and agitation were standardized for both groups using the Richmond AgitationSedation Scale (RASS) score [12]. The RASS scores were evaluated at 2 h, 4 h, 6 h, 8 h, 12 h, and 24 h postoperatively.

3.1.3. Postoperative sedation

Was measured using the Ramsay sedation score (RSS) in the first 24 hours after surgery.

3.1.4. Adverse effects

Any side effects such as respiratory depression, pruritus, or PONV were recorded. Respiratory depression was a decrease in oxygen saturation (SpO2) of less than 92%.

3.1.5. The cortisol level

Another 3 ml blood sample was collected from the cortisol subgroup patients six hours after anesthesia recovery. Serum cortisol samples were received in the chemistry lab unit in the clinical pathology department of Assiut University Hospitals after they had been collected, labelled, and registered. Then the samples were loaded on the APTIO module, centrifuged, and processed to Centaur equipment. Cortisol test kits were used on equipment Centaur, XPT module, which has serial no. IRL20131804, manufactured by Siemens Healthcare.

At discharge, all children were prescribed oral paracetamol (20 mg/kg) as required (a maximum of four doses in 24 h).

4. The outcomes

The primary outcome was the duration of postoperative analgesia, referred to as the time to rescue analgesia. Secondary outcomes included the total dose of rescue analgesics, sequelae such as respiratory depression, pruritus, postoperative nausea and vomiting (PONV), RASS score, and the influence of nalbuphine on cortisol levels.

5. Study power

The primary objective of the study was the time to initial analgesic request. Based on a preliminary analysis using t-tests to find a difference between two independent means (two groups) at a one-tailed type I error of 0.05, a power of 0.7, and an effect size of 0.6 using the G-Power calculator 3.1.9.7, it was determined that a total sample size of 54 patients (27 in each group) was sufficient for statistical testing. To make up for the expected patient dropout, three extra people were added to each group.

6. Statistical analysis

For statistical analysis, IBM SPSS Statistics version 20 (SPSS Inc., Chicago, IL, USA) was used. The chi-square test was used to compare groups in categorical data. For continuous data, the Shapiro-Wilkes test was used, and the findings were presented as mean S.D. The Student's T-test was used for group comparisons, and the Mann-Whitney test was used for non-normally distributed data. The two groups' differences in intraoperative data and postoperative scores were compared using a one-way repeated measures ANOVA. The interaction between time and groups was examined using a two-way repeated-measures ANOVA with "group" (a between-subjects variable) and "time" (a within-subjects variable) as the major components. The paired t-test was used for quantitative data that were normally distributed (pre- and post-cortisol levels). Spearman correlation coefficients were used to analyze the correlation between quantitative parameters. A P-value less than 0.05 was considered significant.

7. Results

Among the 69 participants screened for eligibility, 60 patients were enrolled in the present study; Patients were divided into three groups containing 30 patients each. We encountered no instances of failed blockage in either group (Figure 1).

7.1. Patient characteristics and clinical data

No statistically significant differences existed between groups in age, weight, duration of operation, and anesthesia (Table 1).

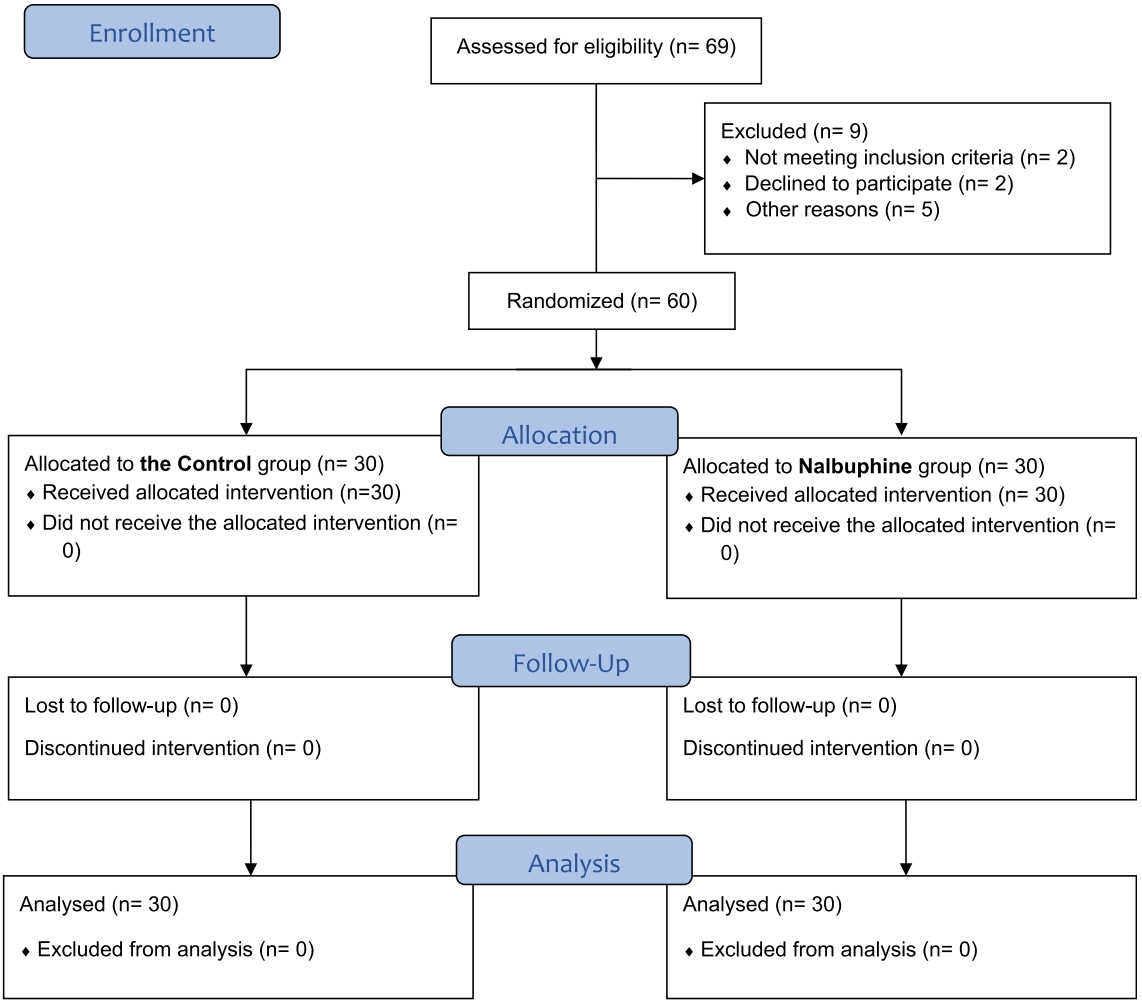

Figure 1. CONSORT flow diagram.

Table 1. Baseline characteristics of studied groups.

	Control ($n = 30$)	Nalbuphine ($n = 30$)	*P*- value
Age (years)	5.1 ± 2.6	4.7 ± 2.3	.512
Weight (kg)	16.7 ± 5.8	17.5 ± 4.7	.559
Operation time (min)	70.0 ± 15.8	75.0 ± 12.2	.175
Anesthesia time (min)	95.0 ± 15.8	1.0 ± 12.2	.176

Data are presented as mean ± SD. No statistically significant differences ($P > 0.05$) by the independent sample t-test or Chi-squared test.

7.2. Hemodynamics

At any point during the trial, there was no evidence of a significant difference between the groups in terms of mean arterial pressure (MAP), mean heart rate (HR), or mean oxygen saturation (SpO2) (data not presented).

7.3. Postoperative pain profile

7.3.1. The FLACC score

The FLACC was lower in the nalbuphine group compared to the control group at all time points and statistically significant from 2 hours postoperatively to the end of the observation period (Figure 2).

7.3.2. Analgesic request and consumption

The duration of postoperative analgesia was significantly longer in the nalbuphine group (21.5 ± 1.3) than in the control group (7.1 ± 0.89) hours ($p < 0.001$). The number of patients who developed pain and needed rescue analgesia was significantly reduced in the nalbuphine group compared with the control group ($p < 0.001$). The mean total consumption of rescue analgesia in the first 24 h postoperatively was significantly lower in the nalbuphine group ($p < 0.001$) (Table 2). None of the patients in both studied groups needed intravenous nalbuphine supplementation during 24 h postoperatively.

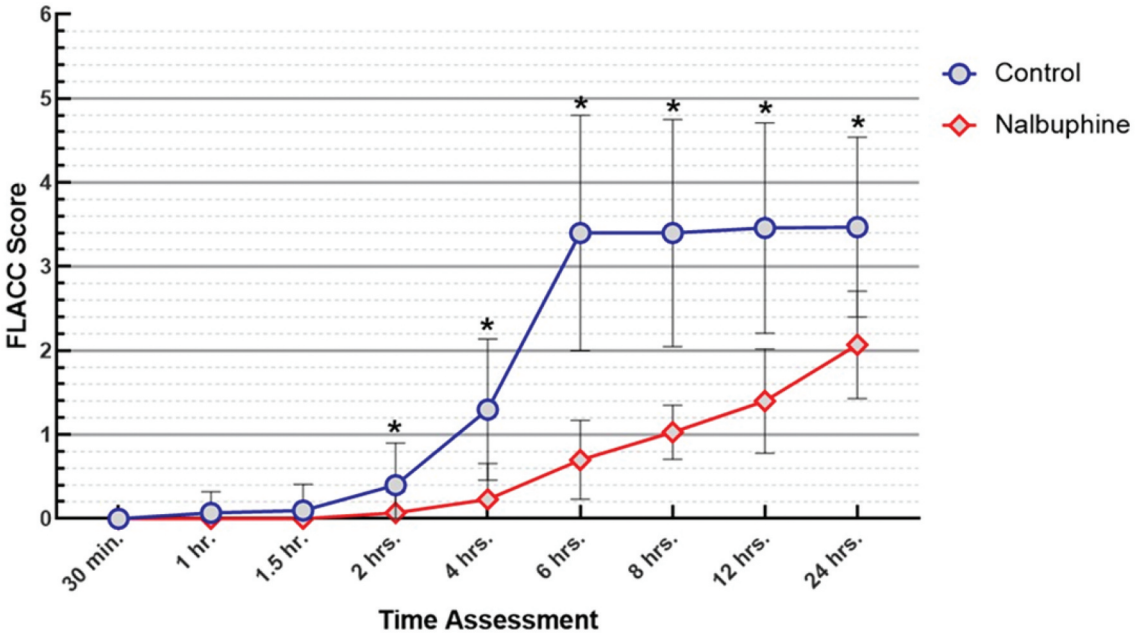

Figure 2. The Face, Legs, Activity, Cry, Consolability (FLACC) pain scale changes for both studied groups. Note: * *Significant p-value*.

Table 2. Postoperative analgesia and sedation in both studied groups.

Variable	Control ($n = 30$)	Nalbuphine ($n = 30$)	*P*- value
The number of patients who needed paracetamol	28 (93.3%)	13 (43.3%)	<.001
Total Paracetamol consumption (mg/24 hrs.)	341.5 ± 74.8	18.0 ± 58.6	<.001
Time to first analgesic requirement (Hrs.) (Duration of postoperative analgesia)	7.1 ± 0.89	21.5 ± 1.3	<.001
Number of patients sedated.	3 (10%)	20 (66.66%)	<.001

Data are presented as mean ± SD and number (%). No statistically significant differences ($P > 0.05$) by the independent sample t-test or Chi-squared test.

7.4. Sedation and Agitation assessment

The RASS was significantly lower in the nalbuphine group than in the control group at all time points (Figure 3).

7.5. Ramsey sedation score

The mean sedation values in the nalbuphine group were significantly higher than in the control group postoperatively. The number of patients who were sedated was significantly higher in the nalbuphine group ($p < 0.001$) (Table 2).

7.6. Side effects

None of the patients in both groups developed bradycardia, hypotension, pruritus, or respiratory depression. However, three patients (10%) suffered from PONV in the nalbuphine group ($p = 0.119$).

7.7. Serum cortisol levels

Serum cortisol levels were tested for a sub-group of studied patients (10 patients from each group). The preoperative cortisol levels were statistically non-significant between both groups. However, postoperative cortisol levels were significantly lower in the nalbuphine group compared to the control group ($p < 0.001$). When comparing the levels in each group pre- and postoperative, the nalbuphine group showed a significant decrease in cortisol levels postoperatively. Postoperative cortisol levels showed a non-significant increase in the control group compared to the baseline (Table 3). The reference range for cortisol levels was 4.3–22.4 mcg/dl.

8. Discussion

The current study found that the duration of postoperative analgesia in the nalbuphine group was much longer than in the control group. In addition, patients in the nalbuphine group had considerably fewer dosages of paracetamol within the first 24 hours after surgery.

Nalbuphine functions as a KOR and MOR agonist, producing analgesia via two distinct pathways (supraspinal analgesia via MORs and spinal analgesia and sedation via KORs) and protects against receptor blockade-dependent respiratory failure [8]. It had fewer side effects, a better pharmacological profile, and better postoperative analgesia quality [13].

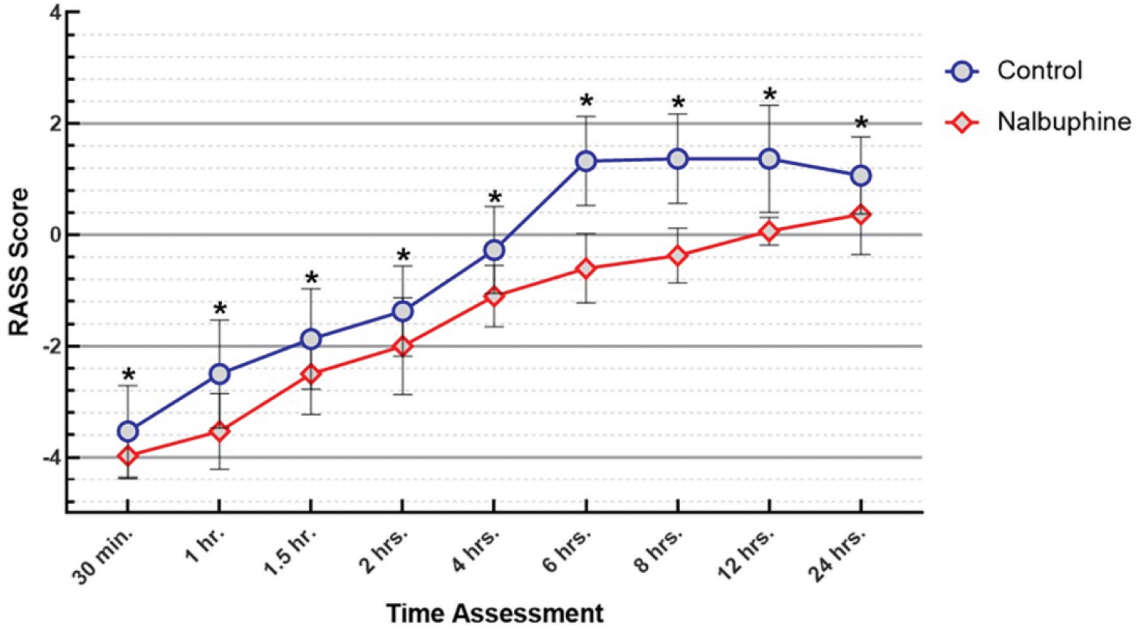

Figure 3. Richmond Agitation sedation scale (RASS) changes for both studied groups. Note: * *Significant p-value*

Table 3. Serum cortisol levels (mcg/dl) in sub-group of study groups.

	Control ($n = 10$)	Nalbuphine ($n = 10$)	*P*- value
Pre-operative	20.1 ± 1.0	19.5 ± 1.2	0.240
Postoperative	22.8 ± 2.3	13.2 ± 1.9	<0.001
P- value	0.214	0.037	

Data expressed as mean ± S.D. *P* value was significant if < 0.05.

Verma et al. discovered that combining Nalbuphine with strong bupivacaine for subarachnoid block considerably improved postoperative analgesic duration for lower limb orthopaedic operations [14].

In the nalbuphine group, most patients were more sedated but arousable, especially during the first 8 hours postoperatively. This can be explained by the agonist effect of nalbuphine on kappa receptors which is responsible for spinal analgesia and sedation. However, none of the patients in the nalbuphine group developed respiratory depression at any time in the postoperative period. Fewer side effects of nalbuphine may be attributed to its central antagonist activity on the mu receptors.

In line with our results, Mohamed et al. found that nalbuphine added to bupivacaine in caudal anesthesia provides longer postoperative analgesia and sedation without respiratory depression in children who underwent lower abdominal surgery. Furthermore, they reported more sedation scores at 30 minutes and 1 hour postoperatively in the bupivacaine-nalbuphine group. However, they used a different sedation score, an objective score based on eye-opening [15]. Also, Salama et al. found that caudal anesthesia using levobupivacaine and nalbuphine provided a longer duration of analgesia with no reported side effects compared to the levobupivacaine group. They found that FLACC pain scores were significantly lower in the levobupivacaine-nalbuphine group compared to the levobupivacaine group. Also, they found that the total dose of postoperative paracetamol consumption in the first 12 h was significantly lower in the levobupivacaine-nalbuphine group compared to the levobupivacaine group. All patients recorded no serious adverse effects in the first 12 h [9].

Abdallah et al. compared postoperative pain with adding fentanyl or nalbuphine to caudal bupivacaine in children who underwent hernia repair surgery. Consistent with our results, they reported that adding nalbuphine to caudal bupivacaine prolonged the duration of postoperative analgesia, decreased paracetamol consumption, and lessened requests for postoperative analgesia [16].

The present study agreed with Ahuja et al., who found that the addition of fentanyl or ketamine to caudal bupivacaine was able to blunt the neuroendocrine stress response (blood glucose, serum cortisol, and insulin levels) in children who underwent infra-umbilical surgery [17].

In contrast to our findings, Gaitini et al. investigated the effect of fentanyl added to bupivacaine versus bupivacaine alone on the stress response. They found that combining fentanyl with bupivacaine in children's caudal block did not affect catecholamine plasma levels [18].

9. Limitations of the study

The present study has a few limitations. First, evaluating inadequate analgesia during the intraoperative period was challenging, and we could not measure the block's onset time as patients were under GA. Second, we did not evaluate blocking properties such as the maximum level of sensory block and time to two dermatome regression of analgesia. The Pinprick method of assessing analgesia is problematic in children as it causes discomfort, pain, and restlessness. Third, only one dose of nalbuphine was tested, and different doses should be tested in further studies to determine the best dose without adverse effects. Lastly, due to financial problems, serum cortisol levels were assessed only in a subgroup of patients.

10. Conclusions

Based on our results, adding 0.1 mg/kg of nalbuphine to caudal bupivacaine 0.25% provides better postoperative pain control than caudal bupivacaine alone in children undergoing hypospadias repair without increasing the risk of side effects.

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Disclosure statement

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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