Cai *et al. BMC Anesthesiology* (2025) 25:172
https://doi.org/10.1186/s12871-025-03053-7

BMC Anesthesiology

RESEARCH Open Access

Effect of hydromorphone combined with ropivacaine caudal block on immune function after hypospadias surgery in children

Yuzhu Cai[1], Mingwen Yang[1], Xinghui Liu[1], Lingli Zhang[1], Jun Wang[1] and Yingying Sun[1*]

Abstract

Background This study aimed to evaluate the effects of caudal block anesthesia with hydromorphone-ropivacaine compared to ropivacaine alone on postoperative immune function and pain management in children undergoing hypospadias surgery.

Methods A total of 100 pediatric patients were randomly assigned to two groups: the Hydromorphone-Ropivacaine (HR) group and the Ropivacaine (R) group for caudal block anesthesia, with 50 patients in each group. The R group received 0.25% ropivacaine at a dose of 1 ml/kg, while the HR group received 0.25% ropivacaine (1 ml/kg) combined with hydromorphone (10 μg/kg). The maximum dose for both groups was capped at 30 ml (1 ml/kg). Anesthesia induction included intravenous administration of pentobarbital (0.01 mg/kg) and dexamethasone (0.15 mg/kg), followed by sevoflurane inhalation. All patients underwent ultrasound-guided caudal block anesthesia administered by the same anesthetist. Primary outcomes included the distribution of T lymphocyte subsets (CD3+, CD4+, CD8+, and CD4+/CD8 + ratios) measured at five time points: pre-anesthesia (T0), end of surgery (T1), 24 h postoperatively (T2), 48 h postoperatively (T3), and 72 h postoperatively (T4). Secondary outcomes included postoperative pain scores assessed using the Modified Children's Hospital of Eastern Ontario Pain Scale (M-CHEOPS) at 1, 6, 12, 18, and 24 h postoperatively, sedation levels evaluated using the Ramsay sedation scale at the same time points, and the incidence of postoperative adverse events.

Results The HR group exhibited significant reductions in $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ ratios at T1, T2, and T3 compared to baseline (T0) ($p < 0.001$). At all postoperative time points (T1, T2, T3, T4), the HR group demonstrated significantly higher levels of $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ ratios compared to the R group ($p < 0.001$). By T4 (72 h postoperatively), immune markers in the HR group had largely normalized to baseline levels, whereas those in the R group remained significantly lower ($p < 0.001$). Postoperative pain, assessed using the Modified Children's Hospital of Eastern Ontario Pain Scale (M-CHEOPS), was significantly lower in the HR group at 6, 12, and 18 h postoperatively compared to the R group ($p < 0.001$). The HR group also exhibited a longer duration of analgesia and required fewer doses of rescue analgesia within the first 24 h postoperatively ($p = 0.046$). Sedation levels, evaluated using the Ramsay sedation scale, showed significant differences between the groups at 1 h ($p = 0.0087$) and 6 h ($p < 0.0001$) postoperatively, with higher sedation scores observed in the HR group. There were no significant differences in heart

*Correspondence:
Yingying Sun
sunyy168@126.com

Full list of author information is available at the end of the article

rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, or oxygen saturation between the groups at any time point ($p > 0.05$). No significant differences were observed between the two groups in terms of postoperative adverse reactions (all $p > 0.05$).

Conclusion Caudal block anesthesia with hydromorphone-ropivacaine offers enhanced postoperative pain relief and a lesser impact on immune function compared to ropivacaine alone in children undergoing hypospadias surgery. Further studies are warranted to explore the long-term effects on immune function.

Keywords Hydromorphone, Ropivacaine, Caudal block, Hypospadias surgery, Immune function, T lymphocyte subsets, Anesthesia

Introduction

Hypospadias is a common congenital disorder in males, characterized by abnormal urethral development and affecting approximately 1 in every 125 newborns [1]. Unlike many other conditions, hypospadias not only causes significant physical impairment but also leads to a range of physical and psychological challenges, especially in less developed regions [2]. Surgical repair remains the only definitive treatment, though expectant management may be considered for minor cases. Even after surgery, patients may continue to face functional and psychological issues throughout their lives [3]. The primary objective of surgical intervention is to restore both the appearance and function of the penis, but outcomes vary significantly. These are influenced by factors such as the type and severity of the abnormality, patient condition, specific surgical techniques, and surgeon skill. Common complications include urethrocutaneous fistula, bleeding, catheter blockage, urine leakage, wound infection, glans dehiscence, penile shaft torsion, and meatal stenosis. Achieving optimal outcomes with minimal complications requires a comprehensive preoperative assessment, careful selection of surgical approach, meticulous tissue handling, and diligent postoperative follow-up [4]. Despite advancements in surgical techniques, hypospadias repair remains challenging, with a high complication rate even among experienced surgeons [5, 6].

Various factors—such as surgery duration, repair type, patient age, and postoperative inflammation—significantly impact surgical outcomes and may exacerbate immune impairment, an issue with critical clinical implications [7–10]. A compromised immune system during the perioperative period is linked to an increased risk of postoperative infections and sepsis [11]. Cellular immunity, primarily mediated by T lymphocytes, is crucial for the body's defense against infections. $CD3^+$ serves as a marker for total T cells [12], $CD4^+$ T-helper cells activate both cellular and humoral immunity [13], while $CD8^+$ T cells primarily function as cytotoxic lymphocytes, playing a crucial role in targeting and eliminating infected or malignant cells [14]. A reduced $CD4^+/CD8^+$ ratio is typically associated with disease severity and poor prognosis [15]. As well as a decrease in T lymphocyte numbers surgery also causes a shift in the balance between the immune-suppressive regulatory T lymphocytes and the immune promoting helper T and cytotoxic T cells. This shift results in a predominance of T regulatory cells in the post-operative period [16].

Anesthetic agents also play a significant role in modulating immune function, potentially affecting perioperative infection rates and surgical outcomes. The immune system comprises innate and adaptive components; the former provides immediate, non-specific pathogen defense, while the latter recognizes specific antigens and establishes immune memory. Various anesthetic agents and perioperative drugs can influence both innate and adaptive immunity, potentially affecting the interplay between these immune components. Compared to general anesthesia alone, combining caudal block with general anesthesia has been shown to reduce postoperative pain and complications in pediatric hypospadias surgeries [17]. Regional anesthesia, such as caudal block, has been associated with immune benefits, including reduced anesthetic consumption, surgical stress, enhanced pain management, and decreased opioid use [18]. Effective postoperative analgesia helps preserve immune function in surgical patients [19]. Compared to general anesthesia alone, epidural anesthesia reduces neuroendocrine responses, aiding in immune homeostasis [20–22]. Caudal block anesthesia, a form of epidural block, is commonly used in pediatric surgeries. While traditional single-shot caudal blocks with local anesthetics are effective for acute and chronic pain management, their limitations include short action duration and dose-dependent side effects on cardiovascular and central nervous systems. To prolong sensory and motor blocks and reduce cumulative anesthetic doses, adjuvants or additives are often used. A wide range of adjuvants have been explored, from classical opioids to other agents with varying mechanisms of action. Numerous opioids, such as morphine, fentanyl, sufentanil, buprenorphine, and tramadol, have been used with variable success [23, 24]. Hydromorphone, a semi-synthetic morphine derivative, has a balanced solubility and lipophilicity profile, making it particularly suitable for this purpose. Compared to morphine, hydromorphone has a faster onset and a longer

duration of action than fentanyl, without causing delayed respiratory depression. Current evidence supports the safe use of hydromorphone in pediatric neuraxial anesthesia [25]. Hydromorphone-ropivacaine combinations have demonstrated superior analgesia compared to ropivacaine alone, reducing the need for systemic opioids and minimizing opioid-related adverse effects. Studies in pediatric populations undergoing urological, abdominal, and orthopedic procedures have shown that this combination enhances postoperative analgesia, facilitates early mobilization [26], and may improve surgical outcomes by reducing opioid-induced side effects such as nausea, vomiting, and pruritus [27, 28]. The current study builds upon this foundation by evaluating its immunomodulatory effects in addition to its analgesic efficacy.

Despite the improvements in appearance and function achieved through hypospadias surgery, the impact of surgical stress and anesthesia on the immune system remains a major concern. Studies have shown that surgical stress can trigger the release of stress hormones and inflammatory mediators, inducing systemic inflammatory response syndrome (SIRS) and suppressing immune function. This immune suppression is particularly pronounced in children, whose immune systems are still developing, increasing their susceptibility to infections and other complications. This study aims to explore the effects of combining hydromorphone and ropivacaine in caudal block anesthesia on postoperative immunosuppression. It seeks to provide new anesthetic strategies for hypospadias repair, with the goal of reducing postoperative immunosuppression and promoting recovery.

Patients and methods

Patients

This prospective, randomized, controlled trial was conducted in the Department of Anesthesiology and Perioperative Medicine at Anhui Provincial Children's Hospital (Anhui, China) from June 2023 to August 2024. The study protocol was approved by the Ethics Committee of Anhui Children's Hospital (Approval Number: ETYY-2022-025). Written informed consent was obtained from the guardians of all participants in accordance with the principles of the Declaration of Helsinki. Inclusion criteria consisted of: (1) Children diagnosed with hypospadias requiring urethroplasty at Anhui Children's Hospital. (2) Ages 1 to 3 years. (3) ASA classification I or II. (4) Complete medical records without prior treatment at other facilities. Exclusion criteria included: (1) Children with severe hypovolemia and shock. (2) Children with thrombocytopenia or coagulopathy. (3) Children with infections at the puncture site. (4) Patients with central nervous system disorders, particularly those with spinal cord or nerve root abnormalities.(5) Patients exhibiting signs of intracranial hypertension preoperatively. (6) Children with acute or severe bronchial asthma.

Methods

Patients were randomly assigned to two groups: the Ropivacaine group (R group), which received sacral block anesthesia with ropivacaine (0.25% ropivacaine at 1 ml/kg) combined with general anesthesia, and the Hydromorphone group (HR group), which received hydromorphone plus ropivacaine (hydromorphone at 10 μg/kg combined with 0.25% ropivacaine at 1 ml/kg) [29]. The attending physician independently assessed patient eligibility based on medical history. Randomization was performed using a computer-generated randomization table ($n = 50$ per group). The attending physician was also responsible for drug preparation to ensure consistency throughout the study.

Preoperative requirements included fasting: clear liquids for 2 h, formula milk for 6 h, and solid food for 8 h. Patients received a topical application of lidocaine ointment (a 1:1 soluble mixture of 2.5% lidocaine and 2.5% prilocaine) the night before surgery and had a peripheral intravenous catheter placed. All patients were accompanied by a parent into the operating room, where they were connected to monitors (Philips Medizin System Boeblingen GmbH) to assess blood pressure (BP), heart rate (HR), and pulse oximetry (SpO_2).

Anesthesia induction

Induction agents included 0.01 mg/kg of pentobarbital (Jinzhou Aohong Pharmaceutical Co., Ltd., National Drug Code H20020606) and 0.15 mg/kg of dexamethasone (Hainan Betters Pharmaceutical Co., Ltd., National Drug Approval Code H32021561) (maximum dose 5 mg). Sevoflurane (Maruishi Pharmaceutical Co., Ltd., H20150020) was initiated at 8% and then reduced to 5%. Once the child exhibited no spontaneous movement, regular breathing, and centered gaze, a laryngeal mask was placed. For patients with airway hyperreactivity, an orotracheal tube was inserted. Patients requiring intubation received cisatracurium (Jiangsu Hengrui Medicine Co., Ltd., National Drug Approval Code H20183042) (0.1 mg/kg) four minutes prior. Following mechanical ventilation, respiratory parameters were adjusted to maintain end-tidal carbon dioxide levels at 30–35 mmHg. All patients underwent sacral block anesthesia administered by the same anesthetist, while another monitored vital signs.

The child was positioned on their left side, with knees drawn toward the abdomen. Midpoints of the sacral angles were marked, and the injection site and surrounding area were sterilized after handwashing. Using an ultrasound diagnostic system (Mindray Resona 7EXP, Shenzhen Mindray Bio-Medical Electronics Co., Ltd.,

China) with a sterile sheath, the sacral canal was visualized. The ultrasound transducer was positioned perpendicular to the midline to obtain transverse views, scanning from the coccyx to the head. Once a cross-sectional image of the sacral angle was obtained, the transducer was rotated 90° for a longitudinal view. The probe was then moved toward the coccyx and head to observe the S5-S1 junction. Using the spinous process as a guide, the echogenic sacral ligament was visualized, allowing for clear identification of the needle's trajectory.

After confirming no blood or cerebrospinal fluid upon aspiration, anesthetic was slowly injected into the sacral canal in a stepwise manner. In the R group, 0.25% ropivacaine (Shijiazhuang Fourth Pharmaceutical Co., Ltd., National Drug Approval Code H20203107) (1 ml/kg) was administered; in the HR group, 0.25% ropivacaine (1 ml/kg) combined with hydromorphone (Yichang Renfu Pharmaceutical Co., Ltd., National Drug Approval Code H20120100) (10 μg/kg) was used. The maximum dose for both groups was capped at 30 ml (1 ml/kg) [30]. The delay for sacral block was set to 60 s. Post-injection, subcutaneous swelling was examined. General anesthesia was maintained with sevoflurane, adjusting the inhalation concentration to ensure hemodynamic stability (changes in mean arterial pressure [MAP] and heart rate [HR] not exceeding 20% of baseline). After the return of spontaneous breathing and full consciousness, the laryngeal mask or endotracheal tube was removed, and the patient was transferred to the recovery room for observation. Patients met discharge criteria (Aldrete score ≥ 9) before being transferred to the surgical ward [31]. If MAP and/or HR increased more than 20% from baseline or if the child exhibited movement during the procedure, sacral block anesthesia was deemed unsuccessful. If intravenous sufentanil (Yichang Renfu Pharmaceutical Co., Ltd., National Drug Approval Code H20054171) > 0.1 μg/kg was required 20 min post-sacral puncture, the patient was excluded from the study. All patients received 0.1 mg/kg of Tropisetron (Hangzhou Minsheng Pharmaceutical Co., Ltd., National Drug Approval Code H20052664) intravenously after surgery.

T lymphocyte subset analysis

Five milliliters of venous blood were collected at the following time points: pre-anesthesia (T0), end of surgery (T1), 24 h postoperatively (T2), 48 h postoperatively (T3), and 72 h postoperatively (T4), mixed with anticoagulant tubes. After centrifugation at 3000 rpm for 5 min at room temperature, plasma was stored at -40 °C for analysis. Flow cytometry (FACS Calibur, BD Company) was used to analyze the anticoagulated blood samples, counting T lymphocyte subsets ($CD3^+$, $CD4^+$, and $CD8^+$).

Postoperative pain management

Pain was assessed at 1, 6, 12, 18, and 24 h postoperatively using the Modified Children's Hospital of Eastern Ontario Pain Scale (M-CHEOPS) [32], with scores exceeding 6 indicating inadequate analgesia [33]. Acetaminophen (Shanghai Johnson Pharmaceutical Co., Ltd., National Drug Approval Code H19990007) (20 mg/kg) was administered orally as needed. Pain assessments and duration of analgesia were recorded during the first 24 h post-surgery, defined as the time from surgery completion to the first dose of acetaminophen. If pain persisted, doses were repeated every 4 h until alleviation was achieved. Total acetaminophen dosage, intervals, and consumption were documented.

Observation indicators

Basic information and Surgery/Anesthesia-Related data

Basic demographic and anesthesia-related data collected included patient gender, age, weight, height, duration of surgery (from incision to dressing completion), duration of anesthesia (from induction to extubation), recovery of spontaneous breathing (from cessation of sevoflurane to resumption of breathing), eye-opening time (from cessation of sevoflurane to eye-opening), extubation time, and PACU stay duration.

Primary outcome measures

Distribution of T cell subsets ($CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ ratios) at T0, T1, T2, T3, and T4.

Secondary outcome measures

Postoperative pain scores were assessed using the modified M-CHEOPS at 1, 6, 12, 18, and 24 h. Postoperative sedation levels were evaluated using the Ramsay sedation scale at the same time points [34]. Blood pressure, MAP, heart rate, and pulse oximetry were recorded at multiple points: pre-anesthesia, post-induction, post-sacral block, before transfer to recovery, and immediately after extubation. The occurrence, timing, and dosage of rescue analgesia during the perioperative period were documented, along with any postoperative adverse events. The use of airway devices (endotracheal tube/laryngeal mask) during general anesthesia was recorded for each patient.

Statistical analysis

The sample size calculation for this study was based on detecting significant differences in postoperative immune function and pain management between the Hydromorphone-Ropivacaine (HR) group and the Ropivacaine (R) group. Based on previous studies assessing similar outcomes, a medium effect size (Cohen's $d \approx 0.5$) was assumed for differences in T lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ ratios) and pain scores (M-CHEOPS) between the two groups. A two-sided

significance level of 0.05 was used for statistical testing. The power was set at 80% to ensure the study had sufficient sensitivity to detect meaningful differences between groups. To account for potential loss to follow-up, we estimated a dropout rate of 10%. Using these parameters, the sample size was calculated using standard sample size estimation formulas for comparing means between two independent groups. The final estimated sample size was a minimum of 50 patients per group, for a total of 100 patients.

Data were analyzed using SPSS software (version 20.0). Descriptive statistics were applied to summarize demographic data and surgical/anesthetic-related variables. Continuous variables, such as patient age, weight, surgery duration, and anesthesia duration, were expressed as mean ± standard deviation (SD) and compared using independent samples *t*-tests for normally distributed data, or Mann-Whitney *U* tests for non-normally distributed data. Categorical variables, including gender and airway management tools, were presented as frequencies (n) and percentages (%) and analyzed using chi-square tests or Fisher's exact tests, as appropriate. Repeated measures analysis of variance (ANOVA) was used to evaluate changes in T lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$, and the $CD4^+/CD8^+$ ratio), pain scores (M-CHEOPS), and sedation scores (Ramsay) over time (T0, T1, T2, T3, T4 for lymphocyte subsets; 1, 6, 12, 18, and 24 h post-surgery for pain and sedation scores). In cases where the ANOVA results showed significant differences, post hoc analyses were conducted using the least significant difference (LSD) test to identify specific time points with differences. Vital signs (blood pressure, mean arterial pressure, heart rate, and oxygen saturation) were compared between groups at various time points using repeated measures ANOVA. The need for rescue analgesia and the incidence of postoperative adverse reactions were analyzed using chi-square or Fisher's exact tests. A *p*-value of < 0.05 was considered statistically significant for all comparisons.

Results

Study population and baseline characteristics

A total of 111 patients were assessed for eligibility to participate in this study. Six patients were excluded due to the intraoperative administration of opioid analgesics for hemodynamic instability, and five patients declined to participate. Ultimately, 100 patients completed the study and were included in the statistical analysis, with 50 patients in each group (Fig. 1). No significant differences were found between the two groups regarding demographic factors (age, gender, height, weight) or clinical characteristics (diagnosis) ($p > 0.05$; Table 1). Additionally, there were no significant differences between the groups in terms of surgery duration, anesthesia duration, time to return of spontaneous respiration, time to eye opening, extubation time, PACU stay, or length of hospital stay (all $p > 0.05$; Table 1).

Immune function

At baseline (T0), no significant differences were observed between the two groups in terms of T lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ ratios) ($p > 0.05$). However, compared to T0, the HR group showed significant reductions in $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ ratios at T1, T2, and T3 ($p < 0.001$). Similarly, the R group demonstrated significant decreases in these subsets at T1, T2, T3, and T4 (Except for the T0 VS T4 $p = 0.01$, all other $p < 0.001$). At T1, T2, T3, and T4, the HR group had significantly higher levels of $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ ratios compared to the R group ($p < 0.001$). By T4, the levels of $CD3^+$, $CD4^+$, and the $CD4^+/CD8^+$ ratio in the HR group had essentially normalized to baseline levels (T0) ($CD3^+$: $p = 0.184$; $CD4^+$: $p = 0.090$; $CD8^+$: $p = 0.932$; $CD4^+/CD8^+$: $p = 0.236$).the HR group still exhibited elevated levels of $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ ratios relative to the R group ($p < 0.001$). Importantly, there were no significant changes in $CD8^+$ levels at any of the five time points for either group (Table 2). These findings suggest that the HR treatment has a lesser impact on cellular immune function compared to the R treatment.

Postoperative pain and analgesia

Postoperative pain, assessed using M-CHEOPS scores, was significantly lower in the HR group at 6, 12, and 18 h postoperatively compared to the R group ($p < 0.001$; Table 3). Additionally, 38 children (38%) did not require rescue analgesia within the first 24 h postoperatively. Of these, 24 (48%) were in the HR group and 14 (28%) were in the R group, with an analgesia duration exceeding 24 h in all cases. Among the children who required rescue analgesia ($n = 62$), those in the HR group required less postoperative rescue analgesia ($p = 0.046$) and had a longer duration of analgesia ($p < 0.001$) compared to the R group (Table 4).

Postoperative sedation levels

The comparison of Ramsay Sedation Scores between the two groups after surgery revealed that the HR group had significantly higher sedation scores than the R group at 1 h ($p = 0.0087$) and 6 h ($p < 0.0001$) postoperatively. However, no significant differences in sedation scores were observed between the two groups at 12 h ($p = 0.435$), 18 h ($p = 1$), and 24 h ($p = 1$) postoperatively (Table 5).

Vital signs and airway devices

There were no significant differences between the groups in terms of heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, or oxygen

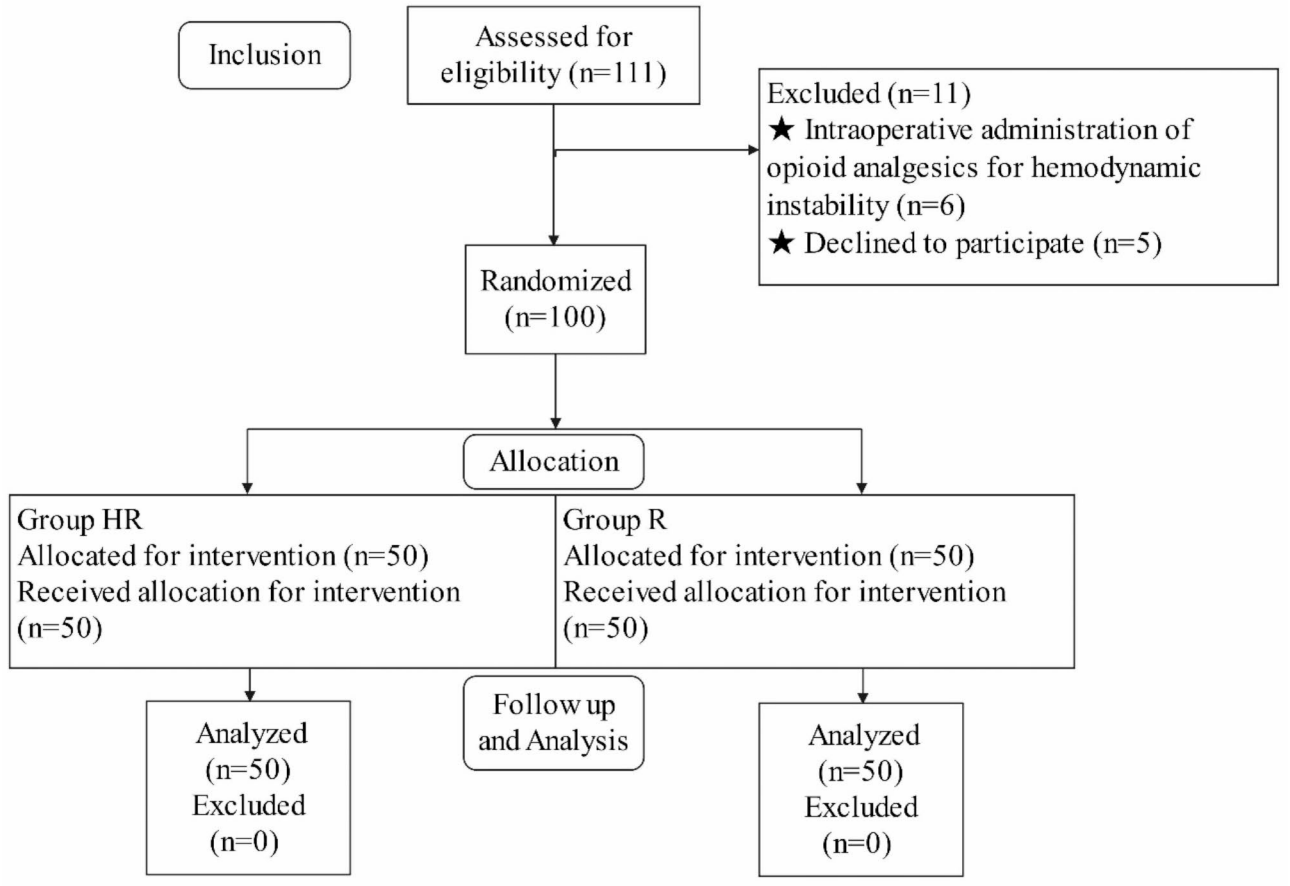

Fig. 1 Flowchart for selection of study participants

Table 1 Comparison of baseline characteristics of patients between the HR and R groups (Mean ± SD)

Variable	HR	*R*	*p*
Age (years)	1.75 ± 0.81	1.82 ± 0.76	0.657
Height (cm)	86.52 ± 6.85	87.01 ± 7.03	0.725
Body Mass Index (kg/m^2)	16.84 ± 1.92	17.22 ± 1.81	0.311
Time of Surgery (min)	141.29 ± 52.66	138.42 ± 48.14	0.777
Time of Anesthesia (min)	175.27 ± 61.15	179.95 ± 67.11	0.716
Time of Spontaneous Breathing Recovery (min)	5.64 ± 3.15	5.99 ± 2.99	0.570
Time of Eyes Opening (min)	17.35 ± 4.17	17.97 ± 5.59	0.531
Time of Extubation (min)	12.07 ± 5.10	12.72 ± 6.23	0.569
PACU Stay Time (min)	31.48 ± 7.36	32.67 ± 8.15	0.445
Length of Hospital Stay (days)	10.1 ± 1.4	10.6 ± 1.7	0.112

HR (n = 50), Hydromorphone-Ropivacaine Composite Group; R (n = 50), Ropivacaine Group

saturation at any of the following time points: pre-anesthesia, immediately after intubation, post-sacro-coccygeal block, immediately before surgery, immediately after surgery, or immediately after extubation (all $p > 0.05$; Fig. 2). The use of laryngeal masks and endotracheal intubation was also comparable between the groups: HR group (LMA = 48; ETT = 2) and R group (LMA = 47; ETT = 3) ($p = 0.617$).

Complications

No significant differences were observed between the two groups in terms of postoperative adverse reactions (all $p > 0.05$; Table 6).

Discussion

This study reveals that both groups experienced a decrease in $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ ratios at T1, T2, and T3 compared to T0, indicating post-surgical immunosuppression. However, the HR group (hydromorphone combined with ropivacaine) demonstrated a more robust recovery in immune markers than the R group (ropivacaine alone). By T4, immune markers in the HR group had largely returned to preoperative levels, whereas markers in the R group remained lower, suggesting an immunoprotective advantage of the HR approach. The observed T-cell subset changes imply that the HR group may better mitigate postoperative immunosuppression, a particularly relevant effect in pediatric postoperative recovery, where the underdeveloped immune system in children makes them more

Table 2 Comparison of T lymphocyte subsets in patients with hypospadias before and after receiving hydromorphone-ropivacaine caudal block anesthesia and ropivacaine caudal block anesthesia treatment (Mean ± SD)

Time point	Group	$CD3^+$	$CD4^+$	$CD8^+$	$CD4^+/CD8^+$
T0	HR	68.73 ± 2.00	38.86 ± 1.84	26.56 ± 1.74	1.47 ± 0.14
	R	67.67 ± 5.58	38.96 ± 1.44	26.81 ± 0.94	1.47 ± 0.09
T1	HR	62.22 ± 3.94[a]	35.55 ± 2.08[a]	26.26 ± 1.09	1.35 ± 0.08[a]
	R	56.27 ± 4.51[a, b]	29.59 ± 4.21[a, b]	26.52 ± 0.98	1.12 ± 0.18[a, b]
T2	HR	53.73 ± 1.98[a]	26.84 ± 1.90[a]	26.23 ± 0.79	1.02 ± 0.15[a]
	R	50.09 ± 4.89[a, b]	23.12 ± 2.59[a, b]	26.50 ± 0.70	0.87 ± 0.10[a, b]
T3	HR	61.88 ± 4.21[a]	34.93 ± 4.60[a]	26.18 ± 2.80	1.33 ± 0.18[a]
	R	54.27 ± 4.51[a, b]	27.29 ± 4.21[a, b]	26.50 ± 2.66	1.03 ± 0.20[a, b]
T4	HR	68.20 ± 1.96	38.23 ± 1.84	26.53 ± 1.73	1.44 ± 0.11
	R	63.67 ± 5.58[a, b]	34.86 ± 6.19[a, b]	26.61 ± 1.33	1.31 ± 0.24[a, b]

[a] $p<0.05$ vs. T0 in the same group; [b] $p<0.05$ vs. the CGEA group at the same time point. T0, before anesthesia; T1, at the end of surgery; T2, 24 h after surgery; T3, 48 h after surgery; T4, 72 h after surgery. HR ($n=50$), Hydromorphone-Ropivacaine Composite Group; R ($n=50$), Ropivacaine Group; CD, cluster of differentiation

Table 3 Comparison of M-CHEOPS score for postoperative analgesia time between the two groups of children (Mean ± SD)

Time Point	HR	*R*	*p*
1 h	4.72 ± 0.55	4.83 ± 0.71	0.448
6 h	5.69 ± 0.62	6.51 ± 0.70	0.00006
12 h	6.49 ± 0.52	7.42 ± 0.69	0.00002
18 h	6.97 ± 0.67	8.60 ± 0.63	0.00001
24 h	6.23 ± 0.56	6.45 ± 0.71	0.315

HR ($n=50$), Hydromorphone-Ropivacaine Composite Group; R ($n=50$), Ropivacaine Group

Table 4 Comparison of the number of acetaminophen doses received by children, the dosage of acetaminophen used, and postoperative analgesia duration under two different caudal administration regimens

	HR ($n=50$)	R ($n=50$)	*p*
n (%)	26 (52%)	36 (72%)	0.039
Dose[a]	35 (22–46)	45 (22–65)	0.046
Time[b]	732 (425–860)	390 (182–468)	0.001

HR, Hydromorphone-Ropivacaine Composite Group; R, Ropivacaine Group. Dose and time presented as median M (P_{25} ~ P_{75}). [a]Acetaminophen dose in mg.kg − 1 in 24 h. [b]Analgesia time in minutes

Table 5 Frequency of patients with different intensities of sedation assessed using Ramsay scale in the postoperative period in the two groups of children undergoing caudal epidural anesthesia with different anesthetic solutions

Time point	Group	Mild	Moderate	Deep
1 h	HR	30	16	4
	R	36	12	2
6 h	HR	38	12	0
	R	47	3	0
12 h	HR	46	4	0
	R	47	3	0
18 h	HR	50	0	0
	R	50	0	0
24 h	HR	50	0	0
	R	50	0	0

HR ($n=50$), Hydromorphone-Ropivacaine Composite Group; R ($n=50$), Ropivacaine Group. Sedation intensity was classified as mild (0–2 points on Ramsay scale), moderate (3–4 points on Ramsay scale) or deep (5–6 points on Ramsay scale)

susceptible to infection. Previous studies have established a link between postoperative immunosuppression and an increased risk of complications such as infection and delayed healing [15]. Additionally, the HR group's faster recovery in immune function could be associated with hydromorphone's immunomodulatory properties, aligning with research that suggests hydromorphone reduces postoperative inflammation [35]. Hydromorphone has been shown to lessen postoperative immunosuppression by inhibiting the release of inflammatory cytokines, enabling a more rapid immune recovery following surgical stress. This effect may not only enhance postoperative infection resistance in children but also reduce the incidence of postoperative complications [36]. Interestingly, no significant changes in $CD8^+$ levels were observed between the groups at any postoperative time point. One possible explanation is that the groups of patients were treated with the same surgical procedures and the degrees of injury of the two groups were not significantly different from each other. Therefore, the direct cell killing effect of $CD8^+$ T cells on target cells was not obviously affected [37]. Additionally, the duration of immune monitoring (up to 72 h postoperatively) may not have been sufficient to capture delayed changes in $CD8^+$ levels. Further studies measuring longer-term immune responses and additional immune markers could provide deeper insights into these mechanisms.

From an analgesic perspective, the HR group demonstrated superior postoperative pain control, as evidenced by lower M-CHEOPS scores at 6, 12, and 18 h post-surgery compared to the R group. Patients in the HR group also exhibited longer pain-free intervals and required fewer doses of rescue analgesia. When administered via caudal block, hydromorphone has shown to be a safe and effective method for managing perioperative pain in pediatric patients [25]. Research by Hong et al. corroborates these findings, showing that hydromorphone

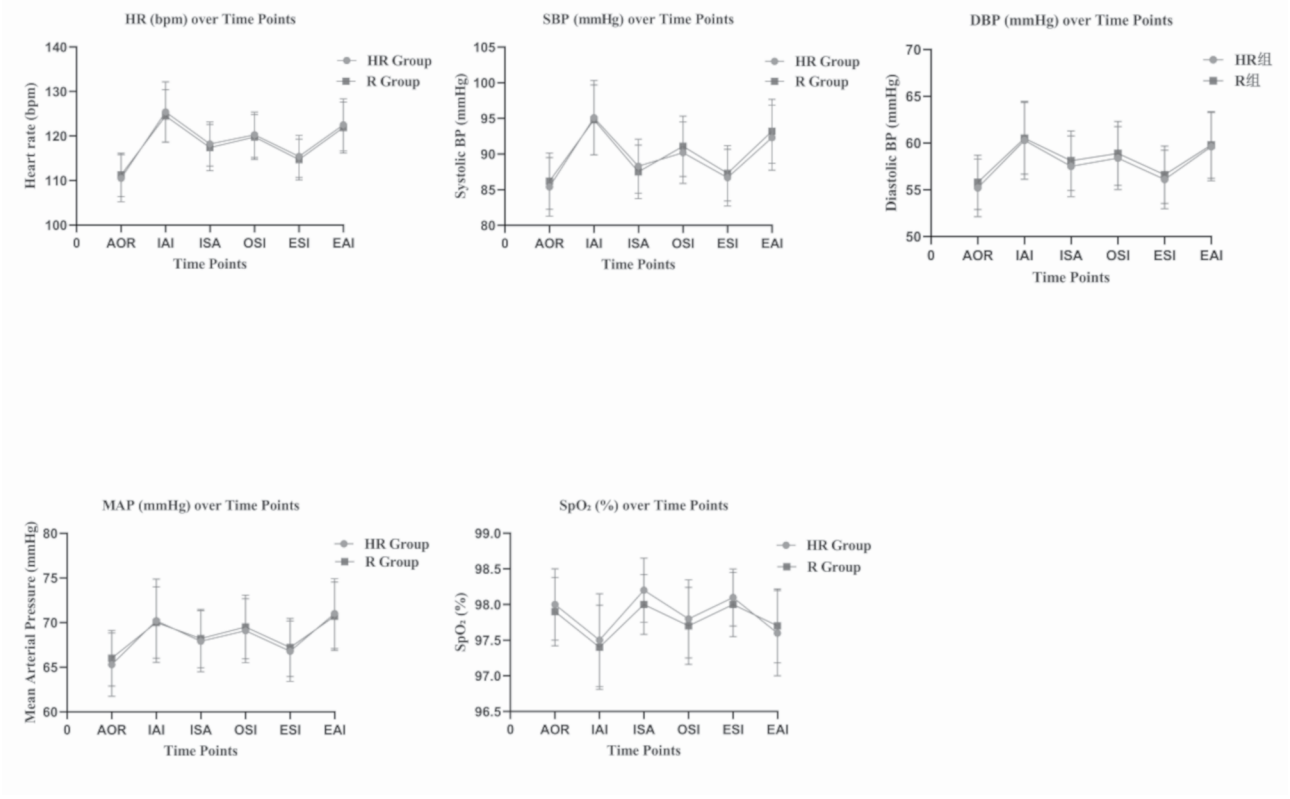

Fig. 2 Comparison of perioperative basic vital signs in children under general anesthesia combined with caudal block using two different caudal administration regimens. HR ($n=50$), Hydromorphone-Ropivacaine Composite Group; R ($n=50$), Ropivacaine Group, all $p>0.05$

Table 6 Comparison of the incidence of postoperative adverse complicaitons between the two groups of children

Group	Nausea and Vomiting	Hypoxemia	Respiratory Depression/Apnea	Pruritus	Bronchospasm	Laryngeal Spasm
HR	5 (10%)	5 (10%)	4 (8%)	0	0	0
R	7 (14%)	5 (10%)	5 (10%)	3 (6%)	0	0
p	0.538	1	1	0.242		

HR ($n=50$), Hydromorphone-Ropivacaine Composite Group; R ($n=50$), Ropivacaine Group; The data in the table are example, example (%)

provides comparable pain relief to intravenous PCA in pediatric spinal surgeries, with fewer adverse effects [38]. Other studies, such as Yang et al., have shown that hydromorphone combined with local anesthetics provides extended analgesia across various surgeries, likely due to hydromorphone's opioid receptor-mediated reduction of pain signal transmission [39]. In our study, the HR group did not require additional analgesia postoperatively, further supporting the efficacy of this combination for prolonged analgesia. This effect is particularly beneficial in pediatric patients, as it reduces the need for higher opioid doses, lowering the risk of adverse effects, including excessive sedation and respiratory depression, consistent with findings from other studies [40].

Sedation levels, measured via the Ramsay scale, revealed statistically significant differences between the two groups at 1 h and 6 h post-surgery ($p<0.05$), though no significant differences were observed at later time points. This suggests that hydromorphone may cause a slight increase in sedation levels early on, with the effect diminishing over time. Early sedation in the perioperative period can alleviate patient anxiety and stress responses, thereby enhancing surgical safety and patient comfort. Importantly, none of the patients experienced excessive sedation or related complications, nor were there significant hemodynamic changes. These results highlight the safety of the hydromorphone dose used in caudal anesthesia in this study. Related studies indicate that hydromorphone has relatively few side effects, and its pharmacologic properties support an effective balance between analgesia and side effect management, making it an attractive choice in pediatric anesthesia [41].

Despite the HR group's better outcomes in immune function and analgesia, there were no significant differences between the two groups in terms of surgical time, anesthesia time, or recovery time. This suggests that the combination of hydromorphone and ropivacaine did not impact the overall duration of surgery or anesthesia

nor the recovery times. Additionally, there were no significant differences in physiological parameters such as heart rate, blood pressure, and oxygen saturation, indicating that both anesthetic approaches were equally safe and effective in maintaining intraoperative and postoperative stability. Hydromorphone, while effective for analgesia, carries potential risks such as respiratory depression, pruritus, nausea, vomiting, urinary retention, and prolonged sedation. In our study, adverse effects were minimal, likely due to careful dosing and adjunctive administration of dexamethasone and antiemetics, which are known to reduce the incidence of nausea and vomiting [42]. However, hydromorphone's opioid nature necessitates caution, as pediatric patients are particularly vulnerable to opioid-induced respiratory depression, which may require close postoperative monitoring. Additionally, prolonged sedation can impact early mobilization and recovery, potentially delaying discharge. Some studies have also linked opioids to immunosuppressive effects through modulation of cytokine release and T-cell function, which warrants further investigation. Clinicians should carefully weigh the benefits of enhanced analgesia against these potential risks, ensuring individualized dosing strategies and proper monitoring protocols.

The findings from this study suggest several clinical implications. First, adding hydromorphone to a ropivacaine caudal block may effectively balance analgesia with immunoprotection, potentially reducing the risk of postoperative infections and other immune-related complications in children. This strategy could be particularly advantageous for high-risk pediatric patients, such as those with immunodeficiencies. Secondly, this method effectively prolongs analgesia, reduces the need for postoperative opioids, and further enhances pediatric surgical safety [43]. Furthermore, the immunomodulatory effects observed in this study may have broader implications beyond hypospadias repair. Given that postoperative immunosuppression is a concern in many pediatric surgeries, the ability of the combination of hydromorphone and ropivacaine caudal block to preserve immune function may reduce the incidence of postoperative infections and enhance overall recovery. The observed impact of this combination on maintaining T-cell homeostasis suggests its potential for improving surgical outcomes in a broader range of pediatric surgeries, such as inguinal hernia repair, orchiopexy, and lower limb orthopedic procedures.

In conclusion, this study demonstrates that the combination of hydromorphone and ropivacaine for caudal block in hypospadias repair surgery holds considerable potential for success. Compared with ropivacaine alone, the HR group exhibited significantly enhanced recovery of immune function and superior postoperative pain control, with immune markers returning more rapidly to preoperative levels and lower postoperative pain scores, as well as prolonged analgesia, and higher sedation scores in the early postoperative period. Additionally, the HR group showed no significant differences in surgical time, anesthesia time, or recovery time compared with the R group, indicating that the combination did not increase the complexity of surgery or anesthesia. These findings suggest that the combination of hydromorphone and ropivacaine not only optimizes perioperative management but also potentially reduces postoperative complications, thereby further enhancing surgical success rates, especially in pediatric patients with underdeveloped immune systems. Although our results suggest potential clinical benefits of combining hydromorphone with ropivacaine, further large-scale, multicenter randomized controlled trials are required to validate its applicability across different surgery types and pediatric populations. Additionally, variations in surgical techniques and surgeon expertise must be considered, as these factors may influence immune responses and overall outcomes. Future studies should also examine the long-term effects on immune function and analgesia to more comprehensively evaluate the clinical feasibility and safety of this anesthetic approach. This study primarily focused on T lymphocyte subsets as markers of immune function. However, incorporating inflammatory cytokines such as IL-6, IL-2, cortisol, and C-reactive protein (CRP) could have provided a more comprehensive assessment of perioperative immune modulation. Future studies should consider measuring these biomarkers to elucidate the full spectrum of immune changes induced by hydromorphone.

Conclusion

In summary, this study demonstrates that hydromorphone combined with ropivacaine for caudal block more effectively alleviates postoperative cellular immune suppression following hypospadias surgery compared to ropivacaine alone. Additionally, it provided superior postoperative analgesia and early sedation without causing any additional clinical complications.

Abbreviations

ASA	American Society of Anesthesiologists
HR	Hydromorphone-Ropivacaine Group
R	Ropivacaine Group
LMA	Laryngeal Mask Airway
ETT	Endotracheal Tube
PACU	Post Anesthesia Care Unit
M-CHEOPS	Modified Children's Hospital of Eastern Ontario Pain Scale
AOR	After entering the Operating Room
IAI	Immediately After Intubation
ISA	Immediately After Spinal Anesthesia
OSI	Onset of Surgery Immediately
ESI	End of Surgery Immediately
EAI	Extubation Immediately
MAC	Minimum Alveolar Concentration
Ramsay	Ramsay sedation scores

$PetCO_2$	Partial pressure of end-tidal carbon dioxide

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-03053-7.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Acknowledgements
Authors would like to thank all the patients, nurses, people who helped collect the data and the hospital authorities.

Author contributions
Yuzhu Cai and Mingwen Yang wrote the main manuscript text, Xinghui Liu and Lingli Zhang prepared Figures 1- 2; Tables 1-6, Jun Wang and Yingying Sun were responsible for the statistical analysis. All authors reviewed the manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Anhui Children's Hospital Ethics Committee (Ethics Number: ETYY-2022-025). Informed consent was obtained from all participants or their legal guardians prior to participation in the study. The purpose, procedures, potential risks, and benefits of the study were explained to each participant, and written informed consent was obtained. For participants under the age of 18, informed consent was obtained from their parents or legal guardians. All personal data were handled confidentially, and all efforts were made to ensure the privacy and anonymity of the participants throughout the study. It was registered with the Chinese Clinical Trial Registry (https://www.chictr.org.cn) with registration number: ChiCTR2300072599, registration date: 2023-06-19.

Consent for publication
This study does not contain any individual person's data in any form (including any individual details, images or videos) that compromise anonymity. Therefore, it is not applicable to include a consent for publication statement in this section.

Competing interests
The authors declare no competing interests.

Clinical implications
a. What is already known about the topic: Caudal block anesthesia, particularly when combined with general anesthesia, has been shown to effectively reduce postoperative pain and limit immunosuppression in pediatric surgeries by lowering the release of stress hormones and inflammatory mediators.
b. What new information this study adds: This study demonstrates that the combination of hydromorphone with ropivacaine for caudal block anesthesia results in superior postoperative pain relief and a faster recovery of immune function, as indicated by higher levels of T lymphocyte subsets ($CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ ratios) compared to ropivacaine alone.
In accordance with BMC Series editorial policies, this study adheres to the CONSORT guidelines for reporting clinical trials. A completed CONSORT checklist is available as a supplementary file.

Author details
[1]Department of Anesthesiology, Anhui Provincial Children's Hospital, Hefei 230051, China

Received: 29 October 2024 / Accepted: 2 April 2025
Published online: 10 April 2025

References

1. Lavoie C, Chun B, Au M, et al. Prevalence of disorders of sex development in patients with hypospadias and cryptorchidism. J Pediatr Urol. 2025;21(1):71–7.
2. Yang Q, Qu WY, Yang L, et al. Literature on the aetiology of hypospadias in the last 5 years: molecular mechanism and environmental factors. Andrologia. 2014;46(6):583–91.
3. Pippi Salle JL, Romao RL, Chua M. Redo surgery to improve urinary function, sexual function and cosmesis in male patients with exstrophy-epispadias complex complications. Technical principles and pearls based on case scenarios. J Pediatr Urol. 2024;20(Suppl 1):S26–34.
4. Rasool N. Outcome of hypospadias surgery in children. TPMJ. 2024;26:3368.
5. Soave A, Riechardt S, Engel O, et al. Komplikationen Bei Hypospadiekorrekturen Urologe A. 2014;53(7):1001–5.
6. Örtqvist L, Fossum M, Andersson M, et al. Long-term follow-up of men born with hypospadias: urological and cosmetic results. J Urol. 2015;193(3):975–81.
7. Kim MH, Im YJ, Kil HK, et al. Impact of caudal block on postoperative complications undergoing tubularized incised plate urethroplasty for hypospadias repair: A retrospective analysis. Anaesthesia. 2016;71:773–8.
8. Ayob F, Arnold R. Do caudal blocks cause complications following hypospadias surgery in children? Anaesthesia. 2016;71:759–63.
9. Taicher BM, Routh JC, Eck JB, et al. The association between caudal anesthesia and increased risk of postoperative surgical complications in boys undergoing hypospadias repair. Paediatr Anaesth. 2017;27:688–94.
10. Saavedra-Belaunde JA, Soto-Aviles O, Jorge J, et al. Can regional anesthesia have an effect on surgical outcomes in patients undergoing distal hypospadia surgery. J Pediatr Urol. 2017;13:e451–4.
11. Guo R, Yang WW, Zhong ML, et al. The relationship between anesthesia, surgery and postoperative immune function in cancer patients: a review. Front Immunol. 2024;15:1441020.
12. Luo L, Ji J, Dong J, et al. Infiltration and subtype analysis of CD3 + CD20 + T cells in lung cancer. BMC Cancer. 2025;25(1):179.
13. Aarntzen EH, De Vries IJ, Lesterhuis WJ, et al. Targeting CD4(+) T-helper cells improves the induction of antitumor responses in dendritic cell-based vaccination. Cancer Res. 2013;73(1):19–29.
14. Reina-Campos M, Scharping NE, Goldrath AW. CD8 + T cell metabolism in infection and cancer. NAT REV IMMUNOL. 2021;21(11):718–38.
15. Liu Q, Wang Y, Cao X, et al. IL-6 and CD4+/CD8 + are important indicators for predicting prognosis in elderly AECOPD patients: A retrospective study. J Inflamm Res. 2023;18:2601–11.
16. Hogan BV, Peter MB, Shenoy HG, et al. Surgery induced immunosuppression. SURG-J R COLL SURG E. 2011;9(1):38–43.
17. Zhu C, Wei R, Tong Y, Liu J, et al. Analgesic efficacy and impact of caudal block on surgical complications of hypospadias repair: A systematic review and meta-analysis. Reg Anesth Pain Med. 2019;44(2):259–67.
18. Aliena SP, Lini C, Chirayath JJ. Comparison of postoperative analgesic effect of caudal bupivacaine with and without ketamine in pediatric subumbilical surgeries. J Anaesthesiol Clin Pharmacol. 2018;34(3):324–7.
19. Cho JS, Lee MH, Kim SI, et al. The effects of perioperative anesthesia and analgesia on immune function in patients undergoing breast cancer resection: A prospective randomized study. Int J Med Sci. 2017;14(10):970–6.
20. Reysner T, Wieczorowska-Tobis K, Kowalski G, et al. The influence of regional anesthesia on the systemic stress response. Reports. 2024;7(4):89.
21. Agarwala R, Morrison B. Neuraxial anaesthesia and its role in enhanced recovery after surgery: a narrative review. Dig Med Res. 2022;5:20–20.
22. Yen FY, Chang WK, Lin SP, et al. Association between epidural analgesia and cancer recurrence or survival after surgery for renal cell carcinoma: A propensity weighted analysis. Front Med (Lausanne). 2022;8:782336.
23. Bodenbender JP, Eberhart L, Paul C, et al. Efficacy of adjuvants in ophthalmic regional anesthesia: A systematic review and network meta-analysis. Am J Ophthalmol. 2023;252:26–44.
24. Swain A, Nag DS, Sahu S, Samaddar DP. Adjuvants to local anesthetics: current Understanding and future trends. World J Clin Cases. 2017;5(8):307–17.

25. Evans MA, Monahan A, Abhold E, et al. The utilization of caudal hydromorphone for fast-tracking in congenital cardiac surgery in a tertiary-care children's hospital: an audit. J Clin Anesth. 2021;72:110314.
26. Lin H, Nie L. Application of hydromorphone and ropivacaine in Ultrasound-Guided brachial plexus block of children. J Perianesth Nurs. 2022;37(5):662–8.
27. Luo X, Xia Y, Gu M, Yao J. Analgesic effect of ropivacaine combined with hydromorphone following surgery for mixed hemorrhoids: A pilot study. Pain Res Manag. 2022;2033580.
28. Cao X, Bao M, Ma Y, et al. Hydromorphone combined with ropivacaine for erector spinae plane block in patients undergoing modified radical mastectomy: A prospective randomized controlled trial. Med (Baltim). 2024;103(26):e38758.
29. Vetter TR, Carvallo D, Johnson JL, Mazurek MS, Presson RG. A comparison of single-dose caudal clonidine, morphine, or hydromorphone combined with ropivacaine in pediatric patients undergoing ureteral reimplantation. Anesth Analg. 2007;104(6):1356–63.
30. Sato M. Ultrasound-guided quadratus lumborum block compared to caudal ropivacaine/morphine in children undergoing surgery for vesicoureteric reflux. Paediatr Anaesth. 2019;29(7):738–43.
31. El Aoufy K, Forciniti C, Longobucco Y, et al. A comparison among score systems for discharging patients from recovery rooms: A narrative review. Nurs Rep. 2024;14(4):2777–94.
32. Zieliński J, Morawska-Kochman M, Zatoński T. Pain assessment and management in children in the postoperative period: A review of the most commonly used postoperative pain assessment tools, new diagnostic methods and the latest guidelines for postoperative pain therapy in children. Adv Clin Exp Med. 2020;29(3):365–74.
33. Guo J, Zhuang P, Liu K, et al. Effects of an individualized analgesia protocol on the need for medical interventions after adenotonsillectomy in children: A randomized controlled trial. BMC Anesthesiol. 2021;21(1):41.
34. Ramsay MA, Savege TM, Simpson BR, et al. Controlled sedation with alphaxalone-alphadolone. Br Med J. 1974;2(5920):656–9.
35. Alinejadfard M, Rajai Firouzabadi S, Mohammadi I, et al. Efficacy and safety of hydromorphone for cancer pain: a systematic review and meta-analysis. BMC Anesthesiol. 2024;24(1):283.
36. Sayed JA, Abd Elshafy SK, Kamel EZ, et al. The impact of caudally administrated Tramadol on immune response and analgesic efficacy for pediatricpatients: a comparative randomized clinical trial. Korean J Pain. 2018;31(3):206–14.
37. Song P, Dong T, Zhang J, et al. Effects of different methods of anesthesia and analgesia on immune function and serum tumor marker levels in critically ill patients. EXP THER MED. 2017;14(3):2206–10.
38. Hong RG, Gauger V, Caird MS, Burke C. Narcotic-only epidural infusion for posterior spinal fusion patients: A single-center, retrospective review. J Pediatr Orthop. 2016;36(5):526–9.
39. Yang M, Wang L, Chen H et al. Postoperative analgesic effects of different doses of epidural hydromorphone coadministered with ropivacaine after Cesarean section: A randomized controlled trial. Pain Res Manag. 2019;9054538.
40. Luo X, Xia Y, Gu M et al. Analgesic effect of ropivacaine combined with hydromorphone following surgery for mixed hemorrhoids: A pilot study. Pain Res Manag. 2022;2033580.
41. Xu Y, Chen Q, Li P, et al. Safety and efficacy of Esketamine for postoperative analgesia in pediatric patients with hypospadias. Front Surg. 2023;10:1131137.
42. Sridharan K, Sivaramakrishnan G. Drugs for preventing post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: Network meta-analysis of randomized clinical trials and trial sequential analysis. Int J Surg, 2019,69.
43. Cramer J. Comparison of Morphine- and Hydromorphone-Containing Patient-Controlled epidural analgesia solutions in pediatric postoperative patients. J Pediatr Pharmacol Ther. 2019;24(1):22–6.

Publisher's note