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Hydromorphone Combined with Ropivacaine for Caudal Block Reduce Early Postoperative Pain in Children: A Randomized Clinical Trial

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Abstract

Purpose: This prospective, randomized, double-blinded study aimed to evaluate the effectiveness and safety of hydromorphone combined with ropivacaine for caudal block in children.

Patients and Methods: One hundred children scheduled to undergo hypospadias repair or congenital hip arthroplasty at West China Hospital were included. The patients were randomly allocated into the HR group (hydromorphone combined with ropivacaine) or the R group (ropivacaine only). In the HR group, patients received a single-shot caudal block with hydromorphone 10 μg/kg combined with 0.2% ropivacaine 1 ml/kg. In the R group, only 0.2% ropivacaine 1 ml/kg was administered for the single-shot caudal block. The primary outcome was the postoperative pain score for the first 72 hours in both groups.

Results: A total of 106 eligible children were screened, and 100 were included in this trial, with 50 in the HR group and 50 in the R group. The average postoperative FLACC pain score within 12 hours after surgery was significantly lower in the HR group compared to the R group ($P < 0.05$). The pain scores at 1 h, 6 h, and 12 h post-surgery in the HR group were significantly lower than those in the R group ($P < 0.05$). The incidence of moderate-to-severe pain in the HR group was markedly lower than that in the R group ($P < 0.05$).

Conclusion: The use of hydromorphone 10 μg/kg combined with 0.2% ropivacaine for single-shot caudal block in children can effectively reduce early postoperative pain scores and the incidence of moderate-to-severe pain. No adverse reactions were noted from hydromorphone, except pruritus.

Keywords

Hydromorphone, Caudal Block, Children, Postoperative Analgesia

Introduction

Despite recent advances in understanding pediatric pain pathophysiology and improvements in perioperative pain management, literature continues to report inadequacies in assessing and treating children's pain [1]. The incidence of postoperative pain in children is estimated to be around 33%-50%, with acute pain within 24 hours after surgery reported as high as 87% [2,3]. Children who experience severe postoperative pain often face delayed wound healing, prolonged hospital stays, and a higher incidence of emergence delirium, sleep disturbances, and other maladaptive behavior changes that may persist for weeks after surgery [4,5]. Effective postoperative pain management

is crucial to minimize the organic, functional, and psychological impact of surgery.

As a postoperative pain prevention strategy, caudal anesthesia is notable for its technical ease and favorable risk-benefit ratio [6-8]. Ropivacaine, a local anesthetic, is commonly used in caudal blocks at concentrations between 0.1% and 0.375% [9,10]. Previous studies have shown that 0.2% ropivacaine provides analgesia for approximately 4-6 hours [6,11]. Caudal blocks are generally performed after the induction of general anesthesia; therefore, for surgeries lasting 2-3 hours, the postoperative analgesia from the caudal block may last only 2-3 additional hours. To address the limitations of local anesthetics, adjuvant medications have been added to caudal blocks to enhance pain control and prolong postoperative analgesia [12,13].

The evolution of local anesthetic adjuvants has progressed from traditional opioids to a diverse array of drugs. Commonly used adjuvants include opioids, dexmedetomidine, clonidine, and dexamethasone. Opioids, which have been utilized in neuraxial blocks for over 50 years, remain conventional adjuvants [14]. Studies indicate that combining ropivacaine with small doses of morphine can significantly prolong postoperative analgesia, although its use is limited by adverse effects such as respiratory depression, nausea, vomiting, and pruritus, particularly in neuraxial applications [15].

Hydromorphone, a semi-synthetic opioid analgesic, has shown efficacy as an adjuvant in intrathecal anesthesia at a dosage of 100 μg, with fewer adverse effects compared to morphine [16,17]. Hydromorphone primarily acts on opioid receptors to exert its analgesic effect [18]. Structurally, hydromorphone hydrochloride is a hydrogenated ketone derivative of morphine with a keto-group instead of a hydroxyl group at position 6 of the benzoyl ring, making it 5-10 times more potent than morphine and facilitating greater brain penetration, thus potentially offering more controllable analgesia [19,20]. Being moderately lipid-soluble—between morphine and fentanyl—hydromorphone has a faster onset than morphine and a longer duration of analgesia than fentanyl [21,22]. Additionally, its lower incidence of adverse effects and lack of risk for delayed respiratory depression make it a promising option for caudal anesthesia [23-25].

Ropivacaine combined with hydromorphone has demonstrated safety in adult caudal blocks, significantly enhancing postoperative analgesia and prolonging its duration with a low incidence of adverse effects [26]. According to pediatric anesthesia management guidelines from Stanford University, the recommended epidural hydromorphone dose for children is 5-10 μg/kg. Another study reported that 10 μg/kg hydromorphone provided effective analgesia with a low incidence of adverse effects in children [15]. Therefore, hydromorphone compounded with ropivacaine for caudal block is considered appropriate for pediatric use.

Rebound pain (RP), defined as severe pain (NRS >7), may also occur after the effects of the caudal block subside. Studies report that approximately 20-40% of patients experience severe postoperative pain following nerve blocks, although the pathogenesis of RP remains unclear [27-29].

Despite several advantages over other opioids, including morphine, limited studies have examined hydromorphone's use in pediatric patients. This study aims to evaluate the effectiveness and safety of hydromorphone combined with ropivacaine for caudal block in children and to determine if this combination reduces early postoperative pain and the incidence of moderate-to-severe pain in children compared to ropivacaine alone.

Methods

Study Design:

This study is a randomized, controlled, prospective, single-center study. The patient recruitments are showed on a flowchart (**Fig-1**). The study protocol was approved by the ethics committee of West China Hospital of Sichuan University (2020-207). This study was registered at Chinese Clinical Trial Registry (https://www.chictr.org.cn/) (Ref. No. ChiCTR2000032806, Date of registration:11/05/2020, Patient enrolment Date:21/05/2020).

Participants:

Children aged 1-6 years undergoing elective hypospadias repair, phalloplasty, or congenital hip

dislocation surgeries with an estimated operation time of more than 30 minutes at West China Hospital were included. Children were excluded if they met any of the following criteria: (1) contraindications for caudal block, (2) sacral canal closure, (3) congenital heart disease, (4) epilepsy, (5) communication difficulties or mental retardation, (6) obesity (BMI > 26), (7) known drug allergies, (8) severe liver or kidney dysfunction, severe genetic or metabolic diseases, or (9) if their guardian refused to participate in the study.

Outcome Measures:

The primary outcome was the postoperative pain scores for the first 72 hours in both groups. Parents assessed the postoperative pain of children at 6, 12, 24, 48, and 72 hours after surgery using the FLACC score.

Secondary outcomes included the duration of postoperative analgesia from the caudal block, defined as the time from the completion of the caudal block to the first press of the PCIA. The incidence of moderate-to-severe pain, defined as the proportion of patients with a FLACC score ≥ 4 out of the total number of follow-up patients, was also recorded, as well as the use of postoperative rescue analgesics, the total number of effective PCIA compressions after the operation, parental satisfaction scores for postoperative analgesia, children's postoperative sleep quality scores, length of hospital stay, and hospitalization expenses. The incidence of postoperative nausea, vomiting, pruritus, urinary retention, bleeding at puncture sites, and serious adverse events—including cardiac arrest, severe hypoxemia, shock, central nervous system injury, and unplanned ICU admission during treatment—was documented.

Randomization and Blinding:

Randomization was performed by a research assistant not otherwise involved in the study, using SPSS software to assign participants at a 1:1 ratio. Sealed, opaque, and numbered envelopes containing the group assignments were prepared. Once consent was obtained, the envelopes were provided to an anesthetic nurse who was not involved in patient care. The anesthetic nurse prepared the drugs according to the group assignment specified in the envelope. This study was blinded to participants, parents, investigators, anesthesiologists, follow-up personnel, statisticians, and ward physicians and nurses, who were also unaware of the children's group assignments.

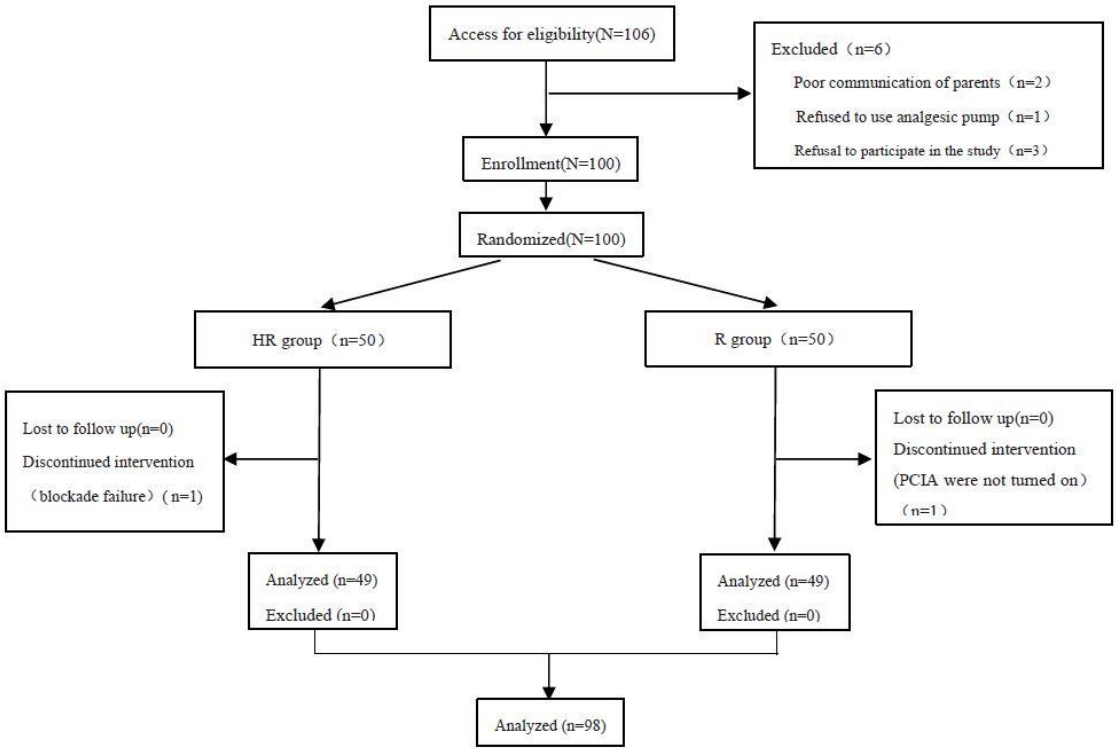

Fig-1: Study Flowchart

Procedures:

Patients undergoing elective hypospadias repair, phalloplasty, and congenital hip dislocation surgeries were screened for eligibility. Children meeting the inclusion and exclusion criteria were selected, and informed consent was obtained from their parents. Before the study procedure, all parents were trained to use the electronic PCIA pump and instructed on the use of the FLACC scale to assess pain severity.

On the morning of surgery, children were brought to the operating room by their parents. Heart rate, non-invasive blood pressure, and pulse oximetry were monitored. Children with established intravenous access in the ward were induced with intravenous anesthesia, while those without access initially received inhalation anesthesia, followed by intravenous induction. General anesthesia was induced in both groups with intravenous midazolam (0.1 mg/kg), fentanyl (3 μg/kg), propofol (3 mg/kg), and cisatracurium (0.15 mg/kg). An LMA or endotracheal tube was placed approximately 3 minutes later. Meanwhile, the anesthetic nurse prepared the caudal block drugs according to the group assignment concealed in the envelope. The hydromorphone and ropivacaine group (HR group) received 0.2% ropivacaine with hydromorphone (10 μg/ml), while the ropivacaine-only group (R group) received 0.2% ropivacaine. The syringes containing the drugs were labeled as study drugs. Caudal block was performed after securing the airway, administered by a senior resident with more than 10 caudal block experiences, supervised by a pediatric anesthesia specialist. Both the resident and specialist were blinded to the caudal block agents. The caudal block injection volume was 1 ml/kg for all surgical categories in this study. All children received 0.8-1 MAC sevoflurane to maintain unconsciousness and to keep hemodynamic parameters (heart rate and mean arterial blood pressure) within 20% of baseline preoperative values. Remifentanil infusion was administered if there were signs of inadequate analgesia during the operation. No significant changes in heart rate or blood pressure at the start of surgery indicated a successful caudal block.

An electronic parent-controlled intravenous analgesia pump was used immediately at the end of surgery. Sufentanil (2 μg/kg), granisetron (0.2 mg/kg), and tramadol (10 mg/kg) were added to 100 ml of normal saline. The PCA pump settings included a continuous infusion rate of 1 ml/h, a single dose of 0.2 ml, and a 10-minute lockout period. Parents assessed the postoperative pain of children at 6, 12, 24, 48, and 72 hours after surgery using the FLACC score. Parents could press the PCIA pump to treat pain with FLACC pain scores ≥ 4. The FLACC pain scores were recorded by blinded assessors during ward visits.

Sample Size Calculation and Statistical Analysis:

The primary outcome was the postoperative pain scores at 1 h, 6 h, 12 h, 24 h, 48 h, and 72 h, which were repeated measurements. The sample size was calculated for repeated measurements using PASS 11 software. Based on a previous study, the minimum clinically significant difference in pain scores for children is 1 point [30]. In a pilot study, the standard deviation between groups was 1.5. Assuming an intraclass correlation coefficient of 0.75, a type I error of 0.05, and a power of 90% (α=0.05, β=0.1), with a 1:1 sample size ratio between the two groups, we planned to enroll 49 children in each group, accounting for a 20% follow-up loss.

SPSS 25 statistical software was used for statistical analysis. Demographic data and baseline indicators were compared to assess the comparability of the two groups. Two-way repeated measures ANOVA was used to evaluate postoperative pain scores up to 72 hours after surgery. Normality of continuous data was assessed using the Kolmogorov-Smirnov test. Normally distributed data were represented by mean ± SD, and Student's t-tests were used to compare anesthesia and operation times. Non-normally distributed data were represented by median (P25, P75), and the rank-sum test was used to analyze age, height, weight, number of effective PCIA compressions, parental satisfaction score, sleep quality scores, length of hospital stay, and hospitalization expenses. Categorical data were presented as frequencies and percentages, with the chi-square test used to compare the incidence of moderate-to-severe pain, use of postoperative rescue analgesics, and incidence of adverse events. Hypotheses were tested using a 2-tailed approach, with $P < 0.05$ considered statistically significant.

Results

One hundred and six American Society of Anesthesiologists (ASA) I–II children were eligible for this study, but 6 were excluded. In total, 100 children were enrolled, with 50 in the HR group and 50 in the R group. However, 1 case from each group was withdrawn from the study due to caudal block failure or PCA pump malfunction. Thus, 48 children from each group were included in the analysis (**Fig-1**). The groups were similar with respect to age, sex, height, and weight ($P > 0.05$). There were no statistically significant differences between the two groups in anesthesia time, operation time, anesthesia recovery time, PACU residence time, or intraoperative opioid use ($P > 0.05$) (**Table-1**).

The average postoperative FLACC pain scores within the first 12 hours were significantly lower in the HR group compared to the R group [2 (1, 4) vs. 3 (2, 4); $P < 0.05$]. No significant difference was found in FLACC pain scores at 24 hours' post-surgery. Pain scores at 1, 6, 12, and 72 hours were significantly lower in the HR group compared to the R group [1 h: 0 (0, 1) vs. 1 (0, 2); $P < 0.05$; 6 h: 2 (0, 3) vs. 3 (2, 4); $P < 0.05$; 12 h: 2 (1, 4) vs. 3 (2, 4); $P < 0.05$; 72 h: 0 (0, 0) vs. 0 (0, 1); $P < 0.05$]. There was no significant difference at 24 and 48 hours between the groups [24 h: 2 (1, 3) vs. 3 (1, 5); $P > 0.05$; 48 h: 1 (0, 2) vs. 1 (1, 3); $P > 0.05$]. Postoperative pain scores were lower in the HR group than in the R group, showing a rise over time that peaked at 12 hours and gradually declined (**Fig-2**). A few missing FLACC pain scores at 24, 48, and 72 hours' post-surgery were imputed with the median of two neighboring time points.

Table-1: Demographic Data

	HR group	R group	*P* value
Age (year)	3 (2, 4)	2 (2, 4)	0.232
Gender (male/female)	29/20	24/25	0.159
Height (cm)	96 (88, 108)	91 (83, 102)	0.204
Weight (kg)	14 (12.5, 19)	13 (10.5, 15.5)	0.176
ASA grade (I/II)	0/49	0/49	
Anesthesia time (min, x±s)	134.2±31.4	131.7±28.2	0.527
Operation time (min, x±s)	90.7±25.4	93.0±30.1	0.322

**Significant at level 0.05*

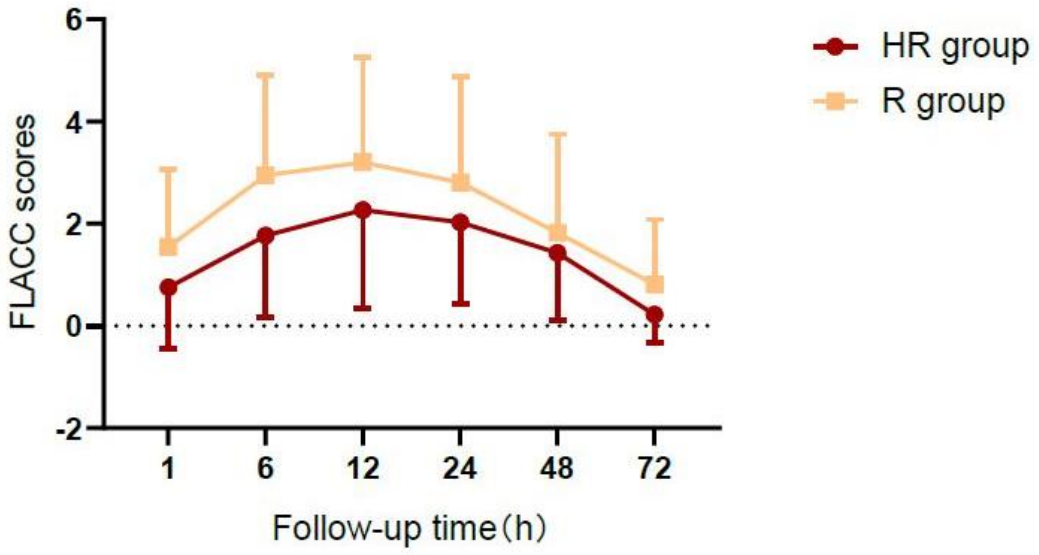

Fig-2:

Trend chart of pain scores between the 2 groups at different postoperative time points, HR group: hydromorphone combined with ropivacaine group, R group: ropivacaine group. Pain scores at 1,6, 12, 24,48 and 72 hours postoperatively.

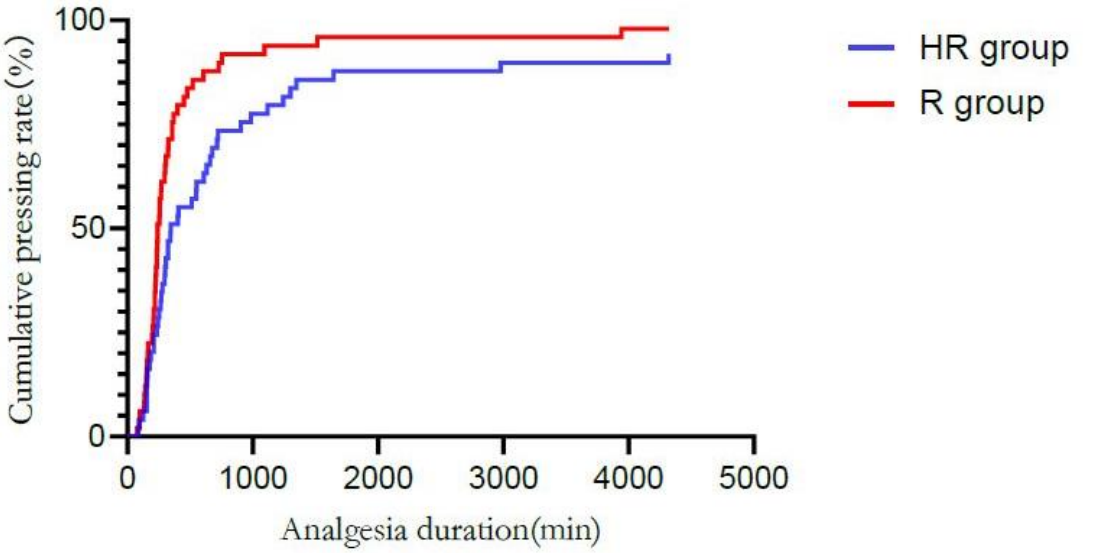

Fig-3:

*PCIA compression counts analysis of analgesia duration (*Significant at level 0.05). HR group: Hydromorphone combined with ropivacaine group, R group: ropivacaine group. analgesic duration: The time between caudal block completed and the first press of PCIA. Cumulative pressing rate: Cumulative rate of compressions for first compression of PCIA.*

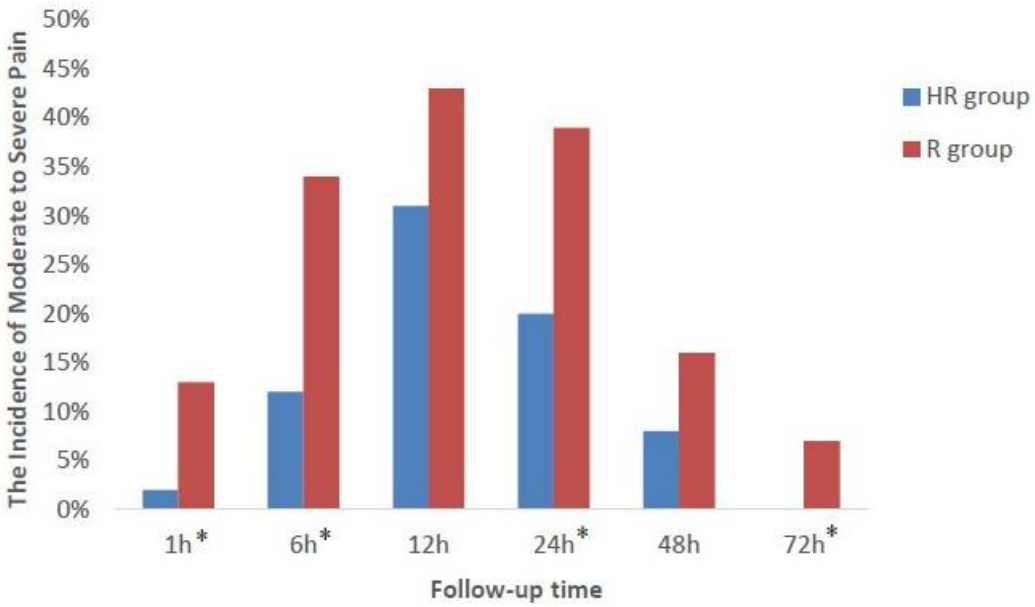

Fig-4:

*The incidence of moderate to severe pain between the 2 groups during the 72-hour postoperative period (*Significant at level 0.05). Moderate to Severe pain: FLACC score≥4.Pain scores at 1,6, 12, 24,48 and 72 hours postoperatively.*

The time from caudal block completion to the first PCIA press was longer in the HR group than in the R group. The postoperative analgesia duration was 3-11 hours in the HR group [5.4 h (3.5 h, 11.1 h)] and 3-6 hours in the R group [4 h (3.4 h, 6 h)]. In the HR group, the analgesia duration was 346 minutes (5.8 h), compared to 239 minutes (4 h) in the R group when the cumulative compression rate reached 50%. The cumulative incidence of compressions in the HR group was significantly lower than in the R group for the same analgesia duration ($P < 0.05$) (**Fig-3**).

The incidence of moderate to severe pain was significantly lower in the HR group than in the R group at 1 h, 6 h, 24 h, and 72 h [1 h: 2% vs. 13% ($P < 0.05$); 6 h: 12% vs. 34% ($P < 0.05$); 24 h: 20% vs. 39% ($P < 0.05$); 72 h: 0% vs. 7% ($P < 0.05$)] (**Fig-4**).

No statistically significant differences were found between the groups regarding the use of postoperative rescue analgesics [10% vs. 12%; P > 0.05], the number of effective PCIA compressions within 72 hours [9 (2, 19) vs. 11 (5, 26); P > 0.05], parental satisfaction scores [10 (8, 10) vs. 10 (8, 10); P > 0.05], sleep quality scores [8 (6, 10) vs. 8 (5, 10); P > 0.05], length of hospital stay [7 (4, 9) vs. 8 (5, 9); P > 0.05], and hospitalization expenses [23,397.34 RMB (20,813.06, 33,272.68) vs. 31,252.20 RMB (20,999.03, 33,843.47); P > 0.05]. The incidence of postoperative pruritus was almost twice as high in the HR group as in the R group [28% vs. 12%; P < 0.05] (**Table-2**).

There were no statistically significant differences in the incidence of adverse events such as nausea and vomiting, drowsiness, urinary retention, or bleeding at puncture sites (P > 0.05) between the groups (**Table-3**). Death, cardiac arrest, severe hypoxemia, shock, central nervous system injury, and unplanned ICU admissions did not occur in either group.

Discussion

The main findings of this study were as follows: (1) The use of hydromorphone 10 μg/kg combined with 0.2% ropivacaine for single-shot caudal block in children can effectively reduce early postoperative pain scores. (2) It can also reduce the incidence of moderate to severe pain as well as prolong the postoperative analgesia duration of the caudal block. (3) There were no adverse events resulting from hydromorphone application except pruritus.

Caudal block is one of the most widely administered techniques of regional anesthesia in pediatric patients who undergo lower urological tract, lower abdominal, and lower limb surgeries. However, the anesthesia duration of a caudal block with ropivacaine alone is too short for the prevention of postoperative pain. Children undergoing hypospadias repair, phalloplasty, and congenital hip dislocation surgery often experience severe postoperative pain, although PCIA is routinely applied. In our study, we found that children experienced moderate to severe pain in the ropivacaine group, with an incidence as high as 34% at 6 hours after surgery in the R group, while the HR group was only 12%. This may be related to the diminishing or disappearance of the analgesic effect of ropivacaine at 6 hours' post-surgery. The use of hydromorphone combined with ropivacaine for single-shot caudal block in children can reduce the incidence of moderate to severe pain.

Table-2: Comparison of the Secondary Outcomes (N=98)

	HR group（n=49）	R group（n=49）	*P* value
The use of postoperative rescue analgesics	5 (10)	6 (12)	0.907
The number of effective PCIA compressions within 72 hours	9 (2,19)	11 (5,26)	1.333
The parental satisfaction score	10 (8,10)	10 (8,10)	0.837
The sleep quality scores	8 (6,10)	8 (5,10)	0.37
The length of hospital stay	7 (4,9)	8 (5,9)	0.323
Hospitalization expenses	23397.34 (20813.06, 33272.68)	31252.20 (20999.03, 33843.47)	0.836

Table-3: Comparison of Adverse Events (N=98)

Adverse vents	HR group (n=49) (%)	R group (n=49) (%)	P value	RR
Nausea and vomiting	5 (10)	2 (4)	0.239	0.374
Pruritus	14 (28)	6 (12)	0.045*	2.867
Drowsiness	8 (16)	10 (20)	0.602	1.314
Urinary retention	1 (2)	0 (0)	0.315	0.98
Bleeding at puncture points	0 (0)	0 (0)	/	/

In this study, we found that the pain score in the HR group was significantly lower than that of the R group within 12 hours' post-surgery, indicating that the analgesic effect of hydromorphone combined with ropivacaine was stronger than that of ropivacaine alone. The result of our study is consistent with the results of previous studies [31-33]. Hydromorphone is a synthetic opioid analgesic that exerts its analgesic effect on the spinal nerves and spinal cord surface, mostly through paraspinal tissues and subarachnoid blocks after caudal administration. A small fraction diffuses cephalad, penetrates the blood-brain barrier, and acts on central opioid receptors to exert analgesia.

Postoperative analgesia duration was 3-6 hours in the R group and 3-11 hours in the HR group, indicating that hydromorphone could prolong the postoperative analgesia duration. Previous studies showed that the analgesia duration of 0.2% ropivacaine after single caudal block was about 3-15 hours [35], and the analgesia duration of hydromorphone after single epidural administration was 7.7-19.3 hours [36]. The analgesia duration in our study was shorter than in previous studies, possibly due to the following reasons. Firstly, such data can be misleading in the pediatric population, as pain is subjective and difficult to assess, and multiple factors can modify pain perception. Secondly, the parents were especially concerned about the postoperative pain of their children, which led to aggressive pain management. Therefore, the duration of postoperative analgesia in our study was shorter than that in previous studies.

This study found that the majority of children developed mild to moderate pain at each observation point within 72 hours' post-surgery, and only a small proportion of children developed severe pain. The incidence of moderate to severe pain at 72 hours postoperatively in the HR group was 20%, which is lower than the 33-50% mentioned in a previous study [2]. The possible reason for the lower incidence of moderate to severe pain in our study is that all the included children used PCA with sufentanil post-surgery, which greatly reduced the incidence of moderate to severe pain.

This study found that the incidence of pruritus was high in both groups, possibly due to the use of PCA with sufentanil. However, the pruritus was transient and usually relieved within 1-hour post-surgery. No patients experienced severe pruritus requiring naloxone administration. In our study, the incidence of pruritus in the HR group was 28%, two times higher than in the R group. This incidence is consistent with Marroquin's study [37].

This study has limitations. Firstly, there were six follow-up time points, which might have made it difficult for parents to assess the pain score at 6 or 12 hours' post-surgery, so we used the average pain scores of the two time points (one each before and after the intervention) instead. Secondly, the caudal block in this study was performed by residents under the guidance of attending physicians on the same day as the operation. Different operators might have led to different effects of sacral block, and the caudal block was implemented after general anesthesia, making it difficult to evaluate the success of the sacral block. Ultrasound visualization could be used in future studies to ensure the success of caudal block.

In conclusion, the use of hydromorphone 10 μg/kg combined with 0.2% ropivacaine for single-shot caudal block in children can effectively reduce early postoperative pain scores, reduce the incidence of moderate to severe pain, and prolong the postoperative analgesia duration of ropivacaine. There were no adverse events resulting from hydromorphone caudal administration except for pruritus.

Conflict of Interest

The author has read and approved the final version of the manuscript. The author has no conflicts of interest to declare.

References

[1] Rnneberg M, Tjlsen A. Pain in neonates. Tidsskrift for Den Norske Lgeforening Tidsskrift for Praktisk Medicin Ny Rkke. 1998;118(23):3610.

[2] Cummings EA, Reid GJ, Finley AG, McGrath PJ, Ritchie JA. Prevalence and source of pain in pediatric inpatients. Pain. 1996 Nov;68(1):25-31. [**PMID**: 9251995]

[3] Vejzovic V, Bozic J, Panova G, Babajic M, Bramhagen AC. Children still experience pain during hospital stay:

a cross-sectional study from four countries in Europe. BMC Pediatr. 2020 Jan 29;20(1):39. [**PMID**: 31996162]

[4] Brasher C, Gafsous B, Dugue S, Thiollier A, Kinderf J, Nivoche Y, Grace R, Dahmani S. Postoperative pain management in children and infants: an update. Paediatr Drugs. 2014 Apr;16(2):129-40. [**PMID**: 24407716]

[5] Pagé MG, Stinson J, Campbell F, Isaac L, Katz J. Identification of pain-related psychological risk factors for the development and maintenance of pediatric chronic postsurgical pain. J Pain Res. 2013;6:167-80. [**PMID**: 23503375]

[6] Tsui BC, Berde CB. Caudal analgesia and anesthesia techniques in children. Curr Opin Anaesthesiol. 2005 Jun;18(3):283-88. [**PMID**: 16534352]

[7] Mauch J, Weiss M. Kaudalanästhesie bei Kindern : Stellenwert und Aspekte zur Sicherheit [Pediatric caudal anesthesia: importance and aspects of safety concerns]. Schmerz. 2012 Aug;26(4):443-53; quiz 454. German. [**PMID**: 22855315]

[8] Suresh S, Long J, Birmingham PK, De Oliveira GS Jr. Are caudal blocks for pain control safe in children? an analysis of 18,650 caudal blocks from the Pediatric Regional Anesthesia Network (PRAN) database. Anesth Analg. 2015 Jan;120(1):151-56. [**PMID**: 25393589]

[9] Tsui BCH, Boretsky K, Berde C. Maximum Recommended Dosage of Ropivacaine and Bupivacaine for Pediatric Regional Anesthesia. Reg Anesth Pain Med. 2018 Nov;43(8):895-96. [**PMID**: 30339619]

[10] Suresh S, Ecoffey C, Bosenberg A, Lonnqvist PA, de Oliveira GS Jr, de Leon Casasola O, de Andrés J, Ivani G. The European Society of Regional Anaesthesia and Pain Therapy/American Society of Regional Anesthesia and Pain Medicine Recommendations on Local Anesthetics and Adjuvants Dosage in Pediatric Regional Anesthesia. Reg Anesth Pain Med. 2018 Feb;43(2):211-16. [**PMID**: 29319604]

[11] Pathak A, Yadav N, Mohanty SN, Ratnani E, Sanjeev OP. Comparison of Three Different Concentrations 0.2%, 0.5%, and 0.75% Epidural Ropivacaine for Postoperative Analgesia in Lower Limb Orthopedic Surgery. Anesth Essays Res. 2017 Oct-Dec;11(4):1022-25. [**PMID**: 29284868]

[12] Ismail AA, Mohamed Hamza H, Ali Gado A. Efficacy of Dexmedetomidine Versus Morphine as an Adjunct to Bupivacaine in Caudal Anesthesia for Pediatric Thoracic Surgeries: A Randomized Controlled Trial. Anesth Pain Med. 2021 May 3;11(2):e112296. [**PMID**: 34336616]

[13] Richa F, Chalhoub V. Dexmedetomidine as an adjunct for pediatric caudal anesthesia: how useful? Minerva Anestesiol. 2018 Jul;84(7):780-82. [**PMID**: 29774731]

[14] Wang JK, Nauss LA, Thomas JE. Pain relief by intrathecally applied morphine in man. Anesthesiology. 1979 Feb;50(2):149-51. [**PMID**: 373503]

[15] Vetter TR, Carvallo D, Johnson JL, Mazurek MS, Presson RG Jr. A comparison of single-dose caudal clonidine, morphine, or hydromorphone combined with ropivacaine in pediatric patients undergoing ureteral reimplantation. Anesth Analg. 2007 Jun;104(6):1356-63, table of contents. [**PMID**: 17513626]

[16] Rauch E. Intrathecal hydromorphone for postoperative analgesia after cesarean delivery: a retrospective study. AANA J. 2012 Aug;80(4 Suppl):S25-32. [**PMID**: 23248827]

[17] Hong D, Flood P, Diaz G. The side effects of morphine and hydromorphone patient-controlled analgesia. Anesth Analg. 2008 Oct;107(4):1384-89. [**PMID**: 18806056]

[18] Farid IS, Lewis JM, Kendrick EJ. The safety and efficacy of hydromorphone via patient controlled analgesia or patient controlled analgesia by proxy for pediatric postoperative pain control. J Clin Anesth. 2020 Mar;60:65-66. [**PMID**: 31466034]

[19] MacKenzie M, Zed PJ, Ensom MH. Opioid Pharmacokinetics-Pharmacodynamics: Clinical Implications in Acute Pain Management in Trauma. Ann Pharmacother. 2016 Mar;50(3):209-18. [**PMID**: 26739277]

[20] Rodrigues S, Shin D, Conway M, Smulski S, Trenker E, Shanthanna H, Vanniyasingam T, Thabane L, Paul J. Hydromorphone versus morphine: a historical cohort study to evaluate the quality of postoperative analgesia. Can J Anaesth. 2021 Feb;68(2):226-34. English. [**PMID**: 33170454]

[21] Felden L, Walter C, Harder S, Treede RD, Kayser H, Drover D, Geisslinger G, Lötsch J. Comparative clinical effects of hydromorphone and morphine: a meta-analysis. Br J Anaesth. 2011 Sep;107(3):319-28. [**PMID**: 21841049]

[22] Bernards CM, Hill HF. Physical and chemical properties of drug molecules governing their diffusion through the spinal meninges. Anesthesiology. 1992 Oct;77(4):750-56. [**PMID**: 1416173]

[23] Swain A, Nag DS, Sahu S, Samaddar DP. Adjuvants to local anesthetics: Current understanding and future

trends. World J Clin Cases. 2017 Aug 16;5(8):307-23. [**PMID**: 28868303]

[24] Evans MA, Monahan A, Abhold E, Hajduk J, Vu E, Suresh S. 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 Sep;72:110314. [**PMID**: 33895545]

[25] Zeng H, Li J, Zhou S. Application of hydromorphone combined with ropivacaine in modified caudal block in anorectal surgery. Sichuan Medical Journal. 2017;38(9):1036-39.

[26] Zeng X, Zhang X. Possible Mechanisms of Rebound Pain After Peripheral Nerve Block Subsides and Preventive Therapy Measures. International Journal of Anesthesia and Clinical Medicine. 2023;11(2):82-87.

[27] Sunderland S, Yarnold CH, Head SJ, Osborn JA, Purssell A, Peel JK, Schwarz SK. Regional Versus General Anesthesia and the Incidence of Unplanned Health Care Resource Utilization for Postoperative Pain After Wrist Fracture Surgery: Results From a Retrospective Quality Improvement Project. Reg Anesth Pain Med. 2016 Jan-Feb;41(1):22-27. [**PMID**: 26650425]

[28] Barry GS, Bailey JG, Sardinha J, Brousseau P, Uppal V. Factors associated with rebound pain after peripheral nerve block for ambulatory surgery. Br J Anaesth. 2021 Apr;126(4):862-71. [**PMID**: 33390261]

[29] Powell CV, Kelly AM, Williams A. Determining the minimum clinically significant difference in visual analog pain score for children. Ann Emerg Med. 2001 Jan;37(1):28-31. [**PMID**: 11145767]

[30] Wang B, Hu B, Zhong H, Zhao C. Study on the Effect of Different Doses of Hydromorphone on the Time Response and Postoperative Analgesia of Ropivacaine in Ultrasound-Guided Suprailiac Fascia Inguinal Block. Evid Based Complement Alternat Med. 2021 Oct 14;2021:9691062. doi: 10.1155/2021/9691062. Retraction in: Evid Based Complement Alternat Med. 2023 Dec 13;2023:9869058. [**PMID**: 34691231]

[31] Yang M, Wang L, Chen H, Tang Y, Chen X. Postoperative Analgesic Effects of Different Doses of Epidural Hydromorphone Coadministered with Ropivacaine after Cesarean Section: A Randomized Controlled Trial. Pain Res Manag. 2019 Mar 3;2019:9054538. [**PMID**: 30944686]

[32] Saisai H. The effect of hydromorphone as an adjuvant to ropivacaine in brachial plexus block. J Clin Anesth. 2019 May;54:111. [**PMID**: 30439607]

[33] Mazer-Amirshahi M, Ladkany D, Mullins PM, Motov S, Perrone J, Nelson LS, Pines JM. Trends in and predictors of hydromorphone administration in US emergency departments (2007-2014). J Opioid Manag. 2018 Jul/Aug;14(4):265-72. [**PMID**: 30234923]

[34] Ivani G, De Negri P, Lonnqvist PA, L'Erario M, Mossetti V, Difilippo A, Rosso F. Caudal anesthesia for minor pediatric surgery: a prospective randomized comparison of ropivacaine 0.2% vs levobupivacaine 0.2%. Paediatr Anaesth. 2005 Jun;15(6):491-94. [**PMID**: 15910350]

[35] Murray A, Hagen NA. Hydromorphone. J Pain Symptom Manage. 2005 May;29(5 Suppl):S57-66. [**PMID**: 15907647]

[36] Marroquin B, Feng C, Balofsky A, Edwards K, Iqbal A, Kanel J, Jackson M, Newton M, Rothstein D, Wong E, Wissler R. Neuraxial opioids for post-cesarean delivery analgesia: can hydromorphone replace morphine? A retrospective study. Int J Obstet Anesth. 2017 May;30:16-22. [**PMID**: 28185794]

[37] Ko MC, Song MS, Edwards T, Lee H, Naughton NN. The role of central mu opioid receptors in opioid-induced itch in primates. J Pharmacol Exp Ther. 2004 Jul;310(1):169-76. [**PMID**: 15044556]