

# Comparative Efficacy of Different Hydromorphone Doses for the Prevention of Catheter-Related Bladder Discomfort in Elderly Men

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**Background:** The high incidence of postoperative catheter-related bladder discomfort (CRBD) in elderly male patients is associated with intraoperative urinary catheterization. In this study, we aimed to investigate the efficacy of perioperative intravenous hydromorphone administration in alleviating postoperative CRBD.

**Methods:** This prospective study enrolled 220 elderly male individuals receiving ureteroscopic lithotripsy and randomly assigned them into four groups with 55 cases in each group. The L group was given intravenous hydromorphone at a dosage of 6 µg/kg, the N group received intravenous hydromorphone at a dosage of 10 µg/kg, the K group received intravenous (0.2 mg/kg) esketamine, and the C group received an equivalent volume of normal saline intravenously. Postoperative severity of CRBD was evaluated. The duration of anesthesia, surgical duration, alert time, extubation time, blood pressure, heart rate, pulse oxygen saturation, and MMSE scores were also evaluated.

**Results:** Significantly lower postoperative CRBD severity was observed in the N, L, and K groups than in the C group at 2, 4, and 24 hours after surgery ( $p < 0.001$ ). Furthermore, the N group had lower pain severity, compared to the L group, at 2, 4 and 24 hours postoperatively ( $p < 0.05$ ). Moreover, the N group, compared to the K group, had lower pain severity at 2 and 24 hours postoperatively ( $p < 0.05$ ). Notably, there were no significant differences in the other assessed outcome parameters ( $p > 0.05$ ).

**Conclusions:** Administration of intravenous hydromorphone during surgery can mitigate the postoperative severity of CRBD, and the standard anesthetic dose of 10 µg/kg hydromorphone used in this research may represent the optimal regimen.

**Clinical Trial Registration:** Chinese Clinical Trial Registry (ChiCTR2500112701).

**Keywords:** catheter-related bladder discomfort; hydromorphone; esketamine; flexible ureteroscopic lithotripsy

## Introduction

For individuals undergoing urinary catheterization under general anesthesia before awakening, urinary catheter retention often results in postoperative catheter-related bladder discomfort (CRBD), with a notably high incidence ranging from 47% to 90% [1]. However, due to the high prevalence of comorbidities such as benign prostatic hyperplasia and urethral stricture in this patient population, the risk of developing CRBD is further increased [2].

In recent years, the treatment options for CRBD have expanded considerably, consisting mainly of two categories [3]: M-receptor antagonists and anesthetic or adjuvant anesthetic agents. M-receptor antagonists can inhibit M-type cholinergic receptors and relax bladder smooth muscle, thereby alleviating CRBD. Preoperative oral administration [4] of tolterodine, oxybutynin, or solifenacin can effectively abate the incidence of postoperative CRBD and decrease postoperative analgesic requirements. Research on anesthetic and adjuvant anesthetic agents has demonstrated that sevoflurane [5], ketamine [6], and dexmedeto-

midine [7] can exert similar effects on postoperative CRBD. However, several limitations exist among the currently available medications for CRBD. M-receptor antagonists may cause adverse reactions such as dry mouth, urinary retention, and cognitive disturbance, especially in elderly patients [8]. Some anesthetic and adjuvant anesthetic agents could potentially elevate the risk of postoperative agitation, drowsiness, or delayed recovery, which may compromise early postoperative rehabilitation [9,10]. In addition, the optimal analgesic regimen for preventing CRBD remains controversial. Therefore, exploring a safe and effective pharmacological strategy to alleviate postoperative CRBD in elderly male patients is urgently needed.

Hydromorphone, a morphine derivative, exerts its primary analgesic effect via  $\mu$ -opioid receptor agonism [11], with mild agonistic activity on the  $\delta$ -receptor and no activity on the  $\kappa$ -receptor and  $\epsilon$ -receptor. It is characterized by its rapid onset, potent analgesia, and favorable safety profile, and has gained widespread use in the management of both acute pain and cancer pain in recent clinical practice [12], with particular benefits observed in elderly patients. Stud-

ies have identified that intraoperative intravenous administration of hydromorphone can reduce pain scores at admission to the post-anesthesia care unit, along with the peak pain scores observed during the initial 48 hours postoperatively [13]. Compared with propofol-dexmedetomidine infusion, propofol-hydromorphone infusion following maxillofacial plastic surgery has been shown to offer advantages in relieving pain and discomfort, attenuating sympathetic hyperactivity, and decreasing stress responses. Given its effects, it could be hypothesized that intraoperative administration of hydromorphone may help prevent the occurrence and reduce the severity of CRBD.

This study sought to determine if the intraoperative use of hydromorphone is effective in alleviating the severity of CRBD. Furthermore, we compared the efficacy of two hydromorphone dosing regimens (6 and 10  $\mu\text{g}/\text{kg}$ ) with that of esketamine administered at a dose of 0.2 mg/kg.

## Methods

### *Research Plan and Participants*

This prospective, double-blind, randomized, controlled clinical trial (Clinical Trial Registration No. ChiCTR2500112701, <https://www.chictr.org.cn/hvshowprojectEN.html?id=288244&v=1.0>) was approved by the Affiliated Hospital of Chengdu University Medical Ethics Committee on March 14, 2025 (PJ2025-016-03). Written informed consent was obtained from all patients prior to study enrollment.

Eligibility screening was performed among patients undergoing flexible ureteroscopic lithotripsy from March to September 2025. The following were regarded as inclusion criteria: male gender, age >65 years, and ASA physical status II–III. The exclusion criteria included: hypersensitivity to hydromorphone hydrochloride, opioids, or esketamine; patients with a history of psychiatric conditions; patients with a history of long-term psychotropic and analgesic medication use; patients with severe liver or kidney impairment, bladder outlet obstruction, prior preoperative intensive care unit admission, urethral anatomical anomalies, overactive bladder syndrome (nocturia  $\geq 3$  episodes or total urination frequency >8 times in 24 hours), as well as paralytic ileus were also excluded.

### *Randomization, Allocation Concealment, and Blinding*

A simple randomization sequence was generated by an independent statistician who did not participate in the subsequent procedures, group allocation, or clinical intervention. Sequentially numbered, sealed, opaque envelopes were employed to ensure concealment of the random allocation sequence. The envelopes were securely sealed to prevent inadvertent or intentional opening before participant enrollment. After eligibility was confirmed, the next sequentially numbered envelope was opened by a design-

nated researcher to assign the participant to a group. Investigators responsible for participant recruitment and outcome assessment were not involved in random sequence generation or envelope preparation, thus ensuring adequate allocation concealment. Patients were allocated into four groups as follows: Group C (control group): intravenous administration of normal saline; Group L (low-dose hydromorphone): intravenous hydromorphone (Lot No. [H20120100], Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China) at 6  $\mu\text{g}/\text{kg}$ ; Group N (standard-dose hydromorphone): intravenous hydromorphone at 10  $\mu\text{g}/\text{kg}$ ; Group K (subanesthetic dose esketamine): intravenous esketamine (Lot No. [H20193336], Jiangsu Hengrui Medicine Co., Ltd., Lianyungang, China) at 0.2 mg/kg. Group assignment was performed by the primary investigator, with randomization codes stored in sequentially numbered, opaque sealed envelopes. These envelopes were then delivered to a second investigator who prepared the study medications. Normal saline, esketamine 0.2 mg/kg, hydromorphone 6  $\mu\text{g}/\text{kg}$ , and hydromorphone 10  $\mu\text{g}/\text{kg}$  were prepared in an identical set of medical devices, labeled only with each patient's name and hospital identification number. A third investigator, blinded to group allocation, administered the study drugs 30 minutes prior to the completion of surgery and was also responsible for anesthesia monitoring, intraoperative care, and management of adverse events. A fourth independent investigator, who remained unaware of treatment assignments, performed all postoperative follow-up evaluations and data collection. All participants and investigators, with the exception of the first two researchers responsible for randomization and drug preparation, were kept blinded to group assignments.

### *Study Procedure*

Standard monitoring, such as non-invasive blood pressure, body temperature, pulse oximetry, capnography, bispectral index (BIS) by Disposable Non-invasive EEG Sensor (Medlinket®), Model B-BIS-4A (Shenzhen Med-link Electronics Tech Co., Ltd., Shenzhen, China), 3-lead electrocardiography, and train-of-four (TOF) neuromuscular monitoring by Mindray BeneVision N15 patient monitor (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China), was performed in all patients. Intravenous induction agents were administered sequentially: midazolam 0.05 mg/kg (Lot No. [H10980025], Jiangsu Nhwa Pharmaceutical Co., Ltd., Xuzhou, China), sufentanil 0.3  $\mu\text{g}/\text{kg}$  (Lot No. [H20054171], Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China), propofol 1–1.5 mg/kg (Lot No. [H20213013], Yangtze River Pharmaceutical Group Co., Ltd., Taizhou, China), and rocuronium 0.6 mg/kg (Lot No. [H20183264], Zhejiang Huahai Pharmaceutical Co., Ltd., Linhai, China). Following tracheal intubation, mechanical ventilation was set to volume-controlled mode. Ventilator parameters were adjusted to an 8–10 mL/kg tidal volume, 10–15 breaths/min respiratory rate,

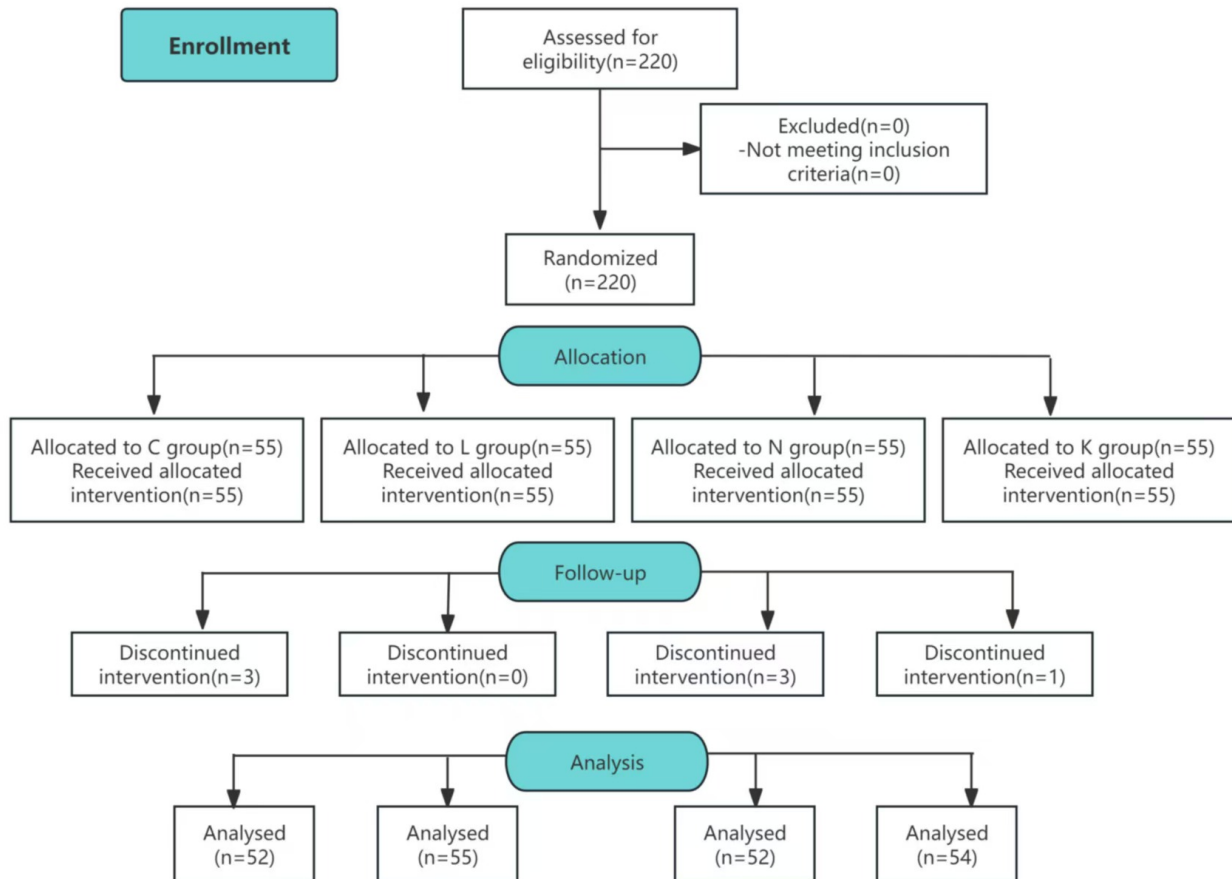


Fig. 1. CONSORT flow diagram.

1:2 inspiratory-to-expiratory ratio, and 50% inspired oxygen fraction, with PetCO<sub>2</sub> maintained within 35–45 mmHg. Anesthesia was maintained via target-controlled infusion (TCI) by Target Controlled Infusion Pump, Model CP-730TCI (Beijing Silugao Medical Technology Co., Ltd., Beijing, China) of propofol at a plasma concentration of 2.0–3.0 ng/mL and remifentanyl (Lot No. [H20030197], Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China) at 2.0–5.0 ng/mL, with BIS values kept within 40–60. Supplemental rocuronium was given based on clinical need to keep TOF count between 1 and 2, and mean arterial pressure was maintained within  $\pm 20\%$  of baseline levels. All surgical manipulations were performed uniformly by a senior urologist during the operation.

Study medications were administered intravenously 30 minutes prior to the completion of surgery. Patients in the N group and L group received 10  $\mu\text{g}/\text{kg}$  and 6  $\mu\text{g}/\text{kg}$  of intravenous hydromorphone, respectively. The subanesthetic-dose esketamine group (K group) was given 0.2 mg/kg of intravenous esketamine, whereas the C group received an identical volume of normal saline. All intravenous injections were delivered over 30 seconds.

Upon completion of surgery, all anesthetics were discontinued, and patient-controlled intravenous analgesia (PCIA) was initiated. The analgesic formulation consisted of sufentanil 50  $\mu\text{g}$ , tramadol 500 mg (Lot No. [HJ20140813], Grünenthal GmbH, Stolberg, Germany), and ondansetron 16 mg (Lot No. [H10960148], Fuan Pharmaceutical Group Ningbo Tianheng Pharmaceutical Co., Ltd., Ningbo, China) diluted to a total volume of 200 mL, with a background infusion rate of 3 mL/h, a bolus dose of 4 mL, and a lockout interval of 30 minutes. Once patients achieved full consciousness (BIS >90) and satisfactory neuromuscular recovery (TOF ratio >0.9), they were transferred to the post-anesthesia care unit.

#### Outcome Assessments

The primary endpoints were Visual Analogue Scale (VAS) scores measured at 2, 4, and 24 hours following tracheal extubation. Secondary outcome measures encompassed anesthesia duration, operative time, emergence time, extubation time, blood pressure, heart rate, as well as oxygen saturation and Mini-Mental State Examination (MMSE) scores assessed at 4 and 24 hours following surgery. At preoperative screening, preoperative counsel-

**Table 1. Patient characteristics.**

Variables	C	L	N	K	Statistic value	<i>p</i> value
Age (years)	68.7 ± 3.6	68.8 ± 2.9	68.3 ± 2.8	68.8 ± 3.3	0.349	0.7899
Male, n (%)	52 (100%)	55 (100%)	52 (100%)	54 (100%)	-	-
BMI (Kg/m <sup>2</sup> )	24.5 ± 1.4	23.8 ± 1.5	24.3 ± 1.5	24.0 ± 1.6	1.814	0.1456
ASA physical status, n (%)					0.675	0.8790
II	51 (98.1%)	54 (98.2%)	50 (96.2%)	53 (98.2%)		
III	1 (1.9%)	1 (1.8%)	2 (3.8%)	1 (1.8%)		
HR (beat/min)	76.9 ± 11.2	73.1 ± 7.8	75.9 ± 9.5	75.5 ± 9.5	1.511	0.2127
SBP (mmHg)	128.8 ± 13.1	126.7 ± 13.1	127.5 ± 14.3	129.7 ± 14.8	0.508	0.6769
DBP (mmHg)	82.5 ± 9.8	80.3 ± 8.9	83.0 ± 10.4	83.0 ± 12.6	0.781	0.5060
SpO <sub>2</sub> (%)	96.6 ± 1.2	97.3 ± 1.0	96.9 ± 1.2	97.0 ± 1.3	2.412	0.0678
Duration of anesthesia (min)	100 (80, 125)	62.5 (40, 81)	90 (68.5, 110)	100 (73.75, 115)	2.823	0.4198
Length of surgery (min)	62.5 (41.25, 93.75)	60 (40, 90)	50 (31.25, 75)	62.5 (40, 81)	3.117	0.3740
Time from drug administration to the end of surgery (min)	31 (26, 42.25)	30 (26, 38.5)	31 (27, 36.75)	30.5 (25, 35.5)	0.485	0.7263

ing on CRBD manifestations and VAS assessment was conducted. Typical CRBD consists of suprapubic burning pain radiating to the penis, graded into four severity tiers: absent (no report of CRBD upon questioning), mild (reported only when specifically inquired about), moderate (spontaneous complaint of discomfort without obvious behavioral reactions), and severe (spontaneous complaint accompanied by behavioral signs such as restlessness, verbal complaints, and attempts to remove the urinary catheter). Postoperative pain severity was assessed using the VAS, a 0–10 scale where 0 signifies no pain and 10 indicates the worst imaginable pain.

### Statistical Analysis

SPSS 22.0 statistical software (IBM Corp., Armonk, NY, USA) was used to conduct the data analysis. The sample size was estimated based on the primary outcome measure of this study. According to previous similar clinical studies, a two-sided  $\alpha$  level of 0.05 and a statistical power of  $1-\beta = 0.90$  were set. The effect size of the primary outcome among groups was determined as a clinically meaningful difference, and the variance or event rate was derived from published literature and pilot data. Sample size calculation was performed using the formula for one-way analysis of variance (four-group comparison). Continuous variables conforming to a normal distribution were reported as the mean ± standard deviation, whereas non-normally distributed continuous data were described using the median and interquartile range. Categorical variables were summarized as frequencies and percentages, and intergroup comparisons were performed using the Chi-square test. In this study, normality tests were first performed for all continuous variables, and the Shapiro-Wilk test was used to determine the distribution characteristics of the data. For data that were normally distributed and satisfied homogeneity of variance, one-way ANOVA was applied for intergroup comparisons, and pairwise comparisons between groups

were performed using the Tukey's test. For data that were not normally distributed or had unequal variances, the non-parametric Kruskal-Wallis H test was used for analysis, and post hoc pairwise comparisons were further performed using the Dunn's test. A *p*-value < 0.05 was regarded as statistically significant.

### Results

A total of 220 cases were initially included in this clinical investigation. All 220 participants were formally enrolled, of whom 213 completed the full trial protocol, with no loss to follow-up throughout the study period, while 7 patients voluntarily withdrew from the research (Fig. 1). Participants were allocated to four groups: Group K, Group N, Group L, and Group C, which respectively received 0.2 mg/kg esketamine intravenous administration, 10 µg/kg hydromorphone, 6 µg/kg hydromorphone, and an equal volume of normal saline. The corresponding number of subjects in each group was 54, 52, 55, and 52, respectively. Baseline demographic and clinical characteristics were comparable across the four groups, with no statistically significant differences observed (Table 1).

### Primary Outcomes

At 2 hours postoperatively, patients in all four groups reported mild pain. In terms of pain intensity, there were statistically significant differences in VAS scores among the four groups (2 (1, 2) vs. 1 (0, 1) vs. 2 (0, 3) vs. 3 (2, 3),  $p < 0.0001$ ). Notably, VAS scores in the C group were significantly higher than in the K group ( $Z = 49.08$ ,  $p < 0.001$ ), the N group ( $Z = 79.93$ ,  $p < 0.001$ ) and the L group ( $Z = 41.87$ ,  $p < 0.01$ ). When comparing the N and L groups, the N group had significantly lower VAS scores ( $Z = -38.06$ ,  $p < 0.05$ ). Similarly, the N group also had significantly lower VAS scores ( $Z = 30.85$ ,  $p < 0.05$ ), compared with the K group. However, VAS scores did not differ significantly between the K and L groups at 2 hours postoperatively.

**Table 2. Primary outcomes (median (Q1, Q3)).**

Primary outcomes	C	L	N	K	H value	p value
2 h VAS	3 (2, 3)	2 (0, 3)	1 (0, 1)	2 (1, 2)	47.14	<0.0001
4 h VAS	3 (2, 3)	2 (1, 2)	1 (0, 1)	1 (1, 2)	45.93	<0.0001
24 h VAS	2 (1, 2)	1 (0, 1)	0 (0, 0)	0 (0, 1)	56.96	<0.0001

**Table 3. Primary outcomes (mean rank diff).**

Primary outcomes	L vs. C	N vs. C	K vs. C	L vs. K	N vs. K	L vs. N
2 h VAS	41.87 ●	79.93 ▲	49.08 ▲	-7.215	30.85 ■	-38.06 ■
4 h VAS	37.25 ■	77.86 ▲	52.07 ▲	-14.81	25.79	-40.60 ●
24 h VAS	36.51 ■	82.21 ▲	51.67 ▲	-15.16	30.54 ■	-45.71 ▲

▲:  $p < 0.001$ ; ●:  $p < 0.01$ ; ■:  $p < 0.05$ .

**Table 4. Secondary outcomes.**

Secondary outcomes	C	L	N	K	H value	p value
Alert time (min)	10 (7, 14.75)	10 (8, 14)	10 (8, 15)	10 (7, 14.25)	1.860	0.6021
Extubation time (min)	10 (5, 13)	13 (9.5, 15)	10 (6, 15)	11.5 (8.5, 15)	5.988	0.1122
					F value	p value
2 h HR (beat/min)	71.4 ± 9.1	70.6 ± 8.9	70.0 ± 9.1	72.0 ± 9.7	0.4745	0.7004
4 h HR (beat/min)	71.4 ± 6.7	72.0 ± 9.1	73.0 ± 10.3	75.5 ± 10.5	1.9820	0.1177
2 h SpO <sub>2</sub> (%)	98.0 ± 1.1%	98.2 ± 1.2%	98.3 ± 1.5%	98.3 ± 1.2%	0.9326	0.4257
4 h SpO <sub>2</sub> (%)	97.7 ± 1.2%	97.6 ± 1.0%	97.8 ± 1.3%	97.5 ± 1.4%	0.6360	0.5926
2 h SBP (mmHg)	117.6 ± 12.9	114.3 ± 10.3	119.8 ± 9.3	119.7 ± 13.2	2.4330	0.0661
4 h SBP (mmHg)	117.4 ± 9.6	116.9 ± 10.9	118.6 ± 10.2	119.3 ± 10.7	0.6356	0.5929
2 h DBP (mmHg)	76.4 ± 9.5	72.3 ± 7.6	76.8 ± 9.0	76.5 ± 9.2	1.0970	0.3516
4 h DBP (mmHg)	75.0 ± 7.8	77.4 ± 8.9	75.5 ± 8.4	73.3 ± 6.4	2.4420	0.0653
4 h ΔMMSE	-0.32 ± 1.26	-0.65 ± 1.05	-0.69 ± 1.99	-0.57 ± 1.26	0.6859	0.5616
24 h ΔMMSE	-1.05 ± 1.98	-1.16 ± 1.35	-1.61 ± 1.78	-1.24 ± 1.55	1.0870	0.3556

4 h ΔMMSE, Preoperative MMSE - 4 h postoperative MMSE; 24 h ΔMMSE, Preoperative MMSE - 24 h postoperative MMSE.

At 4 hours postoperatively, significant differences in VAS scores were observed among the K, N, L and C groups regarding pain intensity (1 (1, 2) vs. 1 (0, 1) vs. 2 (1, 2) vs. 3 (2, 3),  $p < 0.0001$ ). VAS scores in the C group were significantly higher than those in the K group ( $Z = 52.07$ ,  $p < 0.001$ ), the N group ( $Z = 77.86$ ,  $p < 0.001$ ) and the L group ( $Z = 37.25$ ,  $p < 0.05$ ). However, VAS scores did not differ significantly among the N, L and K groups. Nevertheless, the N group exhibited lower VAS scores than the L group ( $Z = -40.6$ ,  $p < 0.01$ ).

At 24 hours postoperatively, statistically significant differences in VAS scores were observed among the K, N, L and C groups in terms of pain intensity (0 (0, 1) vs. 0 (0, 0) vs. 1 (0, 1) vs. 2 (1, 2),  $p < 0.0001$ ). VAS scores in the C group were significantly higher than in the K group ( $Z = 51.67$ ,  $p < 0.001$ ), the N group ( $Z = 82.21$ ,  $p < 0.001$ ), and the L group ( $Z = 36.51$ ,  $p < 0.05$ ). Additionally, compared to the K group, VAS scores were lower in the N group ( $Z = 30.54$ ,  $p < 0.05$ ), whereas there was no significant difference in VAS scores between the L and K groups (Tables 2,3). However, the N group had significantly lower VAS scores ( $Z = -45.71$ ,  $p < 0.001$ ) compared with the L group.

### Secondary Outcomes

No significant intergroup differences were observed in awakening time or extubation time (Table 4,  $p > 0.05$ ). In addition, no statistically significant variations in systolic or diastolic blood pressure, heart rate, or pulse oximetry saturation were detected at 2 hours postoperatively among the four groups (Table 4,  $p > 0.05$ ). Similarly, MMSE scores did not differ significantly at 4 and 24 hours following surgery (Table 4,  $p > 0.05$ ).

### Discussion

Patients who undergo flexible ureteroscopic lithotripsy require indwelling urinary catheterization to preserve urethral patency and promote the drainage of urine and residual stone fragments [14]. However, this intervention also predisposes them to CRBD. Currently, the underlying mechanisms of CRBD are complex [3], and potential mechanisms that may contribute to its occurrence include detrusor muscle contraction mediated by M-type muscarinic receptors [15], heightened sensitivity to stimuli due to the dense innervation of the urinary

tract, male gender, urological surgery, and the volume of the catheter balloon [16]. Severe CRBD can trigger behavioral responses in patients such as restlessness, confusion, and whole-body writhing, which may lead to various complications [17]. Reducing the incidence and severity of perioperative CRBD is a crucial aspect of anesthetic care. The findings of this trial not only confirm the reproducibility of previous studies but also provide an alternative novel and effective preventive measure for CRBD.

Hydromorphone, as a  $\mu$ -receptor agonist, exhibits an analgesic potency 5 to 10 times greater than that of morphine [18]. Furthermore, hydromorphone exhibits low plasma protein binding, ranging from 8% to 19%, and this binding is not affected by variations in drug dose, concentration, or fluid therapy. This characteristic minimizes the risk of metabolic interference when hydromorphone is co-administered with other medications [19]. Upon systemic administration, hydromorphone acts on central opioid receptors, with a small portion binding to central opioid receptors or spinal dorsal horn opioid receptors, thereby inhibiting the amplitude and conduction velocity of nerve trunk action potentials and exerting a potent analgesic effect [20]. In this study, intraoperative administration of 10  $\mu$ g/kg and 6  $\mu$ g/kg hydromorphone reduced the severity of CRBD at 2 hours, 4 hours, and 24 hours postoperatively, suggesting that hydromorphone may exert preventive effects against CRBD.

Recent studies have found that urethral hypersensitivity, catheter-induced detrusor contraction, and inflammatory mediator-driven prostaglandin synthesis may contribute to the pathogenesis of CRBD [21]. As an opioid drug, hydromorphone activates  $\mu$ -opioid receptors and two distinct downstream pathways. One pathway, primarily mediated by G proteins, leads to analgesic effects, while the other, potentially mediated by  $\beta$ -arrestin, may cause adverse reactions [22]. Bershad *et al.* [23] found that hydromorphone could alleviate patients' physiological responses to acute stress. Another study by Ershoff *et al.* [13] discovered that each 0.2-mg increase in intraoperative hydromorphone dosage was associated with lower pain scores on admission to the post-anesthesia care unit, as well as reduced peak and time-weighted average pain scores during the first two postoperative days. Consistent with these findings, 10  $\mu$ g/kg hydromorphone significantly reduced CRBD severity at 2, 4, and 24 hours postoperatively compared with 6  $\mu$ g/kg of hydromorphone. Although hydromorphone is widely used in the management of acute and chronic pain, a literature search using the keywords "hydromorphone", "urological surgery", and "CRBD" revealed that evidence regarding its efficacy in preventing CRBD is limited.

Of note, the clinical use of esketamine is restricted by several labeled contraindications, including uncontrolled hypertension, risks of elevated intraocular and intracranial pressure, preeclampsia or eclampsia, uncontrolled hyper-

thyroidism, and situations requiring uterine muscle relaxation. These contraindications limit the application of esketamine, whereas hydromorphone may serve as a complementary option in these restricted scenarios. This study found that 6  $\mu$ g/kg and 10  $\mu$ g/kg hydromorphone, as well as 0.2 mg/kg esketamine, were effective in reducing CRBD severity. Moreover, 10  $\mu$ g/kg hydromorphone reduced CRBD severity more significantly at 2 and 24 hours postoperatively. Together, this study showed that hydromorphone could reduce the severity of CRBD within 24 hours, potentially through its anti-inflammatory and analgesic effects.

To our knowledge, this is the first study to evaluate the impact of intraoperative hydromorphone administration on postoperative CRBD. Nevertheless, this study has several limitations: it was a single-center study, and future multi-center studies are needed for validation; the optimal dosage and timing of hydromorphone administration require further investigation; the use of opioids as part of the intraoperative anesthetic and analgesic regimen may influence the incidence of early postoperative CRBD, but since the dosage of opioids was comparable across the three study groups, the impact of this potential confounding factor is likely minimal; and the use of a pain rating scale to evaluate the severity of CRBD may be constrained by the measurement method itself, potentially failing to comprehensively assess the behavioral symptoms of CRBD. Owing to the limited number of enrolled patients, no subgroup analysis was performed for key variables; thus, a larger patient cohort is urgently needed to further reveal differential responses to hydromorphone across patient subgroups. Additionally, the time interval from drug administration to the end of surgery deviated from the planned schedule. Although we compared these actual time intervals among groups and found no significant between-group differences, suggesting that this variable was well balanced across groups and unlikely to introduce substantial confounding, this finding should be verified in a larger patient cohort given the time-dependent effect of the study drug. Therefore, further studies are warranted, and the results should be interpreted with caution.

## Conclusions

Intraoperative intravenous administration of hydromorphone may reduce the severity of CRBD in elderly male patients undergoing ureteroscopic lithotripsy. The conventional dose of 10  $\mu$ g/kg hydromorphone demonstrates superior efficacy compared with a sub-anesthetic dose of 0.2 mg/kg esketamine or 6  $\mu$ g/kg hydromorphone. Furthermore, for patients with contraindications to esketamine, hydromorphone may serve as an alternative option for clinicians. However, further research is needed to determine the optimal timing and dosage for hydromorphone administration.

## Availability of Data and Materials

The data presented in this study are available on reasonable request from the corresponding author.

## Author Contributions

SY and SFL designed the study and collected the raw data. YWZ, HJC, YHQ and SMX analyzed the data. SY and SMX prepared the manuscript draft. All authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

## Ethics Approval and Consent to Participate

This study was approved by the Affiliated Hospital of Chengdu University Medical Ethics Committee on March 14, 2025 (PJ2025-016-03). All patients provided written consent before participating, and all procedures were conducted strictly in accordance with the Declaration of Helsinki.

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Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

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