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Effects of nefopam on catheter-related bladder discomfort in patients undergoing ureteroscopic litholapaxy

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Background: Patients who undergo urinary catheterization may experience postoperative catheter-related bladder discomfort (CRBD). Previous studies have indicated that drugs with antimuscarinic effects could reduce the incidence and severity of CRBD. Accordingly, this study was carried out to investigate whether nefopam, a centrally acting analgesic with concomitant antimuscarinic effect, reduces the incidence and severity of CRBD.

Methods: Sixty patients with American Society of Anesthesiologists physical status I and II and aged 18–70 years who were scheduled to undergo elective ureteroscopic litholapaxy participated in this double-blinded study. Patients were divided into control and nefopam groups, comprising 30 patients each. In the nefopam group, 40 mg nefopam in 100 ml of 0.9% saline was administered intravenously. In the control group, only 100 ml of 0.9% saline was administered. All patients had a urethral catheter and ureter stent inserted during surgery. The incidence and severity of CRBD, numerical rating scale (NRS) score of postoperative pain, rescue pethidine dose, and side effects were recorded in the post-anesthesia care unit after surgery.

Results: The incidence (P = 0.020) and severity (P < 0.001) of CRBD were significantly different between the control group and the nefopam group. The NRS score of postoperative pain (P = 0.006) and rescue dose of pethidine (P < 0.001) were significantly higher in the control group than in the nefopam group.

Conclusions: Intravenous administration of nefopam in patients scheduled to undergo ureteroscopic litholapaxy reduced the incidence and severity of CRBD, NRS score of postoperative pain and analgesic requirements.

Keywords: Complications; Nefopam; Ureteroscopy; Urinary catheterization.

Introduction

In patients who undergo ureteroscopic litholapaxy, a postoperative Foley catheter and ureter stent can cause catheter-related bladder discomfort (CRBD), which may worsen postoperative pain and compromise patient safety. CRBD is a reaction mediated by the muscarinic receptor activity of the bladder muscles. Symptoms of CRBD include a burning sensation in the suprapubic area and an urge to void. The mechanism of CRBD is similar to that of overactive bladder [1,2]. CRBD develops in 58% to 80% of patients treated with urethral catheters [3–5]. In a previously reported patient-control study, ketamine, anticholinergic

drugs, tramadol, gabapentinoids, and dexmedetomidine, which have antimuscarinic effects, have been shown to reduce the incidence and severity of CRBD [3–6].

Nefopam is a centrally acting, non-opioid, non-steroidal, antinociceptive drug, commonly used as a perioperative analgesic agent [7]. If administered during the perioperative period, it reduces the use of opioids and non-steroidal anti-inflammatory drugs employed for analgesia and postoperative complications such as respiratory depression, sedation and renal toxicity [8]. The mechanism of action of nefopam is not fully elucidated; however, its central analgesic effect might be mediated by inhibiting the reuptake of serotonin, dopamine, and norepinephrine [9,10].

In this study, nefopam was administered intravenously to patients undergoing ureteroscopic litholapaxy, and its effect on the incidence and severity of postoperative CRBD was investigated.

Materials and Methods

This prospective, randomized, double-blinded, placebo-controlled study was approved by the Institutional Review Board of our hospital and was performed after obtaining consent from all the participating patients. The study included 18- to 70-year-old patients with American Society of Anesthesiologists physical status I and II, who underwent elective ureteroscopic litholapaxy under general anesthesia between August 2016 and April 2017.

The exclusion criteria included bladder outflow obstruction and overactive bladder (frequency > 3 times per night or more than 8 times per 24 h), epilepsy, myocardial infarction, arrhythmia, heart failure, renal and hepatic diseases, current use of monoamine oxidase inhibitors, a history of drug or alcohol abuse, angle-closure glaucoma, morbid obesity (body mass index > 30 kg/m^2), a history of chronic pain, and a history of psychiatric conditions.

The patients were divided into control and nefopam groups by using a computer-generated random number table (www.randomization.com). Anesthesia was performed by the anesthesiologist assigned to the surgery. Immediately after arrival at the operating room, 40 mg nefopam, diluted in 100 ml of 0.9% saline, was administered intravenously at a rate of 150 ml/h to patients in the nefopam group, while patients in the control group were administered only 100 ml of physiological saline intravenously. To ensure that the patients and anesthesiologists were blinded to the group assigned, the study medications were packaged in an identical manner and provided to the anesthesiologist in a black plastic bag. Except for nefopam, no other medications were administered before anesthesia.

Induction of anesthesia was performed by inserting a laryngeal mask airway (LMA, I-gel^{TM}, Intersurgical Ltd., UK) after administering 2 mg/kg propofol and 0.6 mg/kg rocuronium bromide.

Anesthesia was maintained with 2.0–3.0 vol% of sevoflurane and a fraction of inspired oxygen of 0.5. During surgery, hypotension (mean arterial pressure < 65 mmHg) was treated with 5 to 10 mg ephedrine or 20 to 40 μg phenylephrine, and bradycardia (heart rate < 40 beats/min) was treated with 0.25 or 0.5 mg atropine. Patients in whom hypotension or bradycardia developed were excluded from the study. A systolic blood pressure (SBP) value higher than 140 mmHg, or a diastolic blood pressure (DBP) value higher than 90 mmHg were recorded as cases of hypertension. Patients whose SBP exceeded 150 mmHg or DBP exceeded 100 mmHg were administered nicardipine or labetalol as appropriate. In cases of tachycardia (heart rate > 100 beats/min), the concentration of the inhalation gas was increased and an additional 10 mg of esmolol was administered.

After the ureteral stones were removed using ureteroscopy, a 6 Fr ureteral stent and a 16 Fr urethral catheter were inserted. Sugammadex 2 mg/kg was used to reverse muscle relaxation. LMA was removed after spontaneous respiration was confirmed and the patient's eyes opened. Then, the patient was transferred to the post-anesthesia care unit (PACU) and observed.

The severity of CRBD was classified as follows: patient had no complaints of CRBD (none); patient complained of CRBD when he/she was asked about CRBD (mild); patient self-reported CRBD (moderate), and patient complained of CRBD and tried to remove the catheter, shook hands and feet, or made sounds indicative of pain (severe). Postoperative pain was recorded using the numeric rating scale (NRS) score (0: no pain; 10: worst imaginable pain). The incidence and severity of CRBD, and the NRS score of postoperative pain were assigned by the anesthesiology resident, who was unaware of the study, for 1 h at 10-min intervals, when the patients' level of sedation was 1 or 2 based on the Ramsay sedation score. Patients whose NRS score was 5 or higher received repeated intravenous injections of 25 mg pethidine until the score went below 5. Severity of CRBD and NRS score of postoperative pain recorded the highest score during observation period. Postoperative nausea and vomiting (PONV), somnolence, hyperhidrosis, headache, and blurred vision were recorded. The primary endpoint was the incidence of CRBD, and the secondary endpoints were the severity of CRBD, NRS score of postoperative pain, rescue dose of pethidine, and side effects.

Assuming that nefopam would reduce the incidence of CRBD by 50%, the power analysis with α = 0.05 and β = 0.8 indicated that we would need 30 patients in each group. When the dropout rate was set at approximately 5%, the study was designed to include a total of 64 patients, with 32 patients in each group. Statistical analyses were conducted using SPSS ver. 19.0 (IBM Corp., USA). The Chi-square test, Fisher's exact test (if cell size ≤ 5), or linear by linear association were used to compare

the incidence and severity of CRBD, PONV, dry mouth, hyperhidrosis, intraoperative hypertension, and tachycardia; the *t*-test was used for the analysis of NRS score of postoperative pain and rescue dose of pethidine. A P value less than 0.05 was considered statistically significant.

Results

A total of 64 patients participated in this study. A computer-generated random number table was used to select 32 patients for the control group and 32 patients for the experimental group. Two patients without the ureteral stent in each group were excluded from the study, resulting in 30 patients per group being analyzed. There was a statistically significant difference in height between the control group and nefopam group (168.2 ± 7.9 vs. 161.9 ± 9.3, P = 0.006). However, there was no statistically significant difference in BMI between the control and nefopam

groups (24.9 ± 2.7 vs. 25.5 ± 3.0, P = 0.645) (Table 1).

CRBD was classified as none, mild, moderate, or severe according to severity. The incidence of CRBD was 86.7% (26 patients) in the control group compared to 60.0% (18 patients) in the nefopam group (P = 0.039), indicating a significant difference. The severity of CRBD decreased in the nefopam group compared to that in the control group; this decrease was significant (P < 0.001) (Table 2).

NRS scores of postoperative pain were significantly higher in the control group (3.6 ± 2.5) than in the nefopam group (1.8 ± 1.8) (P = 0.006). Additionally, there was a significant difference in the rescue dose of pethidine (P < 0.001) between the control group (18.3 ± 18.5) and the nefopam group (2.5 ± 7.6) (Table 2).

There were no significant intergroup differences in terms of intraoperative hypertension (systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg), tachycardia (heart rate > 100 beats/min) and postoperative side effects including PONV, somnolence, hyperhidrosis, headache, and blurred vision (Table 3).

Table 1. Demographic Data

Parameters	Control group (n = 30)	Nefopam group (n = 30)
Age (yr)	49.8 ± 15.3	53.1 ± 11.8
Sex (M/F)	21/9	16/14
ASA classification (I/II)	16/14	17/13
Weight (kg)	70.5 ± 10.2	67.2 ± 11.1
Height (cm)*	168.2 ± 7.9	161.9 ± 9.3
BMI (kg/cm^2)	24.9 ± 2.7	25.6 ± 3.0
Stone size (mm)	5.8 ± 1.9	5.6 ± 1.6
Ureter stone position		
Upper	3	5
Mid	2	4
Lower	25	21
Duration of operation (min)	27.0 ± 23.8	22.5 ± 17.6
Duration of anesthesia (min)	42.5 ± 22.4	40.0 ± 17.2

Data are presented as mean ± SD values or the number of patients. There were no significant differences between the two groups. ASA: American Society of Anesthesiology. *P < 0.05.

Table 3. Incidence of Side Effects

Side effects	Control group (n = 30)	Nefopam group (n = 30)
Intraoperative		
Hypertension (SBP > 140 mmHg or DBP > 90 mmHg)	16 (53.3)	18 (60.0)
Tachycardia (heart rate > 100 beats/min)	4 (13.3)	1 (3.3)
Postoperative		
Nausea and vomiting	1 (3.3)	0
Somnolence	0	0
Hyperhidrosis	0	0
Headache	0	0
Blurred vision	0	0

Data are presented as the number of patients (%). SBP: systolic blood pressure, DBP: diastolic blood pressure.

Table 2. Incidence and Severity of Catheter-related Bladder Discomfort

	Control group (n = 30)	Nefopam group (n = 30)	OR or MD	95% CI	P value
CRBD					
Incidence	26 (86.7)	18 (60.0)	0.23	0.06–0.83	0.039
Severity					< 0.001
Mild	8 (26.7)	15 (50.0)			
Moderate	14 (46.7)	3 (10.0)			
Severe	4 (13.3)	0 (0.0)			
Postoperative NRS score	3.6 ± 2.5	1.8 ± 1.8	1.83	0.69–2.97	0.006
Rescue dose of pethidine (mg)	18.3 ± 18.5	2.5 ± 7.6	15.83	8.52–23.14	< 0.001

Data are presented as mean ± SD values or the number of patients (%). CRBD: catheter-related bladder discomfort, NRS: numerical rating scale, OR: odds ratio, MD: median difference. A P value < 0.05 was considered statistically significant.

Discussion

After ureteroscopic litholapaxy, a ureteral stent and a urethral catheter are inserted to remove residual stone fragments and prevent ureteric obstruction [11]; this may cause postoperative CRBD. CRBD involves visceral pain that develops in the ureter and bladder, which are sensitive to stimulation stemming from catheter-induced irritation, resulting in the involuntary contraction of the smooth muscles of the bladder [1,12]. CRBD is a postoperative complication that could lead to emergence agitation in the PACU and thus, should be actively treated [13].

Previous studies have reported that tolterodine, oxybutynin, gabapentinoids, tramadol, butylscopolamine, dexmedetomidine, and ketamine are effective in preventing CRBD [3–5,14–17]. Glycopyrrolate, a muscarinic receptor antagonist, has recently been shown to be effective for the treatment of CRBD [18,19]. The mechanism of CRBD is similar to that of overactive bladder with respect to urotheliogenic factor. Urothelium is a responsive structure that is capable of detecting thermal, mechanical and chemical stimuli. Transmitters released from urothelium by stimulation may alter the excitability of afferent neurons and affect detrusor muscle contractility [2]; therefore, drugs that are effective for the treatment of overactive bladder can be used to treat CRBD. To date, no study has investigated the effect of nefopam on CRBD. To the best of our knowledge, this is the first study to assess the effect of nefopam on CRBD.

The structure of nefopam is similar to that of orphenadrine, an antimuscarinic agent [20]; however, the mechanism of action of nefopam is similar to those of triple receptor (serotonin, norepinephrine, and dopamine) reuptake inhibitors and anticonvulsants. Laboratory studies show that nefopam acts predominantly on the serotonergic receptors and dopamine D1 transporter; among the serotonergic receptors, nefopam binds most strongly to the 2A receptor [21]. Because of these mechanisms, nefopam has been used to treat shivering, alleviate postoperative pain, and prevent hyperalgesia via the blockade of the N-methyl-D-aspartate receptor [7].

In this study, the incidence of CRBD in the nefopam group was significantly lower than that in the control group. First, the decreased incidence of CRBD in the nefopam group may have been attributable to triple receptor reuptake inhibition by nefopam. The major sources of serotonin-containing terminals in the spinal cord are the raphe nuclei. Lumbosacral autonomic nuclei, also known as the sphincter motor nuclei, receive serotonergic input from the raphe nuclei, and stimulation of the raphe nuclei was found to inhibit bladder contraction reflexes in studies performed in cats and rats [22,23]. Selective serotonin uptake inhibitors exert an inhibitory effect on overactive bladder, which is mediated by a similar mechanism [24]; therefore, we presumed that nefopam could also inhibit bladder activity by increasing

serotonin in the central nervous system (CNS). Interestingly, in a number of serotonin subtypes in the experimental studies, the activation of serotonin 2A receptor in the bladder induced bladder contraction. However, considering that the CNS is the most affected area and that most serotonin receptors are distributed not in the end organ but in the CNS, the nefopam-induced inhibitory effect of the bladder contraction response is expected to be greater than the activation effect.

Second, the effect of nefopam may be attributable to dopamine transporter activation. The relationship between dopamine and bladder dysfunction is already well known.

Animal studies indicate that D1 receptors inhibit micturition reflexes, while D2 receptors act reversely, and overactive bladder is associated with dopamine receptors [25]. In addition to the effects of serotonin, the activation of D1 receptors, specifically induced by nefopam, facilitates the relief of CRBD symptoms. Unlike the serotonin, which mainly affects the CNS, analgesic pathway mediated by nefopam-induced activation of the dopamine receptors, has not been elucidated. However, according to animal study, dopaminergic analgesic pathway by nefopam is not observed at the spinal level and may be possible at the supraspinal level [26].

Third, it can be assumed that nefopam inhibits calcium influx [27]. While the activation of the detrusor muscle via muscarinic receptors and noradrenergic pathways requires extracellular calcium influx through the calcium channel [28], nefopam appears to inhibit detrusor hyperactivity by interfering with calcium influx.

When comparing hemodynamic changes during surgery, hypertension was observed in 53.3% of patients in the control group and in 60.0% of patients in the nefopam group. Based on previous studies, the nefopam group in this study should have a similar or lower incidence of hypertension than the control group [29,30]. However, there was no statistically significant difference between the incidences of hypertension in the two groups. Postoperative follow-up by the surgeon revealed that intraoperative hypertension did not worsen the prognoses of the patients. One patient in the nefopam group developed tachycardia during surgery, the incidence of which is very low compared to that in the glycopyrrolate pretreatment group in a study by Kim et al. [19]. Nausea, vomiting, somnolence, hyperhidrosis, headache and blurred vision are symptoms that may occur when nefopam is administered, and there was no significant difference between the two groups. These indicate that intravenous administration of nefopam did not affect hemodynamic instability during surgery and can be used relatively safely.

There are several limitations to this study. First, because the dose of nefopam was limited to 40 mg, it was not possible to analyze the difference in effect with respect to the dose or the minimum effective dose. Therefore, further studies should be

performed to investigate the effects of different other, lower and higher, doses. Second, patients were not at the same level of consciousness while recording the outcomes, as patients with a Ramsay sedation score of 1 or 2 were asked about their condition.

In conclusion, intravenous administration of nefopam in patients undergoing ureteroscopic litholapaxy reduced the incidence and severity of CRBD, postoperative pain, and analgesic requirements without side effects.

Acknowledgments

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