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Prophylactic Tramadol versus Nefopam for Post-operative Catheter-Related Bladder Discomfort in Patients Undergoing Elective Percutaneous Nephrolithotomy: Randomized Controlled Trial

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ABSTRACT

Background: Individuals waking from general anesthesia frequently experience disagreeable symptoms of catheter-related bladder discomfort (CRBD) due to intraoperative catheterization.

Objective: Comparing efficacy of nefopam versus tramadol to prevent (CRBD) after percutaneous nephrolithotomy (PCNL) surgery.

Patients and methods: This was a prospective double-blind study conducted on a total of 150 adult patients between the ages of 18 and 60, of both sexes, who were undergoing percutaneous nephrolithotomy (PCNL) for a renal upper ureteric stone. They were divided into three groups; Tramadol group, Nefopam group and Control group.

Results: The demographic data showed no statistically significant differences between the three groups (P value >0.05). Average fentanyl use after surgery was much higher in the control group (326.50±35.14 mcg/24 hours) compared with both tramadol (165.00±15.15 mcg/24 hours) and nefopam groups (183.00±21.69 mcg/24 hours) (P value <0.001**).** The severity of CRBD, when comparing the control group to the tramadol and nefopam groups, the control group had significantly higher post-operative pain and rescue analgesic use throughout all study timeframes (P value <0.05). Sedation, an increase in the number of patients reporting post-operative nausea and vomiting (PONV), and dry mouth were all significantly more common in the tramadol group than in the nefopam or control groups (P value<0.05).

Conclusions: Intra-operative administration of both tramadol and nefopam significantly reduced post-operative CRBD, pain together with reduced consumption of post-operative fentanyl requirements in patients undergoing PCNL. However, nefopam was superior to tramadol as it was not associated with post-operative sedation and had lesser incidence of post-operative adverse events.

Keywords: Catheter-related bladder discomfort, Tramadol, Nefopam, Percutaneous Nephrolithotomy.

INTRODUCTION

With the development of Enhanced Recovery After Surgery (ERAS) protocol, there is a new trend for a more satisfying post-operative pain control and early discharge following short-lasting surgery as recovery and discharge from the hospital are often held back by inadequate pain management[(1)].

Patients who have urinary catheterization as part of their surgery experience a painful side effect known as catheter-related bladder discomfort (CRBD)[(2)]. It's characterized by symptoms including an urgent need to urinate and burning pain above the pubic bone, and it's sometimes linked to abnormal behavior [(3)]. This symptom can be explained by the stimulation of muscarinic receptors, namely type 3 muscarinic receptors (M3) due to release of acetylcholine from irritated cholinergic nerves secondary to involuntary contraction of the proximal urethra or bladder by the indwelling catheter, which results in the frequent urge to void [(4)].

The reported prevalence of CRBD ranges from 58% to 80% [(5)], in addition to mild to severe males are more likely to be affected by CRBD [(6)].

There are a number of anesthetics with anti-muscarinic characteristics that have been claimed to be useful in preventing CRBD[(7-10)].

For pain relief, tramadol is a synthetic, centrally-acting Mu1 (U1) agonist analgesic that also blocks the activity of M1 and M3 muscarinic receptors [(11)]. Further, tramadol has been shown in animal experiments to have a suppressive impact on both detrusor hyperactivity and normal micturition [(12)].

In the field of perioperative analgesia, nefopam stands out as a popular choice due to its centrally acting, non-opioid, non-steroidal analgesic properties. Reuptake inhibition of serotonin, dopamine, and norepinephrine may be responsible for its central analgesic action [(13)].

Patients undergoing elective percutaneous nephrolithotomy were included in this trial to evaluate the efficacy of prophylactic tramadol against nefopam in reducing post-operative CRBD. Reducing the occurrence or severity of CRBD was the primary aim, while minimizing the need for post-operative fentanyl and the occurrence of adverse effects such sedation, PONV, and respiratory depression were secondary endpoints.

PATIENTS AND METHODS

This is randomised, placebo-controlled, double-blind trial. Adult patients (aged 18-60) of either sex who were undergoing PCNL for a renal upper ureteric stone and required urinary bladder catheterization were included in the trial. Patients had to be ASA I or II status to be eligible. Nephrostomy and post-operative bladder drainage for 12-24 hours are common after this operation.

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The current investigation was conducted at Qena University Hospitals. The patients were divided into three groups (with 50 people in each group) using a computer-generated random number table (www.randomization.com).

Patients who had undergone transurethral resection of the prostate for benign prostatic hypertrophy or who had ha history of bladder outflow blockage or overactive bladder (frequency > 3 times per night or more than 8 times/24 hours) were not included, as well as, liver or renal disorders, heart failure, myocardial infarction, epilepsy, arrhythmia, diabetes mellitus, regular usage of a monoamine oxidase inhibitor or nonsteroidal anti-inflammatory medication, addiction, angle-closure glaucoma, severe obesity (BMI>30), and chronic pain in the past.

All eligible patients were kept fasting six hours for solids and two hours for clear fluid.

As soon as they got to the operating room (OR), a 20-gauge catheter was put in their veins and pumping in 500 millilitres of lactated ringer was started. All patients were monitored using a 5-lead ECG, non-invasive blood pressure, peripheral oxygen saturation, end-tidal carbon dioxide (maintained at 32-36 mmHg), and temperature.

Anesthesia was induced using 1 microgram per kilogram of fentanyl and 2 milligrams per kilogram of propofol.

The 0.5 mg/kg dose of atracurium used for tracheal intubation was very successful. To drain urine into a urinary bag, a 16 Fr. Foley catheter with an inflatable balloon filled with 10 ml of distilled water was placed in the supra-pubic region using an adhesive tape and never subjected to traction.

Maintaining unconsciousness required 2.0-3.0 vol% sevoflurane and a 50% FiO_2 fraction.

Three groups of patients were chosen at random to receive either 1.5 mg/kg of tramadol diluted in 10 ml at 15 minutes before scheduled extubation. Isotonic saline solution (Group T, n=50), nefopam diluted to 0.15 mg/kg in 10 ml. isotonic saline solution (Group N, n=50), or isotonic saline 10 ml (Group C, n=50). I.V. administration was used for all medications in the studies (one minute duration). An anesthesiologist who was not engaged in the study delivered these drugs.

Following extubation and administration of a combination of neostigmine 0.04 mg/kg and atropine 0.01 mg/kg, patients regained their normal muscular tone and reflexes and were moved to the post-anesthesia care unit (PACU).

At t=0 (the end of surgery), t=1, t=2, t=6, and t=4 (minutes 1, 2, 6, and 12 after surgery), patients were evaluated for CRBD, pain, PONV, and sedation. The post-operative evaluation was carried out by an anesthesiologist who was also blinded to the patients' identities.

Using a four-point scale, the severity of CRBD was determined by: 1-none (none of CRBD were complained); 2- mild (when answered yes if asked they had CRBD); 3- moderate (when they complained that they had CRBD by themselves without asking and without behavioral changes), and 4- severe (when they complained that they had CRBD by themselves and showed behavioral changes like they were twisting around, trying to get out the catheter by thrashing their arms and legs) [(9)].

The patients' NRS scores for post-operative pain were recorded (0:no pain,10: worst imaginable pain)[(14)].

I.V. fentanyl 25 ug was given as a rescue analgesic if severe CRBD was present or the patient's NRS score was greater than 3.

Early (within 6 post-operative hours) and late (between 6 and 24 post-operative hours) PONV were defined according to a four-point ordinal scale from 0 to 3 (0 = no nausea; 1 = mild nausea; 2 = moderate nausea; 3 = severe nausea with vomiting) [(15)].

All patients with PONV grade 3 were given 4 mg I.V. of ondansetron as a rescue antiemetic.

The Ramsay Sedation Scale was used to determine how sedated a patient was: 1 = alert, agitated, or restless; 2 = cooperative, oriented, and tranquil; 3 = asleep, responsive to commands; 4 = rapid response to loud glabellar tap or loud noise; 5 = slow response to light glabellar tap or loud noise; 6 = no response at all [(16)].

If a patient's sedation level was higher than 4, they were regarded to be sedated. Having a ventilator frequency of 8 breaths per minute (bpm) and an oxygen saturation of 90% without supplemental oxygen was considered to be a sign of respiratory depression.

Facial flushing, dry mouth, blurred vision and other possible post-operative adverse events were noted and recorded if present.

Sample size calculation:

Graph Pad Instat 3.0 was used to estimate a sample size of 45 cases for each group (completed to 50 cases). It has been estimated that CRBD occurs in 60% of cases [(8)]. Both tramadol and nefopam have been shown to reduce the occurrence by about 30 percent, so that therapy with either drug is likely to have a positive effect. 45 patients would be required in each group with 80% power and α =0.05 to be statistically significant. To reduce the possible dropouts, 50 patients in each group were required.

Ethical consent:

Ethical Committee approval was obtained from Qena University Hospitals Institutional Review Board in September 2017 and written informed consent was obtained from every patient participating in the study. There is a record for this trial in the Australian and New Zealand Clinical Trials Registry (ANZCTR) under the identification: ACTRN12618002054291 and website: http://www.ANZCTR.org.au/ACTRN12618002054291.aspx This work has been carried out in accordance with The Code of Ethics of the World

Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

The analysis was performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was utilised to check for the normality of the numeric variables. Mean and standard deviation were reported for numerical variables that follow a normal distribution, whereas the median and range were reported for those that did not. Quantitative and percentage representations of categorical variables were used. The chi-square test was used to compare groups based on continuous or discrete categories. In this study, statistical significance was determined by a P-value of less than 0.05.

RESULTS

The current study was conducted on a total of 195 patients who were evaluated for eligibility. Five participants declined to take part, 10 patients were excluded for chronic use of pain medications, 5 patients for age >60 years, 5 patients for transurethral resection of prostate, 10 patients for diabetes mellitus, and 10 patients for history of lower urinary tract surgery. Totally, 150 people participated in the study, 50 in each of the three groups (Table 1).

Patients' age, sex, ASA I/II classification, anesthetic time, and surgical time were not significantly different between the three groups. Mean post-operative fentanyl consumption was highly statistically significant greater in the control group compared with both tramadol group and nefopam group with (Table 1).

Table (1): Demographic data

	Group T (n=50)	Group N (n=50)	Group C (n=50)	P value
Age (years):	35.14 ± 10.99	34.66 ± 11.19	33.48 ±11.53	0.7495
Sex (M/F):	37/13	33/17	39/11	0.3907
ASA I/II:	37/13	38/12	41/9	0.6150
Duration of Anesthesia(min):	108.30 ± 9.93	108.20 ±10.39	107.60 ± 10.65	0.9351
Duration of surgery(min):	94.50 ±11.21	93.20 ± 10.49	93.70 ± 10.63	0.8314
Post-operative fentanyl requirement (mcg/24 hr):	165.00 ± 15.15	183.00 ± 21.69	326.50 ± 35.14	<0.0001 ***

Data are presented as mean ±SD, or as number
Group T= Tramadol group, Group N= Nefopam group, Group C= Control group.
***= Very highly significant.

When comparing the severity of CRBD in the control group to that of the tramadol and nefopam groups across the study's several post-operative time points, the severity was statistically significantly more only in the control group at 0, 1, 2, 6 and 12 hours (Table 2).

Table (2): Severity of CRBD at different times of post-operative periods

	Group T (n=50)	Group N (n=50)	Group C (n=50)	P value
0 hr.(T_0)	1.34 ± 0.38	1.18 ± 0.39	2.28± 0.61	<0.0001 ***
1 hr.(T_1)	1.34±0.28	1.60 ± 0.41	2.26±0.60	<0.0001 ***
2 hr.(T_2)	1.58±0.30	1.52±0.31	2.08± 0.49	<0.0001 ***
6 hr.(T_3)	1.50 ± 0.31	1.48± 0.31	1.74 ± 0.39	0.0347 *
12hr (T_4)	1.30 ± 0.36	1.60 ± 0.32	2.06 ± 0.24	<0.0001 ***

Data are presented as mean ±SD.
Group T= Tramadol group, Group N= Nefopam group, Group C= Control group.
*=Significant, ***= Very highly significant.

It was found that after 0, 1, 2, 6, 12, and 24 hours after surgery, the VAS scores for pain in the control group were significantly greater than those in the tramadol and nefopam groups (Table 3).

Table (3): Severity of post-operative pain score in the studied three groups at different times

VAS	Group T(n=50)	Group N(n=50)	Group C(n=50)	P value
0 hr.(T_0)	2.0 (2.0-4.0)	2.0 (1.0- 4.0)	4 (2.0 -6.0)	<0.0001 ***
1 hr.(T_1)	2.0 (1.0 -4.0)	2.0 (1.0-3.0)	4.0 (3.0-7.0)	<0.0001 ***
2 hr.(T_2)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	4.0 (3.0-5.0)	<0.0001 ***
6 hr.(T_3)	2.0 (1.0-2.0)	2.0 (1.0-3.0)	3.0 (2.0-5.0)	0.0168 *
12 hr.(T_4)	2.0 (1.0-2.0)	2.0 (1.0-2.0)	2.0 (1.0-5.0)	0.0143*
24 hr.(T_5)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	2.0 (1.0-3.0)	0.0020**

Data are presented as median (range).
Group T= Tramadol group, Group N= Nefopam group, Group C= Control group.
*=Significant, **= Highly significant, ***= Very highly significant.

The tramadol group experienced significantly more sedation at 0, 1, and 2 hours after surgery compared to the nefopam group and the control group (Table 4).

Table (4): Post-operative sedation in the studied three groups

Variable	Group T(n=50)	Group N(n=50)	Group C(n=50)	P value
0 hr.(T_0)	3.0 (2.0-4.0)	2.0 (1.0-2.0)	1.0 (1.0-2.0)	<0.0001 ***
1 hr.(T_1)	1.0 (1.0-3.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.0239 *
2 hr.(T_2)	2.0 (1.0-3.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.0103*
6 hr.(T_3)	1.0 (1.0-3.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.2351
12 hr.(T_4)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.3508
24 hr.(T_5)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.8785

Data are presented as median (range).
Group T= Tramadol group, Group N= Nefopam group, Group C= Control group.
*=Significant, ***= Very highly significant.

In comparison to the tramadol and nefopam groups at 0 hours, 1 hours, 2 hours, and 6 hours, the control group had a significantly higher number of patients requiring rescue analgesics after surgery. There was statistically significant increase in the number of patients experiencing PONV and dry mouth in the tramadol group compared with both nefopam group and control group. (Table 5).

Table (5): Post-operative side effects

Use of post-operative rescue analgesic	Group T (n=50)	Group N (n=50)	Group P (n=50)	P value
0 hr.	2(4%)	4(8%)	19 (37.3%)	P<0.0001***
1 hr.	5(10%)	6 (12%)	25(50%)	P<0.0001***
2 hr.	7(14%)	9(18%)	32(64%)	P<0.0001***
6 hr.	4(8%)	5(10%)	26 (52%)	P<0.0001***
12 hr.	2(4%)	3(6%)	5(10%)	0.4723
24 hr.	1(2%)	1(2%)	2(4%)	0.7734
2- PONV:	7(14%)	1(2%)	2(4%)	0.0361*
3- Dry mouth:	6(12%)	0(0%)	0(0%)	0.0019**

Data are presented as number and percentage (%).
Group T= Tramadol group, Group N= Nefopam group, Group C= Control group.
PONV=Post-operative nausea and vomiting.
*=Significant, **= Highly significant, ***= Very highly significant.

DISCUSSION

Researchers found that giving patients tramadol and nefopam during surgery helped lessen their need for post-operative rescue analgesics and the severity of post-operative CRBD and pain. However, the reported adverse effects of tramadol like sedation, dry mouth and PONV, make nefopam superior to tramadol.

Although there are a number of drugs available to counteract CRBD, many questions remain unanswered in clinical practice. Adverse effects, some of which are quite serious, are a reality with all of the effective treatments for CRBD. Even more, they may be inappropriate for use right after surgery. In other words, this kind of management is not always in place. Overactive bladder, characterized by urine frequency and urgency, with or without the sense of urge incontinence, is a common cause of intensive care unit admissions. Muscarinic receptor antagonists, which have been proven helpful in multiple studies, are currently used extensively in the pharmaceutical management of this uncomfortable symptom [7-10]. Although this approach has been effective in reducing pain and discomfort, it is not without drawbacks due to the availability of pain and discomfort processes that do not appear to be linked to muscarinic receptors. This also clarifies why so many articles advocate for non-muscarinic receptor antagonist drugs like paracetamol [17], ketamine [18] and pregabalin [19] to treat these symptoms.

Tramadol is a synthetic, opioid analgesic of the aminocyclohexanol group that has a central nervous system effect and primarily inhibits serotonin reuptake but has a poor affinity for opioid receptors. Also, it has an inhibitory effect on M_1 and M_3 muscarinic receptors, thus postulated to be effective for CRBD [20].

Two trials looked at the effects of intravenous tramadol 1.5 mg/kg before surgery and reported a significant reduction in the incidence of CRBD up to 6 hours after surgery. However, increased adverse effects like sedation, dry mouth, nausea and vomiting were also observed [11, 21]. The results of these other investigations corroborate those of the current research. Tramadol's active metabolite, O-desmethyl, is responsible for its blatantly negative after-surgery effects [22].

Nefopam is a centrally acting analgesic that is produced from benzoxazocine, which is not a sedative. It shares structural similarities with the antimuscarinic agent orphenadrine [23]. However, nefopam's mode of action is similar to that of anticonvulsants and other drugs that block the uptake of the neurotransmitter's serotonin, norepinephrine, and dopamine [13]. Nefopam has been used to treat shivering, reduce surgical pain, and avoid hyperalgesia as a result of its ability to block the N-methyl-D-aspartate receptor [24]. For this reason, nefopam is widely utilised as an efficient analgesic adjuvant for perioperative pain, and is well-documented to lessen the need for opioids in the post-operative term [13].

Inhibition of triple receptor reuptake by nefopam has been linked to a significant reduction in post-operative CRBD and pain in the nefopam group, as seen in the current study.

Consistent with **Cheon *et al.*** [25]**,** who looked at the impact of nefopam on CRBD in patients having ureteroscopic litholapaxy, we found that it reduced both the frequency and severity of the condition.

While nefopam is not an opioid, it nonetheless has the potential to cause a number of unpleasant side effects in the post-operative time.

LIMITATIONS

The current study does have a few caveats. Initially, it is a small-scale, single-center study. Second, we did not assess the dose-response titration nor the effects of continuing the drugs in the post-operative period, and instead employed a fixed dose for each drug. Finally, a patient's pain tolerance and prior experience with a urinary catheter can affect the severity of CRBD. Finally, we hadn't compared the medications under study across the spectrum of surgical procedures that call for urinary catheterization.

CONCLUSIONS

Intra-operative administration of both tramadol and nefopam significantly reduced post-operative CRBD, discomfort and pain in patients undergoing PCNL. However, nefopam was associated with no post-operative sedation and lesser incidence of post-operative adverse events when compared with tramadol.

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