Section: Anaesthesiology and Critical Care

Original Research Article

COMPARISON BETWEEN PRE-EMPTIVE INTRAVENOUS NEFOPAM AND TRAMADOL FOR ATTENUATION OF CATHETER RELATED BLADDER DISCOMFORT AND SURGICAL STRESS RESPONSE IN PATIENTS UNDERGOING TURBT

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Received : 02/11/2023
Received in revised form : 02/12/2023
Accepted : 16/12/2023

Keywords:
Nefopam, tramadol.

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DOI: 10.47009/jamp.2023.5.6.221

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (6); 1078-1082

Abstract

Background: Urological procedures involving urinary catheterization, as an intervention leads to Catheter Related Bladder Discomfort (CRBD). Patients often experience distressing symptoms after surgery. Although drugs with anti-muscarinic effects have been used for the treatment of CRBD, the search for best drug is still on. Hence, this study was carried out to investigate whether nefopam, a centrally acting analgesic with concomitant anti-muscarinic effect, reduces the incidence and severity of CRBD. **Materials & Methods:** A prospective, randomised double-blind study was conducted on 90 patients of the American Society of Anaesthesiologists (ASA) status of I-II, aged 18-70 years of either sex undergoing elective TURBT surgery. Patients were divided into three groups, comprising 30 patients each; Group A received 100mg tramadol, Group B received 20 mg nefopam and Group C received 2ml NS; as intravenous infusion in 100 ml normal saline 30 mins before surgery. The incidence and severity of CRBD, VAS score for postoperative pain, rescue analgesia and other side effects were recorded postoperatively. Serum cortisol and blood sugar levels before and after the procedure were noted. **Results:** The incidence and severity of CRBD were significantly lower in nefopam group ($p<0.0001$), 2h after the surgery compared to tramadol and control group. The VAS score of postoperative pain ($P <0.001$) and rescue dose of paracetamol ($P < 0.001$) were significantly higher in the group C. Postoperatively, serum cortisol and blood sugar levels were significantly lower in Group B ($P < 0.0001$) than group A and group C. **Conclusion:** Premedication with intravenous nefopam reduced the incidence and severity of CRBD, postoperative pain and surgical stress response in patients undergoing transurethral resection of bladder tumour.

INTRODUCTION

Urological procedures involving urinary catheterization, as an intervention lead to Catheter Related Bladder Discomfort (CRBD) in immediate post-operative period. Incidence of CRBD ranges from 47-90%.[1] Clinically, patients with CRBD present with burning sensation spreading from supra-pubic area to penis, urinary urgency and urinary frequency with or without urge incontinence. Behavioral responses include flailing limbs, vocal response, pulling out of urinary catheter.[1,2]

CRBD has distressing consequences like increased postoperative agitation, unsatisfied patient and attendants, prolonged hospital stay thus increasing workload on medical staff and cost of stay at hospital.[3] Also there is increased incidence of various postoperative complications like surgical site dehiscence, cardiovascular instability , arrhythmias.[1]

Mechanism involved in bladder irritation and contraction from foley catheter are mediated by stimulation of muscarinic receptors. Also, prostaglandins have an excitatory role in causing bladder contractility.[4] Hence anti-muscarinic drugs and prostaglandin inhibitors prevent bladder contractility and thus relieve the symptoms of CRBD. Various drugs like anti-muscarinic agents, tapentadol, ketamine, parecoxib, dexmedetomidine, NSAIDS, gabapentin and general anaesthetic agents like sevoflurane and propofol have shown proven benefits in prevention of CRBD.[1]

Nefopam is a centrally acting, non-opioid, non-steroidal, anti-nociceptive drug, used as a perioperative analgesic agent. When administered during the perioperative period, it has shown to reduce the use of opioids and NSAIDS for analgesia

ISSN (O): 2687-5365; ISSN (P): 2753-6556

and decreased postoperative complications such as respiratory depression, sedation and renal toxicity. 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.[5] Nefopam is a novel drug and has limited studies on its efficacy in prevention of CRBD.

Tramadol is a centrally acting opiod analgesic with anti-muscarinic effect and has proven to decrease incidence and severity of CRBD by inhibition of noradrenaline (NA) and serotonin (5HT) reuptake.[3] This study hereby compares the efficacy and tolerability of nefopam and tramadol in prevention of CRBD in patients undergoing transurethral resection of bladder tumour (TURBT). The primary objective was to compare the efficacy of tramadol and nefopam with control group in reducing incidence and severity of postoperative CRBD. The secondary objective was to compare the surgical stress response and side effects of the drugs.

MATERIALS AND METHODS

Study Type

A prospective, randomized study.

Source of Data

After obtaining written informed consent from the participants, the study was conducted in Government Doon Medical College, Dehradun after clearance from institutional ethical board.

Duration of Study

The study was done from August 2022 to August 2023.

Method of Collection of Data

The study included 90 patients of the American Society of Anaesthesiologists (ASA) status of I-II, aged 18-70 years of either sex undergoing elective TURBT under subarachnoid block. All patients were made aware of the symptoms of CRBD (presented with burning sensation with urgency to micturate or supra-pubic discomfort) and Visual Analogue Scale (VAS) during pre-anaesthetic visit. Patients who refused or with significant cardiac, respiratory or GI disease, renal failure, diabetes mellitus, history of chronic drug intake or allergy to the study drug, psychiatric illness were excluded from the study.

All the study participants were pre-medicated with 0.25 mg oral Tab. Alprazolam and 150 mg Tab. Ranitidine on night before surgery. Patients were randomized using computer generated random number in either of the three groups (n=30). Group A received intravenous infusion of 100mg tramadol in 100 ml NS; Group B received intravenous infusion of 20 mg nefopam in 100 ml NS and Group C was given 100 ml + 2ml NS infusion 30 mins prior to surgery. The anaesthesiologist who randomised the patients administered the medications and had no further role in the study.

This study was conducted to assess the efficacy of the study drugs in reducing the incidence and severity of postoperative CRBD as a primary outcome. Secondary outcomes included the difference in serum cortisol and blood sugar levels, the need for rescue analgesic and adverse effects including postoperative nausea and vomiting (PONV), respiratory depression, sedation, drowsiness, confusion and dry mouth.

Baseline vitals were recorded. Blood samples for serum cortisol level and Random Blood Sugar (RBS) was sent 1 h before surgery and 2 h after completion of surgery. Preoperative sedation was evaluated by the Ramsay Sedation Scale (RSS) before shifting to operation theatre (Grade 1 – patient appears anxious, agitated, or restless; Grade 2 – patient is cooperative, tranquil, and oriented; Grade 3 – patient responds to verbal command; Grade 4 – patient is asleep and shows response only to light glabellar tap, or loud auditory stimuli; Grade 5 – patient is asleep and shows sluggish response to light glabellar tap or loud auditory stimulus and Grade 6 – patient is asleep and shows no response to glabellar tap or loud auditory stimulus). Standard monitors like electrocardiography, non-invasive blood pressure, and pulse oximetry were attached in the operation theatre. Subarachnoid block was performed in L4-L5 space using 25G Quincke's needle and injected 2.5 mL of 0.5% bupivacaine heavy after free flow of CSF. The patient was positioned in lithotomy, after achieving a block level of T8. Hemodynamic parameters like systolic (SBP), diastolic(DBP)and mean arterial pressure, heart rate and peripheral oxygen saturation (SpO2) were recorded before premedication, after shifting to OT, at the time of spinal anaesthesia, at 5, 10, 15 min and then every 15 min till the end of surgery. At the end of surgery, urinary bladder was catheterized using 18 F Foley catheter after lubricating with 2% lignocaine jelly and the balloon was inflated with 10 mL NS. After shifting to the post-operative care unit (PACU), the severity of CRBD was evaluated at intervals of 0, 0.5, 1, 2, 3, 4, 5 and 6 h postoperatively on a four-point severity scale by a blinded assessor. [Grade1 - No pain; 2 - Mild pain (revealed by asking the patient);3 - Moderate pain (spontaneous complaint by the patient); 4 - Severe discomfort (agitation, loud complaints and attempts to remove catheter)]. Also, suprapubic pain was assessed by VAS with scores ranging between 0-10 (where 0 is no pain and 10 is worst imaginable pain) postoperatively. The first analgesic requirement (VAS ≥3) was recorded and 1 gm of paracetamol was administered intravenously with an interval of atleast 6 hrs. Intravenous 40 mg parecoxib was administered to patients who had a VAS >5 even after receiving paracetamol and were noted. Postoperatively, patients with a sedation score of more than or equal to 4 were considered sedated. The presence of PONV was assessed on a score of 0, 1 or 2 (0 = no nausea or vomiting; 1 = tolerable nausea or vomiting; 2 = intractable nausea or vomiting). Rescue anti-emetic, intravenous ondansetron 4 mg was given to the patients with PONV of grade >1. Other complaints like respiratory

ISSN (O): 2687-5365; ISSN (P): 2753-6556

depression, drowsiness, confusion and dry mouth were also assessed.

Statistical Analysis

The data was analyzed using IBM SPSS statistical version 20 (Statistical Package for Social Science, IBM 2011). Frequencies and percentages were computed for qualitative data (age, ASA physical status, sedation score, CRBD score and postoperative symptoms), and mean and standard deviation for quantitative data (height, weight, hemodynamic parameters, VAS, duration of surgery, serum cortisol and blood sugar levels). Hemodynamic parameters were compared with t-test. The means of continuous variables were compared among the three groups using analysis of variance (ANOVA). P <0.05 was considered as statistically significant.

RESULTS

A total of 90 patients completed the study with no dropouts. Demographic profile of patients were comparable in all three groups (Table 1). There were no significant differences among the three groups (p>0.05). The levels of serum cortisol and random blood sugar after 2 hrs of surgery among the 3 groups showed Group C > A > B and it was highly significant (p<0.0001). [Table 2]

The incidence of CRBD among 3 groups is depicted in Figure1. There was no difference in CRBD incidence and severity at 0 and 0.5 h postoperatively in Group A and B, but there was significant incidence and severity of CRBD in Group C on first assessment in PACU (0 h). At 2 h postoperatively, incidence of CRBD was lower in group B (B<A<C), which was statistically significant (P<0.0001). Similarly, at 3,4,5 and 6 h postoperatively, the incidence and severity of CRBD was much lower in group B followed by Group A and Group C, which was statistically highly significant(P<0.001). [Table 3]

On comparison of mean VAS score at different time intervals postoperatively, the score was higher in Group C followed by Group A and Group B. The difference was highly significant (p<0.001). [Figure 2]

Figure 3 depicts the side effects where none of the patients complained of dry mouth, nausea and vomiting, drowsiness, respiratory depression in either of the groups. Confusion was observed in 1 patient in Group A and B and were comparable. RSS of 4 was present in 2 patients in Group A,1 patient in Group B and none in Group C. Need for rescue analgesia, paracetamol was highest in group C (n=26) followed by Group A (n=2) and none required in Group B patients. There was no need for parecoxib in either of the groups.

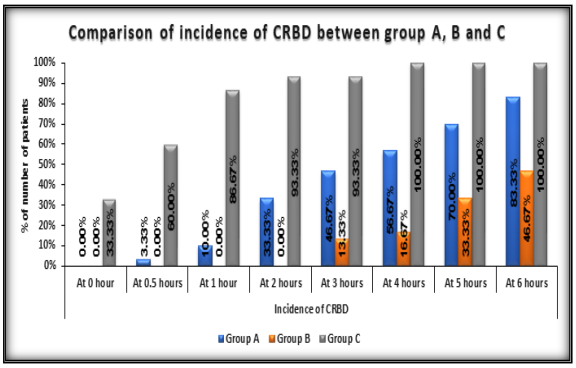

Figure 1: Comparison of incidence of CRBD between group A, B and C

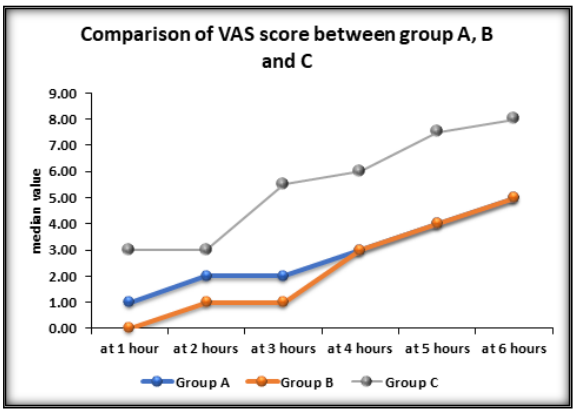

Figure 2: Comparison of VAS score at different time intervals between group A, B and C

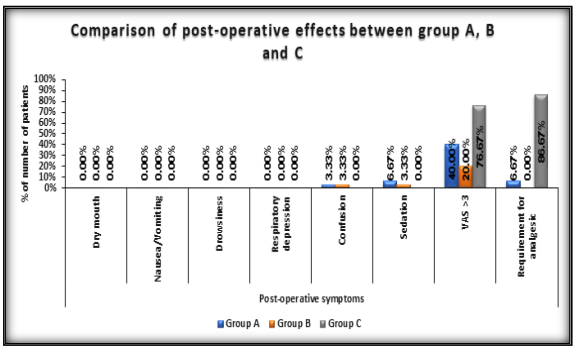

Figure 3: Comparison of post-operative symptoms between group A, B and C

Table 1: Distribution of Lesion According to Age and Sex

Demographic characteristics	Group A(n=30)	Group B(n=30)	Group C(n=30)
ASA I	8 (26.67%)	8 (26.67%)	6 (20%)
II	22 (73.33%)	22 (73.33%)	24 (80%)
Age(years)	65.03 ± 6.99	64.57 ± 4.56	64.4 ± 3.89
Height(cm)	165.27 ± 7.51	164.13 ± 3.58	165.67 ± 3.3
Weight(kg)	65.73 ± 5.35	65.1 ± 3.9	64.63 ± 3.71

Table 2: Comparison of surgical characteristics between group A, B and C

Patient details	Group A(n=30)	Group B(n=30)	Group C(n=30)	P value
Duration of surgery(minutes)	40.82 ± 5.64	41.43 ± 5.37	42.73 ± 5.34	0.786

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Serum cortisol after 2 hours(ng/dL)	164.73 ± 12.12	125.47 ± 5.58	194.9 ± 3.76	<0.0001 A vs B:<0.0001 A vs C:<0.0001 B vs C:<0.0001
RBS after 2 hours(mg/dL)	115.3 ± 3.06	102.5 ± 2.45	133.77 ± 2.4	<0.0001 A vs B: <0.0001 A vs C: <0.0001 B vs C: <0.0001

Table 3: Comparison of severity of CRBD between group A, B and C

Time	Group A				Group B				Group C				P value
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	
0	30	0	0	0	30	0	0	0	20	15	5	0	< 0.0001 A vs B: NA A vs C :0.0008 B vs C: 0.0008
0.5	29	1	0	0	30	0	0	0	12	12	6	0	< 0.0001 A vs B: 1 A vs C: <.0001 B vs C: <.0001
1	27	3	0	0	30	0	0	0	3	17	8	2	<0.0001 A vs B:0.237 A vs C:<.0001 B vs C:<.0001
2	20	10	0	0	30	0	0	0	0	4	21	5	<0.001
3	16	14	0	0	26	4	0	0	0	4	18	8	<0.0001
4	13	17	0	0	25	5	0	0	0	2	16	12	<0.0001
5	6	12	9	3	20	9	1	0	0	0	12	18	<0.001
6	3	6	9	5	16	12	2	0	0	0	7	23	<0.0001

DISCUSSION

After transurethral resection of bladder tumour, a foley catheter is left in place to empty and heal the urinary bladder, which may cause postoperative CRBD. The visceral pain that develops in the bladder is due to stimulation stemming from catheter-induced irritation, resulting in the involuntary contraction of the smooth muscles of the bladder [6,7]. CRBD is a postoperative complication that can lead to emergence agitation in the PACU and thus, should be actively treated.[8]

Various studies have shown promising results that tolterodine, oxybutynin, gabapentinoids, tramadol, tapentadol, butylscopolamine, dexmedetomidine, and ketamine are effective in preventing CRBD.[9-15]

The mechanism of CRBD is similar to that of overactive bladder with respect to urotheliogenic factor,[16] hence drugs that are effective for the treatment of overactive bladder can be used to treat CRBD. There are limited studies on efficacy of nefopam on CRBD.

Nefopam has a similar structure to that of orphenadrine, an antimuscarinic agent.[17] The mechanism of action of nefopam is similar to those of triple receptor (serotonin, norepinephrine, and dopamine) reuptake inhibitors and anticonvulsants. Studies have shown that nefopam acts predominantly on the serotonergic receptors and dopamine D1 transporter; among the serotonergic receptors, nefopam binds most strongly to the 2A receptor.[18] 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.[19]

In this study, overall incidence of CRBD was 77 %. The incidence of CRBD in nefopam group was significantly lower (47 %) as compared to tramadol (83 %) and control group (100%). The mechanisms attributed for decreased incidence of CRBD in Nefopam group are related to animal studies. Firstly, triple receptor reuptake inhibition by nefopam. The major sources of serotonin-containing terminals in the spinal cord are the raphe nuclei. Few studies performed in cats and rats reported that 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.[20,21] Selective serotonin uptake inhibitors exert an inhibitory effect on overactive bladder, which is mediated by a similar mechanism,[22]; therefore, we presumed that nefopam could also inhibit bladder activity by increasing serotonin in the central nervous system (CNS).

Secondly, the effect of nefopam may be attributable to dopamine transporter activation, where D1 receptors inhibit micturition reflexes, while D2 receptors act reversely, and overactive bladder is associated with dopamine receptors.[23] The combined effects of serotonin and the activation of D1 receptors by nefopam resulted in the relief of CRBD symptoms. Third, it can be assumed that nefopam inhibits calcium influx.[24] While the activation of the detrusor muscle via muscarinic

ISSN (O): 2687-5365; ISSN (P): 2753-6556

receptors and noradrenergic pathways requires extracellular calcium influx through the calcium channel.[25]

The incidence as well as severity of CRBD was lower at all-time intervals after 2h in Nefopam group compared to other groups, indicating better efficacy and tolerability postoperatively. The VAS was lower in group B at 3, 4, 5, and 6 h than group A indicating IV Nefopam to be more effective in relieving postoperative pain than IV tramadol.

Recently, the degree of stress response to surgery is related to serum cortisol and blood sugar levels.[26] This study reported the extent of systemic stress response to transurethral resection of bladder tumour (TURBT) by measuring serum cortisol levels and blood sugar levels. A significant decrease in the serum cortisol and blood sugar levels was found in nefopam group as compared to tramadol and control group and was statistically highly significant ($P < 0.0001$).

In this study, 1 patient presented with confusion in both nefopam and tramadol group. Sedation was observed in 2 patients in tramadol group and 1 in nefopam group ($P = 1$). Several authors have observed an increased incidence of sedation and PONV with tramadol.[3,14]

The limitations of this study is the dose of nefopam, which was limited to 20 mg. Hence, further studies can be performed to investigate the effects of different doses in urological procedures.

CONCLUSION

To conclude, intravenous administration of nefopam in patients undergoing transurethral resection of bladder tumour reduced the incidence and severity of postoperative CRBD and pain.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556