Original Article

Comparison between pre-emptive oral tramadol and tapentadol for attenuation of catheter-related bladder discomfort and surgical stress response in patients undergoing transurethral resection of prostate: A prospective, randomised, double-blind trial

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ABSTRACT

Background and Aims: Surgical interventions involving urinary catheterisation often lead to catheter-related bladder discomfort (CRBD). With a very high incidence rate of 47%–90%, CRBD often leads to a distressing and painful recovery after surgery. Although many opioids have been used for the treatment of CRBD, the search for the best is still going on. This study investigated the efficacy and tolerability of oral tapentadol and tramadol on postoperative CRBD. **Methods:** This was a prospective, randomised double-blind study. 100 patients, undergoing transurethral resection of the prostate were randomly assigned into two groups to receive tramadol 100 mg (Group A) or tapentadol 50 mg (Group B) orally 1 h before surgery. CRBD was evaluated on a 4-point severity scale in the post-operative area at 0, 0.5, 1, 2, 3, 4, 5 and 6 h. Pain and adverse effects were assessed postoperatively. Serum cortisol levels before and after the procedure were noted. Statistical analysis was done with the analysis of variance, *t* test. **Results:** Postoperative CRBD, 2 h after surgery was significantly reduced in group B than group A ($P = 0.012$). Cortisol levels, postoperatively were significantly lower in Group B (113 ± 65.45) ($P = 0.001$) than group A (162.64 ± 118.84 ng/dL). Dry mouth was seen in four, nausea in eight and sedation in six patients in group A while none in group B. 14 patients in Group A and one patient in Group B needed intravenous paracetamol ($P = 0.000$). **Conclusions:** Premedication with tapentadol was more effective in reducing CRBD and pain postoperatively. The surgical stress response and side effects were significantly reduced with tapentadol.

Key words: Tapentadol, tramadol, transurethral resection of prostate, urinary catheterisation

INTRODUCTION

Surgical interventions involving urinary catheterisation often lead to catheter-related bladder discomfort (CRBD). It is one of the most crucial clinical entities and possesses an incidence rate of 47%–90%.[1] CRBD is associated with a burning sensation involving the suprapubic area and penis with discomfort in voiding. These complaints lead to varied behavioural responses including pulling out the urinary catheter, strong vocal response, and flailing limbs.[1,2] The

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features of CRBD are almost similar to overactive bladder as the clinical symptoms of both entities are related to involuntary contraction of the detrusor muscle.[3] The bladder irritation and contraction from a Foley catheter appears to be mediated by stimulation of muscarinic receptors. Therefore, the agents with anti-muscarinic activity such as oxybutynin, butyl scopolamine and tolterodine form the mainstay of therapy.[4] Secondly, prostaglandin appears to have an excitatory role in bladder contractility. So, prostaglandin inhibitors surely help to prevent bladder contractility and thus relieve symptoms of CRBD.[5] Thirdly, agents modulating the inflammatory or pain pathway also influence the pain management modalities of CRBD.[5-7]

Drugs like ketamine, tramadol, paracetamol, parecoxib, gabapentin and pregabalin have also shown benefits in remitting the symptoms of CRBD.[1] Tapentadol is a novel opioid that acts centrally and exerts its analgesic effects through a two-fold mechanism: by mu-opioid receptor agonism and additionally via noradrenaline re-uptake inhibition, with both mechanisms residing in the single molecule. These mechanisms complement each other and clearly have a role in nociceptive and neuropathic pain management.[8] Tapentadol is one of the most promising opioid analgesics and has never been tested for its potential in the management of CRBD.

This study therefore compared the efficacy and tolerability of tapentadol and tramadol in the treatment of CRBD in patients recovering from transurethral resection of prostate (TURP). The primary objective of the study was to compare the efficacy of tramadol and tapentadol in reducing the incidence and severity of postoperative CRBD. The secondary objective was to compare the surgical stress response and side effects of the drugs.

METHODS

This prospective, randomised study was conducted in a tertiary care hospital after clearance from the institutional ethical board. During the pre-anaesthetic visit, written informed consents were taken from all patients and they were made aware of the symptoms of CRBD (manifested as a burning sensation with urgency to micturate or supra-pubic discomfort) and of the visual analogue scale (VAS).

From November 2018 to November 2019, 100 patients of the American Society of Anesthesiologists (ASA) physical status grade I and II, undergoing elective TURP under subarachnoid block were included. Patients with significant cardiac disease, renal failure, asthma, refusal or contraindication for spinal anaesthesia, patient on chronic analgesic use, psychiatric disease, paralytic ileus and recent use of monoamine oxidase inhibitors (within 14 days) were excluded from the study.

All eligible patients were premedicated with 0.25 mg oral alprazolam and 150 mg ranitidine on the night before surgery.

The anaesthesiologist responsible for randomisation used opaque envelopes to place random numbers generated by a computer. These numbers indicated the group assigned to the participants. Group A received oral tramadol 100 mg and Group B received oral tapentadol 50 mg 1 h before the surgery. All the medications were administered by an anaesthesiologist responsible for randomisation with no further involvement in the study. The anaesthesiologist who assessed the outcome of the disease and the participants were blinded to the group allocation.

The primary outcome was to assess the efficacy of the study drugs in reducing the incidence and severity of postoperative CRBD. Secondary outcomes included the difference in cortisol levels post-surgery, the need for additional analgesic and adverse effects including postoperative nausea and vomiting (PONV), respiratory depression, sedation, drowsiness, confusion and dry mouth.

Sample for serum cortisol level was sent 2 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.

Patients were attached with standard monitors like electrocardiography, non-invasive blood pressure, and pulse oximetry. All patients were administered subarachnoid block in space L4-L5 using Quincke

needle by injecting 2.5 mL of 0.5% bupivacaine heavy. After achieving a block level of T8, the patient was positioned in the lithotomy position. Systolic, diastolic and mean arterial pressure, heart rate and peripheral oxygen saturation (SpO_2) were recorded before premedication, after shifting to operation theatre, at the time of spinal anaesthesia, at 5, 10, 15 min and then every 15 min till the end of surgery. Urinary catheterisation was done using 18- French Foley catheter after applying 2% lignocaine jelly for lubrication. The balloon was inflated with 10 mL normal saline.

After shifting to the post-operative care unit (PACU), the severity of CRBD was evaluated by a blinded assessor at intervals of 0, 0.5, 1, 2, 3, 4, 5 and 6 h postoperatively on a four-point severity scale. 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). Postoperatively, suprapubic pain was assessed by the VAS with scores ranging between 0-10 (where 0 is no pain and 10 is worst imaginable pain). The first analgesic requirement (VAS ≥3) was recorded and such patients were administered 1 gm of paracetamol intravenously with the shortest interval of at least 6 h between each dose. Intravenous parecoxib 40 mg was administered to those patients in the PACU who had a VAS >5 even after receiving paracetamol. The total numbers of patients requiring paracetamol/parecoxib were noted.

The level of sedation was recorded postoperatively. Patients with a sedation score of more than or equal to 4 were considered sedated. The presence of PONV was assessed as a score of 0,1 or 2 (0 = no nausea or vomiting, 1 = tolerable nausea or vomiting, and 2 = intractable nausea or vomiting). Rescue anti-emetic was given to the patients with PONV of grade >1 with intravenous ondansetron 4 mg. Other complaints like respiratory depression, drowsiness, confusion and dry mouth were also assessed.

Based on a previous study, we estimated the sample size with an incidence of CRBD as 60%.[9] Considering a decrease in the severity of CRBD by30% with a power of 0.85 and alpha error of 0.05, 48 patients per group were needed to detect significance. In order to consider any dropouts, we included 50 patients in each group.

Statistical Package for the Social Sciences (SPSS South Asia Pvt., Ltd., Bengaluru, India) version 22, and Microsoft Office Excel 2010 for statistical testing was used. The quantitative data (height, weight, duration of surgery, haemodynamic parameters, SpO2, VAS and serum cortisol levels) were expressed as mean and standard deviation while qualitative data (age, ASA physical status, sedation score, CRBD, other complaints) were expressed in terms of frequencies and percentages. The means of the continuous variables were compared among the two groups using analysis of variance (ANOVA). Haemodynamic changes were compared with the help of *t*-test statistics. We considered $P \leq 0.05$ as statistically significant.

RESULTS

A total of 100 patients fulfilling the eligibility criteria were included from November 2018 to November 2019. All patients completed the study, and there were no dropouts [Figure 1]. Demographic data were comparable in both the groups [Table 1].

The incidence of CRBD in both groups is shown in Figure 2. Between the two groups, there was no difference in CRBD incidence and severity at the first assessment in the PACU and 0.5 h postoperatively. At 2 h postoperatively, the incidence of CRBD in group B was lower than in Group A, which was statistically significant ($P = 0.012$). Similarly, at 3, 4, 5 and 6 h postoperatively, the incidence and severity of CRBD in group B was much lower than in Group A, which was statistically highly significant with a *P* value < 0.0001 [Table 2].

Table 1: Demographic profile and surgical characteristics of patients

	Tramadol group (*n*=50)	Tapentadol group (*n*=50)	*P*
Age (years)	67±8	65±8	0.459
Height (cm)	167.93±7.41	168.41±8.02	0.427
Weight (kg)	60.44±8.21	62.5±9.28	0.395
ASA I/II	12/38	14/36	
Duration of surgery (min)	40.8±14.23	39.9±12.72	0.894
Serum cortisol levels (ng/dL) 2 h after surgery	162.64±118.84	113±65.45	0.001**

Data are presented as mean±standard deviation or numbers. ***P*<0.01 (highly significant). ASA: American Society of Anesthesiologists

Table 2: Incidence and severity of catheter related bladder discomfort in group A and B at different time intervals

Time (h)	Tramadol Group (A)					Tapentadol Group (B)					*P*
	Incidence	None (Grade1)	Mild (Grade2)	Moderate (Grade3)	Severe (Grade4)	Incidence	None (Grade1)	Mild (Grade2)	Moderate (Grade3)	Severe (Grade4)	
0	0	50	0	0	0	0	50	0	0	0	-
0.5	0	50	0	0	0	0	50	0	0	0	-
1	2	48	2	0	0	0	50	0	0	0	0.495
2	7	43	7	0	0	0	50	0	0	0	0.012*
3	18	32	18	0	0	1	49	1	0	0	<.0001**
4	30	20	30	0	0	3	47	3	0	0	<.0001**
5	41	9	33	8	0	14	36	14	0	0	<.0001**
6	42	8	28	14	0	25	25	24	1	0	<.0001**

*P<0.05 statistically significant. **P value highly significant

On comparison of the postoperative mean VAS score at different time intervals, the score was higher in Group A starting from 2 h, but the difference was highly significant between the two groups at 3 h ($P = 0.003$), 4 h ($P = 0.0003$), 5 h ($P < 0.0001$) and 6 h ($P < 0.0001$) [Table 3]. On comparison of mean serum cortisol levels between Group A and Group B, the cortisol levels postoperatively were higher in group A (162.64 ± 118.84 ng/dL) as compared to Group B (113 ± 65.45) and the difference was highly significant statistically ($P = 0.001$) [Table 1].

Side effects such as dry mouth and tolerable nausea were present in 8% and 16% patients in the tramadol group, while none were observed in tapentadol group. Patients did not complain of vomiting in both the groups. RSS of 3 was present in 12% of patients in Group A and 0% in Group B. None of the patients had RSS of 4 or higher. Additional need for analgesic like paracetamol was present in 14 patients of group A and one patient of group B in the postoperative period. There was no need for the second rescue analgesic parecoxib in both groups. Other complaints like respiratory depression, drowsiness or confusion were not seen in either of the groups [Table 4].

Table 3: Comparison of visual analogue scale (VAS) scores between group A and B

Time (h)	Tramadol Group (A)	Tapentadol Group (B)	*P*
0	0±0	0±0	-
0.5	0±0	0±0	-
1	0±0	0±0	-
2	0.04±0.2	0±0	0.155
3	0.16±0.37	0±0	0.003**
4	0.28±0.45	0.02±0.14	0.0003**
5	0.68±0.62	0.08±0.27	<.0001**
6	0.94±0.62	0.32±0.51	<.0001**

*P<0.05 statistically significant. **P value highly significant. VAS: Visual analogue scale

Table 4: Comparison of postoperative side effects

	Tramadol group	Tapentadol group	*P*
Dry mouth	4 (8%)	0 (0%)	0.117
Nausea/vomiting	8 (16%)	0 (0%)	0.014*
Drowsiness	0 (0%)	0 (0%)	-
Respiratory depression	0 (0%)	0 (0%)	-
Confusion	0 (0%)	0 (0%)	-
Sedation	6 (12%)	0 (0%)	0.027*
VAS >3	14 (28%)	1 (2%)	0.000**
Requirement for rescue analgesic	0 (0%)	0 (0%)	-

*P<0.05 statistically significant. **P<0.01 highly significant. VAS: Visual analogue scale

DISCUSSION

This study compared the efficacy of pre-emptive oral tramadol and tapentadol in reducing CRBD as well as their tolerability in the postoperative period. The study depicted the overall incidence of CRBD as 67%. The incidence in tramadol group was 84% as compared to 50% in tapentadol group.

Postoperatively, the incidence as well as severity of CRBD in tapentadol group was lower at all time intervals after 2 h, indicating its better efficacy than tramadol. In this study, the VAS was lower in group B than group A postoperatively at 3, 4, 5, and 6 h indicating oral tapentadol to be more effective in relieving postoperative pain than oral tramadol. The CRBD and VAS scores were comparable in both the groups in the first hour. This was because the analgesic effect of spinal anaesthesia lasts longer in the perineal region.

The urinary bladder receives parasympathetic supply from the pelvic nerves (S2-S4) and sympathetic supply from hypogastric nerves (T12–L2). Increased signals from the pelvic nerve cause contraction of the detrusor muscle, stimulating micturition. Receptor binding assays have identified M1, M2 and M3 receptor subtypes in the bladder. Even though the M2 receptor predominates, as shown by ligand receptor binding studies, it is the M3 receptors that are primarily

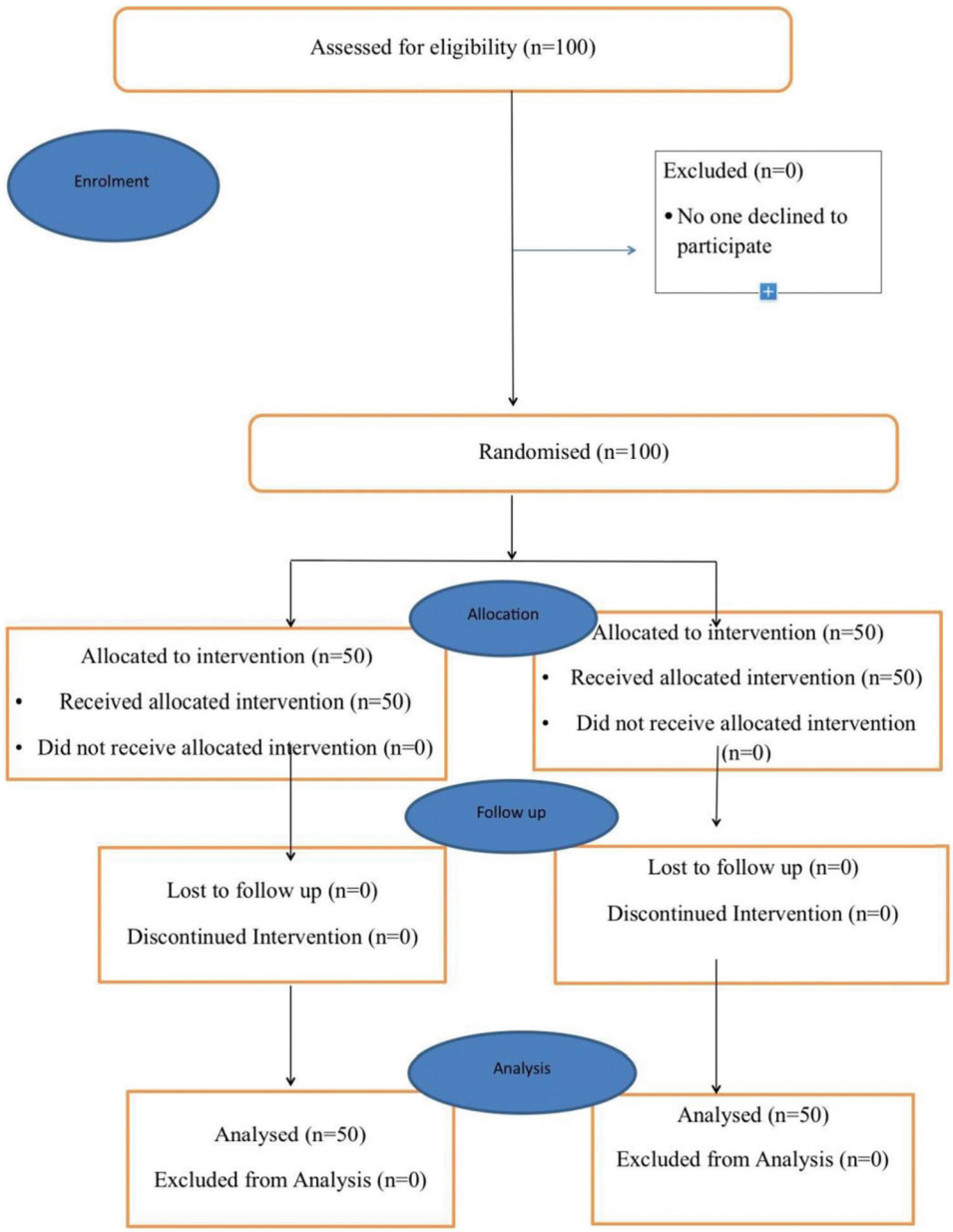

Figure 1: CONSORT flow diagram

responsible for bladder contraction. M3 receptor stimulation using acetylcholine leads to smooth muscle contraction. Coactivation of M2 receptors leads to increase in response to M3 stimulation.[1,10]

Catheterisation results in the release of acetylcholine by stimulation of bladder afferent nerves. This results in involuntary contractions of the detrusor urinae mediated by the M3 muscarinic receptor.[11] Prostaglandin synthesis also plays a significant role in the occurrence of CRBD. Its synthesis is triggered by detrusor muscle contraction, bladder mucosal damage and release of inflammatory mediators after urinary catheterisation. This leads to CRBD with lower urinary tract symptoms.[5]

Tramadol, a commonly used postoperative analgesic, is a synthetic centrally acting opioid analgesic. The various actions include inhibition of noradrenaline and serotonin reuptake, and also inhibition of M1 and M3 muscarinic receptors. Previous studies have shown the role of tramadol in reducing the symptoms of CRBD.[9,11-13]

Tapentadol is a novel centrally-acting synthetic analgesic used for treating both acute and chronic, moderate to severe pain, which can only be treated with opioid analgesics. The analgesic effect is due to mu-opioid receptor agonism, and nor-adrenaline

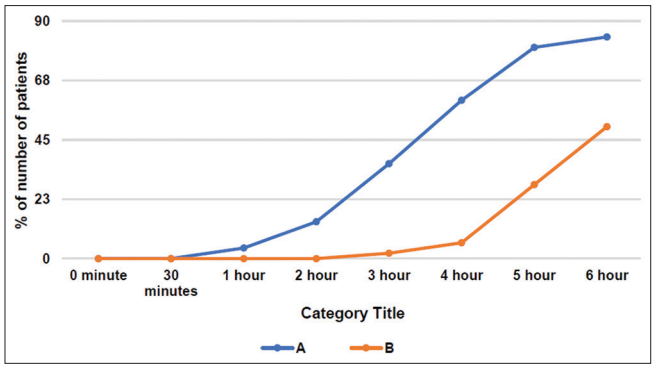

Figure 2: Comparison of incidence of catheter related bladder discomfort between groups A and B

reuptake inhibition. Its potency at the mu-opioid receptor is much greater than tramadol and it does not possess any serotonin activity. Tapentadol does not have anti-muscarinic effects. Its action through suppression of C-afferent neuronal activity and neural excitability in dorsal horn neurons, by modulating spinal interneurons may play a role in decreasing CRBD.[14] Currently, we have not found any study showing the role of tapentadol on CRBD.

Several researchers have evaluated the role of tapentadol as a postoperative analgesic with improved postoperative pain scores and gastrointestinal tolerability.[15,16]

The relationship between serum cortisol levels and surgical stress has generated interest recently, with more studies investigating the degree of surgical stress.[17] This study determined the extent of systemic stress response to transurethral resection of prostate (TURP) by measuring serum cortisol levels. A significant difference in the serum cortisol levels was found between the two groups. The stress response to the surgery was significantly reduced in tapentadol group as compared to tramadol group ($P = 0.001$).

In this study, four and eight patients presented with dry mouth and tolerable nausea, respectively, in the tramadol group while no patient complained of these side effects in the tapentadol group. Tramadol is metabolised to an active O-desmethyl metabolite which is responsible for these side effects.[8,18,19] Several authors have observed an increased incidence of PONV and sedation with tramadol.[4,9] Sedation was observed in six patients in tramadol group and none in tapentadol group ($P = 0.027$) in this study; nevertheless, tapentadol appears to have a better central nervous system and gastrointestinal tolerability profile owing to lack of significant serotonergic activity.[8]

The limitations of this study are that the sample size is small and it was only associated with male patients. Hence, this protocol cannot be superimposed on patients undergoing all kind of surgeries. Furthermore, in our study, we limited VAS scores evaluation to only 6 h. A longer observation time might be feasible as the half-life of tramadol is 6 h.

CONCLUSION

In conclusion, oral premedication with tapentadol is superior to an equi-analgesic dose of tramadol in reducing the incidence and severity of postoperative CRBD and pain after TURP.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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