

# Evaluation of intra-operative tramadol for prevention of catheter-related bladder discomfort: a prospective, randomized, double-blind study

A. Agarwal<sup>1\*</sup>, G. Yadav<sup>1</sup>, D. Gupta<sup>1</sup>, P. K. Singh<sup>1</sup> and U. Singh<sup>2</sup>

<sup>1</sup>Department of Anaesthesiology and <sup>2</sup>Department of Biostatistics, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow 226014, India

\*Corresponding author. E-mail: aagarwal@sgpgi.ac.in

**Background.** Catheter-related bladder discomfort (CRBD) is defined as an urge to void or discomfort in the supra-pubic region; reported postoperatively in patients who have had urinary catheterization intra-operatively. We have evaluated tramadol, a centrally acting opioid analgesic with muscarinic receptor antagonist properties for prevention of CRBD.

**Methods.** Fifty-four adults (18–60 yr), ASA physical status I and II of either sex, undergoing elective percutaneous nephro-lithomy were randomly divided into two groups of 27 each. Control (C) group received normal saline (NS; 2 ml), whereas Tramadol (T) group received tramadol 1.5 mg kg<sup>-1</sup>. All medications were diluted in 2 ml NS and administered 30 min before extubation. Intra-operatively, urinary catheterization was performed with a 16 Fr Foley's catheter, and the balloon was inflated with 10 ml distilled water. The CRBD was assessed at 0, 1, 2, and 6 h after patient's arrival in the post-anaesthesia care unit along with total postoperative fentanyl requirement. Severity of CRBD was graded as none, mild, moderate and severe. Data were analysed by one-way ANOVA, Z-test, and Fisher's exact test.  $P < 0.05$  was considered significant.

**Results.** Incidence and severity of CRBD was reduced in T group compared with C group at all time points ( $P < 0.05$ ). Postoperative pain as assessed by visual analogue scale and total postoperative fentanyl requirement ( $\mu\text{g kg}^{-1}$ ) was also reduced in the T group [176 (SD 26.5)] compared with C group [210 (34.6)] ( $P < 0.05$ ).

**Conclusions.** Tramadol 1.5 mg kg<sup>-1</sup> administered i.v. 30 min before extubation decreases the incidence and severity of CRBD and postoperative fentanyl requirement.

*Br J Anaesth* 2008; **101**: 506–10

**Keywords:** complications, catheter-related bladder discomfort; pharmacology, tramadol

Accepted for publication: June 20, 2008

Catheter-related bladder discomfort (CRBD) is defined as an urge to void or discomfort in the supra-pubic region; observed after operation in patients who are awakening from anaesthesia and have had an urinary catheterization during operation.<sup>1</sup> This symptom complex is extremely distressing to the patient in the postoperative setting and may lead to exacerbated postoperative pain and reduced quality of life.<sup>2</sup> Muscarinic receptor antagonists such as tolterodine and oxybutynin have been reported to be effective in preventing CRBD.<sup>1–3</sup> I.v. ketamine in sub-hypnotic doses has also been identified as an effective treatment of CRBD.<sup>4</sup>

Tramadol, a synthetic opioid of the aminocyclohexanol group, is a centrally acting opioid analgesic which also has inhibitory effect on M1 and M3 muscarinic receptors.<sup>5–6</sup>

Recently, an inhibitory action of tramadol on the normal micturition and detrusor over-activity has been reported in animal studies.<sup>7</sup> So far, a literature search did not reveal any information regarding the effect of tramadol in patients suffering from CRBD. The present study was therefore planned to evaluate the efficacy of intra-operative administration of tramadol on the incidence and severity of CRBD.

## Methods

This prospective, randomized, double-blind, placebo controlled study was conducted after approval from the Institute's ethics committee and written informed consent

from the patients. Adult patients (18–60 yr) with an ASA physical status I and II of either sex, undergoing elective percutaneous nephro-lithomy (PCNL) for renal and upper ureteric stone, were included. Patients with a history of bladder outflow obstruction, transurethral resection of prostate for benign prostate hyperplasia, elderly patients (age >60 yr), overactive bladder (frequency: more than three times in the night or more than eight times in 24 h) and end-stage renal disease (urine output <500 ml per 24 h), morbid obesity, disturbance of central nervous system, chemical substance abuse, chronic pain, chronic analgesic usage and cardiovascular, and hepatic or any psychiatric disease were excluded from the study.

Assuming that tramadol would reduce the incidence of CRBD by 30%, power analysis with  $\alpha=0.05$ ,  $\beta=0.8$  showed that we would need to study 24 patients in each group. To make provision for dropouts if any, we enrolled 27 patients in each group. The study therefore consisted of 54 patients. Patients who could not be extubated at the end of the surgery or who were re-explored within the study period were considered as dropouts.

Patients meeting the inclusion criteria during the pre-anaesthetic checkup were randomly assigned into two groups of 27 each with the help of computer-generated table of random numbers. Depending on the results of the randomization process, patients received medication [diluted in 2 ml of normal saline (NS)], i.v. 30 min before extubation. Patients in the control (C) group received NS (2 ml) whereas patients in the Tramadol (T) group received tramadol 1.5 mg  $\text{kg}^{-1}$  (Cipla Health Biotech Private Limited, Solan, India). These medications were administered by a blinded anaesthesia registrar who was not involved in the study.

Premedication consisted of oral lorazepam 0.04 mg  $\text{kg}^{-1}$  the night before and 2 h before surgery. Induction of anaesthesia was done with fentanyl 2  $\mu\text{g kg}^{-1}$  and propofol 2 mg  $\text{kg}^{-1}$ . Tracheal intubation was facilitated by vacuronium bromide 0.1 mg  $\text{kg}^{-1}$ . Urinary catheterization was done using 16 Fr Foley's catheter and its balloon was inflated with 10 ml distilled water after induction of anaesthesia. Urinary catheter was inserted after its lubrication with K-Y jelly (a water base lubricating gel) and was fixed in the suprapubic area with an adhesive tape without any traction and was always left to free drainage into an urobag. Anaesthesia was maintained using 70% nitrous oxide in oxygen, propofol infusion at 50–150  $\mu\text{g kg}^{-1} \text{min}^{-1}$  and intermittent dosage of fentanyl and vecuronium as and when required. Inadequate analgesia was defined as an increase in systolic blood pressure, heart rate, or both by >20% of baseline value for >5 min in response to a surgical stimulus. In cases of inadequate analgesia, patients were given bolus doses of fentanyl 0.5  $\mu\text{g kg}^{-1}$ . Last dose of fentanyl was administered 30 min before completion of surgery.

At the end of the surgery, all patients received a combination of neostigmine 0.05 mg  $\text{kg}^{-1}$  and glycopyrrolate 0.01 mg  $\text{kg}^{-1}$  for reversal of vacuronium and were transferred to the post-anaesthesia care unit (PACU) after

extubation. In the PACU, all patients received i.v. fentanyl via patient-controlled analgesia for their postoperative pain management.

Primary outcomes were defined as reduction in the incidence or severity of CRBD, whereas secondary outcomes were defined as reduction in postoperative fentanyl requirement. Another independent anaesthesia registrar (G.D.Y.) blinded to the group allocation observed the incidence and severity of CRBD, postoperative fentanyl requirement, and side-effects such as the level of sedation, postoperative nausea vomiting (PONV), and respiratory depression immediately after extubation (0 h); and thereafter at 1, 2 and 6 h after operation.

Severity of CRBD was recorded as none when patients did not complain of any CRBD even on asking, as mild when reported by patients only on questioning, as moderate when reported by the patients on their own (without questioning and not accompanied by any behavioural responses), and as severe when reported by patients on their own along with behavioural responses. Behavioural responses observed were flailing limb, strong vocal response, and attempt to pull out the catheter.<sup>2</sup> Postoperative pain was assessed by a visual analogue scale (VAS) (between 0 and 100; where 0 means no pain and 100 means worst imaginable pain). The severity of PONV was graded on a four-point ordinal scale from 0 to 3 (0=no nausea, 1=mild nausea, 2=moderate nausea, and 3=severe nausea with vomiting). Ondansetron 4 mg i.v. was given to all patients with PONV of grade 3 as rescue anti-emetic. The level of sedation was assessed by the Ramsay sedation scale (1: anxious, agitated or restless; 2: co-operative, oriented, and tranquil; 3: responds to command; asleep; 4: brisk response to light glabellar tap or loud noise; 5: a sluggish response to light glabellar tap or loud noise; 6: no response). Patients with a sedation scale of  $\geq 4$  were considered sedated.<sup>8</sup> Respiratory depression was defined as ventilatory frequency <8 bpm and oxygen saturation <90% without oxygen supplementation.

The method of statistical analysis was decided prospectively and incorporated into the intention-to-treat principle. Patient characteristic data were analysed with one-way ANOVA for continuous variables and  $\chi^2$  test for categorical variables. Data regarding incidence of CRBD were compared with test of proportions (Z-test), whereas severity of CRBD (none, mild, moderate, and severe) was analysed by Fisher's exact-test. SPSS 14.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.  $P<0.05$  was considered significant.

## Results

A total of 62 consecutive patients were evaluated between September 2006 to March 2007, out of which eight patients were excluded from the study on account of H/O end-stage renal disease,<sup>4</sup> chronic analgesic consumption,<sup>3</sup> and morbid obesity.<sup>1</sup> Therefore, 54 patients were included in the study

and received study medication after randomization. Four patients (two from each group) were considered as dropped from the study as one could not be extubated at the end of the surgery and another three were re-explored within the study period on account of postoperative bleeding. Therefore, these four patients were not subjected for further statistical analysis and only 50 patients completed the study (25 in each group) (Fig. 1). There was no substantial difference among the groups with regard to age, sex, weight, height, intra-operative fentanyl consumption, and duration of anaesthesia ( $P>0.05$ ) (Table 1).

All the patients ( $n=25$  in each group) received a combination of neostigmine  $0.05 \text{ mg kg}^{-1}$  and glycopyrrolate  $0.01 \text{ mg kg}^{-1}$  at the end of surgery. Incidence and severity of CRBD was reduced in the T group compared with the C group at all time points ( $P<0.05$ ) (Table 2). Median VAS was reduced in the T group compared with the C group at 0 and 1 h after operation (Table 2). After operation, less fentanyl requirement ( $\mu\text{g}$ ) was used in the T group [176 (26.5)] than in the C group [210 (34.6)] ( $P<0.05$ ) (Table 2).

Tramadol was associated with a higher incidence of PONV compared with the C group ( $P<0.05$ ). Ten patients

in the T group and three patients in the C group received ondansetron (Table 3).

Tramadol was associated with higher incidence of sedation compared with the C group ( $P<0.05$ ) (Table 3). None of the patients were deeply sedated in any group (Ramsay sedation scale of  $>4$ ).

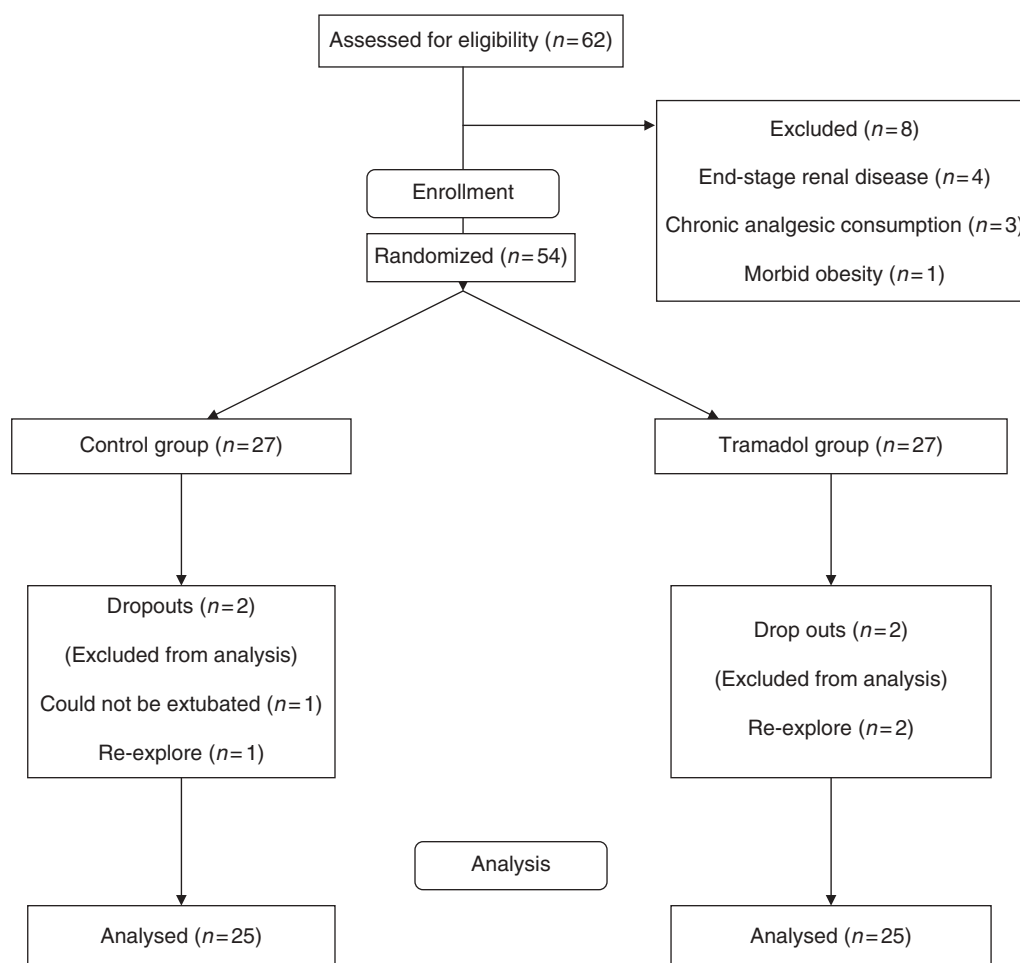
Three patients in the T group developed an oxygen saturation of  $<90\%$  on air in the postoperative period, which was antagonized after oxygen supplementation as compared with none in the control group.

Absolute risk reduction and the number-needed-to-treat in the T group was 32% and 3, respectively, in relation to CRBD.

## Discussion

In the present study we observed that intra-operative tramadol administered i.v. 30 min before extubation lead to a reduction in the incidence and severity of CRBD and post-operative fentanyl requirement ( $P<0.05$ ).

Contraction of the bladder, voluntary or involuntary, involves detrusor activity, mediated by stimulation of the



**Fig 1** Flow chart.

**Table 1** Patient details and intra-operative fentanyl consumption. Data are numbers or mean (SD)

Variables	Group	
	Control (n=27)	Tramadol (n=27)
Age (yr)	42.9 (15.6)	43.4 (11.8)
Sex (male/female)	20/5	19/6
Weight (kg)	56.5 (7.0)	55.8 (5.4)
Heights (cm)	163.6 (7.1)	162.8 (4.9)
Duration of surgery (min)	143 (24.8)	141 (26.3)
Intra-operative fentanyl requirement ( $\mu\text{g h}^{-1}$ )	73.8 (36.6)	70.8 (28.7)

**Table 3** Incidence of side-effects. Data presented as numbers. \* $P<0.05$  during inter-group comparison

Side-effects	Groups	
	Control (n=25)	Tramadol (n=25)
Nausea	5	14*
Vomiting	3	10*
Sedation	4	15*
Respiratory depression	1	3
Drowsiness	3	5
Dizziness	2	3
Dry mouth	10	12

muscarinic receptors by acetylcholine, released from activated cholinergic nerves. Two components of detrusor contraction have been demonstrated, the dominating one mediated by muscarinic receptors and the other by ATP (atropine-resistant component).<sup>9</sup> The evidence suggests that muscarinic receptors located in the urothelium/suburothelium and on afferent nerves may contribute to the pathophysiology of overactive bladder and CRBD. Muscarinic receptor antagonists such as oxybutynin, tolterodine, and ketamine are the basis of medical treatment for CRBD.<sup>1 3 4</sup> Gabapentin has also been reported to be effective in preventing CRBD by modulating the afferent input from the bladder and the excitability of the sacral reflex centre.<sup>10</sup>

Tramadol is a centrally acting, synthetic opioid analgesic with weak opioid agonist properties. It inhibits the detrusor activity by inhibition of type-1 muscarinic ( $M_1$ ) and type-3 muscarinic ( $M_3$ ) receptors.<sup>5 6</sup> Epidural tramadol increases the bladder capacity along with compliance and delays filling-sensation; thus, might decrease the need of catheterization of urinary bladder in the postoperative period.<sup>11</sup> Onset of action of tramadol is within 10 min and peak effect occurs in about 30 min. Tramadol neither impairs the cognitive function nor produces hallucination like ketamine.

Tramadol is a potent analgesic routinely used for postoperative pain relief with minimal respiratory depression, major organ toxicity, depression of gastrointestinal motility, and low risk of abuse.<sup>12–14</sup> We report another interesting dimension to its growing popularity [i.e. reduction in the incidence and severity of CRBD (50%) along with its

observed reduction in the postoperative fentanyl requirement (20%); if tramadol is administered i.v. 30 min before the end of surgery]. Thus, the observed reduction in CRBD was higher compared with reduction in the postoperative pain, which might have been because of the pre-dominant anti-muscarinic effects of tramadol.

Tramadol was associated with a higher incidence of sedation compared with the control group; however, none of the patients were deeply sedated in any group (Ramsay sedation scale of  $>4$ ). All these patients had a brisk response to light glabellar tap or loud auditory stimulus. At this sedation score, all patients were communicable and therefore it is very unlikely that sedation of this magnitude would have affected the assessment of CRBD.

Three patients in the T group developed oxygen saturation  $<90\%$  on air in the postoperative period requiring oxygen supplementation via face mask compared with none in the C group. This does not seem to be a big concern as, routinely, patients are administered oxygen via a face mask in the postoperative setting. However, observed high incidence of PONV with tramadol is a matter of concern and prophylactic anti-emetic may be considered as a viable option.

Sublingual oxybutynin administered after operation has recently been reported to reduce bladder discomfort and postoperative pain;<sup>2</sup> however, authors of this study recorded postoperative discomfort in the supra-pubic region as incisional pain contrary to established norm of

**Table 2** Incidence and severity of CRBD presented as numbers and postoperative pain (VAS) presented as median (inter-quartile range). Asterisk denotes  $P<0.05$  during inter-group comparison

Groups		Time (h)							
		Control				Tramadol			
Time periods (h)		0	1	2	6	0	1	2	6
N		25	25	25	25	25	25	25	25
CRBD	No	10	9	11	13	18*	17*	18*	20
	Yes	15	16	14	12	7*	8*	7*	5*
Severity of CRBD	Mild	8	8	7	7	4	6	6	4
	Moderate	5	6	6	4	2	1	1	1
	Severe	2	2	1	1	1	1	0	0
Postoperative pain		45 (20)	25 (10)	20 (12)	10 (10)	20 (5)*	20 (5)*	15 (12)	10 (7)
Postoperative fentanyl requirement ( $\mu\text{g}$ )		210 (34.6)				176 (26.5)*			

treating this symptom as manifestation of catheter-related bladder discomfort.<sup>1 3 10</sup> However, tramadol offers the advantage over oxybutynin and tolterodine that it could be administered i.v. and as such administered conveniently perioperatively as and when required.

Several limitations of the study should be acknowledged. Tramadol was administered i.v. 30 min before the time of extubation; so as to achieve peak effect of tramadol at the time of extubation with maximum anti-muscarinic effect; however, at times, it is difficult to predict the exact time of completion of surgery. Further, in this study we have evaluated the response of a single dose of tramadol on the prevention of CRBD in patients undergoing urologic surgery. We did not evaluate the dose-response titration and effect of tramadol in treating CRBD.

Administration of tramadol intra-operatively prevents CRBD and reduces postoperative fentanyl consumption. We therefore conclude that i.v. tramadol 1.5 mg kg<sup>-1</sup> administered 30 min before extubation results in reduction in the incidence and severity of CRBD and postoperative fentanyl requirement.

## References

- 1 Agarwal A, Raza M, Singhal V, et al. Evaluation of efficacy of tolterodine for prevention of catheter related bladder discomfort: a prospective, randomized, placebo-controlled double blind study. *Anesth Analg* 2005; **101**: 1065–7
- 2 Tauzin-Fin P, Sesay M, Svartz L, Krol-Houdek MC, Maurette P. Sublingual oxybutynin reduces postoperative pain related to indwelling bladder catheter after radical retropubic prostatectomy. *Br J Anaesth* 2007; **99**: 572–5
- 3 Agarwal A, Dhiraaj S, Singhal V, Kapoor R, Tandon M. Comparison of efficacy of oxybutynin and tolterodine for prevention of catheter related bladder discomfort: a prospective, randomized, placebo-controlled, double-blind study. *Br J Anaesth* 2006; **96**: 377–80
- 4 Agarwal A, Gupta D, Kumar M, Dhiraaj S, Tandon M, Singh PK. Ketamine for treatment of catheter related bladder discomfort: a prospective, randomized, placebo controlled and double blind study. *Br J Anaesth* 2006; **96**: 587–9
- 5 Shiraishi M, Minami K, Uezono Y, Yanagihara N, Shigematsu A. Inhibition by tramadol of muscarinic receptor-induced responses in cultured adrenal medullary cells and in *Xenopus laevis* oocytes expressing cloned M<sub>1</sub> receptors. *J Pharmacol Exp Ther* 2001; **299**: 255–60
- 6 Shiga Y, Minami K, Shiraishi M, et al. The inhibitory effects of tramadol on muscarinic receptor-induced responses in *Xenopus* oocytes expressing cloned M (3) receptors. *Anesth Analg* 2002; **95**: 1269–73
- 7 Pehrson R, Stenman E, Andersson KE. Effects of tramadol on rat detrusor overactivity induced by experimental cerebral infarction. *Eur Urol* 2003; **44**: 495–9
- 8 Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *Br Med J* 1974; **2**: 656–9
- 9 Andersson KE, Schroder A. Changes in muscarinic receptors of the aging bladder. *Urologe A* 2004; **43**: 552–6
- 10 Agarwal A, Dhiraaj S, Pawar S, Kapoor R, Gupta D, Singh PK. An evaluation of the efficacy of gabapentin for prevention of catheter-related bladder discomfort: a prospective, randomized, placebo-controlled, double-blind study. *Anaesth Analg* 2007; **105**: 1454–7
- 11 Singh SK, Agarwal MM, Batra YK, Kishore AV, Mandal AK. Effect of lumbar-epidural administration of tramadol on lower urinary tract function. *Neurourol Urodyn* 2008; **27**: 65–70
- 12 Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. *Drugs* 2000; **60**: 139–76
- 13 Budd K, Langford R. Tramadol revisited. *Br J Anaesth* 1999; **82**: 493–5
- 14 Wilder-Smith CH, Hill L, Wilkins J, Denny L. Effect of morphine and Tramadol on somatic and visceral sensory function and gastrointestinal motility after abdominal surgery. *Anaesthesiology* 1999; **91**: 639–47