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ORIGINAL ARTICLE

The efficacy of pregabalin for prevention of catheter-related bladder discomfort: a prospective, randomized, placebo-controlled double-blind study

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Abstract
Objective The present study evaluated the efficacy of preoperative pregabalin for prevention of catheter-related bladder discomfort.
Design Prospective, randomized, placebo controlled, double blinded study.
Materials and methods Sixty patients of either sex undergoing elective spine surgery and requiring urinary bladder catheterization were randomly assigned to two groups. The patients in Group P (pregabalin group) received 150 mg of pregabalin orally 1 h prior to induction of anesthesia with sips of water and the patients in Group C (control group) received placebo. Anesthesia technique was identical in both the groups. Catheter-related bladder discomfort (CRBD) was evaluated on a 4-point scale (1 = no discomfort, 2 = mild, 3 = moderate, 4 = severe), on arrival (0 h) and again at 1, 2, and 6 h postoperatively. Patients were provided patient-controlled analgesia with fentanyl for postoperative pain relief.
Results The incidence of CRBD was significantly less in the pregabalin group compared with the control group at all time intervals ($P < 0.05$). The severity of CRBD was reduced in the pregabalin group compared with the control group at all time intervals except 6 h. The postoperative consumption of fentanyl was significantly less in group P, while the sedation score was significantly higher in the group P compared to group C.
Conclusion Pretreatment with pregabalin 150 mg prevents CRBD and also decreases postoperative fentanyl consumption. Clinical Trials.gov identifier: (ref: CTRI/2013/11/004170).

Keywords Pregabalin · Catheter-related bladder discomfort · Analgesia

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Introduction

Postoperative urinary bladder catheterization symptoms (urinary urgency, frequency and urge incontinence) are labeled as catheter-related bladder discomfort (CRBD) [1]. It is a distressing feeling to the patient which at times requires urgent treatment. The role of detrussor muscle spasm and muscuranic effects on the detrussor muscle is a common culprit. Various groups of drugs such as tolterodine, oxybutynin [2], butylscopolamine [3], ketamine [4], tramadol [5], gabapentin [6] and paracetamol [7] have been tried and found to have a variable success rate in decreasing the symptoms. The use of antiepileptics (gabapentin and pregabalin) was recently introduced for the treatment of resistant cases of overactive bladder (OAB) [8]. As the symptoms of OAB are similar to CRBD, we planned this study to evaluate the efficacy of pregabalin for prevention of CRBD.

Materials and methods

This prospective, randomized, placebo-controlled study was conducted after approval from the Institutional Ethics

Committee. Written informed consent was obtained from patients undergoing elective spine surgery under general anesthesia who required catheterization. The study was registered at Clinical Trials.gov http://www.ctri.nic.in (ref: CTRI/2013/11/004170).

Sixty-eight patients aged 20–60 years, ASA physical status I or II, of either sex, and scheduled for elective spine surgical procedures requiring catheterization were included in this study. Patients with a history of preoperative neurological bladder/bowel involvement secondary to spinal pathology, bladder outflow obstruction, overactive bladder (frequency >3 times in the night or >8 times in 24 h), end-stage renal disease (urine output <500 ml per 24 h), morbid obesity, disturbance of the central nervous system, chemical substance abuse, chronic pain, and cardiovascular, hepatic or any psychiatric disease were excluded from the study. Patients were randomly allocated to two equal groups of 30 using a computer-generated table of random numbers.

Group P (Pregabalin group)	These patients received pregabalin 150 mg orally with sips of water, 1 h before the induction of anesthesia
Group C (Control group)	The patients received a similar-looking placebo tablet orally with sips of water, 1 h before the induction of anesthesia

All the patients were premedicated with lorazepam 2 mg and ranitidine 150 mg the night before, and 2 h prior to surgery. The study drugs were given to the nurse attendant in identical envelopes marked P and C. The nature of the medications was not known to the nurse attendant who administered the drugs as per instructions.

In the operating room, after establishing the basic monitoring, anesthesia was induced by injecting fentanyl 1.5 μg/kg and propofol 1.5–2.0 mg/kg followed by vecuronium 0.1 mg/kg body weight. Orotracheal intubation was performed with the correct size of cuffed endotracheal tube. Urinary bladder catheterization was performed with a 16F Foley catheter after lubrication with jelly (Lubic; Neon Laboratories) and its balloon was inflated with 10 ml of normal saline. Thereafter, the catheter was fixed in the suprapubic region with adhesive tape without traction. Maintenance of anesthesia was carried out with oxygen:nitrous oxide (O_2:N_2O; 33:66), sevoflurane, and intermittent boluses of vecuronium (0.015 mg/kg) and fentanyl (0.5 μg/kg) as required. After completion of surgery, neuromuscular blockade was reversed and the patients were moved to the post-anesthesia care unit (PACU).

In the PACU, CRBD was evaluated with a 4-point scale (1 = no discomfort; 2 = mild, revealed on questioning only; 3 = moderate, stated by the patient without being questioned; 4 = severe, urinary urgency demonstrated by behavioral responses such as attempts to remove the urinary catheter, restless extremity movements, verbal responses) on arrival in the PACU (0 h) and again at 1, 2, and 6 h postoperatively.

The patients in both groups received postoperative analgesia with fentanyl (5 μg/ml) through a patient-controlled analgesia (PCA) pump (Smith Medical ASD, Inc., USA). The total fentanyl requirement in the first 6 h was recorded. Any complications like postoperative nausea, vomiting, dizziness, somnolence, vertigo, confusion, blurred vision and dry mouth were also recorded and managed accordingly.

The postoperative sedation level was assessed by the Ramsay sedation score which consists of the following six grades—anxious (1), cooperative and tranquil (2), responding to commands only (3), brisk response to light glabellar tap (4), sluggish response to light glabellar tap (5), and no response to light glabellar tap (6).

Assuming there would be a 30 % reduction in incidence of CRBD following therapy one would need to include 25 patients in each group for results to be significant (with $\alpha = 0.05$ and $\beta = 0.80$); therefore, we enrolled 30 patients in each group to account for potential dropouts or protocol violations.

Statistical analysis was performed using the Graph pad prism 6.0 statistical software. Patient characteristic data were analyzed with Student *t* test for continuous variables and chi-squared test for categorical variables. The incidence of bladder discomfort between groups was analyzed by a test of proportions (*Z* test), whereas the severity of discomfort (mild, moderate, and severe) was analyzed by Fisher's exact test. Sedation score was analyzed by the Mann–Whitney test. A *P* value of <0.05 was considered statistically significant.

Results

Sixty-eight patients were assessed for eligibility between October 2013 and March 2014. Sixty patients were included in the study after randomization and all patients completed the study (Fig. 1). Eight patients were excluded on account of patient refusal (four patients), and history of preoperative use of analgesics (four patients). There were no significant differences between the two groups with respect to age, gender, body weight, type and duration of surgery and intraoperative fentanyl requirements ($P > 0.05$) (Table 1).

The incidence of CRBD was significantly less in the pregabalin group compared with the control group at all time intervals ($P < 0.05$) (Table 2). Severity of CRBD was reduced in the pregabalin group compared with the

Fig. 1 Study design

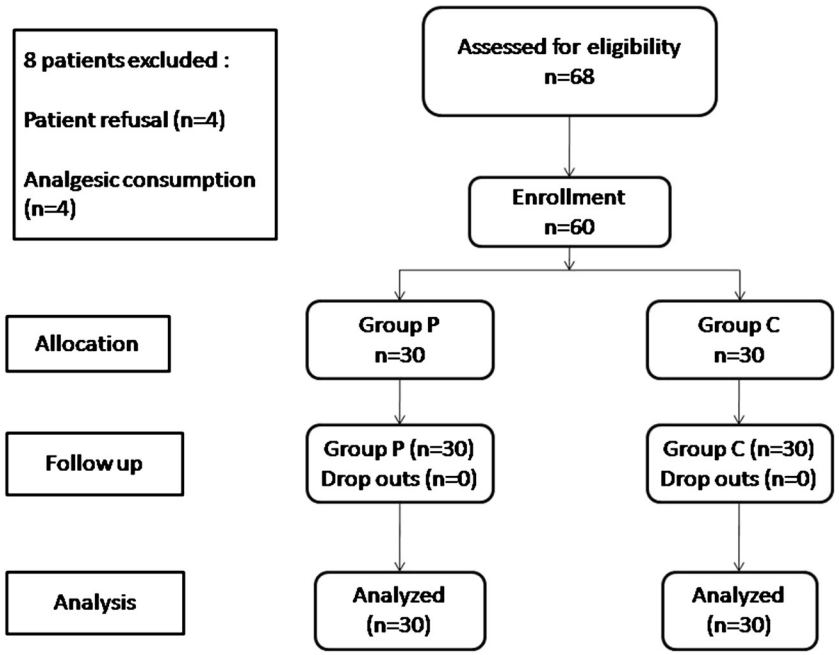

Table 1 Demographic data

	Group C ($n = 30$)	Group P ($n = 30$)	P value
Mean age (years)	43.63 ± 13.61	46.23 ± 8.43	0.377
Male/female	24/6	22/8	0.761
Weight (kg)	59.63 ± 8.35	62.63 ± 10.70	0.230
Spine surgery			
Cervical/lumbar	9/21	11/19	0.784
Duration of surgery (min)	147.83 ± 33.26	154.17 ± 37.92	0.494
Intra-operative fentanyl requirement (μg)	144.17 ± 29.19	135.33 ± 25.96	0.110

Data are presented as either mean values ± SD or by absolute numbers

Table 2 Incidence and severity of CRBD

Time (h)	0		1		2		6	
Groups	C	P	C	P	C	P	C	P
N	30	30	30	30	30	30	30	30
Bladder discomfort								
No	9	19	10	19	12	21	15	25
Yes	21	11	20	11	18	9	15	5
P value (incidence)	0.009		0.019		0.019		0.006	
Grading of discomfort								
Mild	4	7	5	8	7	8	9	4
Moderate	5	4	4	2	5	1	4	1
Severe	12	0	11	1	6	0	2	0
P value (severity)	0.004		0.021		0.039		0.617	

Data are presented as numbers

control group at 0, 1 and 2 h ($P < 0.05$) (Table 2). No difference was observed in the severity of bladder discomfort in these groups at 6 h ($P > 0.05$). None of the patients in group P had a severe grade of discomfort at all time intervals except 1 patient at 1 h postoperatively. The maximum number of patients in group P had mild discomfort only (Fig. 2).

The consumption of fentanyl in the first 6 h was significantly less in group P compared to group C (211.83 ± 43.54 vs 355.33 ± 51.44 μg) ($P < 0.0001$). Sedation score was significantly higher in group P ($P = 0.002$) (Table 3). There were no significant differences in side-effects between the two groups.

Discussion

CRBD is a common and distressing problem in the postoperative period leading to increased morbidity and need of analgesics. Symptoms of CRBD secondary of an indwelling urinary catheter mimic those of OAB. Therefore, drugs effective in treating OAB have a role in prevention of CRBD [9].

Current treatments for CRBD include oxybutynin, tolterodine, butylscopolamine, ketamine, tramadol and gabapentin. Muscarinic receptor antagonists (oxybutynin, tolterodine and butylscopolamine) are effective in reducing the incidence and severity of CRBD by suppressing

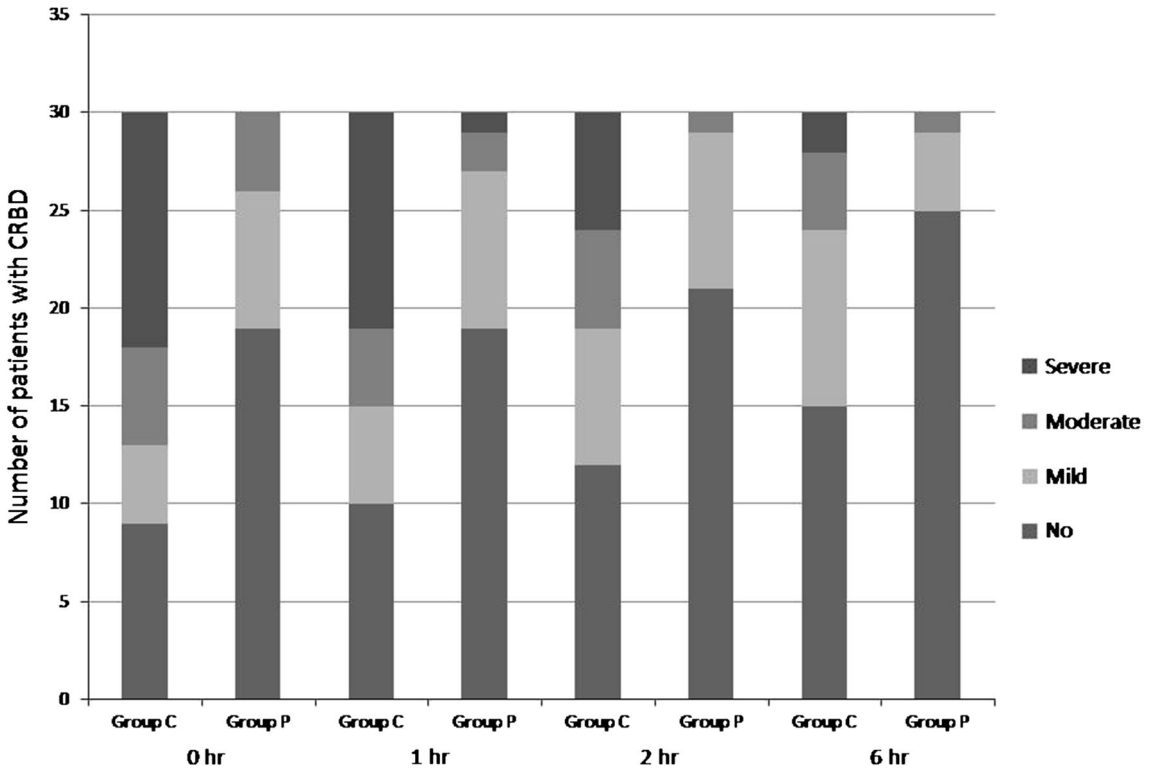

Fig. 2 Incidence and severity of CRBD

Table 3 Postoperative sedation score (Ramsay sedation score) and fentanyl consumption within 6 h after surgery

	Group C ($n = 30$)	Group P ($n = 30$)	P value
Fentanyl requirements (μg)	355.33 ± 51.44	211.83 ± 43.54	<0.0001
Sedation score	2.10 ± 0.61	2.63 ± 0.67	0.002

Data are presented as mean values ± SD

involuntary bladder contractions; however, treatment with these agents is not free of side-effects, such as dry mouth, facial blushing, and blurred vision. Furthermore, they have no role in postoperative analgesia [10]. Ketamine, which binds with *N*-methyl-D-aspartate, muscarinic, and cholinergic receptors, has also been effective in the management of CRBD. However, intravenous ketamine has been found to be associated with increased levels of sedation despite the use of subhypnotic doses [4]. Tramadol inhibits detrussor activity by inhibition of muscarinic (M1 and M3) receptors and decreases the incidence and severity of CRBD and postoperative fentanyl requirement, but its use is associated with nausea, vomiting, sedation and dry mouth [5]. 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 center, which is similar to OAB [6].

Pregabalin is an analog of the inhibitory neurotransmitter GABA, but does not interact with GABA receptors or mimic the actions of GABA. Pregabalin interacts with an auxiliary subunit (alpha2-delta subunit) of voltage-gated calcium channels [11]. Potent binding at this site attenuates depolarization-induced calcium influx at nerve terminals, with a subsequent reduction in the central release of excitatory neurotransmitters (e.g., glutamate, substance P, calcitonin, noradrenaline, gene-related peptide) [12, 13]. Peripheral release may lead to the subsequent inhibition of bladder smooth muscle contraction and to decreased amplitude of detrussor contractions [14]. Pregabalin's capacity to suppress the release of excitatory neurotransmitters is probably responsible for its analgesic properties. This analgesic effect may increase the intervals between urgency episodes, helping to augment bladder capacity [15].

Pregabalin was associated with a higher incidence of sedation compared with the control group and this side-effect is dose related [16]. We chose to study a dose of 150 mg because the recommended starting dose is 150 mg/day and, as a result, none of the patients in the pregabalin group were deeply sedated (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.

Spine surgery may also lead to bladder and bowel disturbance with an incidence is 0.2–1 % of the surgeries for lumbar disc herniation [17]. In our study, no patients complained of any disturbance in the bladder and bowel and all catheters were removed 12–24 h after surgery and none of the patients required recatheterization.

A limitation of our study is that we evaluated the response of a single and fixed dose of pregabalin on CRBD. We did not evaluate the dose−response titration, nor did we evaluate the effect of continuing therapy in the postoperative period. We did not evaluate its role in patients undergoing all types of surgical procedures, as well as in patients who are catheterized for other medical procedures not requiring any surgical intervention. Another limitation of our study is that we neither evaluate CRBD in relation to patient gender nor the beneficial effect of pregabalin in decreasing CRBD in relation to patient gender. This was due to the fact that a larger number of males presented for surgery compared to females in our study. However, as there was no significant sex difference between the two groups in our study, it may not affect the outcome of CRBD. Research regarding effectiveness of different dosages of pregabalin and their effect according to patient gender for decreasing the incidence and severity of CRBD needs further evaluation.

In conclusion, oral pregabalin (150 mg) administered 1 h before induction of anesthesia significantly reduced the incidence and severity of bladder discomfort along with a reduction in postoperative fentanyl consumption but at the cost of increased sedation.

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