

Duloxetine in Reducing Catheter-Related Bladder Discomfort: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study

ABSTRACT

Objective: The excessive desire to void with discomfort in the supra-pubic region, which is experienced postoperatively by patients who underwent urinary catheterization, is known as catheter-related bladder discomfort. In this study, we evaluated duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, in preventing catheter-related bladder discomfort.

Material and methods: Around 64 adults (18-60 years), of either sex, with American Society of American Society of Anesthesiologists (ASA) physical status I and II, scheduled to undergo elective gastrointestinal carcinoma surgeries under general anesthesia were analyzed in the final assessment of 2 comparative groups C and D of 32 patients each. Group D received 1 ranitidine tablet of 150 mg and 1 duloxetine tablet of 60 mg, while group C patients received 2 tablets of ranitidine of 75 mg 2 hours prior to induction. A 16 F Foley catheter was used to catheterize bladder intra-operatively, and 10 mL of distilled water was used to fill the balloon. At 0, 1, 2, and 6 hours, the catheter-related bladder discomfort was evaluated, and categorized into none, mild, moderate, and severe. The study drug's adverse effects, if any, were reported.

Results: At all-time intervals, group D had lower incidence and severity of catheter-related bladder discomfort than group C ($P < .05$). Compared to group C, patients in group D had a higher incidence of nausea, dizziness, and vomiting; nevertheless, the difference was statistically insignificant ($P > .05$).

Conclusion: Duloxetine of 60 mg given orally 2 hours before induction decreases the incidence and severity of catheter-related bladder discomfort.

Keywords: Catheter-related bladder discomfort, duloxetine, overactive bladder.

Introduction

Urinary catheterization in post-operative patients is often associated with burning sensation, increased frequency, urgency, or discomfort in suprapubic region, and the condition is well defined as catheter-related bladder discomfort (CRBD).¹ Catheter-related bladder discomfort may cause prolongation in hospital stay by aggravating post-operative pain and increasing the incidence of post-operative complications.^{2,3} Patients frequently exhibit agitation, flailing limbs, and intense verbal responses.^{1,2}

A number of drugs such as oxybutynin, tolterodine, butylscopolamine, solifenacin, darifenacin, ketamine, butorphanol, paracetamol, tramadol, resiniferatoxin, gabapentin, pregabalin, dezocine, amikacin, and dexmedetomidine have been assessed for their efficacies in preventing CRBD in various patient populations.⁴⁻¹⁶ The descending inhibitory pain pathways in the central nervous system may be affected by serotonin and norepinephrine.¹⁷ It has been demonstrated that duloxetine, a strong selective serotonin and norepinephrine reuptake inhibitor (SNRI), is useful in managing chronic pain.¹⁸ From the supraspinal or spinal levels, duloxetine reduces pain by concurrently modulating norepinephrine and serotonin in the descending analgesic pathway. Duloxetine may inhibit the N-methyl-D-aspartate (NMDA) receptors in mice implicated in pain perception, according to a new study.¹⁹

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Materials and Methods

Around 68 consecutive adult patients posted for gastrointestinal (GI) carcinoma surgery were assessed for eligibility. Patients aged between 18 and 60 years, with ASA physical status I or II, of either sex, undergoing elective surgery for GI carcinoma under general anesthesia, who were catheterized after induction, were included in this prospective, randomized, double-blind, placebo-controlled study after receiving approval from the Ethics Committee of Banaras Hindu University (Approval no: Dean/2013-14/EC/285) and written informed consents from the patients. The trial registry number was CTRI/2014/07/004781. Elderly patients (age > 60 years), morbid obesity, benign prostatic hyperplasia, history of bladder outflow obstruction, overactive bladder, end-stage renal disease, cardiovascular diseases, hepatic disease, chronic analgesic usage, chemical substance abuse, chronic pain, disturbance of central nervous system, or any psychiatric disease, and pregnancy and lactating mothers were excluded from the study.

The night before the procedure and 2 hours before the induction of anesthesia with sips of water, the patients received oral lorazepam of 0.04 mg/kg as a premedication. A computer-generated table of random numbers was used to divide the patients into 2 equal groups. Two tablets were given to each patient by nursing staff 2 hours prior to induction. Group D received 1 ranitidine tablet of 150 mg and 1 duloxetine tablet of 60 mg, while group C patients received 2 tablets of ranitidine of 75 mg. It was done to ensure blinding and also as part of the standard of care. The tablets used to deliver each drug were similar looking to prevent any observer bias.

Fentanyl of 3 µg/kg, propofol of 2 mg/kg, and vecuronium of 0.1 mg/kg were used to produce anesthesia and aid in orotracheal intubation. After lubricating it with K-Y jelly, a 16 F Foley catheter was used to catheterize the urinary bladder, and its balloon was inflated with 10 mL of distilled water. The catheter was then anchored in the suprapubic area without traction using adhesive tape. Propofol was infused at a rate of 50–200 µg/kg, intermittent fentanyl and vecuronium were administered as needed, and normal ASA monitoring was used to maintain anesthesia. Neostigmine (0.04 mg/kg) and glycopyrrolate (0.01 mg/kg) were used to counteract neuromuscular inhibition following surgery. The patients were extubated and transferred to the post-anesthesia care unit (PACU) after a successful

recovery. The patients were given intravenous fentanyl in the PACU using patient-controlled analgesia with a 20 µg/mL patient-activated dose and a 5-min lockout interval. An anesthesia registrar who was unaware of the patient's study groups evaluated bladder discomfort at the point of patient's entry into the PACU (0 hour), as well as at 1, 2, and 6 hours after surgery. The frequency and severity of CRBD were recorded.

Primary outcome: The primary outcome was the incidence of CRBD in both groups.

Secondary outcomes included: The 4-point scale used to rate CRBD severity is as follows: 0 = none, no CRBD reported even when requested; 1 = minimal, only disclosed upon questioning; 3 = extreme, declared on their own and followed by behavioral responses such as a strong verbal response, flailing limbs, or even attempting to rip out the urinary catheter.¹ Levels 2 and 3 correspond to complaints that are unprompted yet moderately severe in nature. Headache, nausea, vomiting, dizziness, and somnolence were reported as side effects of the study medicines.

We needed to recruit 30 patients for each group based on power calculations with alpha errors of 5% and beta errors of 20%, if we assumed the incidence of CRBD to decrease from the reported incidence of 60%–20%.² The Z test was used to compare the incidence of bladder discomfort between groups, and Fisher's exact test was used to compare the degree of discomfort (mild, moderate, and severe). We used Shapiro–Wilk test to know the normality distribution of data.

For statistical analysis, Statistical Package for Social Sciences 16.0 (SPSS Inc.; Chicago, IL, USA) was utilized. Statistical significance was defined at $P < .05$.

Results

After getting ethical committee clearance, this study was conducted from 2013 to 2016 in a Tertiary care hospital. Around 68 consecutive patients were assessed for eligibility, of which 3 patients were excluded due to patient refusal. The patients were randomized into 2 groups of 33 and 32 in groups C and D, respectively. One patient in group C lost to follow-up. So, final analysis was carried out among 32 patients in each group (Figure 1). Between the groups, there were no significant differences in the demographic and baseline characteristics of the patients (Table 1). In comparison to group C, group D experienced significantly lower rates of bladder discomfort (5 vs. 17 patients at 0 hour, 6 vs. 18 patients at 1 hour, 7 vs. 16 patients at 2 hours, and 5 vs. 15 patients at 6 hours) ($P < .05$). The relative risk of CRBD incidence is calculated as 0.2941 at 0 hour (95% CI: 0.1234–0.7009), 0.3333 at 1 hour (95% CI: 0.1523–0.7296), 0.4375 at 2 hours (95% CI: 0.2086–0.9177), and 0.3333 at 6 hours (95% CI: 0.1375–0.8082). When compared to group D, the control group's bladder discomfort was much more severe at 1 hour ($P < .05$). The incidence of moderate discomfort at 1 and 2 hours was also higher in group C ($P < .05$) (Table 2). Most of the patients in group D who developed bladder discomfort had mild discomfort at 0, 1, 2, and 6 hours (Table 2). Compared to group C, patients in group D had more instances of nausea, dizziness, and vomiting (Table 3). In terms of adverse effects, however, there were no statistically significant differences between groups ($P > .05$).

MAIN POINTS

- Catheter-related bladder discomfort (CRBD) is a common and annoying post-operative complication that increases patient morbidity and hospital stay.
- Various drugs have been tried for the prevention and management of CRBD with variable success rates.
- Duloxetine is a potent selective serotonin and norepinephrine reuptake inhibitor and has been shown to be effective in the treatment of major depressive disorder, neuropathic pain, stress urinary incontinence, generalized anxiety disorder, and fibromyalgia.
- Our study concludes that pretreatment of duloxetine of 60 mg can reduce the incidence and severity of CRBD in post-operative period, without causing major systemic side effects.

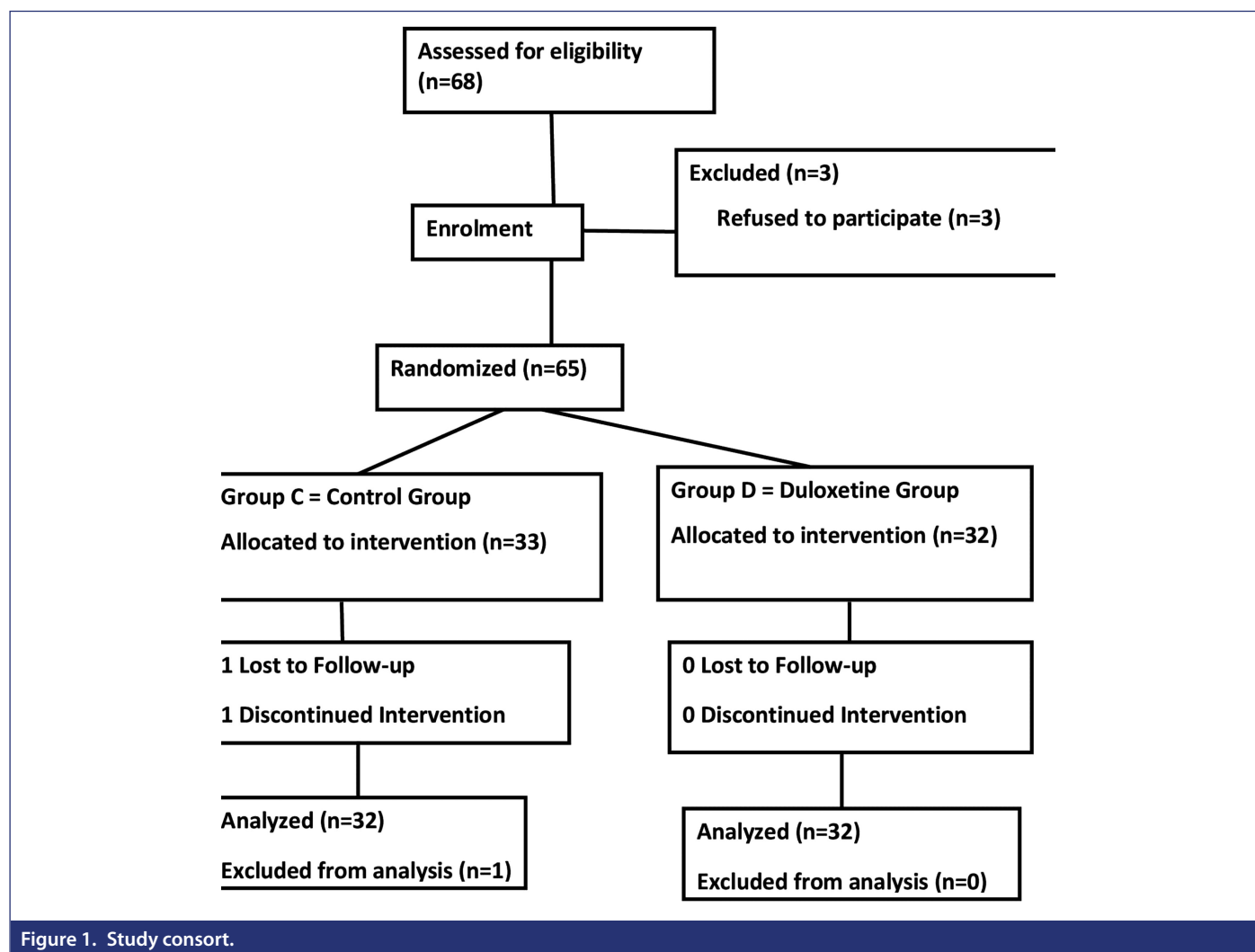


Figure 1. Study consort.

Discussion

The present investigation demonstrates that duloxetine (60 mg) administered orally reduced the incidence and severity of CRBD with little or no increase in the incidence of drug-related side effects.

Urinary urgency and frequency, with or without urge incontinence, are the signs of overactive bladder (OAB). Involuntary bladder contractions caused by muscarinic receptors are the cause of these symptoms. The cornerstone of OAB treatment is antimuscarinic medications. Duloxetine, an effective reuptake inhibitor of serotonin (5-HT) and norepinephrine, has been used to treat a variety of

conditions, including major depressive disorder, generalized anxiety disorder, neuropathic pain, fibromyalgia, and stress urinary incontinence. It modifies simultaneously norepinephrine and serotonin in the descending analgesic pathway at the supraspinal or spinal levels, thereby reducing pain. Duloxetine may block the NMDA receptor too, which is implicated in pain perception, according to a study done in mice.²⁰ Chung-Chih Hsu et al²¹ recently published a case report in which they discovered that the drug duloxetine was successful in treating a patient whose trauma-related bladder pain had not responded well to treatment with gabapentin, nalbuphine, and solifenacin but responded significantly to duloxetine. A single 60 mg dose of duloxetine has an average oral bioavailability of 50%. Maximum plasma concentration happens about 6 hours after the injection, with an average 2-hour delay before absorption starts. So, we gave the dosing 2 hours prior to induction. In our institutional setup, the listed elective surgeries lasted for 2-3.5 hours. So the maximum effect which was achieved at 1 hour in group D can be explained by the fact that peak effect was achieved at 1 hour postoperatively when maximum drug concentration was achieved, i.e., 6 hours after drug administration.

According to our study, there was no significant difference in the frequency of side effects such as sedation and dizziness between the

Table 1. Baseline Characteristics

	GROUP C (n = 32)	GROUP D (n = 32)	P
Sex (male/female)	17/15	16/16	1.000
Age in years	45.7 ± 7.5	46.2 ± 6.4	.77
Weight in kg	57.3 ± 8.2	55.4 ± 7.8	.34
Body mass index (kg/m ²)	21.4 ± 1.2	21.8 ± 1.1	.17
Average surgical time (minute)	127.6 ± 15.1	132.1 ± 12.4	.19
Average anesthesia time (minute)	145.6 ± 13.8	148.6 ± 10.6	.33

Table 2. Incidence and Severity of Catheter-Related Bladder Discomfort.

Time (hours)	0		1		2		6	
Group	C	D	C	D	C	D	C	D
n	32	32	32	32	32	32	32	32
Bladder discomfort	17	5	18	6	16	7	15	5
P		.033*		.0019*		.03*		.01*
Grading								
Mild (%)	7 (41)	3 (60)	7 (39)	5 (83)	7 (44)	6 (86)	10 (67)	5 (100)
Moderate (%)	5 (29)	1 (20)	6 (33)	1 (17)	6 (37)	1 (14)	3 (20)	0
Severe (%)	5 (29)	1 (20)	5 (28)	0	3 (19)	0	2 (13)	0

*P < .05 (statistically significant).

Table 3. Comparison of the Side Effects in Both the Groups

Side Effect	Group C n = 32	Group D n = 32	P
Pruritus	0	0	1.000
Somnolence	0	0	1.000
Headache	1	2	.55
Dizziness	1	3	.3
Nausea and vomiting	1	4	.16

duloxetine and placebo groups. Previous studies comparing gabapentin or pregabalin against placebo showed that these adjuvants enhanced the likelihood of dizziness or drowsiness.^{13,14} Our findings might imply that duloxetine, which does not enhance drug-related side effects, can be a good substitute for gabapentinoids. Nausea and vomiting were noticed in 4 patients out of 32 (12.5%), but they responded to intravenous ondansetron. None of the patients complained of somnolence and pruritus.

Our study has limitations too. In patients undergoing elective non-urolurgical surgery, we assessed the effect of a single dose of duloxetine on CRBD; however, we did not assess the dose–response titration and impact of duloxetine in the postoperative period. We also did not use any established anticholinergics for CRBD as the control group to compare against duloxetine due to their known systemic side effects. We did not use any additional tests for the evaluation of patients' pre- and post-operative mental status as we used a single dose of duloxetine pre-procedure which is very unlikely to affect the mental health of patients below 60 years of age. Additionally, we excluded individuals who were catheterized for non-surgical reasons and for other medical conditions. The post-operative pain score and the need for analgesics to manage the discomfort were also not recorded. In addition, the quantification of CRBD mainly depends upon the patient's ability to understand and the evaluator's assessment. This may be the reason for various articles showing different incidences of CRBD.^{2,22} However, strictly adhering to study protocol can give more accurate data on its incidences and severity.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Banaras Hindu University (Approval no: Dean/2013-14/EC/285).

Informed Consent: Written informed consent was obtained from the patients who participated in the study.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors declare that they have no conflict of interest.

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