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Efficacy of trospium for prevention of catheter-related bladder discomfort: a prospective, randomized, placebo-controlled, double-blind study

Vinit Kumar Srivastava[1], Sanjay Agrawal[2], Sweta Anil Deshmukh[1], Febin Noushad[1], Saima Khan[1], Raj Kumar[3]

Department of Anesthesiology, [1]Apollo Hospitals Bilaspur, Chhattisgarh, [2]All India Institute of Medical Sciences, Rishikesh, Uttarakhand, [3]Department of Neurosurgery, Apollo Hospitals Bilaspur, Chhattisgarh, India

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Corresponding author:
Vinit K. Srivastava, M.D., P.D.C.C.
Department of Anesthesiology, Apollo Hospitals Bilaspur, Chhattisgarh 495006, India
Tel: +91-9755557539
Fax: +91-7752401767
Email: drvinit75@gmail.com
ORCID: https://orcid.org/0000-0002-8430-7290

Background: Catheter-related bladder discomfort (CRBD) is a frequent complaint after awakening from anesthesia in patients receiving perioperative bladder catheterization. Overactive bladder (OAB) and CRBD show similar symptoms; thus, drugs used for the management of OAB influence symptoms of CRBD. Trospium chloride has been found effective in managing resistant cases of OAB. We evaluated the efficacy of oral trospium on CRBD in the postoperative period.

Methods: Sixty-four male and female adult patients, with planned spinal surgery and requiring urinary bladder catheterization, were randomly divided into two groups of 32 each. Group T patients received 60 mg extended-release oral trospium (extended-release) 1 h before induction of anesthesia and Group C patients received a similar-looking placebo. The anesthetic technique was identical in both groups. The CRBD score was evaluated in the postoperative ward using a 4-point scale (1 = no discomfort, 2 = mild, 3 = moderate, 4 = severe). Readings were recorded on arrival (0 h), and 1 h, 2 h, and 6 h postoperatively. All patients received fentanyl for postoperative pain relief.

Results: The incidence of CRBD was significantly higher in Group C than in Group T at 0 h (66% vs. 22%, P = 0.001) and 1 h postoperatively (72% vs. 28%, P = 0.001). The incidence of moderate to severe CRBD was higher in Group C at postoperative 2 h (82% vs. 14%, P = 0.004). There was no significant difference in postoperative fentanyl requirements.

Conclusions: Pretreatment with 60 mg extended release trospium reduced the incidence and severity of CRBD in the early postoperative period.

Keywords: Antimuscarinic Muscarinic antagonists; Muscarinic receptors; Overactive bladder; Postoperative period; Trospium chloride; Urinary catheterization.

Introduction

The salient features of catheter-related bladder discomfort (CRBD) are urinary urgency, frequency with or without urge, and incontinence observed after bladder catheterization [1]. The presence of a urinary catheter may be distressing to the patient and manifests as agitation, restlessness, or pulling out of the catheter. The clinical presentations of overactive bladder (OAB) and CRBD are quite similar, and thus drugs useful in managing OAB could be used in the prevention of CRBD [2,3]. Antimuscarinic agents are the first choice of drugs for OAB [4]. Darifenacin and solifenacin have recently been studied for the prevention of CRDB with varying success rates [5]. Other groups of drugs, such as

antiepileptics (gabapentin and pregabalin) [6,7], ketamine [8], tramadol [9], and dexmedetomidine [10], have shown varying degrees of success for prevention of CRBD.

Trospium chloride [11] is a non-selective muscarinic receptor antagonist and a quaternary ammonium compound found to be effective in treating resistant cases of OAB [12,13]. This study was designed to evaluate the effectiveness of trospium chloride for the prevention of CRBD in patients undergoing spinal surgery and requiring catheterization.

Materials and Methods

After approval from the Institutional Ethical Committee (AHB/CR/95/26-07-2016) and written informed consent from patients, this study was performed on 74 patients with American Society of Anesthesiologists physical status I and II of either sex, aged 20–65 years, who were undergoing elective spinal surgery and required catheterization of the urinary bladder. This study was registered at ClinicalTrials.gov (www.ctri.nic.in, ref: CTRI/2016/11/007423). Exclusion criteria were known sensitivities to study drugs, bladder outflow obstruction, overactive bladder, preoperative neurological bladder/ bowel involvement, chronic pain, drug or alcohol abuse, and cardiovascular or hepatic disease. Eligible patients were randomly distributed into two groups, with the help of a computer-generated table of random numbers. Group T (trospium) received 60 mg of extended release (ER) oral trospium 1 h prior to induction of anesthesia with sips of water. Group C (control) received an oral placebo tablet 1 h prior to induction of anesthesia with sips of water.

In similar-looking envelopes marked T and C, the study drugs were given to the anesthesia registrar who administered the drugs as per instructions with sips of water. In the operating room, after establishing monitoring systems (electrocardiography, pulse oximetry, and noninvasive blood pressure), the patients in both groups received injections of midazolam (0.03 mg/kg), fentanyl (1.5 μg/kg), and propofol (1.5–2.0 mg/kg), followed by vecuronium (0.1 mg/kg) for muscle relaxation. Tracheal intubation was completed with an appropriate-sized cuffed endotracheal tube. Anesthesia was maintained with oxygen:nitrous oxide (O_2:N_2O at a ratio of 33:66), sevoflurane, and intermittent boluses of vecuronium and fentanyl as required. Urinary catheterization was performed under strict aseptic precautions with a 16F Foley catheter after lubricating the urethra with water-soluble lubricating jelly (Neon Laboratories, India) and 10 ml of normal saline was used to inflate its balloon. Catheter fixation was done in the suprapubic region without traction. Perioperative inadequate analgesia was defined as an increase in mean arterial pressure > 20% or heart rate > 30% from baseline in response to a surgical stimulus. In these situations, an intravenous bolus of fentanyl (0.5 μg/kg) was administered. At the end of surgery, the neuromuscular blockade was reversed with neostigmine (40 μg/kg) and glycopyrrolate (10 μg/kg), the trachea was extubated, and patients were moved to the post-anesthesia care unit (PACU). All patients received postoperative analgesia with fentanyl (5 μg/ml) through a patient-controlled analgesia pump (Smiths Medical, USA) in the PACU. Fentanyl requirements in the first 6 hours postoperatively were recorded.

Primary outcome

The primary outcome of this study was the incidence and severity of CRBD, which was recorded on a 4-point severity scale [8] (1 = no discomfort; 2 = mild, admitted on questioning only; 3 = moderate, told by the patient without being questioned; 4 = severe, urinary urgency demonstrated by behavioral changes such as attempts to remove the catheter, verbal responses, and restless movements of extremities) on arrival (0 hour) and again at 1, 2, and 6 hours (h) postoperatively.

Secondary outcome

The secondary outcomes included perioperative fentanyl requirements and side effects of the study drug (such as dry mouth, facial flushing, blurred vision, constipation, agitation, or tachycardia).

Sample size calculation

The sample size was calculated by employing a two-sided P level. The reported incidence of CRBD in our previous study, secondary to intraoperative catheterization, was 70% in spinal surgery at 0 h (primary endpoint) [7]. Assuming that the CRBD incidence in Group C was equal to that of the previous study and the CRBD incidence in Group T was set as 30% (with $\alpha = 0.05$ and $\beta = 0.80$) based on a pilot study, the effect size used was 0.8 based on these proportions (Cohen's $h = 2 * arcsin\sqrt{p_1} - 2 * arcsin\sqrt{p_2} = 0.82$), [14] which resulted in a sample of 25 patients per group to attain the desired effect. Considering a 25% drop-out rate, a sample of 32 patients in each group was targeted.

Statistical analysis

Statistical analysis was done using the statistical software Prism (version 7.0; GraphPad Software, USA). The normality of data was assessed by the Kolmogorov-Smirnov test. Student t-test was

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used for continuous variables and Pearson's chi-squared test was used for categorical variables. Fisher's exact test was used to analyze the incidence and severity of bladder discomfort (mild, moderate, and severe) and the incidence of side effects. An alpha value adjustment with Bonferroni's correction (i.e., the alpha value divided by the number of comparisons) was performed to compare the incidence and severity of CRBD between the two groups at each time point. A P value of < 0.05 was considered statistically significant.

Results

A total of 74 patients were assessed for eligibility, out of which 64 patients were studied after randomization and all patients completed the study (Fig. 1). Ten patients were eliminated from the study due to the preoperative use of pregabalin and analgesics (paracetamol, flupertine, and tramadol). There were no significant differences between patient demographics (P = 0.750), surgery duration (P = 0.627), or intraoperative fentanyl (P = 0.627) requirement between the groups (Table 1).

The incidence of CRBD was 66% in Group C (22% in those <50 yr and 44% in those >50 yr) and 22% in Group T (6% in those <50 yr and 16% in those >50 yr) at 0 h. The overall incidence of CRBD in Group C was significantly higher than in Group T at 0 and 1 h postoperatively. In the subgroup analysis according to age, the incidence of CRBD in Group C was significantly higher than in Group T at all time intervals in the >50 age group (P = 0.004 at 0 h, P = 0.007 at 1 h, P = 0.008 at 2 h, and P = 0.003 at 6 h), but the incidence of CRBD was not significant between the two groups in the <50 age group.

CRBD severity (mild vs. moderate to severe) was significantly decreased in Group T compared to Group C at 2 h postoperatively (P = 0.004). In the subgroup analysis according to age, CRBD severity (mild vs. moderate to severe) was significantly decreased in group T compared to Group C at 1 h (P = 0.006) and 2 h (P = 0.011) postoperatively in the >50 age group, while at other time intervals the severity was not significant between these two groups. The majority of patients in Group T had only mild discomfort (Table 2). The absolute risk reduction with trospium was 44%, the relative risk reduction was 61%, and the number needed to treat was 2.

There were no significant differences in postoperative fentanyl requirements between Group C (342.7 ± 51.8 μg) and T (352.3 ± 66.4 μg) within 6 h postoperatively (P > 0.05). The use of trospium was associated with a higher incidence of dry mouth (15%) compared to the control group (9%). There were no significant differences between the two groups in other side effects (Table 3).

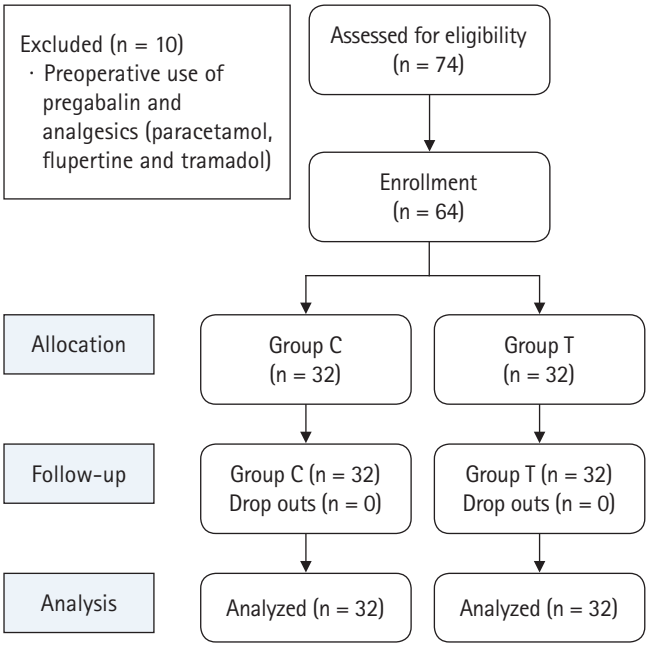

Fig. 1. Study design.

Table 1. Demographic and Clinical Profile of Study Participants

Characteristics	Group C (n = 32)	Group T (n = 32)	P value
Age (yr)	49.6 ± 7.8	52.8 ± 6.1	0.065
Sex (M/F)	25/7	23/9	0.773
Weight (kg)	61.6 ± 8.3	63.7 ± 9.9	0.362
Spine surgery			
Cervical/lumbar	10/22	12/20	0.793
Duration of surgery (min)	148.9 ± 32.6	145.0 ± 36.9	0.655
Intra-operative fentanyl requirement (μg)	118.6 ± 18.3	123.7 ± 20.7	0.296
Post-operative fentanyl requirement (μg)	342.7 ± 51.8	352.3 ± 66.4	0.518

Values are presented as mean ± SD or number. Group C: control group, Group T: trospium group.

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

Postoperation (h)	0 h		1 h		2 h		6 h	
	Group C (n = 32)	Group T (n = 32)	Group C (n = 32)	Group T (n = 32)	Group C (n = 32)	Group T (n = 32)	Group C (n = 32)	Group T (n = 32)
Bladder discomfort								
No	11 (34)	25 (78)	9 (28)	23 (72)	15 (47)	25 (78)	20 (62)	29 (91)
Yes	21 (66)	7 (22)	23 (72)	9 (28)	17 (53)	7 (22)	12 (38)	3 (9)
P value (incidence)	0.001*		0.001*		0.019		0.016	
Relative risk (95% CI)	0.33 (0.16–0.67)		0.39 (0.22–0.71)		0.41 (0.19–0.85)		0.25 (0.07–0.8)	
Grading of discomfort								
Mild	6 (29)	4 (57)	5 (22)	6 (67)	3 (18)	6 (86)	5 (42)	2 (67)
Moderate to severe	15 (71)	3 (43)	18 (78)	3 (33)	14 (82)	1 (14)	7 (58)	1 (33)
P value (severity)	0.207		0.035		0.004*		0.569	

Values are presented as the number of patients (%). Group C: control group, Group T: trospium group. P values are calculated using Pearson's chi-squared test. *Presents statistical significance adjusted for multiple comparisons applying Bonferroni's correction at P = 0.0125.

Table 3. Incidence of Side Effects

	Group C (n = 32)	Group T (n = 32)	P value
Postoperative nausea and vomiting	1 (3)	2 (6)	1.000
Facial flushing	1 (3)	2 (6)	1.000
Dry mouth	3 (9)	5 (15)	0.707
Blurred vision	0	0	
Tachycardia	0	0	

Values are presented as number of patients (%). Group C: control group, Group T: trospium group.

Discussion

CRBD as a postoperative phenomenon is associated with emergence agitation, increased analgesic requirements, and sometimes behavioral changes, and needs active management. The incidence of CRBD varies between 40% and 80% among different surgeries with a maximum incidence reported in genitourinary surgeries [15]. Sometimes it is difficult to differentiate CRBD from spasms or pain associated with genitourinary surgeries. Therefore, we selected spinal surgeries for our study. Other factors influencing the incidence of CRBD are sex (male), catheter diameter [16], and perioperative medications (pregabalin, dexmedetomidine, paracetamol) [7,10,17]. In recent studies, the use of glycopyrrolate as a premedication or part of reversal agents for antagonizing the neuromuscular blockade have been found to influence the incidence of CRBD [18,19]. We did not specifically study this aspect; however, their effect cannot be denied as the incidence of CRBD in our study was 66% (control group) at 0 h, which was similar to other studies. The use of trospium further decreased the incidence of CRBD. The use of sevoflurane has also been shown to decrease the incidence of early CRBD compared to desflurane and propofol [20,21]. It has been postulated that the effect of sevoflurane is short-lived (up to one hour postoperatively) due to its effect on M3 receptors.

There are 5 muscarinic receptor subtypes (M1-M5) present in the human body, each of which have different functions [22]. M2 receptors (70–80%) are the predominant cholinoceptors present in the urinary bladder, while M3 receptors (20–30%) in the bladder mediate detrusor contraction. Hence, selective M2 and M3 receptor antagonists have a therapeutic role in the prevention of CRBD without producing the systemic side effects of anticholinergic drugs. Trospium has a greater affinity for M2 and M3 muscarinic receptors than other muscarinic receptor subtypes.

The mechanism of antimuscarinic agents for the prevention of CRBD is through a reduction of detrusor overactivity by decreasing both contraction frequency and intensity [23]. Additionally, they inhibit bladder afferent mechanisms during the filling phase and increase bladder capacity. Because of these effects, antimuscarinic agents have become a mainstay of treatment for CRBD. Trospium has shown higher tissue selectivity in inhibiting detrusor contraction over salivation, offering an advantage over other agents by reducing detrimental effects and improving compliance. Older antimuscarinic agents, like oxybutynin and tolterodine, have no specificity for any subtype [2].

We administered 60 mg ER trospium, as this is the most effective single daily dose in an overactive bladder [24]. In our institute, most elective spinal surgeries take 2–2.5 h. If anesthesia time is added, then the patients arrive at the PACU after 2.5–3 h. Peak plasma levels of trospium are achieved within 4–5 h. Therefore, trospium administration 1 h before induction roughly corresponded to the peak effect of trospium. The elimination half-life

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of trospium is 10–20 h; therefore, we expected its effect for 12 h postoperatively. In our study, the peak effect of trospium occurs 0–2 h postoperatively, which is why the significant decrease in the incidence and severity of CRBD in our study occurred during this period only. However, we did not assess the CRBD score beyond 6 h due to our study protocol.

Agarwal and colleagues observed that oxybutynin and tolterodine decreased the CRBD incidence by 20–25% [25]. We found a 43% decrease in the CRBD incidence with the use of trospium. Tauzin-Fin et al. [26] also demonstrated that a reduction in the incidence of CRBD was about 48% with 5 mg oxybutynin sublingually. However, the results of this study may have been affected by the use of gabapentin as premedication and tramadol at the timing of wound closure. Both of these drugs also decrease the incidence of CRBD; therefore, this study basically used a cocktail regimen. We also observed a significant decrease in the incidence of dry mouth (15%) and other adverse effects in the trospium group compared with previous studies [25,26] on oxybutynin and tolterodine ($P < 0.05$).

There are certain limitations to this study. It was not possible to analyze the difference in CRBD score with respect to the different doses or a minimally effective dose due to the fixed dose of the drug in this study. Research on the effectiveness of different dosages of trospium, durations of more than 6 h, and their effect by patient sex to decrease the incidence and severity of CRBD score needs further investigation.

In conclusion, 60 mg of ER trospium administered 1 h prior to induction of anesthesia significantly decreased the incidence and severity of CRBD in the early postoperative period, but at the cost of a marginally increased incidence of dry mouth.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Vinit Kumar Srivastava (Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Software; Supervision; Visualization; Writing – original draft; Writing – review & editing)
Sanjay Agrawal (Conceptualization; Methodology; Resources; Supervision; Writing – original draft; Writing – review & editing)
Sweta Anil Deshmukh (Conceptualization; Methodology; Resources; Software; Supervision; Writing – original draft)
Febin Noushad (Methodology; Resources; Software; Visualization)
Saima Khan (Conceptualization; Formal analysis; Investigation; Methodology; Resources)
Raj Kumar (Conceptualization; Methodology; Resources; Supervision; Writing – original draft)

ORCID

Vinit Kumar Srivastava, https://orcid.org/0000-0002-8430-7290
Sanjay Agrawal, https://orcid.org/0000-0002-2806-1943
Sweta Anil Deshmukh, https://orcid.org/0000-0002-5269-8776
Febin Noushad, https://orcid.org/0000-0002-4297-0852
Saima Khan, https://orcid.org/0000-0001-9139-9093
Raj Kumar, https://orcid.org/0000-0002-4896-5229

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