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

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

Running title: Trospium for catheter related bladder discomfort
Abstract

**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 management of OAB influences symptoms of CRBD. Trospium chloride has been found effective in management of resistant cases of OAB. We evaluated effectiveness of oral trospium on CRBD in the postoperative period.

**Methods:** Sixty-four male and female adult patients were randomly divided into two groups, planned for spine surgery and requiring catheterization of urinary bladder. Group T patients received oral trospium 60 mg ER (extended-release) 1 h before induction of anesthesia and Group C patients received a similar looking placebo. Anesthesia technique was identical in both groups. CRBD score was evaluated in postward using 4-point scale (1 = no discomfort, 2 = mild, 3 = moderate, 4 = severe). Readings were recorded on arrival (0 h), 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 postoperative 0 h (66% vs 22%, p=0.001) and 1 h (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 trospium 60 mg ER reduces the incidence and severity of CRBD in the early postoperative period.

**Keywords:** Antimuscarinic agents; Trospium; Muscarinic receptors; Urinary catheterization; Overactive bladder; Postoperative period.
**Introduction**

The salient features of catheter related bladder discomfort (CRBD) are urinary urgency, frequency, with or without urge incontinence observed after bladder catheterization [1]. Presence of urinary catheter may be distressing to the patient and manifests as agitation, restlessness or pulling out of the catheter. It has been observed that the clinical presentation of OAB and CRBD are quite similar, thus the drugs useful in the management of OAB can be used in the prevention of CRBD [2, 3]. Antimuscarinic agents are the first choice drugs for OAB [4]. Darifenacin and solifenacin (newer antimuscarinic agents) have been recently studied for the prevention of CRDB with varying success rates [5]. Other groups of drugs like antiepileptics (gabapentin and pregabalin) [6, 7], ketamine [8], tramadol [9] and dexmedetomidine [10] have shown varying degree of success for prevention of CRBD.

Trospium chloride [11] is a non-selective muscarinic receptor antagonist, a quaternary ammonium compound, found to be effective for the treatment of 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 spine surgery and requiring catheterization.
Materials and Methods

After approval from Institute's Ethical Committee and written informed consent from patients, this study was performed on seventy-four American Society of Anesthesiologist physical status I and II patients of either sex, age 20-65 years, undergoing elective spine surgery and requiring catheterization of the urinary bladder. This study was registered at Clinical Trials.gov www.ctri.nic.in (ref: CTRI/2016/11/007423). Exclusion criteria were known sensitivity to study drug, bladder outflow obstruction, overactive bladder, preoperative neurological bladder/bowel involvement, chronic pain, drug or alcohol abuse, cardiovascular and 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 oral trospium 60 mg ER (extended-release) 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 (SR) who administered the drugs as per instructions with sip of water. In the operation room, after establishing the monitoring (electrocardiography, pulse oximetry and noninvasive blood pressure), the patients in both groups received injection (inj.) midazolam 0.03 mg/kg, inj. fentanyl 1.5 mcg/kg, inj. propofol 1.5-2.0 mg/kg followed by inj vecuronium 0.1 mg/kg for muscle relaxation. Tracheal intubation was completed with an appropriate size cuffed endotracheal tube. Maintenance of anesthesia was done with oxygen: nitrous oxide (O₂:N₂O; 33:66), sevoflurane, intermittent boluses of vecuronium and fentanyl as required. Urinary catheterization was performed under strict aseptic precaution with a 16F Foley catheter after lubrication of urethra by watersoluble lubricating jelly (Neon Laboratories, Mumbai, India) and 10 ml of normal saline was used.
to inflate its balloon. The fixation of catheter was done in 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 the surgical stimulus. In these setting, iv bolus of fentanyl (0.5mcg/kg) was administered. At the end of surgery neuromuscular blockade was reversed with neostigmine (40mcg/kg) and glycopyrrolate (10 mcg/kg), trachea extubated and patients shifted to the post-anesthesia care unit (PACU). All patients received postoperative analgesia with fentanyl (5 mcg/ml) through a patient-controlled analgesia pump (Smith Medical ASD, Inc., USA) in PACU. Fentanyl requirements in the first 6 hours of the postoperative period were recorded.

**Primary outcome**

The primary outcome of the study was the incidence and severity of CRBD, which were recorded on a four 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 behavioural changes such as attempts to remove the catheter, verbal responses, restless movements of extremity) on arrival (0 hour) and again at 1, 2, and 6 hours postoperative period.

**Secondary outcome**

The secondary outcomes included perioperative fentanyl requirements and side effects of study drug (such as dry mouth, facial flushing, blurred vision, constipation, agitation, and 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 spine surgery at 0 h postoperatively (primary endpoint) [7]. Assuming that the CRBD incidence in group C was equal to
that of the previous study and the CRBD incidence in the 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 \( h = 2 \times \arcsin(\sqrt{p_1}) - 2 \times \arcsin(\sqrt{p_2}) = 0.82 \), [14]) which resulted into a sample of 25 patients per group to attain the desired effect. Considering 25% drop outs, a sample of 32 patients in each group were targeted.

**Statistical analysis**

Statistical analysis was done using the statistical software Graph pad prism 7.0. The Normality of data was assessed by the Kolmogorov-Smirnov test. Student “t” test for continuous variables and Pearson’s Chi-square test for categorical variables analyzed patient characteristic data. Fisher’s exact test analyzed the incidence and severity of bladder discomfort (mild, moderate, and severe) and incidence of side effects. The 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 (Figure 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, surgery duration and intraoperative fentanyl requirement between the groups (P>0.05) (Table 1).

The incidence of CRBD was 66% in group C (22% in age <50 yrs and 44% in age >50 yrs) and 22% in group T (6% in age <50 yrs and 16% in age >50 yrs) at 0 h. The overall incidence of CRBD in group C was significantly higher than in group T at 0 and 1 h only. In subgroup analysis according to age, the incidence of CRBD in group C was significantly higher than in group T at all time intervals in age group > 50 yrs (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 incidence of CRBD was not significant between two groups in age group < 50 yrs.

CRBD Severity (mild vs moderate to severe) was significantly decreased in group T compared to group C at 2 h only (P=0.004). In 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) only in age group > 50 yrs, while at other time interval CRBD severity was not significant between these two groups. The maximum number of patients in group T had only mild discomfort (Table 2). 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 mcg) and group T (352.3±66.4 mcg) within 6 h after Surgery (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).
Discussion

CRBD as a postoperative phenomenon is associated with emergence agitation, increased analgesics requirement and sometimes behavioural changes and needs active management. The incidence of CRBD varies between 40-80% among different surgeries with a maximum incidence reported for genitourinary surgeries [15]. Sometimes it is difficult to differentiate CRBD with spasm or pain associated with genitourinary surgeries hence we selected spine surgeries for our subjects. Other factors influencing the incidence of CRBD are male gender, diameter of the catheter [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 antagonising neuromuscular blockade have been found to influence the incidence of CRBD [18, 19]. We specifically did not study this aspect however their effect cannot be denied as the incidence of CRBD in our study was 66% (control group) at 0 hour which was similar to other studies. Use of trospium further decreased the incidence of CRBD. Use of inhalational agent 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 (upto one hour postoperatively) and is due to its effect on M3 receptors.

There are 5 muscarinic receptors subtype (M1-M5) present in the human body and produce different functions according to their receptor subtype [22]. M2 receptors (70-80%) are the predominant cholinoreceptors present in the urinary bladder, while M3 receptors (20-30%) present in bladder mediates detrusor contraction, hence selective M2 and M3 receptors antagonist have a therapeutic role in the prevention of CRBD without producing systemic side effects of anticholinergic drugs. Trospium has a greater affinity for M2 and M3 subtypes of muscarinic receptors than other subtypes of the muscarinic receptors.
The mechanism of antimuscarinic agents for the prevention of CRBD is due to 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 the bladder capacity. Because of these effects, antimuscarinic agents became the mainstay of treatment for CRBD. Trospium has shown higher tissue selectivity to inhibit detrusor contraction over salivation, offering an advantage over other agents by reducing detrimental effects and improving compliance. The older antimuscarinic agents like oxybutynin and tolterodine have no specificity for any subtype [2].

We administered trospium 60 mg ER, because this is the most effective single daily dose in overactive bladder [24]. In our institute, most elective spine surgeries take 2–2.5 h. If anesthesia time was added, then the patients arrive at the PACU after 2.5-3 h. The peak plasma levels of trospium are achieved within 4-5 h. Therefore, trospium administration 1 hour before induction roughly corresponded to the peak effect of trospium. The elimination half-life of trospium is 10–20 h, therefore we expected its effect for 12 h postoperatively. In our study the peak effect of trospium coincides with 0-2 hr postoperative period of surgery, that’s why the significant decrease in the incidence and severity of CRBD in our study during this period only. However, we did not assess the CRBD score beyond 6 hr because of our protocol of the study.

Agarwal and colleagues observed that oxybutynin and tolterodine decreased the CRBD incidence by 20-25% [25]. We found 43% decrease in our study by the use of trospium. Tauzin-Fin et al also demonstrated that a reduction in the incidence of CRBD was about 48% by use of oxybutynin 5 mg sublingually [26]. However, the results of this study may have been affected by use of gabapentin as premedication and tramadol at the timing of wound closure. Both these drugs also decrease the incidence of CRBD, so moreover this study is 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 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 minimally effective dose due to the fixed-dose of the drug in this study. Research on the effectiveness of different dosages of trospium, duration more than 6 h and their effect by patient gender to decrease the incidence and severity of CRBD score needs further investigation.

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


<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group C (n=32)</th>
<th>Group T (n=32)</th>
<th>P-value</th>
<th>Kolmogorov-Smirnov test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yrs)</td>
<td>49.6±7.8</td>
<td>52.8±6.1</td>
<td>0.065*</td>
<td>0.750</td>
</tr>
<tr>
<td>Male/Female</td>
<td>25/7</td>
<td>23/9</td>
<td>0.773#</td>
<td>-</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>61.6±8.3</td>
<td>63.7±9.9</td>
<td>0.362*</td>
<td>0.830</td>
</tr>
<tr>
<td>Spine surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical/lumbar</td>
<td>10/22</td>
<td>12/20</td>
<td>0.793#</td>
<td>-</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>148.9±32.6</td>
<td>145.0±36.9</td>
<td>0.655*</td>
<td>0.627</td>
</tr>
<tr>
<td>Intra-operative fentanyl</td>
<td>118.6±18.3</td>
<td>123.7±20.7</td>
<td>0.296*</td>
<td>0.627</td>
</tr>
<tr>
<td>Post-operative fentanyl</td>
<td>342.7±51.8</td>
<td>352.3±66.4</td>
<td>0.518*</td>
<td>0.830</td>
</tr>
</tbody>
</table>

Data are presented as either mean values ± SD or by absolute numbers. Student *t-test for two independent samples; # Pearson’s Chi-square test
Table 2. Incidence and severity of catheter related bladder discomfort

<table>
<thead>
<tr>
<th>Postoperative (hr)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>T</td>
<td>C</td>
<td>T</td>
</tr>
<tr>
<td>Groups</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Bladder discomfort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11(34)</td>
<td>25(78)</td>
<td>9(28)</td>
<td>23(72)</td>
</tr>
<tr>
<td>Yes</td>
<td>21(66)</td>
<td>7(22)</td>
<td>23(72)</td>
<td>9(28)</td>
</tr>
<tr>
<td>P value (Incidence)</td>
<td>0.001*</td>
<td>0.001*</td>
<td>0.019</td>
<td>0.016</td>
</tr>
<tr>
<td>Relative risk</td>
<td>0.33 (0.16-0.67)</td>
<td>0.39 (0.22-0.71)</td>
<td>0.41 (0.19-0.85)</td>
<td>0.25 (0.07-0.8)</td>
</tr>
<tr>
<td>(95%CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grading of discomfort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>6(29)</td>
<td>4(57)</td>
<td>5(22)</td>
<td>6(67)</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>15(71)</td>
<td>3(43)</td>
<td>18(78)</td>
<td>3(33)</td>
</tr>
<tr>
<td>P value (Severity)</td>
<td>0.207</td>
<td>0.035</td>
<td>0.004*</td>
<td>0.569</td>
</tr>
</tbody>
</table>

Data are presented as number of patients (percentage of patients); p-value is calculated using Pearson’s Chi-square test; *presents statistical significance adjusted for multiple comparisons applying Boneferroni correction at p=0.0125.
Table 3. Incidence of side effects

<table>
<thead>
<tr>
<th></th>
<th>Group C (n=32)</th>
<th>Group T (n=32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative nausea and vomiting</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Facial flushing</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3 (9)</td>
<td>5 (15)</td>
<td>0.707</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as number of patients (percentage of patients). Fisher’s exact test analyzed the data.
10 patients excluded: Preop use of pregabalin and analgesics (paracetamol, flupertine and tramadol)

Assessed for eligibility n=74
Enrollment n=64

Allocation

Group T n=32
Group C n=32

Follow up

Group T (n=32) Drop outs (n=0)
Group C (n=32) Drop outs (n=0)

Analysis

Analyzed (n=32)
Analyzed (n=32)