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Comparison of efficacy of oxybutynin and tolterodine for prevention of catheter related bladder discomfort: a prospective, randomized, placebo-controlled, double-blind study

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Background. Bladder discomfort related to intraoperative catheterization of urinary bladder is a distressing symptom and more so in patients awakening from anaesthesia. These symptoms are similar to symptoms of overactive bladder. Muscarinic receptor antagonists have been reported to be effective in the treatment of overactive bladder. This study was therefore undertaken to evaluate the efficacy of oxybutynin and tolterodine in preventing catheter related bladder discomfort.

Methods. Two hundred and thirty-four consecutive adult patients, ASA I and II, of either sex, undergoing elective percutaneous nephrolithotomy surgery requiring urinary bladder catheterization were randomized into three equal groups of 78 each. Group C (control) received placebo, Group O (oxybutynin) received oxybutynin 5 mg and Group T (tolterodine) received tolterodine 2 mg orally 1 h before surgery. After induction of anaesthesia patients were catheterized with a 16 Fr Foley's catheter and the balloon was inflated with 10 ml distilled water. The bladder discomfort was assessed at 0, 1, 2 and 6 h after patient's arrival in the post-anaesthesia care unit. Severity of bladder discomfort was graded as mild, moderate and severe.

Results. Incidence of bladder discomfort observed in the control group was higher, i.e. 58% (45/78), compared with oxybutynin and tolterodine groups where it was 35% (28/78) and 33% (26/78), respectively ($P<0.05$). Significant reduction in the severity of bladder discomfort was also observed after oxybutynin and tolterodine therapy compared with control ($P<0.05$).

Conclusion. Pretreatment with either oxybutynin or tolterodine reduces the incidence and severity of catheter related bladder discomfort.

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In patients undergoing surgery, where urinary bladder of the patient is catheterized and is left *in situ* for postoperative bladder drainage, patients often complain of bladder discomfort (an urge to void or discomfort in the suprapubic region) in the postoperative period because of catheter related bladder irritation. These symptoms are similar to symptoms of overactive bladder (urinary frequency and urgency, with or without urge incontinence) which are caused by involuntary contractions of the bladder mediated by muscarinic receptors.[1 2] Muscarinic receptor antagonists oxybutynin and tolterodine have been used successfully for the management of overactive bladder.[3]

Tolterodine has been reported to be effective in reducing catheter related bladder discomfort.[4] This study aimed to evaluate the efficacy of oxybutynin and tolterodine in decreasing urinary catheter related bladder discomfort in patients undergoing percutaneous nephrolithotomy (PCNL) for renal and upper ureteric stones.

Methods

After approval from the Institute's Ethics Committee and written informed consent from the patients, this prospective, placebo-controlled study was conducted in a randomized,

double-blind manner. Incidence of urinary catheter related bladder discomfort has been reported to be 55%.[4] Assuming that this incidence would reduce to 30% after therapy we required 78 patients in each group for results to be statistically significant with α=0.05 and β=0.80.

The study therefore consisted of 234 consecutive adults (18–60 yr), ASA I or II, of either sex, undergoing elective PCNL for renal and upper ureteric stone requiring catheterization of urinary bladder. This procedure usually requires postoperative bladder drainage for 12–24 h in addition to nephrostomy. Patients were randomized with the help of a computer generated table of random numbers into three groups. Tablets were peeled off from their packing and placed in identical bottles marked 1, 2 and 3, and were handed over to a nursing staff in the preoperative area. This nurse was not aware of the medication contained in these bottles and administered these to patients depending upon the results of the randomization. Patients belonging to Group C (control) received placebo, Group T received tolterodine 2 mg (Detrusitol; Pharmacia Italia S.p.A) and Group O received oxybutynin 5 mg (Cystran; Intas Pharmaceuticals, India). All the drugs were given orally 1 h before induction of anaesthesia. Patients with a history of overactive bladder (frequency >3 times in the night or >8 times in 24 h) and/or at end-stage renal disease (urine output <500 ml/24 h) were excluded from the study.

The patients were premedicated with lorazepam 0.04 mg kg^{-1} given orally the night before and 2 h before the induction of anaesthesia. Anaesthesia was induced with fentanyl 3 μg kg^{-1} and propofol 2 mg kg^{-1}. Tracheal intubation was facilitated by vecuronium bromide 0.1 mg kg^{-1}. Anaesthesia was maintained using 70% nitrous oxide in oxygen and a propofol infusion 50–150 μg kg^{-1} min^{-1} and intermittent fentanyl and vecuronium as required. Monitoring consisted of five lead ECG, non-invasive blood pressure, pulse oximetry, temperature and end-tidal carbon dioxide (kept between 4.0 and 4.6 kPa). None of the patients received epidural or spinal anaesthesia or were given antiemetics as part of anaesthesia protocol. At the end of surgery the muscle relaxation was reversed by a combination of neostigmine 0.05 mg kg^{-1} and glycopyrrolate 0.01 mg kg^{-1}. After induction of anaesthesia the urinary bladder was catheterized using 16 Fr Foley's catheter and its balloon was inflated with 10 ml distilled water. The urinary catheter was lubricated with K-Y jelly (a water base lubricating gel) before insertion and was fixed in the suprapubic area with an adhesive tape without any traction. It was always left to free drainage into a bag. After surgery the patients were transferred to the post-anaesthesia care unit (PACU) and they received i.v. fentanyl for the postoperative pain using a patient-controlled analgesia device.

Assessment of bladder discomfort (urge to pass urine or discomfort in suprapubic region) was carried out by one of the investigators (V.S.), who was unaware of the group allocation, at 0, 1, 2 and 6 h after arrival of the patients in the PACU. Severity of bladder discomfort was recorded as mild (reported by the patient only on questioning), moderate (reported by the patient without questioning; not accompanied by any behavioural responses) and severe (reported by the patient without questioning and accompanied by behavioural responses). Behavioural responses observed were flailing limbs, strong vocal response and attempts to pull out the urinary catheter. If the patient did not complain of any bladder discomfort then the investigator engaged the patient in a casual conversation (asking patient's name, occupation and place of stay). Thereafter these patients were asked whether they were comfortable and if the patients replied in the affirmative then it was presumed that the patients did not have any bladder discomfort. However, if the patients reported that they had an urge to pass urine or discomfort in the suprapubic region then these patients were included in the mild bladder discomfort group. Presence or absence of adverse effects such as postoperative nausea and vomiting (PONV), facial flushing, dry mouth and blurred vision were noted. Ondansetron 4 mg i.v. was used as the anti-emetic whenever a patient had an episode of vomiting in the postoperative period.

Differences in the age and weight between the groups were compared by one-way ANOVA whereas differences in distribution of gender, incidence of bladder discomfort and side-effects between the groups were compared with the help of test of proportions for large sample (*Z*-test). Severity of bladder discomfort (mild, moderate and severe) was analysed by Fisher's exact test. SPSS 9.0 (SPSS Inc., Chicago, IL) was used for the statistical analysis. $P<0.05$ was considered as significant.

Results

There were no significant differences in the patient characteristics including age, gender and weight between the groups (Table 1). The overall incidence of bladder discomfort was significantly less in oxybutynin and tolterodine groups compared with the control group ($P<0.05$). In the control group, the severity of bladder discomfort at 1 h was significantly higher compared with oxybutynin and tolterodine groups ($P<0.05$) (Table 2). Similarly, incidences of moderate discomfort at 1 and 2 h were higher in the control group ($P<0.05$) (Table 2); the majority of the patients in the oxybutynin and tolterodine group had mild discomfort at 1 and 2 h. No difference was observed in the severity of bladder discomfort in all the three groups at 0 and 6 h. There was no difference in the incidence and severity of

Table 1 Patient characteristics. Data presented as either absolute number of patients or mean (SD)

Groups	Control	Oxybutynin	Tolterodine
n	78	78	78
Age (yr)	43.6 (14.4)	45.6 (13.2)	44.4 (12.8)
Gender (M/F)	42/36	40/38	39/39
Weight (kg)	57.3 (11.4)	55.4 (12.6)	56.9 (10.2)

Table 2 Incidence and severity of bladder discomfort, data presented as number of patients. *$P<0.05$ for comparison between control *vs* tolterodine and oxybutynin. C, control; O, oxybutynin; T, tolterodine

Time (h)	0			1			2			6		
Groups	**C**	**O**	**T**	**C**	**O**	**T**	**C**	**O**	**T**	**C**	**O**	**T**
n	78	78	78	78	78	78	78	78	78	78	78	78
Bladder discomfort	43*	13	12	45*	28	26	38*	21	20	28*	12	14
Grading of discomfort												
Mild	17	9	8	19*	26	24	17*	19	17	22	12	14
Moderate	13	2	2	15*	2	2	16*	2	3	4	0	0
Severe	13	2	2	11*	0	0	5	0	0	2	0	0

Table 3 Incidence of side-effects, data presented in number of patients. *$P<0.05$ for comparison between control *vs* oxybutynin and tolterodine. C, control; O, oxybutynin; T, tolterodine

Time (h)	0			1			2			6		
Groups	**C**	**O**	**T**	**C**	**O**	**T**	**C**	**O**	**T**	**C**	**O**	**T**
n	78	78	78	78	78	78	78	78	78	78	78	78
PONV	4	5	4	5	11	8	5	2	2	1	2	4
Facial flushing	1	6	6	0	4	5	0	4	6	1	2	4
Dry mouth	15*	40	36	19*	46	43	15	18	17	12	15	16
Blurred vision	0	0	0	2	0	0	0	0	0	1	0	0

bladder discomfort between the tolterodine and oxybutynin groups at all time points studied (Table 2).

In the oxybutynin group absolute risk reduction, relative risk reduction and number needed to treat (NNT) with 95% confidence boundary were 17 (2–31), 38 (4–60) and 6 (3–47), respectively. In the tolterodine group absolute risk reduction, relative risk reduction and NNT with 95% confidence boundary were 19 (4–33), 42 (10–63) and 5 (3–23), respectively.

The incidence of dry mouth was significantly higher in the tolterodine and oxybutynin groups compared with control ($P<0.05$) (Table 3). There were no differences in the incidence of other side-effects and fentanyl consumption between the groups. We did not encounter any clinically relevant dysrhythmias in our study.

Discussion

We observed a significant reduction in the incidence and severity of catheter related bladder discomfort in the postoperative period in patients who had received either oxybutynin or tolterodine before operation ($P<0.05$).

The innervations of the urinary tract are derived from three sets of peripheral nerves: sacral parasympathetic, thoraco-lumbar sympathetic and sacral somatic (primarily the pudendal nerves).[5] Overactive bladders are characterized by the symptoms of urinary frequency and urgency, with or without urge incontinence. These symptoms result from involuntary contractions of bladder mediated by muscarinic receptors.[1,2] Although behavioural and surgical interventions may be used to treat overactive bladder, antimuscarinic therapy by suppressing involuntary bladder contractions has been the mainstay of treatment for overactive bladder for almost 30 yr.[6–8] Oxybutynin inhibits the muscarinic effect of acetylcholine on smooth muscle. It also has a moderate anticholinergic effect. Tolterodine is the first antimuscarinic agent to be specifically developed for the treatment of overactive bladder.

Tolterodine is rapidly absorbed after oral administration reaching peak plasma concentration within 1–2 h. Its elimination half-life ranges from 1.9 to 11 h. After oral oxybutynin therapy the peak plasma level is reached at ~1 h and the estimated half-life is <2 h with a duration of action of 6–10 h. Oxybutynin has no significant effects on heart rate. Supra therapeutic dose of tolterodine 4 mg twice daily for 2 weeks have been reported to increase heart rate by 6 beats min^{-1}.[9] We administered single dose of oxybutynin (5 mg) or tolterodine (2 mg) to our patients and observed that these drugs did not influence heart rate, ECG or blood pressure during anaesthesia.

The efficacy of oxybutynin in reducing catheter related bladder discomfort has not been evaluated so far. This study therefore aimed to evaluate the efficacy of oxybutynin and compare it with an equipotent dose of tolterodine[10–12] for attenuating the incidence and severity of catheter related bladder discomfort in patients undergoing PCNL requiring intraoperative catheterization of urinary bladder.

We used 16 Fr catheters in all our patients as we were expecting light haematuria with no or small clot.[13] With respect to balloon inflation, it is kept to ~10 ml as both under- or over-inflation have disadvantages.[13]

Agarwal and colleagues[4] observed that tolterodine 2 mg administered 1 h before surgery reduced the incidence of catheter related bladder discomfort by 19%. We observed a similar reduction of 25% in this study, whereas oxybutynin reduced the incidence by 23%. Reduction in the severity of observed bladder discomfort was similar in both the studies.

We observed significant increase in the incidence of dry mouth in the oxybutynin and tolterodine groups compared with control ($P<0.05$). Tolterodine and its metabolite 5-HM show functional selectivity for the bladder over the salivary glands compared with oxybutynin and thus are expected to cause less dryness of mouth.[14] However, contrary to expectation no difference in the incidence of dryness of mouth was observed between oxybutynin and tolterodine which needs to be explored in future studies. The incidence of other side-effects was similar between all the groups.

In this study we observed significant reduction in the incidence and severity of catheter related bladder discomfort in the postoperative period in patients who had received either oxybutynin or tolterodine before operation ($P<0.05$). There was no difference in the side-effects between these two study drugs. We did not evaluate the dose–response titration, nor have we evaluated the effect of continuing the therapy in the postoperative period. We also did not evaluate the effect of therapy in patients who may be catheterized for other medical reasons but not requiring any surgical intervention and further studies in

these areas are suggested. We, therefore, conclude that pretreatment with both oxybutynin and tolterodine are effective in reducing the incidence and severity of catheter related bladder discomfort.

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