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Effectiveness of Solifenacin for Managing of Bladder Spasms in Patients With Urethroplasty

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Abstract

To evaluate the efficacy and safety of solifenacin in the treatment of bladder spasms after urethroplasty. Patients underwent urethroplasty were randomly assigned to the study group (n = 165) and the control group (n = 150). Patients in the study group were treated with solifenacin for 7 days. Patients in the control group were placebo. Each group was further divided into four subgroups: paracentetic suprapubic cystostomy subgroup, traditional suprapubic cystostomy subgroup, former suprapubic cystostomy subgroup, and urethral catheter subgroup. A visual analogue scale (VAS) was used to measure the severity of bladder spasms. The mean duration of spasms, the frequency of spasms, and the incidences of urine extravasation and radiating pain were recorded each day. There were no significant differences in the VAS scores and mean duration of bladder spasms between the study and control groups . However, there was a significantly lower VAS score in the patients taking solifenacin in the paracentetic suprapubic cystostomy subgroup (p < .05). A similar tendency was noted in the mean duration of bladder spasms in this subgroup. In a comparison of the daily and nightly frequency of spasms within the four subgroups, a significant improvement was noted in the control group within 5 days. A similar difference was not noted within 6 days in the study group. The short-term therapy with solifenacin is an effective and safe method for decreasing the frequency of bladder spasms after urethroplasty. Patients undergoing paracentetic suprapubic cystostomy might be the only subset to benefit from this treatment.

Keywords

bladder spasms, solifenacin, urethroplasty, urethral stricture

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One of the most common complications of lower urinary tract surgery is bladder spasms, which are involuntary contractions of the detrusor muscles, which manifest as intermittent abdominal cramps, perineal pain, and a sensation of urgency to void. Bladder spasms may result in urinary leakage around the urethral catheter when one is in situ (Chiang, Ben-Meir, Pout, & Dewan, 2005). Moreover, the duration of urethroplasty is more than 1 hr, and it is essential to use an indwelling urethral catheter and cystostomy catheter for 3 weeks after the surgery. According to the findings of Yates, Tanner, and Crossley (2004), these factors lead to an increased need for urethral reconstruction due to bladder spasms compared to other operations. The symptoms of bladder spasms affect the recovery of postoperative patients in the units.

In 2002, Anderson and Dewan confirmed the efficacy of the highly selective muscarinic M3 receptor antagonist, solifenacin, in the control of bladder spasms after transurethral prostatectomy (Anderson & Dewan, 2002). After that, there have been only a few domestic and

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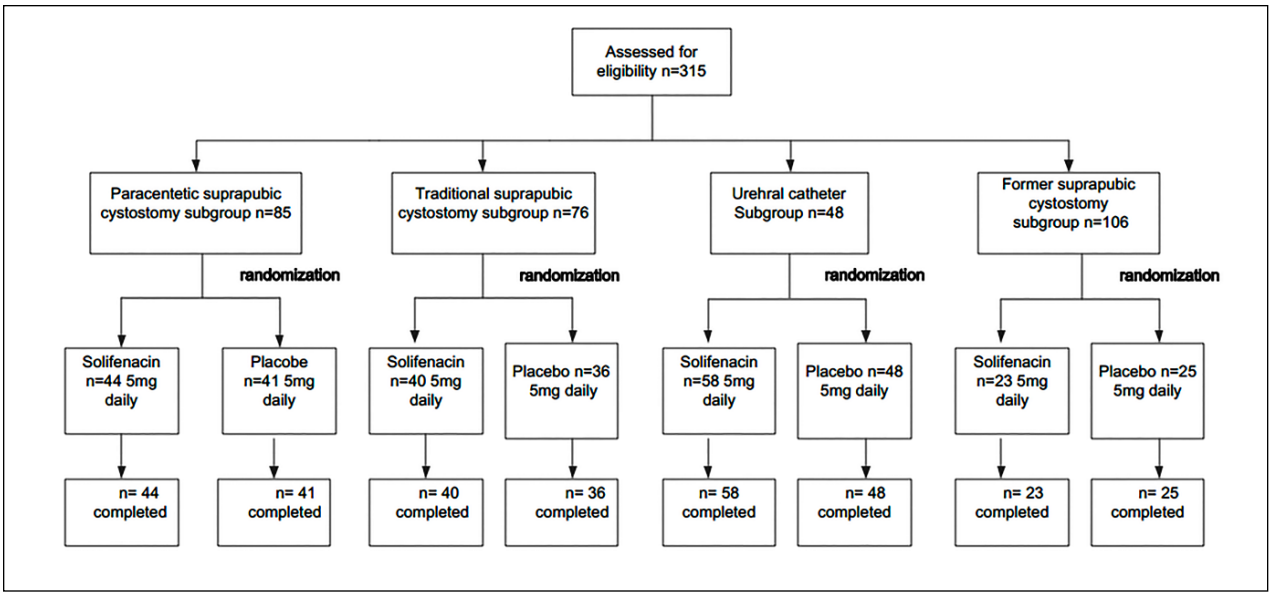

Diagram 1. Summary of patient flow in the study.

international reports on the impact of the drug for the short-term treatment of bladder spasms after urethral reconstruction. From July 2011 to October 2015, 315 patients who underwent urethroplasty were randomized to evaluate the efficacy of solifenacin in the management of bladder spasms.

Materials and Methods

Data were collected from 315 patients who ranged in age from 5 to 85 years old (mean age of 38.5 ± 16.3 years). Seventy-five (23.81%) male patients were identified as anterior urethral stricture; 225 (71.43%) male patients were posterior urethral stricture, bulbar membranous strictures included; and 15 (4.8%) female patients were urethratresia with urethrovaginal fistula. Among them, 70 (22.22%) patients underwent urethroplasty with autologous materials, 213 (67.62%) patients underwent urethra end-to-end anastomosis, 12 (3.81%) patients underwent internal urethrotomy, 5 (1.59%) patients underwent bladder neck reconstruction, 3 (0.95%) patients underwent isolated cystostomy, and 12 (3.81%) patients underwent isolated genitourinary fistula repair. All patients were treated with a urethral indwelling catheter or cystostomy catheter after the operation for 3 weeks. The size of all catheters was F18r. The type of catheter used was based on the surgeon's preference.

The study design is shown in Diagram 1. After the urethroplasty, patients were randomly (coin toss) assigned to either the study group (n = 165) and the control group (n = 150). All patients were blinded during the study. The patients in the study group were treated with solifenacin (5 mg once daily) for 7 days beginning the first day after the operation. The patients in the control group were treated with vitamin C (10 mg once daily) for the same period of time. Each group was further divided into four subgroups based on the use of a urethral indwelling catheter or intraoperative cystostomy (Table 1).

A VAS was used to measure the severity of bladder spasms. The mean duration of spasms, the frequency of spasms, the incidences of urine extravasation and radiating pain, and the side effects associated with using solifenacin were recorded each day on a self-made scale (Table 2).

All patients signed informed consent forms before beginning the study. The Shanghai Sixth People's Hospital ethics committee specifically approved this study (Registration ChiCTR-IPR-17011523).

Statistical Analysis

Statistical analysis was performed using the SPSS 13.0 software program for Windows (SPSS Inc.). All of the results were given as $X \pm SD$ (Standard Deviation). Student's t tests were used for the analyses of the means. The chi-squared test was used to compare the incidence rates between groups. A $p < 0.05$ was considered statistically significant.

Results

All patients were successfully treated by urethroplasty and tolerated the investigation well. There were no significant

Table 1. The Details of the Basic Characteristics of Patients.

	Study group	Control group
Paracentetic suprapubic cystostomy subgroup (No. of pts)	44	41
Age (years)	35 ± 6.8	38 ± 7.8
Gender (% male)	81.82	82.93
Average surgery time (minutes)	78s ± 18.6	76 ± 20.9
Duration of hospitalization (days)	21 ± 6	25 ± 7
Location of the stricture		
Bulbar	28	28
Membranous	16	13
Urine extravasation	8	14
Traditional suprapubic cystostomy subgroup (No. of pts)	40	36
Age (years)	31 ± 8.8	34 ± 7.8
Gender (% male)	100	100
Average surgery time (hours)	86 ± 19.6	89 ± 20.9
Duration of hospitalization (days)	20 ± 8	24 ± 9
Location of the stricture		
Bulbar	24	23
Membranous	16	13
Urine extravasation	8	10
Former suprapubic cystostomy subgroup (No. of pts)	58	48
Age (years)	38 ± 4.6	29 ± 8.9
Gender (% male)	100	100
Average surgery time (hours)	60 ± 29.6	62 ± 26.9
Duration of hospitalization (days)	21 ± 8	22 ± 9
Location of the stricture		
Bulbar	35	33
Membranous	23	15
Urine extravasation	8	12
Urethral catheter subgroup (No. of pts)	23	25
Age (years)	38 ± 8.6	39 ± 10.9
Gender (% male)	100	100
Average surgery time (hours)	62 ± 23.9	66 ± 26.7
Duration of hospitalization (days)	21 ± 3	22 ± 4
Location of the stricture		
Bulbar	17	16
Membranous	6	9
Urine extravasation	7	9

No. of pts = number of patients.

differences in the VAS scores (Fig. 1A) or the mean duration of bladder spasms (Fig. 2A) between the study group and control group (VAS scores: $p = .78 > .05$; the mean duration: $p = .43 > .05$). There was a significantly lower VAS score in those taking solifenacin in the paracentetic suprapubic cystostomy subgroup ($p = .032 < .05$) (Fig. 1B). A similar tendency was noted in the mean duration of bladder spasms in this subgroup ($p = .043 < .05$) (Fig. 2B).

In a comparison of the daily and nightly frequencies of spasms within the four subgroups (Fig. 3), a statistically significant difference was noticed in the control group within 5 days ($p = .042 < .05$). No similar difference was noticed within 6 days in the study group ($p = .13 > .05$). There was no significant difference in the incidence of urine extravasation or radiating pain among the four subgroups (the incidence of extravasation: $p = .67 > .05$; the incidence of radiating pain: $p = .33 > .05$).

During the course of the study, no serious adverse effects were observed. Dry mouth was noted in six patients (3.64%) assigned to the study group. No patients complained of dry mouth in the control group. Ten patients (6.06%) complained of constipation after the operation in the study group, compared with six patients (4%) in the control group. None of the other patients experienced these conditions.

Table 2. The Details of Bladder Spasm After Urethroplasty.

Name:_____Gender:_____Age:_____
Tel: _____Registration No.:_____
Location of stricture: _____Preoperative cystostomy:_____
Date of surgery:_____
Type of operation: _____Type of intraoperative cystostomy: _____
Preventive drugs: _____Usage of preventive drugs: _____
Preoperative uroflowmetry:_____ Preoperative urography: _____.

Day	D1	D2	D3	D4	D5	D6	D7	D8
VAS score								
Urinary extravasation								
Frequency of spasms (daytime)								
Frequency of spasms (nighttime)								
Mean duration of spasms								
Visible Hematuria								
Radiating pain (anus or testes)								

Uroflowmetry following catheter removal: _____
Urography following catheter removal: _____
Special situation during the treatment process: _____
P.S.: Please use 0 or 1 to complete the above table. "0" means "No"; 1 means "Yes".

Discussion

Previous studies reported that bladder spasms often appear after lower urinary tract surgery. Yates et al. (2004) revealed that the patients at the highest risk of experiencing bladder spasms are those who are undergoing surgical procedures lasting more than 25 min and those with catheters inserted. Considering these unfavorable factors, the patients undergoing urethroplasty would be prone to develop bladder spasms. The occurrence of bladder spasms has a large impact on the recovery of patients. Furthermore, a study conducted by Montgomery et al. (2007) identified that extravasation of urine at the anastomosis caused by bladder spasms was independently associated with the formation of a urethral stricture.

The best treatment for postoperative bladder spasms is to remove the catheter (Anderson & Dewan, 2002). Due to the particularities of urethroplasty, it is essential to use an indwelling urethral catheter and cystostomy catheter for 3 weeks after the surgery. Relieving bladder spasms by removing the catheters is not feasible in these cases. The current treatment modalities include opioids, anticholinergics, musculotropic bladder smooth muscle relaxants, and local anesthetics (Park et al., 2000). These strategies are considered efficacious in suppressing postoperative bladder spasms. Side effects from the different agents have also been noted, including a decrease in gastrointestinal motility caused by intravenous morphine (leading to nausea and constipation), dry mouth induced by oxybutynin, and the risk for misplacement of the cannula during epidural anesthesia (Chiang et al., 2005).

As a new-generation antimuscarinic agent, solifenacin is a highly selective muscarinic M3 receptor antagonist. Furthermore, solifenacin has been demonstrated to have apparent tissue selectivity for the bladder over the salivary glands in preclinical models (Ikeda et al., 2002). Clinical trials (Luo, Liu, Han, Wei, & Shen, 2012) have demonstrated that treatment with solifenacin effectively reduced the symptoms of overactive bladder by inhibiting carbachol-induced intracellular calcium mobilization in bladder smooth muscle cells. To date, no studies published have assessed the safety and tolerability of solifenacin in the treatment of bladder spasms after urethroplasty. There is a clear need for a regularly updated and comprehensive systematic study of the effectiveness of solifenacin in the management of patients with bladder spasms.

The OAB symptom score has not gained acceptance as an objective tool to record related symptoms. This is based on the characteristics of urethroplasty. Patients undergoing urethroplasty often require the use of an indwelling urethral catheter and cystostomy catheter for 3 weeks. It is impossible to record the frequency of micturition and the symptoms of urinary incontinence in these patients. To address this issue, a self-made questionnaire was developed to record the mean duration of spasms, the frequency of spasms, the incidence of urine extravasation, and the incidence of radiating pain. A VAS (Wewers

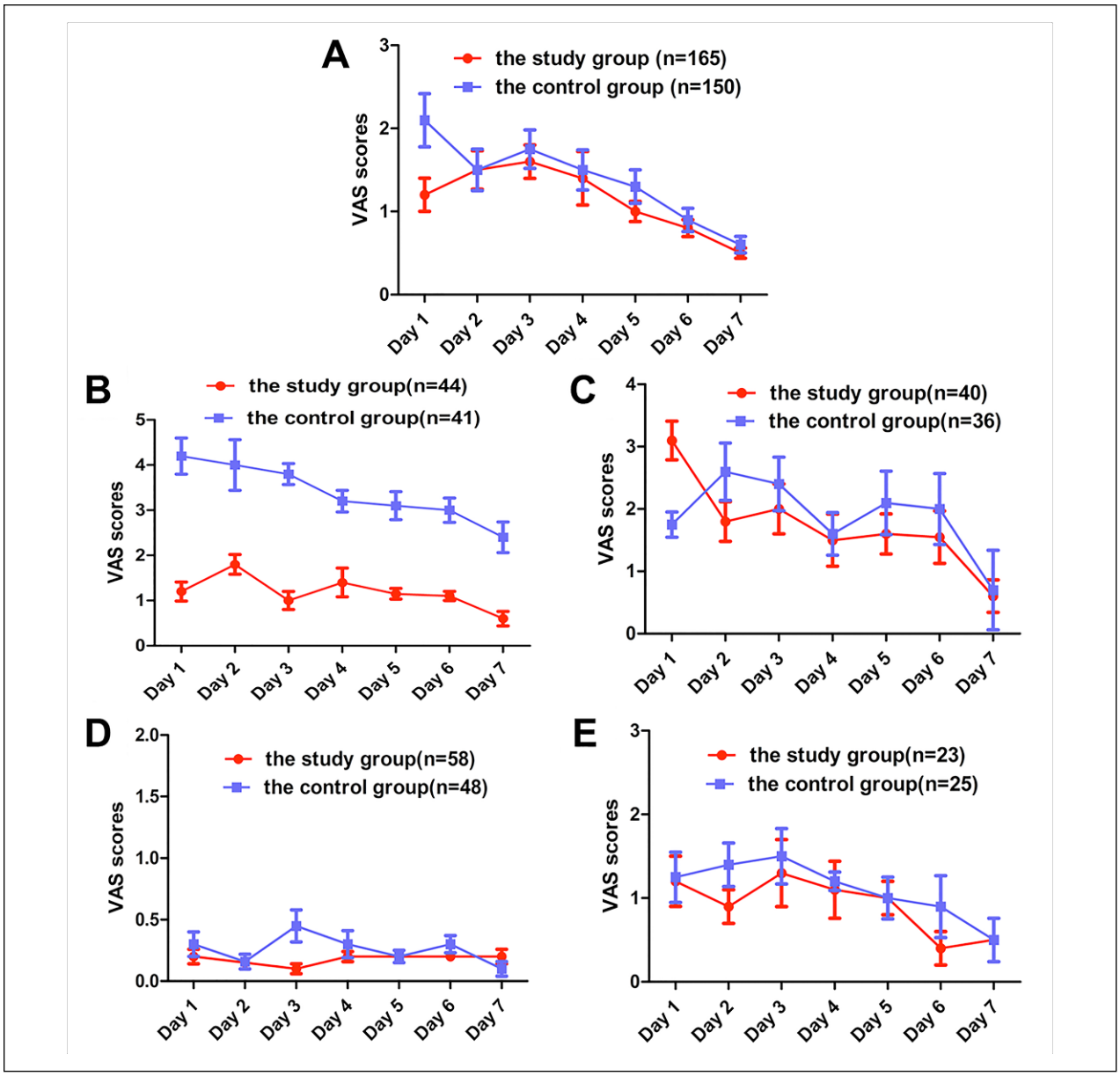

Figure 1. Visual analogue scale (VAS) of patients in study group and control group. (A) The general VAS score in study group and control group; (B) paracentetic suprapubic cystostomy subgroup; (C) traditional suprapubic cystostomy subgroup; (D) urethral catheter subgroup; (E) former suprapubic cystostomy subgroup.

& Lowe, 1990) was used to measure the severity of the bladder spasms. The aim of the present study was to objectively evaluate the efficacy of solifenacin in the short-term treatment of bladder spasms after urethroplasty.

In the present study, none of the paired subgroups (study group and control group) manifested a statistically significant difference in the severity of bladder spasms, the mean duration of spasms, the incidence of urine extravasation, or the incidence of radiating pain. With regard to the frequency of spasms, there were notable differences in each subgroup within the control group, while statistical testing demonstrated no differences among the subgroups in the study group. Previous studies (Chapple, et al., 2004; Chapple, 2004; Luo et al., 2012) of the efficacy of solifenacin for treating overactive bladder reported that it had beneficial effects on the micturition frequency and nocturia and that it decreased the number of micturitions per 24-hr period. Considering the above results, it can be concluded that the main purpose of the application of solifenacin in patients undergoing urethroplasty is to decrease the frequency of spasms. In a

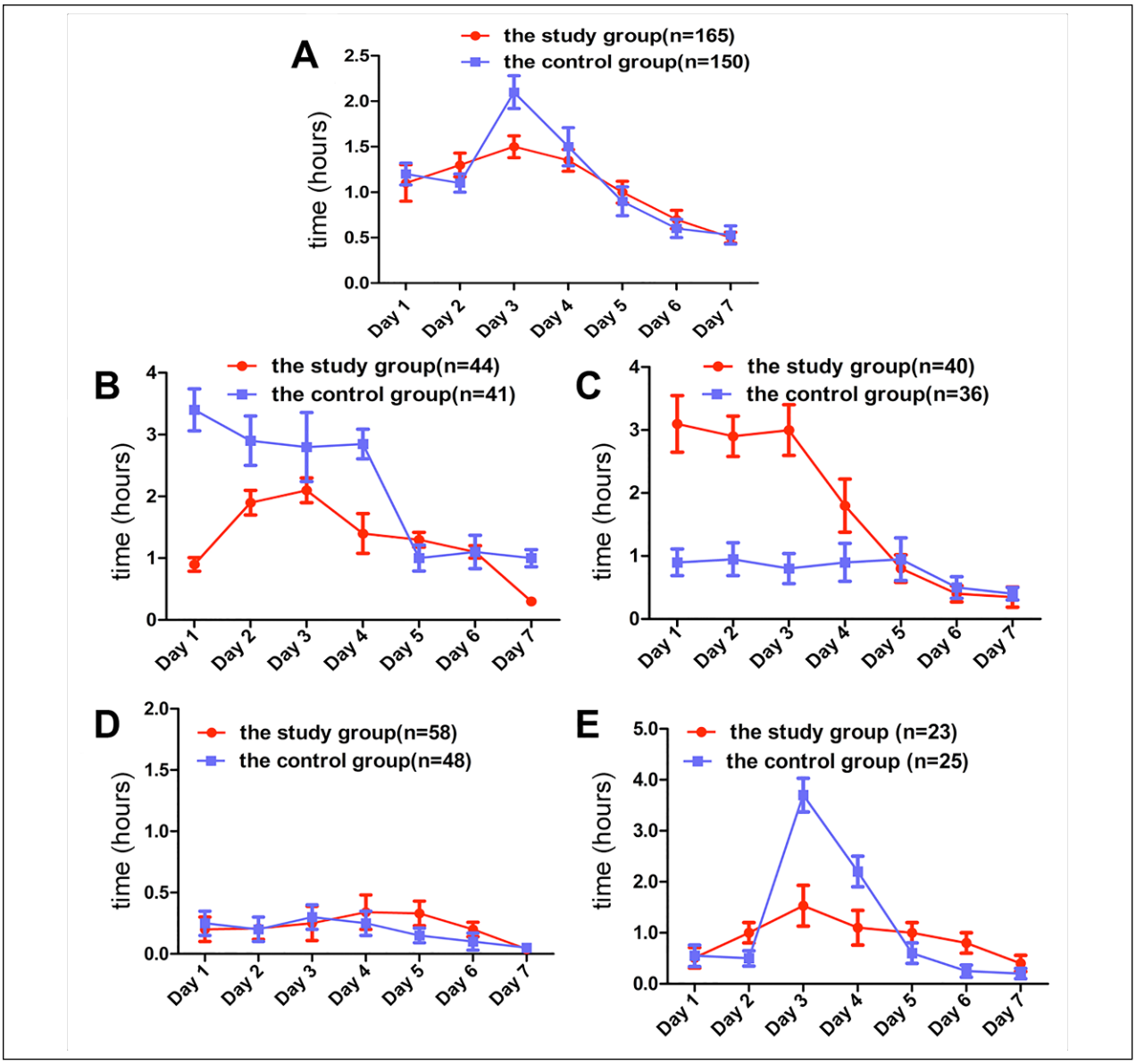

Figure 2. The mean duration of spasm in study group and control group. (A) The general comparison between the study group and control group; (B) paracentetic suprapubic cystostomy subgroup; (C) traditional suprapubic cystostomy subgroup; (D) urethral catheter subgroup; (E) former suprapubic cystostomy subgroup.

comparison of the daily and nightly frequencies of spasms among the four subgroups, a statistically significant difference was noted in the control group within 5 to 6 days. Therefore, it is reasonable to recommend that patients should start the solifenacin immediately within 6 days after surgery. Because urethroplasty does not have a large impact on gastrointestinal functions, the patients who underwent urethroplasty were instructed to take solifenacin 6 hr after the operation to alleviate the postoperative frequency of spasms.

Interestingly, our team observed that there was a significantly lower VAS score, mean duration of spasms, and incidence of spasms in those taking solifenacin in the paracentetic suprapubic cystostomy subgroup. No similar tendency was observed in the traditional suprapubic cystostomy subgroup in which patients experienced more serious surgical trauma. There are at least three possible explanations for this phenomenon. First, the catheter generally sits lower after paracentetic suprapubic cystostomy than after traditional suprapubic cystostomy, which results in a higher incidence of stimulation to the trigonal mucosa of the bladder in paracentetic suprapubic cystostomy patients. Second, the catheter in the paracentetic suprapubic cystostomy subgroup was longer than the

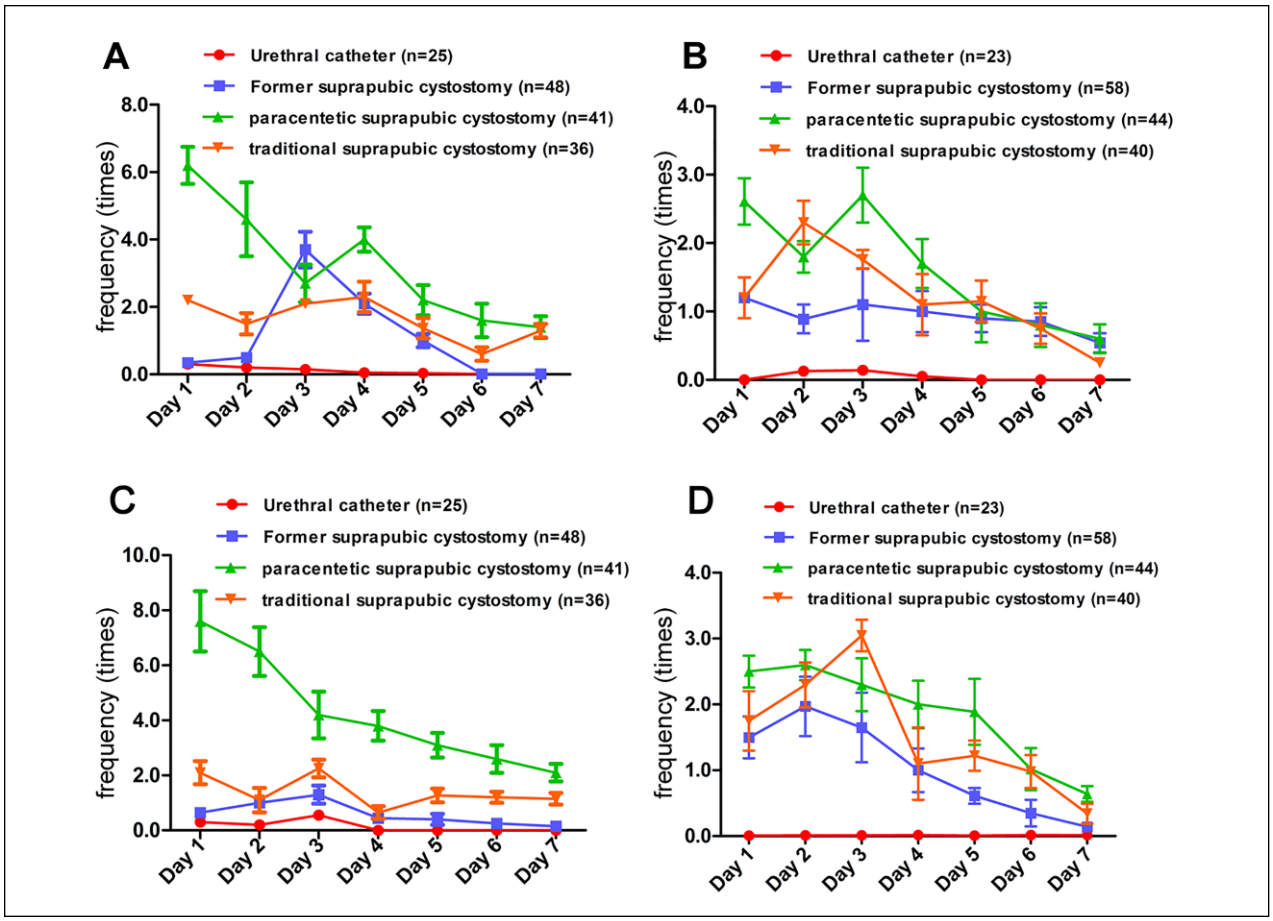

Figure 3. The daily frequency of spasm in study group and control group. (A) The comparison of daily frequency of spasm within four subgroups in control group; (B) the comparison of daily frequency of spasm within four subgroups in study group. The night frequency of spasm in study group and control group; (C) the comparison of night frequency of spasm within four subgroups in control group; (D) the comparison of night frequency of spasm within four subgroups in study group.

mushroom-shaped catheter in the traditional suprapubic cystostomy subgroup, which made it easier for the longer catheter to spiral in the bladder. When the patient changes position, the mushroom-shaped catheter may intermittently rub against the trigonal mucosa of the bladder, eventually leading to bladder spasms. Finally, in contrast to the traditional suprapubic cystostomy, paracentetic suprapubic cystostomy is a blind operation that is more likely to cause postoperative hemorrhage. The presence of blood clots within the bladder might be another cause of postoperative bladder spasms.

With regard to safety, in the study group, dry mouth occurred in 3.6% of the patients and constipation was reported by 7.8%. The incidence of dry mouth is similar to that in previous reports, while the incidence of constipation seems to be slightly higher. The different incidence of constipation might be due to the differences in the patients' diet, daily activity pattern, and surroundings after the operation. There did not appear to be any relationship with solifenacin itself. In the present study, the incidence of constipation in the study group was lower than that in the control group. Combined with previous reports (Haab, Cardozo, Chapple, Ridder, & Solifenacin Study, 2005; Zaitsu, Mikami, Ishida, & Takeuchi, 2011), the patients treated with solifenacin (12–52 weeks) had a significantly higher rate of dry mouth and constipation. Therefore, it could be concluded that patients undergoing urethroplasty can safely take solifenacin for a short-term period.

In the present study, all patients in the study group were treated with solifenacin (5 mg) once daily. However, Chapple, et al. (2004) reported that solifenacin at either 5 mg or 10 mg once daily was effective and well tolerated for treating symptomatic OAB. Further studies will be needed to assess the efficacy, safety, and tolerability of the difference doses of solifenacin. It may be useful to introduce tolterodine as a positive control group for comparisons of the efficacy and safety of treatment.

Admittedly, there are some limitations in this study. This study was unblinded for researchers and relied upon daily recordings that may have led to biased reporting. It also had a small number of participants in the urethral catheter subgroup which may have limited the ability to detect a significant difference.

Conclusion

In summary, the findings of this study demonstrated that short-term therapy with solifenacin is an effective and safe method for decreasing the frequency of bladder spasms after urethroplasty. Patients should start solifenacin immediately within 6 days after surgery. Patients undergoing paracentetic suprapubic cystostomy might be the only subset benefit from this treatment.

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Declaration of Conflicting Interests

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