

Efficacy of solifenacin in the prevention of short-term complications after laparoscopic radical prostatectomy

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Abstract

Objective: To evaluate the efficacy of solifenacin in the prevention of short-term complications after laparoscopic radical prostatectomy (LRP).

Methods: This randomized placebo-controlled study enrolled patients with histologically proven prostate cancer who underwent LRP. The patients were randomized to receive either solifenacin (5 mg once daily; study group) or placebo (control group) for the 15-day period beginning on the first day after surgery. The mean duration of detrusor overactivity (DO), the frequency of DO, the duration of macroscopic haematuria, and the days before catheter removal were recorded. The International Continence Society Short Form Male questionnaire, bladder neck stenosis episodes, and maximum urinary flow rate were evaluated at 1 month after surgery. The side-effects after using solifenacin were also recorded.

Results: A total of 120 patients were randomly assigned to the study group ($n = 62$) or the control group ($n = 58$). There were significantly lower rates of DO episodes during the daytime and night-time, haematuria and transient incontinence in the study group compared with the control group.

Conclusion: Solifenacin was a well-tolerated and effective treatment for the prevention of complications after LRP, with the main advantage compared with placebo being the decreased frequency of DO episodes during the daytime and night-time.

Keywords

Laparoscopic radical prostatectomy, complications, solifenacin

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Introduction

Prostate cancer (PCa) is a significant contributor to morbidity and mortality in males.¹ Although brachytherapy and radiotherapy have achieved much progress, laparoscopic radical prostatectomy (LRP) remains an appropriate method that is universally accepted, especially for localized PCa.² LRP is a challenging operation that demands a high level of surgical expertise and experience. The complications after LRP include urethrovesical anastomotic urinary leakage, urinary incontinence, haematuria, and bladder neck stenosis.³ Detrusor overactivity (DO) is defined by the International Continence Society as the urodynamic observation of involuntary detrusor contractions during the filling phase that can be spontaneous or provoked.⁴ The symptoms of DO usually present a few days or months after LRP.⁵ DO can appear with other complications and the end result would be a delay in healing time.⁶

Antimuscarinics are considered the first-line pharmacotherapy for DO.⁷ Solifenacin, a once-daily competitive muscarinic receptor antagonist has been found to improve DO symptoms, including incontinence, urgency, and frequency, with a low incidence of treatment-limiting adverse events.⁸ Solifenacin has been used in several trials post-radical prostatectomy,⁹⁻¹¹ but there is a lack of research for the application of solifenacin in cases of LRP. The main difference in this current study is that all of the patients had undergone laparoscopic procedures, rather than robotic or open procedures, for which there are few data. The objective of the present study was to evaluate the efficacy of solifenacin in the prevention of complications after LRP.

Patients and methods

Study participants

This randomized placebo-controlled study enrolled a consecutive series of patients with

histologically proven PCa who underwent LRP between March 2011 and October 2016 in the Department of Urology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China. The inclusion criteria included: (i) age <80 years old; (ii) transrectal prostatic biopsy; (iii) Gleason score ≤ 8 ; (iv) preoperative prostate-specific antigen <35 ng/ml; (v) no adjuvant radiotherapy; (vi) transrectal ultrasound; (vii) adenoma volume <80 ml; (viii) not taking medication that might affect bladder function. All of the patients had Clavien Classification of Surgical Complications grades between Grade I and Grade II.¹² Patients with a neurogenic bladder, history of constipation, drug allergy or any urethral, bladder neck, or prostatic surgery were excluded.

The patients were randomly assigned to the study or control group using a computer-generated randomization schedule that was prepared prior to the study commencement by a statistician not otherwise associated with the study. Patients in the study group were treated with solifenacin (5 mg VESicare®; Astellas GmbH, Munich, Germany; oral medication; once a day; for a 15-day period) beginning on the first day after surgery. Patients in the control group were treated with placebo (5 mg vitamin C) for the 15 days. The control and study medications were identical in appearance (white round tablets).

The Ethical Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital approved this study. All patients in this study provided written informed consent.

Study procedures

All procedures were performed under general anaesthesia by laparoscopy using the same approach of radical prostatectomy. The operations are extraperitoneal and antegrade excision. Each patient received a

drainage tube around the bladder and urethral anastomosis, and a 22 F triple lumen catheter was inserted into the bladder. The balloon was inflated within the bladder using the same volume of 15 ml isotonic sodium chloride. The drain was removed after 2 consecutive days of <30 ml output, in the absence of fever. Patients underwent the maximum uroflowmetry after catheter removal and all of the patients were examined by cystoscopy for confirmation at 1 month after surgery.

Study outcomes

The assessed study outcomes included the mean frequency of DO episodes during the day and night, the duration of macroscopic haematuria, the days until catheter removal, International Continence Society Short Form Male questionnaire at 2 weeks after catheter removal (ICSmale-SF),¹³ bladder neck stenosis episodes, and maximum urinary flow rate. A visual analogue scale (VAS) was used to measure the severity of bladder constriction. In addition to these outcomes, the side-effects after using solifenacin were also recorded.

Statistical analyses

All statistical analyses were performed using the SPSS[®] statistical package, version 12.0

(SPSS Inc., Chicago, IL, USA) for Windows[®]. The baseline characteristics and perioperative data were statistically analysed using Student's *t*-test and are presented as mean \pm SD. A two-tailed test was used to compare the postoperative adverse events. A *P*-value <0.05 was considered statistically significant.

Results

The present study enrolled 120 patients with a mean age of 71.3 years (age range, 64–79 years) who had histologically proven PCa and underwent LRP. The patients were randomly assigned to the study group (*n* = 62) or the control group (*n* = 58). The baseline characteristics and perioperative results are summarized in Table 1. The groups were homogenous for age, prostate volume, Gleason score, haemoglobin decrease, operative time and preoperative prostate-specific antigen levels.

All of the patients were followed-up for 1 month postoperatively and the complications were recorded. The frequency of DO during the daytime and night-time was significantly lower in patients in the study group between postoperative day (POD) 3 and POD 9 compared with the control group (*P* < 0.01 for all comparisons) (Figures 1a and 1b). On the first day after

Table 1. Baseline demographic and clinical characteristics and perioperative data for the male patients (*n* = 120) with histologically proven prostate cancer who participated in this study of the efficacy of solifenacin in the prevention of short-term complications following laparoscopic radical prostatectomy.

Characteristic	Study group <i>n</i> = 62	Control group <i>n</i> = 58
Age, years	67.8 \pm 9.1	68.4 \pm 8.7
Prostate volume, ml	52.6 \pm 12.5	56.7 \pm 14.8
Gleason score	6.4 \pm 2.1	6.2 \pm 1.9
Prostate-specific antigen, ng/ml	12.5 \pm 6.5	14.3 \pm 7.3
Operative time, min	220.3 \pm 21.6	202 \pm 26.5
Haemoglobin decrease, g/dl	1.8 \pm 0.9	1.7 \pm 1.1

Data presented as mean \pm SD.

No significant between-group differences (*P* \geq 0.05); Student's *t*-test.

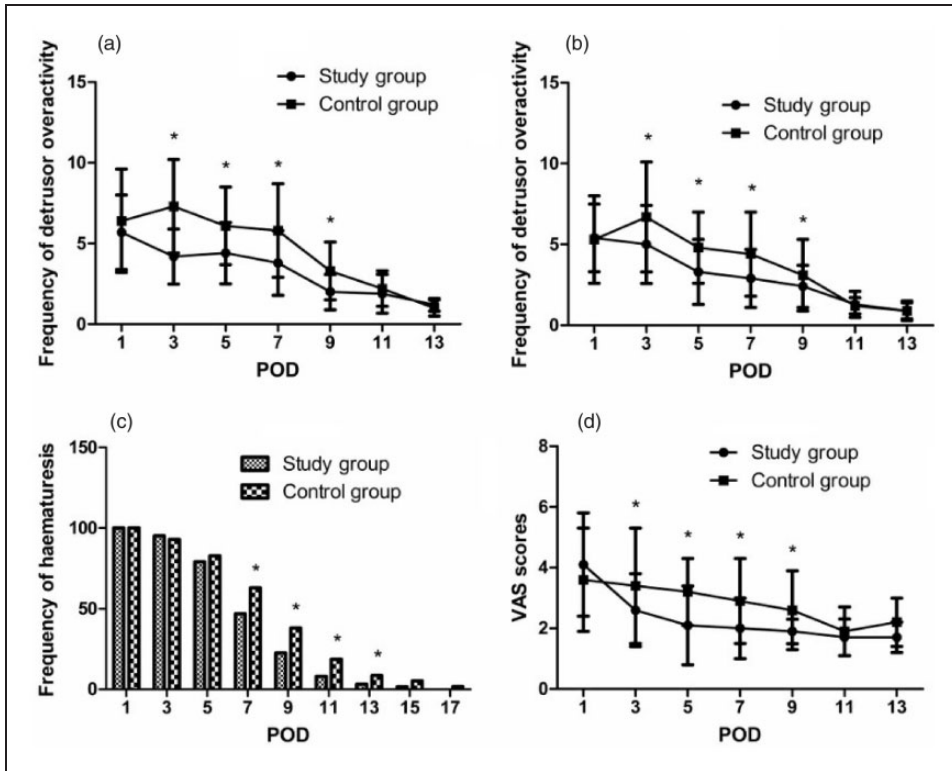


Figure 1. Comparison of data between the study group and the control group after surgery. The frequency of detrusor overactivity between the two groups during the daytime (a) and night-time (b) from postoperative day (POD) 1 to POD 13. The frequency of haematuria after surgery from POD 1 until all of the patients were without haematuria (c). Comparison of the visual analogue scale (VAS) scores between the study group and the control group from POD 1 to POD 13 (d). Data are presented as mean \pm SD. * $P < 0.05$ study group compared with the control group; Student's *t*-test.

surgery, DO was not significantly different between the two groups; and after POD 11, the frequency of DO gradually recovered similarly in the two groups.

The rate of haematuria in the study group was significantly lower than in the control group between POD 7 and POD 13 ($P < 0.01$ for all comparisons) (Figure 1c). All of the patients were discharged without haematuria; and the patient with the longest hospital stay was discharged on POD 18.

Two weeks after catheter removal, the total ICSmale-SF incontinence score was significantly lower in the study group compared with the control group ($P < 0.01$)

(Table 2); with significant differences being observed for the incontinence symptoms assessed by questions i2, i3 and i6 ($P < 0.01$ for all comparisons). There was no significant difference between the two groups in terms of voiding symptoms.

The mean number of days with an indwelling drainage tube and the number of days with an indwelling catheter were significantly lower in the study group compared with the control group ($P < 0.01$ for both comparisons) (Table 3).

The VAS test was conducted from the first day after surgery. The VAS score in the study group was significantly lower

Table 2. International Continence Society Short Form Male (ICSmale-SF) questionnaire results at 2 weeks after catheter removal for the male patients ($n = 120$) with histologically proven prostate cancer who participated in this study of the efficacy of solifenacin in the prevention of short-term complications following laparoscopic radical prostatectomy.

	Study group $n = 62$	Control group $n = 58$	Statistical significance ^a
ICSmale-SF – voiding symptoms			
Total score	6.3 ± 3.1	6.8 ± 2.8	NS
v1 score	1.2 ± 0.5	1.2 ± 0.4	NS
v2 score	0.8 ± 0.3	0.8 ± 0.2	NS
v3 score	1.8 ± 0.9	1.9 ± 0.7	NS
v4 score	0.2 ± 0.1	0.4 ± 0.1	NS
v5 score	2.3 ± 0.9	2.5 ± 1.4	NS
ICSmale-SF – incontinence symptoms			
Total score	6.8 ± 1.6	12.4 ± 2.3	$P < 0.01$
i1 score	1.9 ± 0.5	2.6 ± 1.1	NS
i2 score	1.0 ± 0.4	2.5 ± 1.2	$P < 0.01$
i3 score	1.1 ± 0.5	3.1 ± 0.7	$P < 0.01$
i4 score	1.8 ± 0.4	1.9 ± 0.6	NS
i5 score	0.5 ± 0.3	0.6 ± 0.3	NS
i6 score	0.5 ± 0.2	1.7 ± 0.9	$P < 0.01$

Data presented as mean \pm SD.

^aStudent's *t*-test.

NS, no significant between-group difference ($P \geq 0.05$).

Table 3. Postoperative data recorded at 1 month post-surgery for the male patients ($n = 120$) with histologically proven prostate cancer who participated in this study of the efficacy of solifenacin in the prevention of short-term complications following laparoscopic radical prostatectomy.

	Study group $n = 62$	Control group $n = 58$	Statistical significance ^a
Indwelling drainage tube, days	6.3 ± 2.1	8.6 ± 3.7	$P < 0.01$
Indwelling catheter, days	10.2 ± 2.6	12.7 ± 3.0	$P < 0.01$
Transient incontinence	13 (21.0)	23 (39.7)	$P = 0.03$
Bladder neck stenosis	2 (3.2)	7 (12.1)	NS
QMAX, ml/s	20.8 ± 7.9	18.7 ± 9.1	NS

Data presented as mean \pm SD of *n* of patients (%).

^aStudent's *t*-test.

QMAX, maximum flow rate; NS, no significant between-group difference ($P \geq 0.05$).

compared with the control group on POD 3, POD 5, POD 7 and POD 9 ($P < 0.05$ for all comparisons) (Figure 1d).

The 1-month postoperative data on patient bladder function are shown in Table 3. A total of 13 patients (21.0%) in

the study group and 23 patients (39.7%) in the control group complained of some degree of urinary incontinence ($P = 0.03$). There was no significant difference in the rate of bladder neck stenosis or maximum flow rate between the two groups.

Of the 62 patients in the study group, 12 patients (19.4%) experienced side-effects, including dry mouth (five [8.1%]), constipation (six [9.7%]), and blurred vision (one [1.6%]). Four of 58 patients (6.9%) in the control group had symptoms of constipation.

Discussion

Prostate-specific antigen has been widely used throughout the world as a marker for the diagnosis of PCa. Although the treatment of PCa has achieved great advances in recent decades, LRP is considered the gold standard treatment for localized PCa.¹⁴ Despite increasing understanding of the pelvic anatomy and recent developments in surgical techniques, many postoperative complications occur, such as urethrovesical anastomotic urinary leakage, urinary incontinence, haematuria and bladder neck stenosis.¹⁵ It was reported that the incidence of bladder neck stenosis was between 0.48% and 32%, the incidence of urethrovesical anastomotic urinary leakage was between 0.3% to 15.4%, and the incidence of urinary incontinence was from 6% to 0.8%–87.0%.^{16,17} DO is a characteristic symptom of bladder dysfunction after LRP, which emerges in most patients.¹⁸ Increasing detrusor contractions can induce anastomotic bleeding and urgency, which are associated with increases in other complications.¹⁹

Acetylcholine activates muscarinic receptors on detrusor myocytes and it is the main contractile transmitter.²⁰ Muscarinic receptors consist of five subtypes encoded by five distinct genes.²¹ The mRNAs for all of the muscarinic receptor subtypes have been detected in the human bladder.²² These receptors have been detected in the urothelium, interstitial cells, nerve fibres, and detrusor layers.²³ Detrusor smooth muscle contains muscarinic receptors, mainly of the M2 and M3 subtypes.²⁴ Although M2 receptors have the advantage of greater numbers, M3 receptors in the human detrusor are

believed to be the most important for detrusor contraction.²⁵ Furthermore, it was reported that M3 receptor expression was upregulated more than M2 receptor expression in patents with overactive bladder.²⁶ Solifenacin is an antimuscarinic drug that is approved worldwide at daily doses of 5 mg and 10 mg for the treatment of overactive bladder; and it effectively reduces DO, bothersome storage symptoms and lower urinary tract symptoms.²⁷ Solifenacin is an effective muscarinic receptor antagonist with selectivity for the M3 receptor in the urinary bladder.²⁸ Solifenacin has been widely applied clinically and there are several published studies about the therapeutic effects of solifenacin after radical prostatectomy, but there are some differences in the results for urinary incontinence.^{9–11}

Broad anatomical dissection around the prostate during surgery can disrupt afferent and efferent innervation of the trigone, neobladder neck and posterior urethra, causing outlet incompetence and partial denervation of the detrusor muscle.²⁹ Therefore, in addition to any preoperative pathological conditions, a substantial proportion of patients are subject to various postoperative abnormalities, including DO.³⁰ In the present study, the frequency of DO episodes was significantly lower in the study group compared with the control group during the daytime and night-time from POD 3 to POD 9. This result further confirms that solifenacin was an effective treatment for inhibiting DO. These current data showed that solifenacin was more effective between 3 days and 9 days after surgery, after which the study group showed no significant differences compared with the control group. In our opinion, this phenomenon was primarily due to the surgery, which causes anastomotic inflammation and stimulation of the bladder nervous system. Furthermore, a water-filled catheter can cause bladder irritation symptoms. As the inflammation settles and the catheter

is removed, the bladder stimulus subsides, which in turn decreases bladder irritability. Solifenacin could relax the bladder muscle at the outset by preventing the effects of acetylcholine. This 'silent bladder' could be beneficial to anastomosis healing, decreasing the time required for the vessels around bladder urethral anastomosis to close, thereby reducing the time of persistent leakage of urine or haematuria. It has been shown that the complications of bladder neck stenosis and incontinence are associated with the leakage of urine or haematuria.³¹ However, in this present study, the incidence of bladder neck stenosis exhibited no statistically significant difference regarding the proportion of cases between the two groups.

The ICSmale-SF was devised to evaluate the factors of voiding and incontinence symptoms.¹³ Unlike other questionnaires in the field, it has subscores for the domains of voiding and incontinence, including symptoms as well as separate considerations of frequency, nocturia and impact on daily life.¹³ In the present study, the patients using solifenacin had a significantly lower total score for the ICSmale-SF incontinence symptoms compared with the control group; in particular, for questions i2 (Does urine leak before you can get to the toilet?), i3 (Does urine leak when you cough or sneeze?) and i6 (How often have you had a slight wetting of your pants a few minutes after you had finished urinating and had dressed yourself?). Furthermore, the transient incontinence rate was significantly lower at 1 month after surgery in the study group compared with the control group. These current data demonstrate that solifenacin improved continence after LRP, possibly by reducing postoperative damage to the urethral sphincter by controlling DO.

Previous studies have shown that DO almost always occurs following lower urinary tract surgery, especially with surgical times exceeding 25 minutes.³² Furthermore, indwelling catheters have been correlated

with DO, so after LRP, DO is likely to occur.³² DO not only influences the patient's body state, but it also induces the leakage of urine, and the extravasation of urine can promote scarring the around urethrovesical anastomosis.³³ Early catheter removal has been considered an optimal method for avoiding DO.³⁴ In this current study, the indwelling catheter remained in place until haematuria and urinary leakage has ceased. Furthermore, it was left in place for a minimum of 1 week to ensure adequate anastomotic healing. Many types of medicines can relieve DO, such as nonsteroidal anti-inflammatory drugs and opioids, but these medicines are all limited by their short duration of action or adverse effects.³⁵ Solifenacin is believed to have a longer duration of action and fewer side-effects compared with nonsteroidal anti-inflammatory drugs and opioids.³⁶ Dry mouth, constipation, headache, and blurred vision are generally the most frequently reported adverse events among patients treated with solifenacin.²⁰ In the present study, the incidence of these adverse events was in agreement with those previously reported,³⁷ further illustrating that solifenacin is a well-tolerated choice for the treatment of DO.

In this present study, all of the patients in the study group received 5 mg/day solifenacin, but in previously published literature, both 5 mg/day and 10 mg/day were shown to produce very good effects.³⁸ Future research will be required to explore the most appropriate dosage for the treatment of DO following LRP. Although this study was not a double-blind trial, which results in a low level of evidence, the 1-month follow-up results were still encouraging. Future well-designed, double-blind trials with extended follow-up and larger sample sizes will be needed to better define the role of solifenacin in the prevention of short-term complications after LRP.

In conclusion, this preliminary study showed that solifenacin was a well-tolerated

and effective treatment for the prevention of complications after LRP. Compared with placebo, the main advantage of solifenacin was the decreased frequency of DO episodes during the daytime and night-time. This present study showed that this was associated with a reduction in haematuria, urinary leakage and transient incontinence, which might help patients to recover more quickly.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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