



Does sildenafil enhance the effect of tamsulosin in relieving acute urinary retention?

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ABSTRACT

Objective: To compare the safety and efficacy of combined therapy using sildenafil and tamsulosin for management of acute urinary retention (AUR) with tamsulosin alone in patients with benign prostate hyperplasia (BPH).

Materials and Methods: 101 patients were enrolled in a randomized placebo-controlled study from June 2009 to April 2012. Patients presenting with an initial episode of spontaneous AUR underwent urethral catheterization and then prospectively randomized to receive tamsulosin 0.4mg plus sildenafil 50mg in group A and tamsulosin 0.4mg plus placebo in group B for three days. Urethral catheter was removed three days after medical treatment and patient's ability to void assessed at the day after catheter removal and seven days later. Patients who voided successfully were followed at least for three months.

Results: Mean age of patients was 59.64 ± 3.84 years in group A and 60.56 ± 4.12 years in group B (p value = 0.92). Mean prostate volume and mean residual urine were comparable between both groups (p value = 0.74 and 0.42, respectively). Fifteen patients in group A (success rate: 70%) and nineteen patients in group B (success rate: 62.7%) had failed trial without catheter (TWOC) at 7th day following AUR (p value = 0.3). No significant difference was noted between both groups regarding the rate of repeated AUR at one month and three month follow-up period (p = 0.07 and p = 0.45, respectively).

Conclusion: It seems that combination therapy by using 5-phosphodiesterase inhibitor and tamsulosin has no significant advantages to improve urinary retention versus tamsulosin alone.

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INTRODUCTION

Acute urinary retention (AUR) is one of the most important complications following benign prostate hyperplasia (BPH) that may lead to prostate surgery (1). Previous reports revealed that dynamic factors in bladder outlet have significant role in occurrence of AUR; thus α -blocker agents

such as tamsulosin or alfuzosin-SR are administered as the mainstay treatment after catheterization and significantly reduce the need for prostate surgery (2-4).

There are some evidences about association between lower urinary tract symptoms (LUTS) and erectile dysfunction (5,6). Some previous studies confirmed that combination therapy with

5-phosphodiesterase inhibitors and α -adrenergic blockers resulted in significant improvement of LUTS (7-9). Recently, a meta-analysis of the cross sectional data from twelve articles depicted that 5-phosphodiesterase inhibitors can significantly improve LUTS secondary to BPH in patients with or without erectile dysfunction (10) but there is no obvious data about the role of 5-phosphodiesterase inhibitors in AUR when administered as combination therapy with α -blocker agents.

This randomized placebo-controlled study was conducted to evaluate the safety and efficacy of tamsulosin and sildenafil versus tamsulosin alone in patients presenting with an initial episode of AUR due to BPH.

MATERIALS AND METHODS

Patients younger than 65 years old presenting with an initial episode of spontaneous AUR secondary to BPH were included in this study. Written informed consent was obtained from all patients. Patients with history of urethral stricture, previous urologic surgeries, chronic renal failure, diabetes mellitus, bladder or prostate cancer, prolonged constipation, active urinary tract infection (fever and flank pain and/or nausea and vomiting), gross hematuria, nitrate consumption, addiction to opium and alcohol and residual urine greater than 1000mL were excluded from this study. Likewise, patients with previous use of α -blocker and 5 α -reductase inhibitor were excluded.

Patients were divided into two groups according to a randomized study to assess the safety and efficacy of tamsulosin 0.4mg and sildenafil 50mg versus tamsulosin 0.4mg and placebo in improving the AUR.

We conducted this randomized study on 110 patients (55 men in each group) from June 2009 to March 2012. Patients presenting with an initial episode of spontaneous AUR underwent urethral catheterization and then prospectively randomized to receive tamsulosin 0.4mg plus sildenafil 50mg in group A and tamsulosin 0.4mg plus placebo in group B for three days. No antibiotics were administered to the patients. Urethral catheter was removed three days after medical treatment and patient's ability to void was assessed

at the day after catheter removal and seven days later. The patients who voided successfully were followed at least for three months, while receiving administered medicine (combination therapy vs. monotherapy) unless another episode of AUR occur.

Prostate volume was measured by transrectal ultrasonography. Urinary retention that was refractory to medical therapy was considered an indication for surgical intervention. We had no detailed information about urodynamic parameters of patients because they had not followed their lower urinary tract symptoms previously.

Statistical analysis was performed by SPSS-19 software (Statistical Package for the Social Sciences). Baseline characteristics were compared using t-test and chi-square and Fisher exact tests. TWOC were compared using ANOVA test. $P < 0.05$ was considered as the critical point for significant results.

RESULTS

Two patients in group A and one patient in group B were lost during follow-up and were excluded from analysis. Three patients in group A due to blurred vision and vertigo and three patients in group B due to headache and orthostatic hypotension withdrew from the study. Thus, statistical analysis was done on 50 cases in group A and 51 cases in group B.

Mean age of patients was 59.64 ± 3.84 years in group A and 60.56 ± 4.12 years in group B (p value = 0.92). Mean prostate volume in group A and B was 54.86 ± 19.21 and 52.66 ± 15.48 , respectively (p value = 0.74). Mean residual urine at initial presentation was 717.77 ± 129.75 cc in group A and 738.54 ± 120.83 in group B (p value = 0.42).

Forty one cases (82%) in group A and thirty seven cases (72.5%) in group B had successful trial without catheter (TWOC) after catheter removal during 24 hours after catheter removal. Successful rate of TWOC was significantly better in tamsulosin plus sildenafil group versus tamsulosin at this period (p value = 0.039).

At seven days after catheter removal, six new cases in group A and five new cases in group B had failed TWOC. Thus totally 15 patients in

group A and 19 patients in group B experienced repeated urinary catheterization.

Our findings at early period (after one week) after AUR revealed 70% (35/50) success rate of combination therapy in group A and 62.7% (32/51) success rate of monotherapy in group B. Even though, difference in success rate between these two groups was 8% this difference was not statistically significant (p value = 0.3).

Of 35 patients with successful TWOC in group A, three cases (3/35) at one month follow-up and 6 cases (6/32) at three month follow-up experienced repeated urinary retention. Of 32 cases with successful TWOC in group B, failure of spontaneous voiding was noted in four cases (4/32) at one month follow-up and four other cases (4/28) at three month follow-up. Analysis of these findings revealed no significant difference between groups A and B regarding repeated AUR at one month and three month follow-up period (p = 0.07 and p = 0.45, respectively). These results are listed in Table-1.

We found no significant difference regarding to mean prostate volume and successful or failed TWOC after three months of follow-up. Mean prostate volume in successfully TWOC group and failed TWOC group was 51.53 and 57.35, respectively (P = 0.647).

DISCUSSION

Forty three percent (43%) of men in their life experience LUTS secondary to BPH (11). Obstructive and/or irritative urinary symptoms may be progressed and resulted in occurrence of some adverse events such as renal failure, gross hematu-

ria, bladder stone, urinary tract infection and acute urinary retention (12). Anyone can experience urinary retention, but it is most common in men (15% of men) in their fifties and sixties because of prostate enlargement (1). Painful overdistention of bladder due to bladder outlet obstruction (BOO) mandates emergent urethral catheterization. Following insertion of urethral catheter, medical treatment should be initiated and after a few days, the catheter is removed in order to attempt a trial of voiding without a catheter.

Different protocols of medical therapy have been recommended in the recent years for management of LUTS using different agents including alpha blockers, 5-alpha reductase inhibitors, phytotherapeutic agents, anti-muscarinic drugs and 5-phosphodiesterase inhibitors (13). Alpha adrenergic blockers are the mainstay for treatment of urinary symptoms secondary to BPH. Tamsulosin and alfuzosin SR have high affinity to alpha-1a receptor and do not require dose titration; so these agents are reasonable initial option for managing AUR (14). McNeill et al. revealed that alfuzosin 10mg once daily increases the successful TWOC in men with an initial episode of spontaneous AUR and recommended that this long-acting alpha blocker should be continued after the acute phase (3).

Previous studies evaluated the safety and efficacy of monotherapy with alpha blocker alone versus combination therapy using alpha blocker and 5-alpha reductase inhibitors or anti-muscarinic drugs or 5-phosphodiesterase inhibitors. Medical therapy of prostatic symptoms (MTOPS) study indicated that long-term use of combination therapy with doxazosin and finasteride has significantly greater decrease in LUTS and lowering the rate of

Table 1 - Three month follow-up period of patients after the first episode of spontaneous AUR.

Patients with successful TWOC	Combination therapy	Monotherapy	P value
During 24 hours after catheter removal	(41/50) 82%	(37/51) 72.5%	0.039
7th day after catheter removal	(35/50) 70%	(32/51) 62.7%	0.3
One month following first episode of AUR	(32/50) 64%	(28/51) 55%	0.07
Three months following first episode of AUR	(26/50) 52%	(24/51) 47%	0.45

clinical progression comparing to monotherapy with either drug alone (15). Another study confirmed the aforementioned findings of MTOPS study and revealed that combination therapy of tamsulosin and dutasteride reduced significantly the international prostate symptom score (IPSS) especially in patients with moderate to severe symptoms when compared with monotherapy (16). Likewise, antimuscarinic agents may be useful in combination therapy with alpha blocker in patients with symptoms of BOO and detrusor overactivity without concerns of AUR (17).

LUTS have two components including static and dynamic. Static component is related to the enlargement of prostate and dynamic element comes from contraction of smooth muscle of the prostate. AUR mainly occurs from dynamic component of prostate hyperplasia (18). In addition to corpus cavernosum, there is high expression of PDE-5 mRNA in the bladder and urethra and also a substantial gene expression of PDE-5 has been found in prostate tissue and its smooth muscle (19). Urkert et al. revealed the presence of PDE-5 (cGMP-PDE) mainly in glandular and periglandular areas in transition zone (20). Age-related changes in the nervous system and neuroregulatory factors such as nitric oxide (NO) and RhoA/Rho-kinase may contribute to the pathogenesis of LUTS due to BPH and erectile dysfunction (6). Previous study by Stothers et al. showed that NO may improve LUTS by reducing the smooth muscle tone of the prostate and relaxing the urethra (21). Theoretically, inhibition of 5-phosphodiesterase resulted in increasing of cyclic guanosine mono-phosphate (cGMP). Following accumulation of cGMP, hyperpolarization, rapid drop in intracytoplasmic calcium and finally relaxation of smooth muscle will happen (22,23). In vitro study showed that sildenafil inhibits the growth of prostatic smooth muscle cells (24). Inhibition of PDE-5 in the prostate may have a positive impact on dynamic component of LUTS by decreasing sympathetic tone (7). These findings are in favor of the hypothesis for the use of PDE inhibitors in the pharmacotherapy of LUTS and AUR secondary to BPH. Recently, Angulo et al. described that while tadalafil enhances the effects of sodium nitroprusside induced relaxation and accumulation

of cGMP, combination of tadalafil and tamsulosin resulted in greater decrease in neurogenic contractions of human bladder neck and peripheral prostate (25). According to the aforementioned findings, it seems that PDE-5 inhibitor might act on smooth muscle tone, but cannot influence the bulking effect of the enlarged prostate.

Gacci and their colleagues compared the adverse events and efficacy of tamsulosin 0.4mg/day and vardenafil 10mg/day versus tamsulosin 0.4mg/day alone in reducing LUTS due to BPH in a 12 week follow-up. They concluded that patients in combination therapy group experienced no serious adverse events and this regimen was significantly more effective than tamsulosin alone in improving urinary symptoms (9). Another randomized parallel placebo controlled clinical trial confirmed that tadalafil or tamsulosin has significant and numerically similar effects on improvement of LUTS when comparing to placebo. Even though, only tadalafil was effective in patients with LUTS and erectile dysfunction (26). There are some previous reports regarding the safety and efficacy of sildenafil (25 or 50mg/day) in decreasing of IPSS as monotherapy or in combination with alpha blocker (7-9). A recent systematic review of the prospective and cross sectional studies on 3214 patients suggested that 5-phosphodiesterase inhibitors can significantly improve obstructive urinary symptoms secondary to BPH (10).

There are paradoxical reports regarding the impact of 5-phosphodiesterase inhibitors on maximum urinary flow rate (Q_{max}). Sairam et al. described that inhibition of 5-phosphodiesterase enzyme may increase the urinary flow rate by decreasing the smooth muscle tone of the prostate (27) but Madani et al. indicated that tadalafil improves quality of life and obstructive urinary symptoms (mean 4 scores drop after treatment) but has no significant effect on Q_{max} (28).

There is no clinical study regarding the assessment of efficacy of 5-phosphodiesterase inhibitors as monotherapy or in combination with other agents on AUR following BPH. An interesting double blind placebo controlled crossover study by Datta et al. on 20 women with complete retention or obstructed voiding showed no significant clinical improvement in this group of pa-

tients who had received sildenafil when compared with placebo (29). Some confounding factors that may have influenced the pure effect of 5-phosphodiesterase inhibitor in AUR secondary to BOO were excluded and finally our findings revealed that combination therapy with sildenafil and tamsulosin in patients with AUR has no significant advantages versus monotherapy with tamsulosin in improving retention.

The aim of this study was to assess the efficacy of 5-phosphodiesterase inhibitor as an additive agent to alpha blocker for management of AUR and no voiding diary or IPSS were recorded during follow-up period (early and short-term) and maybe this is the main limitation of our study.

CONCLUSIONS

It seems that combined therapy with 5-phosphodiesterase inhibitor and alpha-blocker has no significant synergistic effects in relieving acute urinary retention when compared with alpha blocker alone in early phase and in a short-term follow-up. Even though no significant side effects were noted, the administration of this agent has some limitations regarding the interference of 5-phosphodiesterase inhibitor with some co-morbidities in older patients with AUR.

CONFLICT OF INTEREST

None declared.

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