

Alfuzosin 10 mg once daily in the management of acute urinary retention of benign prostatic hyperplasia

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Background: Acute urinary retention is regarded as the most serious hazard of untreated benign prostatic hyperplasia. α -blockers is frequently used for acute urinary retention as it is proved to be of value for successful trial without catheter after acute urinary retention and to decrease the need for benign prostatic hyperplasia related surgery. **Objectives:** To evaluate the significance of alfuzosin 10 mg once daily for successful trial without catheter in patients with acute urinary retention and long-term management. **Methods:** Total of 245 enrolled acute urinary retention patients were catheterized and randomized to either alfuzosin 10 mg once daily or placebo for 3 days (first phase), all the failed patients extend their treatment for another 3 days for a second trial without catheter (second phase). The successful patients from both phases were re-randomized for alfuzosin 10 mg once daily or placebo for 12 months, the outcomes were the recurrence of acute urinary retention or the need for surgery (third phase). **Results:** In the first phase alfuzosin have significant value for successful trial without catheter compared with placebo (62.3 vs 32.7%; $p = 0.0001$), in the second phase still of significance in comparison to placebo (32.6 versus 9.5%; $p = 0.002$) while In the third phase, alfuzosin compared with placebo was of statistical significance regarding reducing the recurrence of acute urinary retention only in the first month (1.8 vs 11.3%; $p = 0.04$) and the third month (3.7 vs 16.9%; $p = 0.02$), also regarding the need for surgery (3.7 vs 15.0%; $p = 0.04$) and (7.4 vs 20.7%; $p = 0.04$), respectively. This corresponds to risk reduction of surgery in alfuzosin group of 76% in the first month and 65% in the third month. **Conclusion:** Alfuzosin 10 mg once daily is of value for successful trial without catheter after acute urinary retention and a second trial of voiding in failed first trial is recommended. It reduced the recurrence of acute urinary retention and the need of related surgery especially during first three months of treatment.

Benign prostatic hyperplasia (BPH) is a common disease process which affects an increasing percentage of men as they age, and although it is not a life threatening disease, some patients may have a progression which can be defined by a deterioration in symptoms and health-related quality of life or unfavorable outcomes, such as acute urinary retention (AUR) and BPH-related surgery [1]. A greater risk of progression is associated with certain baseline parameters, such as higher symptoms score, older age, increased prostatic-specific antigen (PSA) and prostatic volume, and reduced maximum flow rate [2,3]. The incidence of AUR in clinical trials of BPH is variable and account for 6–18.3% of overall progression events with accumulative incidence of 2–2.7% [4], and the deterioration in symptoms is the most prevalent progression event in these studies [5].

AUR is considered to be the most serious complication of BPH [6] and even an episode of AUR have a measurable impact on patient health-related quality of life [7].

AUR is treated by catheterization for few days and in most of old studies it was an absolute indication for prostatectomy [8], as it is account for 25–30% of emergency transurethral resection of prostate (TURP) [9,10]. It is found that the prostatectomy performed for AUR is associated with increased risk of intra and postoperative complications, hospital death, and slightly worse outcome than elective prostatectomy [11]. This strongly encourages urologists to advice trial with out catheterization (TWOC), as it succeeds in 23–25% without concomitant medical treatment [12,13] but predicting who will successfully void is not easy. Half of men who initially void successfully will experience recurrent AUR, within a week, 68% will experience a second episode within a year and recurrence is 90% if the initial peak urinary flow rate of less than 5 ml/s [14].

By reducing the bladder outlet resistance through the inhibition of symphatic tone in the bladder neck and prostatic stroma, α -blockers

Keywords: acute urinary retention, alfuzosin, benign prostatic hyperplasia, trial without catheter

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can help relieve AUR and improve the chances of successful TWOC [15]. Early trials used small numbers of patients and various types and formulations of α blockers proved their significance for successful TWOC in comparison to placebo [16,17]. Once-daily formulation of alfuzosin 10 mg (uroselective long acting α -1 blocker) with no dose titration and low incidence of adverse effects was proved to be effective and safe in the treatment of clinical BPH [18] and even to prevent the overall clinical progression of BPH [19].

The largest double-blind, placebo-controlled study (ALFAUR) showed that alfuzosin 10 mg once daily is of significance for successful TWOC and for short- and medium-term (6 months) clinical effectiveness in the management of AUR related to BPH [20].

The present study is designed to investigate the value of alfuzosin 10 mg once daily for successful TWOC, a second TWOC in failed first trial and long-term (1-year) effect in reducing recurrent AUR and BPH-related surgery.

Patients & methods

Since January 2005, and for 6 months then after, cases of first episode spontaneous AUR related to BPH were enrolled in our study (randomized, double-blind, placebo controlled). A written consent was signed by most of enrolled patients. Cases of precipitated AUR or AUR related other than BPH were excluded (e.g., postoperative, drugs precipitated, neurogenic causes, prostatic cancer, vesical stones, urethral stricture, any history of lower urinary tract surgery). All patients were subjected to digital rectal examination (DRE), abdominal ultrasound and serum creatinine (to exclude cases with absolute indications for surgery). Our study of three phases.

Phase I

All those enrolled patients were catheterized at arrival, (urine volume 500–1500 ml only included), and then divided randomly into two groups in 1:1 ratio, to receive either Alfuzosin 10 mg once daily, or placebo for 3 days, TOWC is done after, if succeed then enter Phase III and if failed enter the Phase II.

Phase II

Patients with failure of TWOC in Phase I were re-catheterized, and then extension of their same drug prescriptions (alfuzosin or placebo) for another 3 days, then a second TOWC was done.

All successful voided patients (from both trials) are subjected for Phase III and all failed TWOC patients were excluded from our study. The successful TWOC patients: who can void within 24 h after catheter removal with characters of (flow rate is more than 5 ml/s, voided volume more than 100 ml and residual volume less than 200 ml), these parameters are regarded by many investigators as there is no international definite outcome for the success of TWOC.

Urine culture (catheter aspiration sample) was done for the majority of patients at first catheterization in the first phase (baseline results), and after the first or second TWOC (voided sample) in successful voided patients to detect if there any increasing risk of bacteriuria account for catheterization in the first or the second phase. Culture is considered positive or of significance in catheter aspiration sample if a single recovered organism has more than 10,000 colony-forming unites (CFU)/ml, and more than 100,000 CFU/ml in voided urine sample.

Phase III

The successful TWOC patients were re-randomized in 1:1 ratio to take either alfuzosin 10 mg once daily or placebo for one year, to be evaluated after (1, 3, 6, 9 and 12 months), mainly through assessment of International Prostatic Symptoms Score (IPSS) and Bother Score (as the eighth question of IPSS), serum sample for PSA was taken mainly at the visit of first month, the outcomes of our study are any recurrent attack of AUR, and BPH-related surgery.

Statistical comparisons between alfuzosin and placebo were made using (χ -square) for the results of TWOC, for the recurrence of AUR, and for the need for surgery. While IPSS and bother score were compared using a (*t* test).

Alfuzosin 10 mg once daily used in our study is a product of Synofi-Synthelabo company.

The results

A total of 245 patients with primary spontaneous AUR from BPH were enrolled in our study, were catheterized at emergency unit (91% by transurethral catheter and 9% by suprapubic catheter when it was difficult to be inserted transurethrally) and randomized, 125 patients took alfuzosin 10 mg once daily for 3 days and 120 patients took placebo for the same period. All patients sent home (except 14 patients, 5.7%) where admitted over night to complete their investigations).

Phase I

After completing 3 days of treatment, 21 patients were lost (11 from alfuzosin and 10 from placebo group). a TWOC was done for the remained 224 patients (114 alfuzosin group and 110 placebo group) and the results showed that alfuzosin increases significantly the rate of successful voiding compared with placebo (71/114, 62.3% vs 36/110, 32.7%; $p = 0.0001$), as in Table 1.

Phase II

All the failed voided patients 117 (43 patients from alfuzosin group and 74 patients from placebo group) entered the second phase, were re-catheterized and extend their same treatment either alfuzosin or placebo for another 3 days. A second TWOC was done and it was also significantly more successful in alfuzosin treated patients in comparison to placebo (14/43, 32.6% vs 7/74, 9.5%; $p = 0.002$). So in total of the two phases the successful voiding was significantly more in alfuzosin group than placebo (85/114, 74.6% vs 43/110, 39.1%; $p = 0.0001$) as in Table 1.

Positive culture were found in 19/224 patients (8.4%) at presentation, in 13/107 (12.1%) after first TWOC and in 4/21 (19%) after the second TWOC, so there is no statistical significance ($p > 0.05$) of increase incidence of bacteruria between the baseline, first, and the second TWOC patients.

Phase III

All the failed patients (96 patients) were excluded from our study and all the successful patients (128 patients) entered Phase III. Those successful patients were re-randomized to take either alfuzosin 10 mg once daily or placebo (64 patients for each group) for one year and we continued their follow up after 1, 3, 6, 9, 12 months looking for the recurrence of AUR or the need for BPH-related surgery. A total of 10 patients

were lost during the follow up period (four from alfuzosin and six from placebo group). Withdrawals because of noncompliance or drugs side effects were in 11 patients (six from alfuzosin and five from placebo group). So the net patients for our statistics were 54 for alfuzosin group and 53 for placebo group.

Regarding the recurrence of AUR, our study shows that alfuzosin have statistical significance in reducing its recurrence compared with placebo especially during the first month (1/54, 1.8% vs 6/53, 11.3%; $p < 0.05$) and the third month (2/54, 3.7% vs 9/53; 16.9%, $p < 0.05$) and it is not of statistical significance at 6, 9, 12 months, as in Table 2.

For BPH-related surgery, our results confirmed that alfuzosin treatment is of value in reducing its need in comparison to placebo and this is statistically significant at the first month (2/54, 3.7% vs 8/53, 15.0 %; $p < 0.05$) and at the third month (4/54, 7.4% vs 11/53, 20%; $p < 0.05$) and of no statistical significance at 6, 9, 12 months. Cumulatively over 12 month's period of treatment the need for BPH-related surgery is reduced in alfuzosin treated patients in comparison to placebo (8/54, 14.8% vs 12/53, 22.6%; $p = 0.29$) as in Table 3.

The main indication for surgery was the recurrence of AUR 12/20 (60%), and non compliance or nonsatisfaction from the treatment in the remaining patients 8/12 (40%).

So our results showed that there is significant risk reduction in alfuzosin treated patients regarding AUR specially at 1st and 3rd month (85 and 78%, respectively) and BPH-related surgery (76 and 65%, respectively) as in Figure 1.

There is significant difference in the time when the events of the third phase occurred between alfuzosin and placebo, especially during the first 3 months of treatment, regarding AUR (9/10 patients, 90% in placebo group while only 2/6 patients, 33.3% in alfuzosin group), for BPH-related surgery (11/12 patients, 91% in

Table 1. The success and failure rates after the first and the second trial without catheterization in alfuzpsin and placebo groups.

	Alfuzosin (n = 114)		Placebo (n = 110)		χ^2 ; p-value
	Success	Failure	Success	Failure	
First phase	71 (62.3%)	43 (37.3%)	36 (32.7%)	74 (67.3%)	19.60; 0.0001*
Second phase	14 (32.6%)	29 (67.4%)	7 (9.5%)	67 (90.5%)	9.85; 0.002*
Cumulative	85 (74.6%)	29 (25.4%)	43 (39.1%)	67 (60.9%)	28.76; 0.0001*

*Significant p-value

Table 2. The cumulative incidence of recurrent acute urinary retention in 12 months treatment of alfuzosin and placebo groups.

Duration in months	Alfuzosin (n = 54)		Placebo (n = 53)		χ^2 ; p-value
	Cumulative n	%	Cumulative n	%	
1	1	1.8	6	11.3	3.92, 0.04*
3	2	3.7	9	16.9	5.11, 0.02*
6	5	9.2	10	18.8	2.05, 0.15
9	6	11.1	10	18.8	1.70, 0.26
12	6	11.1	10	18.8	1.70, 0.26

*Significant p-value.

placebo group while only 4/8 patients, 50% in alfuzosin group) and this is of clinical value for alfuzosin as it succeed either to prevent or to delay most of the serious events more than 3 months.

There was no significant statistical difference ($p > 0.05$) in long-term effects between the successful voided patients from the first and the second TWOC regarding the recurrence of AUR (4/6 and 2/6 patients, respectively) and for BPH-related surgery (4/8 and 4/8 patients, respectively).

The mean age of our study populations were 69 ± 2 years, mean PSA was 2.2 ± 0.4 ng/dl, and mean prostatic volume was 65 ± 10 ml. The mean parameters of successful voided patients compared with non successful patients in alfuzosin group regarding the age (69 ± 2 years versus 61 ± 2 years), PSA (1.9 ± 0.3 ng/dl versus 1.2 ± 0.2 ng/d) and for prostatic size (60 ± 10 ml versus 40 ± 10 ml) and this give an idea that the alfuzosin is effective in increasing the successful voiding trials in high risk group of patients for failed TWOC (age >6 years, PSA >1.5 ng/dl, prostatic size >40 mg).

The international prostatic symptoms score (IPSS) was estimated at each visit and it is found that alfuzosin is effective in keeping the patients

in significantly less score ($p = 0.0001$) compared with placebo all over the duration of follow up (12 months), as in Figure 2. Alfuzosin was also successful in reducing the bother score compared with placebo all over 12 months of treatment (Mean: 1.66 ± 0.5 vs 2.27 ± 0.5 ; $p = 0.0001$).

Alfuzosin was well tolerated, as the number of withdrawals is similar with that of placebo (six and five patients, respectively). In alfuzosin group 23 patients (42.5%) and in placebo group 21 patients (39.6%) experienced at least one side effect. Dizziness was the most significant side effect in alfuzosin treated patients and tolerance developed after few days of treatment in the majority of complained patients, as in Table 4.

Discussion

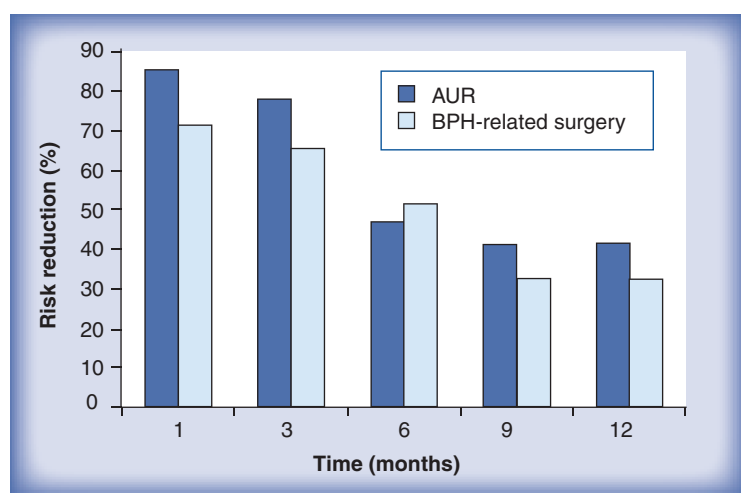
AUR is an important and common public health issue in aging men as it is estimated that more than 1 in 10 men in their 70s will experience AUR within the next 5 years [21], and it is regarded by the patients as the most serious hazard of untreated BPH [22]. AUR was the most important indication for prostatic surgery but after establishing the medical treatment of prostate, the number of patients having surgery for BPH has decreased by 60% over the last decade [23]. α -blockers are the main stay of medical

Table 3. The cumulative need for benign prostatic hyperplasia-related surgery in 12 months treatment of alfuzosin and placebo groups.

Duration in months	Alfuzosin (n = 54)		Placebo (n = 53)		χ^2 ; p-value
	Cumulative n	%	Cumulative n	%	
1	2	3.7	8	15.0	4.11, 0.04*
3	4	7.4	11	20.7	3.95, 0.04*
6	6	11.1	12	22.6	2.54, 0.11
9	8	14.8	12	22.6	1.08, 0.29
12	8	14.8	12	22.6	1.08, 0.29

*Significant p-value.

Figure 1. Risk reduction of AUR and BPH-related surgery during 12 months treatment of alfuzosin.

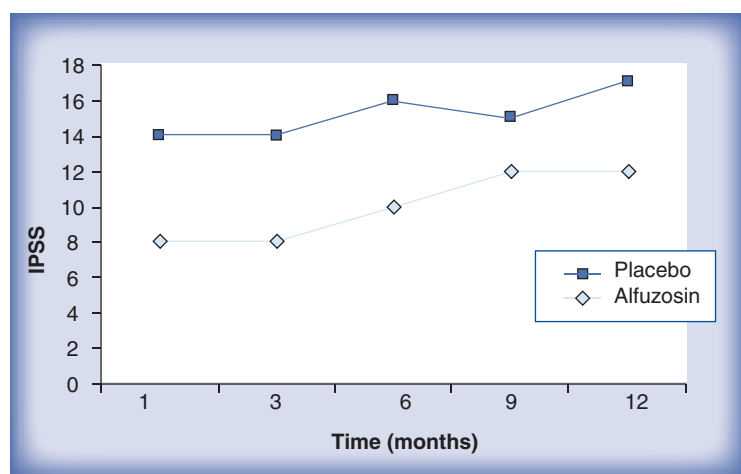


AUR: acute urinary retention; BPH: Benign prostatic hyperplasia.

treatment of BPH, as many studies proved their effectiveness and safety in relieving the symptoms and reducing the overall progression of the disease. Medical therapy of prostatic symptoms (MTOPS) study is one of the important studies in this field and it confirmed that the use of α -blocker (Doxazosin) alone is effective in reducing the overall progression events but it failed to reduce the risk of AUR or the need for related surgery [24].

Our study proved the significance of Alfuzosin 10 mg once daily in increasing the success-

Figure 2. The differences in the international prostatic symptoms score values in alfuzosin and placebo groups during 12 months of treatment.



p = 0.0001 for all values

ful TWOC in AUR related to BPH (62.3%) and this confirmed the results of other two studies ALFAUR [20] and RetenFrance Study [24] as they showed a successful TWOC in 61.9 and 50.2%, respectively. Also our study confirmed the results of the study, which used alfuzosin 5 mg sustained release and showed a successful TWOC of 55% [17]. Most of these results are comparable.

Our study is the first to apply alfuzosin once daily 10 mg and second TWOC on all failed patients in the first trial and proved its success in about third of them (32.6%), although it was applied to only 33.4% of failed first TWOC patients in RetenFrance Study [24] and it was successful in (21.7%) in spontaneous AUR. Our study also proved that the second TWOC was not associated with increase risk of significant bacteriuria ($p > 0.05$), and there was no significant difference in long-term effect between the successful voided patients from the first and the second TWOC regarding the incidence of recurrent AUR and BPH-related surgery and this strongly recommend alfuzosin and a second TWOC to be a model in our practice for all the failed first TWOC.

Our results for long-term effects of alfuzosin in reducing the recurrence of AUR and BPH-related surgery were comparable to the results of ALFAUR study [20], as the reduction was of high significance especially in the first three months of treatment, and this reflect the real value of the drug to prevent the need for surgery or at least to be performed in an elective and in catheter free state. This will reassure the avoidance of severe complications that related to the performance of urgent prostatic surgery in catheterized patients.

Our study proved the effectiveness of alfuzosin in the maintenance of low IPSS and low bothering score compared with placebo as well as the safety of the drug and its negligible significant side effects and this confirm the same results of many studies [18,19,20,25,26].

The cost effectiveness of alfuzosin once daily 10 mg before and after TWOC has both clinical and economic benefits as it decreases the need for emergency surgery for BPH and reduces treatment cost. The cost effectiveness for six months of treatment was confirmed by Lieven and colleagues, and a separated study to evaluate the cost effectiveness of the drug for one year prescription is required [27].

Conclusion

Alfuzosin once daily 10 mg is a very useful in increasing the successful TWOC in spontaneous

Table 4. The incidence of adverse effects in alfuzosin and placebo groups.

Side Effects	Alfuzosin n (%)	Placebo n (%)
Dizziness	4 (7.4%)	2 (3.7%)
Headache	3 (5.5%)	2 (3.7%)
Asthenia	3 (5.5%)	4 (7.5%)
Syncope	0 (0.0%)	0 (0.0%)
Postural hypotension	0 (0.0%)	0 (0.0%)
Impotence	2 (3.7%)	3 (5.6%)
Rhinitis	2 (3.7%)	3 (5.6%)
Arthralgia	3 (5.6%)	2 (3.7%)
Back pain	0 (0.0%)	3 (5.6%)

BPH-related AUR. A second TWOC in failed first trial is of significance, free of adverse effects, and there is no statistical difference in long-term effect between the voided patients in the first and the second TWOC, that is why we recom-

mend it to be a model in urology practice. There is significant risk reduction of recurrent AUR and BPH-related surgery in alfuzosin treated patients in comparison to placebo especially in first 3 months of treatment.

Executive summary

- Acute urinary retention is the most serious hazard of untreated benign prostatic hyperplasia and surgery for acute urinary retention is associated with higher morbidity
- A trial with out catheter after catheterization for acute urinary retention is a recommended step in the management.
- Alfuzosin 10 mg once daily is of value for successful trial without catheter, reducing the recurrence of retention and delaying the need for related surgery to be performed in an elective and catheter free state.
- A second trial with out catheter in patients with failed first trial is valuable, free of adverse effects, and recommended to be a model in urology practice.

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