



## Evaluation the Efficacy of Combined Therapy Ketoconazole and Tamsulosinvs Tamsulosin in AUR Followed BPH Iraqi Patients

Ali Abdulbaqi Ali Ismael\*

Medicine College -Thiqar university/Iraq

\*Corresponding author: [Aliabdulbaqi80@gmail.com](mailto:Aliabdulbaqi80@gmail.com)

### Abstract

The Benin prostate hyperplasia symptom may began with 40years and the incidence increased with increased age to reach 30% in men aged above70 years , this associated with sever complication like AUR which associated with higher morbidity and mortality about 1:7 of patients suffering from AUR dies during the first year, So the study aimed to evaluated the efficacy of mixed therapy versus mono therapy as well as prolong period ( 5 and 8- days ) in success TWOC . This study included 100 AUR as complicated to BPA patients which divided into two groups the 1<sup>st</sup> one 50 patients treated with mixed therapy Ketoconazole and Tamsulosin for 5 Daye (25patients) and 8daye (25 patients) , While the 2<sup>nd</sup> groups treated with immunotherapy Tamsulosin for 5 day and 8 day to 25 patient for each one , then evaluate peak flow rate , Residual urine , voided volume and prostate size to determined efficient type of therapy that gave successful treatment . Results clarified that mixed therapy recorded the best results than mono-therapy and duration for 8 day revealed high PFR, voided volume and low residual urine and prostate size. In conclusion Combination therapy ( Tamsulosin and ketoconazole )augment the prospers rate of treatment without catheter in AUR person this confirmed through that patient void more successfully after catheter removal , according to duration the 8 day revealed high peak flow rate , voided volume and decreased the residual urine also , combination therapy with 8doses recommended to treatment AUR complicated BPH patients

**Keywords:** BPA, AUR, Ketoconazole, Tamsulosin, TWOC, Combined therapy.

### Introduction

Benign prostatic hyperplasia (BPH), is a non-cancerous enlargement in prostate gland so referred to as prostate enlargement. Characteristic may include recursive urination, urination inaccessible, failure in urinates or the bladder became in control (1). Complications can include acute urine retention, bladder disorder, and persistent kidney trouble (2). Incomplete urination lead to urinary as a result of gram positive and gram negative bacteria (3) About 105 million men were affected globally during 2015(4). BPH start after 30yearsand more than half of men are affected after the age of 80 (5) Acute urinary retention (AUR) is a painful and failing in empty the bladder to completion consider a most serious complication in the BPH (6). Symptoms associated with a tensile, discomposed as well as a significant public health problem (7). Up to a third of patients undergoing prostatectomy for BPH associated with AUR that correlated with a higher

morbidity and may causes death after surgery after one month only (8). So increase attention to treatment by using urethral catheterization followed by Trial without Catheter (TWOC) that involves removing a catheter from bladder for a trial period to determine whether can pass urine without it (6). As well as initiate drug therapy by  $\alpha$ -blocker drug that relax the smooth muscle of prostate , prostatic urethra and neck bladder by blocking  $\alpha$  -1a receptors in the prostate, and the  $\alpha$  -1d receptors in the bladder or using 5- are ductase inhibitors drug that reduced prostate size , finally may using combination drug treatment (1). Ketoconazole is an antifungal drug against human fungal infection and has ability to block testosterone synthesis or inhibit testosterone concentration through the effect on several enzymes that transformed cholesterol to steroid hormones(9).Based on these ant androgen; antglucocorticoid impact,

ketoconazole has been used with some success in prostate therapy (10).

### Patients and Method

A prospective hospital based study was adopted, during the period March-2017 till April 2018. The study carried out in AL-Hussein teaching hospital after received the Ethical Considerations which approved by the Medical Ethics Committee of the Ministry of Health in Iraq

### Inclusion and Exclusion Criteria

Patients with AUR secondary to BPH under catheter using , who were agree to participate after explain the experiment purpose and steps were enrolled in study, While Patients suffering from traumatic spinal cord injury, urinary tract disorder , surgery or cancer ; finally vascular and liver disease were excluded.

### Sample Collection

100 patients with median age 69 rang (51-93 years). The patients were distributed randomly into two clinical groups; 1<sup>st</sup>group (50 ) patients received Tamsulosin 0.4mgdaily plus ketoconazole 200mg as 5days for 25 patients and 8 days for the other 25 patients while , 2ed group (50 patients ) had Tamsulosin 0.4 mg daily alone for 5 day and 8 day to 25 patient for each one. The treatment began after at least 3 days from the urethral catheterization and the Tamsulosin

take after a meal and in case ketoconazole most avoid taken anti acid because it needed an acid environment to complete absorbance. All participants during treatment period check the clinical signs, prostate enlargement were checked again by Tran's rectal ultrasound at end the period. Participate were then tested by treatment without catheter and those who completely empty successfully were followed by determination peak flow rate (PFR), the voided volume and the post-void residual urine volume (PVRV; by abdominal ultrasound). Participate with prospers TWO C were maintained on a daily Tamsulosin (0.4 mg) and were re checked after one month to assess the durability of our results.

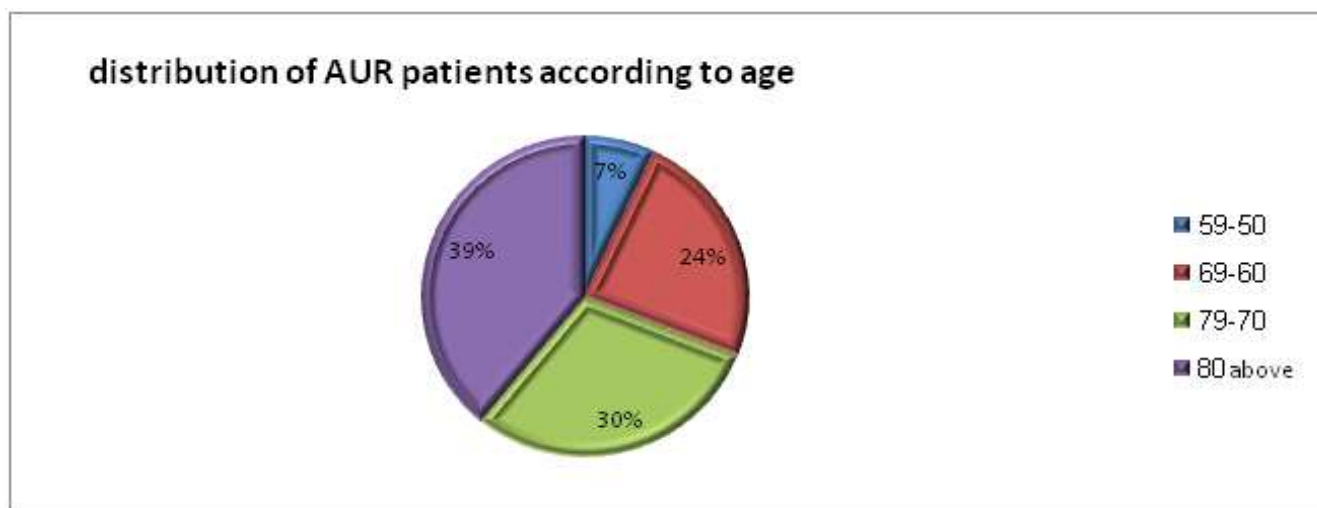
### Statistical Analysis

Statistical analyses using Student's *t* test were done by Graf pad prism 5computer software. Data (mean  $\pm$  standard error) for each group were applied. P-value was considered significant with  $\leq 0.05$ .

### Results

#### Demography Study

The present study show that maximum AUR in BPH cases were observed in the above 80 aged were represent 39 % , 30 % were observed in patients with 70-80 year,24% in 60-70 finally low incidence were found in age 50-59 about 7% Fig (1) .



**Fig 1: Distribution of AUR complicated BPH patients according to age**

### Determination the Success TWOC in Mixed and Mono Therapy Patients

The results showed that treatment were prospers in 41/50participate (82 %) in combination treatments, versus 33/50 patients (66 %) in the Tamsulosin group, this

confirmed the efficacy of combination treatment vs. immunotherapy Fig. (2). The study observed that treatment for 8-days revealed increased succeed trial after catheter removal in both mixed therapy 22/25 (88%) and momo-therapy 18/25 (72%) than 5 days treatment which record 15/25 (60%), 19/25

(76%) in mono and mixed – therapy respectively, this explain that prolong duration of treatment lead to success TWOC in both type Fig (2). The result demonstrate that parameter that associated with success TWOC included increased peak flow which appear that maximum value were in mixed therapy (12.5 ml/s ; 14.3 ml/s) in 5 and 8 day respectively while the Tamsulosin recorded

(6.6 ml/s ; 7.5 ml/s) for 5 and 8 day respectively , and high voided volume also appear in mixed therapy that reach to 186.3 ml ; 212 ml during 5 and 8 doses compare with mono therapy that represent 124 ; 136 during 5 and 8 day . In addition the combination therapy illustrated decreased the residual urine and prostate size Fig (2) Table (1).

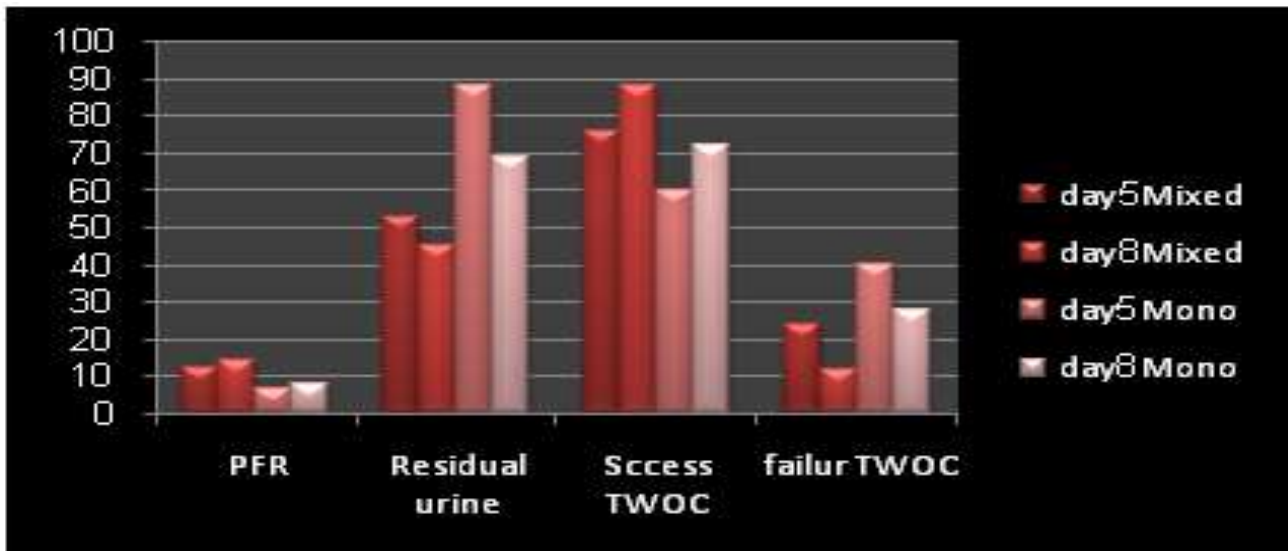


Fig 2: Show the peak flow rate, residual urine, success and failure TWOC in mixed and mono therapy for 5 and 8-day

Table 1: The voided volume, prostate size before and after TWOC in mixed and mon-therapy for 5 and 8 day treatment

| parameter                    | MIXED Therapy |             | Mono-Therapy |             |
|------------------------------|---------------|-------------|--------------|-------------|
|                              | 5 day (n=25)  | 8 day(n=25) | 5 days(n=25) | 8 day(n=25) |
| Voided volume                | 166.33 ± 13.3 | 195 ± 16.4  | 124 ± 8.4    | 136 ± 12.5  |
| Prostate size before therapy | 53± 8.5       | 54 ± 10.7   | 56.4 ± 11    | 53.7 ± 10   |
| Prostate size after therapy  | 51 ± 9.6      | 50.2 ± 13.3 | 56 ± 12.5    | 52 ± 11     |

**Side Effect of Drugs**

The study shown that treatment with combination drug did not reveal serious side effect except dizze, vomiting, headache, nausea which disappear after few time, while treatment with tamsulosin did not recorded any symptoms

**Discussion**

The present study illustrated that older patient have more incidence with AUR by BPH and this consist with several study like (11) who observed that median age of AUR patient was 72years and 50% of patients above 75 years . Nearly in line with, (12) they recorded that mean age of patients were 68 years This study appeared that combination treatment between Tamsulosin and Ketoconazole more efficient in avoid re-catheterized in AUR patients as a result of success voiding volume and increased flow rate that consider predictive marker to evaluated success TWOC in those patients in

compare with groups that treated with Tamsulosin only (13). This finding similar with (14) who observed that treatment with Tamsulosin recorded success rate of TWOC 58.8%, while combined therapy Tamsulosin with Ketoconazole recorded highly increased in the success rate to reach 77.4% ketoconazole lower the testosterone synthesis by human chorionic gonadotropin. Dihydrotestosterone and estradiol binding to sex hormone-binding globulin were inhibited by ketoconazole (15).

In this regard (14) explain that Ketoconazole has the ability to lower serum testosterone to castrate level within 48h which lead to reduce the prostate size and these observation consist with this study which founded that treatment with Tamsulosin slightly reduce the prostate size while combine therapy recorded significant

decreased in prostate size and may be one beneficial effect of ketoconazole.

Similarly (16) demonstrated that ketoconazole can increase the success rate of trial without catheter in patients with benign prostatic obstruction. Tamsulosin alpha 1 -adrenergic blocker play vital role in unclasp smooth muscle fibers located in the prostate and its capsule, bladder neck and prostatic urethra so prevent AUR in symptomatic BPH patients (17).

Also, (18) they shows that Tamsulosin revealed a tendency to be effective in a successful catheter removal. However, Tamsulosin has been shown to be effective in successful TWOC this confirmed by a French cross-sectional study of 2618men, 79% of subjects were treated with  $\alpha$ -blockers during the time of catheter insertion and the TWOC success rate was significantly higher in men who received medical therapy before TWOC, also explain that combination treatment gave doubling success rate of TWOC than Tamsulosin treatment only (11).

The results indicated that prolong duration of treatment lead to high successful trial this accordance with (19) they observed that treatment more than 5 day record 81% Successful voiding versus 77 % in patients treated for less than 5 day. Also, (16) they explain that the patients who received tamsulosin, eight doses after catheterization for AUR were less likely to need re catheterization. Similarly Djavan et al (20) they observed that long period that last to

more than 7 day give significant result in success TWOC reach to 62% than treatment period for two day only 51% This study explain that combination therapy did not recorded any serious side effect and the signs included dizzy and vomiting that disappear after few time from began treatment. This observation is similar to (15) observed that the received Tamsulosinor combined Tamsulosin and Ketoconazole were no recorded any complication or no significant side effects. Also agreement to the results of (21) that used ketoconazole to prevent nocturnal erections after penile surgery.

## Conclusion

benign prostatic obstruction has a serious complication represent by Acute urinary retention that associated with reduced life quality of patient and increased mortality as a result of surgery to prevent this disorder the researcher seek to find effective treatment. In this study evaluated the effect of combine therapy tamsulosin and ketoconazole in compare with tamsulosin and the result revealed increase the success rate of trial without catheter in patients treated with combination therapy and the patient can void more successfully after catheter removal, according to duration the 8 day revealed high peak flow rate, voided volume and decreased the residual urine also, The side-effect profile was not significant in both drug this agree with pharmacology. So, combined therapy can be commends for treating men after catheterization for AUR, and can diminishes their requirements to catheterization.

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