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SAFETY AND EFFICACY OF KETOCONAZOLE IN MANAGEMENT OF ACUTE URINARY RETENTION DUE TO BENIGN PROSTATIC HYPERPLASIA

Urology

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ABSTRACT

Aim: To evaluate safety and efficacy of Ketoconazole in management of acute urinary retention due to benign prostatic hyperplasia.

Material and Method: The study was carried out in Department of Urology, S.M.S. Medical College and attached Hospitals between March 2018 to March 2019. We recruited patients who presented with AUR due to BPH and an informed consent was obtained from each one. A total of 82 patients with acute urinary retention were enrolled and randomized into two groups with 40 patients in group A and 42 patients in group B. Group A received Tamsulosin 0.4mg once daily plus Ketoconazole 200 mg thrice a day, while the category B had Tamsulosin and B- complex as placebo. Those who voided successfully were further evaluated with peak flow rate and USG for post void residual. Patients with successful voiding trial were maintained on a daily Tamsulosin.

Results: After a week of treatment and following removal of urethral catheter 30 patients in group A voided successfully, whereas only 22 patients in group B were able to void and it was statistically significant. On the other hand, the mean peak flow rate of cases with successful voiding trial were 14.87±1.92 in group A in comparison to 12.75±1.22 in group B and the difference between the two groups was found to be statistically significant.

Conclusion: Patients with AUR due to BPH can be treated safely with a combination of Ketoconazole and Tamsulosin to get a better success rate.

KEYWORDS

AUR, BPH, Tamsulosin

INTRODUCTION:

Acute urinary retention (AUR) is one of the most significant complications or long term outcomes resulting from BPH. The etiology of retention is poorly defined as the cause could be obstructive, myogenic or neurogenic.[1] Sympathetic stimulation increases smooth muscle tone of bladder neck and prostatic urethra resulting in AUR. In addition, prostatic infection, bladder overdistention, excessive fluid intake, alcohol consumption, prostatic infarction could be the underlying events resulting in AUR.[2,3]

From a clinical and prognostic point of view, there are two categories of AUR that include spontaneous and precipitated. Precipitated AUR refers to the inability to urinate following a triggering event such as non prostate related surgery, ingestion of some medications as sympathomimetics or anticholinergics.[4]However, in all cases first line treatment is immediate bladder decompression by perurethral catheterization and it has been proved that alpha blockers significantly increase successful catheter free voiding trial in number of these patients.[5,6]

Ketoconazole is an imidazole derivative which has been used as a synthetic antifungal agent for past 50 years. It blocks both gonadal and adrenal testosterone synthesis via cytochrome P450 dependent pathway. By inhibiting 14-methylation it blocks the conversion of lanosterol to cholesterol and it also blocks 17,20-desmolase.[7,8] Its effect is rapid with testosterone levels dropping to the castrate level within 4 hours of administration in some cases. However, this effect is completely reversible and within 24 hours after cessation of the drug, testosterone levels returns to normal.[9,10]

McConnell et al. has proven that some amount of androgen is necessary for prostatic growth maintenance and after androgen blockade there is a significant decrease in its glandular epithelial component and prostatic size.[11] Therefore antiandrogens and 5α-reductase inhibitors are effective in treating prostate cancer and BPH, respectively. Bamberger MH et al.[12] used Ketoconazole in the management and treatment of metastatic prostatic carcinoma, due to its significant antiandrogenic property.

Due to prompt antiandrogenic property of Ketoconazole, it can be used in cases of AUR secondary to BPH. Therefore, this study was undertaken to evaluate the safety and efficacy of Ketoconazole in cases of acute urinary retention due to BPH.

MATERIAL AND METHOD:

The study was carried out in Department of Urology, S.M.S. Medical College and attached Hospitals between March 2018 to March 2019 after approval from our Institutional ethics review board. We recruited patients who presented with AUR due to BPH and an informed consent was obtained from each one. Patients were managed first with urethral catheterization and then they were subjected to careful history taking, clinical examination including digital rectal examination (DRE), abdominal ultrasonography (USG), serum PSA and Liver function test (LFT) and renal function test .

We included patients having prostate size between 30 – 70 gms with grade 1 median lobe and excluded patients in age group less than 40 years, Grade 2 or more median lobe of prostate on USG, chronic retention and suspicious of prostate cancer (abnormal DRE or raised PSA) or acute prostatitis, any concomitant bladder or urethral diseases, past lower tract surgery, patient's unwillingness and allergy to the study drugs.

A total of 82 patients with acute urinary retention were enrolled and randomized into two groups with 40 patients in group A and 42 patients in group B. Group A received Tamsulosin 0.4mg once daily plus Ketoconazole 200 mg thrice a day, while the category B had Tamsulosin and B- complex as placebo. Tamsulosin was administered after dinner and Ketoconazole was taken one hour before food with lemonade.

The urethral catheter was kept in place and drugs were given for 7 days. Liver function test and complete blood count were repeated for all patients at the end of this treatment and any toxicity was recorded. Patients were then put on catheter free trial and those who voided successfully were further evaluated with peak flow rate and USG for post void residual. Patients with successful voiding trial were maintained on a daily Tamsulosin.

STATISTICAL ANALYSIS:

Data was collected and analyzed by Paired t-test and chi-square test with the help of SPSS software version 24.

RESULT:

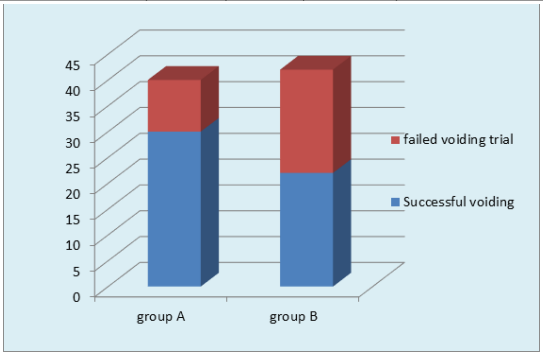
We included 82 patients. Mean prostate size in group A was 64.2gm and in group B was 62.1gm. In both groups, the administered drugs were well tolerated and no patient discontinued the prescribed

medications. Five patients in group A developed nausea & three had dyspepsia but there was no change in LFT and complete blood count in follow-up study.

After a week of treatment and following removal of urethral catheter 30 patients in group A voided successfully, where as only 22 patients in group B were able to void and it was statistically significant. On the other hand, the mean peak flow rate of cases with successful voiding trial were 14.87±1.92 in group A in comparison to 12.75±1.22 in group B and the difference between the two groups was found to be statistically significant. We have also noticed that none of our patients in both groups who had successful voiding developed new episode of AUR on first followup at 1 month (table 1, graph 1).

Table 1: Comparison of successful voiding and peak flow rate among the groups

(n = 82)		Group A (n = 40)	Group B (n = 42)	p-value
Successful voiding	Number	30	22	0.034
	(%age)	75.00	52.38	(chi-square = 4.52)
Peak flow rate	Mean	14.87	12.75	<0.001
	±s.d.	±1.94	±1.22	(t value=4.16)



Graph 1: Distribution of successful voiding in both groups

DISCUSSION:

It is well known that alpha blockers are useful in improving the results of voiding trial in cases of AUR due to BPH[5,6]. These drugs affect only the dynamic component of obstruction by blocking sympathetic receptors leading to relaxation of bladder neck and prostatic urethra. McConnell JD et al.[11] has already proven that androgen deprivation causes involution of prostatic epithelial cells and decreases vascularity and edema of prostate. There is also some evidence in the literature that hyperplasic tissue has more amount of androgen receptors[13] and in addition, Finasteride administration few days before TURP causes decrease in vascularity and bleeding.[14,15] So sharp decline in testosterone secondary to Ketoconazole administration causes decrease in vascularity, edema of epithelial cells and thus subsequent improvement in static component of obstruction.

The success rate of voiding trial in patients taking Tamsulosin in our study (52.38%) was comparable to Lucas et al.[6] (53%). However when combined with Ketoconazole the success rate was 75%. In our study successful voiding patients included mostly those who had post void urine less than 100ml and peak flow rate more than 10ml/min.

In our study, we had not noted any serious complication of drugs administration during study and follow-up. We had not given steroid replacement to patients taking Ketoconazole because of low dose and the short duration of drug administration. In low dose and for short duration, Ketoconazole is already used in some benign conditions such as high flow priapism, Cushing's disease and alopecia[16,17,18] without serious toxicity.

Patients who get a successful voiding trial should be maintained on Tamsulosin to decrease future incidence of AUR. We followed patients at 1 month and 3 months. One patient in group A and two patients in group B developed AUR at 3 months and were operated with TURP. This data showed consistency of Ketoconazole results in followup.

Limitation of our study included the non blinded & single centre study, small sample size and a short followup.

CONCLUSIONS:

Patients with AUR due to BPH can be treated safely with a combination of Ketoconazole and Tamsulosin to get a better success rate, however more studies with larger number of patients are needed to validate our results and reach to a consensus.

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