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The Effect of Oral Tamsulosin vs. Oral Tamsulosin and Oral Isosorbide Dinitrate in Acute Urinary Retention Patients Due to Benign Prostatic Hyperplasia: A Double-Blind Clinical Trial Study

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Abstract

Introduction: Acute urinary retention due to benign prostatic enlargement is one of the clinical complaints that patients refer to the emergency department. Selective α-blockers are used after urinary catheterization. Recently, the use of nitrate compounds has been shown to relieve bladder neck and to treat acute urinary retention.

Objective: The aim of this study was to survey the addition of Isosorbide di nitrate to tamsulosin in the treatment of acute urinary retention in patients with benign prostatic hyperplasia.

Methods: This is a randomized, double-blind placebo-controlled clinical trial. In all, 78 patients with benign prostatic hyperplasia-related acute urinary retention referred to the emergency department were divided into two groups and randomly assigned to receive either 0.4 mg tamsulosin plus placebo or 0.4 mg tamsulosin plus isosorbide dinitrate 40 mg extended-release tablets daily for 3 days. At the same first visit, the catheter was removed and the ability to void in same time and 1 month later was assessed in each group.

Results: After catheter removal, 27 (67.5%) patients in the tamsulosin plus placebo group and 31 (81.6%) in the tamsulosin plus isosorbide dinitrate group voided successfully after 3 days (p = 0.155). After 1 month, 20 (50.0%) patients taking tamsulosin plus placebo and 23 (60.5%) taking tamsulosin plus isosorbide dinitrate could void, yet indicating no significant difference (p = 0.350).

Conclusions: Addition of isosorbide dinitrate to α-blockers has advantage in improving benign prostatic hyperplasia-related acute urinary retention versus tamsulosin alone, although was not statistically significant.

Key words: Acute Urinary Retention; Benign Prostatic Hyperplasia; Isosorbide Dinitrate; Tamsulosin

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a benign prostatic neoplasm and its prevalence is associated with age, affects 75% of people over 70 years old (1). One of the complications in people with BPH is acute urinary retention (AUR) (2). Incidence of AUR is different in various societies and its rate is between 2.2 to 25 per 1000 person-years (3, 4). AUR is an unbearable and painful condition which is associated with pain requiring emergency urinary catheterization procedure (5, 6). On the other hand, there is potential morbidity in using long-term urinary catheterization leading to an increase in the tendency to trial without catheter (TWOC) (7). Using selective α-blockers (alfuzosin, tamsulosin, and silodosin) has resulted in the success of TWOC, a short period of time after catheterization (8, 9). It was reported that, 1-3 days after catheterization in AUR patients, the success rate of TWOC has risen from 23% to 77% (7, 10, 11). It has been indicated that using nitrate compounds relaxes the bladder neck muscles and recovers AUR in patients with BPH (12-14). Some studies have also revealed that daily use of isosorbide dinitrate (ISDN) was not effective in recovering the retention symptoms of the lower urinary tract (15). This study aimed at investigating the effect of adding ISDN to conventional treatment with tamsulosin in AUR patients due to BPH in increasing the success rate of TWOC.

Methods

Study design and setting

This study is double-blind clinical trial research

carried out from 2016 to 2018 in the emergency department (ED) of Imam Khomeini Teaching Hospital, the largest center with patient referral in Sari, the north of Iran. During a year, approximately 70000 patients refer to the hospital and of whom, about 200 refer because of AUR. The convenience sampling conducted this study and researcher in hospital shifts in study period (2016-2018), included all patients who met the study inclusion criteria. It was approved by the Ethics Committee of Mazandaran University of Medical Sciences (code: IR.MAZUMS.IMAMHOSPITAL.REC.95.2440). The research started after registering in the Iranian Registry of Clinical Trials (www.irct.ir) under the code of IRCT2017041724606N3. Written consent was obtained from the patients or their next of kin.

Study population

All patients with BPH who suffered AUR and had referred to the ED entered the study. All had a feeling of urgent urination and complained of pain in the suprapubic area. Bladder distention in these patients was detected by using a portable ultrasound device in the ED. After urinary catheter insertion (Foley catheter), the symptoms disappeared. Those patients with history of renal failure, diabetes, active urinary tract infection, previous urinary tract surgery, urinary system malignancy and contraindications to the use of tamsulosin and ISDN as well as those with unsuccessful urinary catheterization and those who didn't refer for reassessment were all excluded the study (Figure 1).

Protocol

Eligible patients underwent urinary catheterization. All the information about the age, previous history of urinary retention, underlying disorders, and medication were obtained from the patients and their urine voiding volumes were recorded. Then, renal function test requested, and also prostate volume measurement were done by ultrasound. Afterward, the patients were assigned into two groups; the first group (T) included patients who received daily tamsulosin 0.4 mg capsule (Modava Co) and placebo tablet (similar in size, color, and form to ISDN, made in Pharmacology Laboratory, Pharmacy School, Mazandaran University of Medical Sciences). The second group (I) were those who received tamsulosin 0.4 mg capsule (Modava Co.) and ISDN 40 mg extended-release tablets (Aryan Co.) once daily. Computer-generated randomization was utilized to randomize the patients, that is, every other patient was assigned to one of the groups. The medication was prepared in the same number, form, and size and was packed and labeled by a number in opaque envelopes by the principal investigator. Then, the envelopes were given to the pharmaceutic nurse in the emergency department. Each patient was assigned a number by the emergency department pharmaceutic nurse based on the randomization table and consistent with that number, one of the opaque envelopes was given to the patients. The medication in the envelopes sufficed for 3 days and after that period, the patients were reexamined, their urinary catheters were removed, and TWOC was assessed. The patients were followed up weekly for one month and their need to use catheterization was scrutinized. All the information was recorded by the researcher, though none of the patients, pharmaceutical nurse, and researcher knew about the type of medication. The only person who was aware of the codes was the principal investigator who was not involved in the study process.

Outcome

The primary outcome was TWOC rate, and the secondary outcome included urine voiding volume, prostate volume, and catheterization need. The patients were asked about TWOC after 3 days. Urine voiding volume was measured using a urine bag with measured volume meter. A radiology faculty member measured the prostate volume using ultrasound. In a weekly follow up, the patients' need to the second catheterization was recorded.

Statistical Analysis

The data were fed into SPSS version 17. The quantitative data were explained using measures of central tendency, like mean and median with standard deviation (SD) and interquartile range (IQR); the qualitative data were explicated using frequency and percentage. We used Chi-square test for comparing categorical variables and used Fisher's exact test for comparison with 20% of expected count have less than five or the minimum expected count was lower than one. The normality assumption of quantitative variable assessed with Shapiro-Wilk test and graphical approaches, like Q-Q plot and histogram. To compare the quantitative variables in the two groups, we used Independent t-test for normality distributed variable and Mann-Whitney U test was employed in low sample size comparison and non-normality distributed. In all statistical test P-value less than 0.05 was considered as a statistically significant.

RESULTS

During the study period, about 178 patients with AUR had referred to the hospital and finally analyzed data of 40 and 38 patients in tamsulosin-

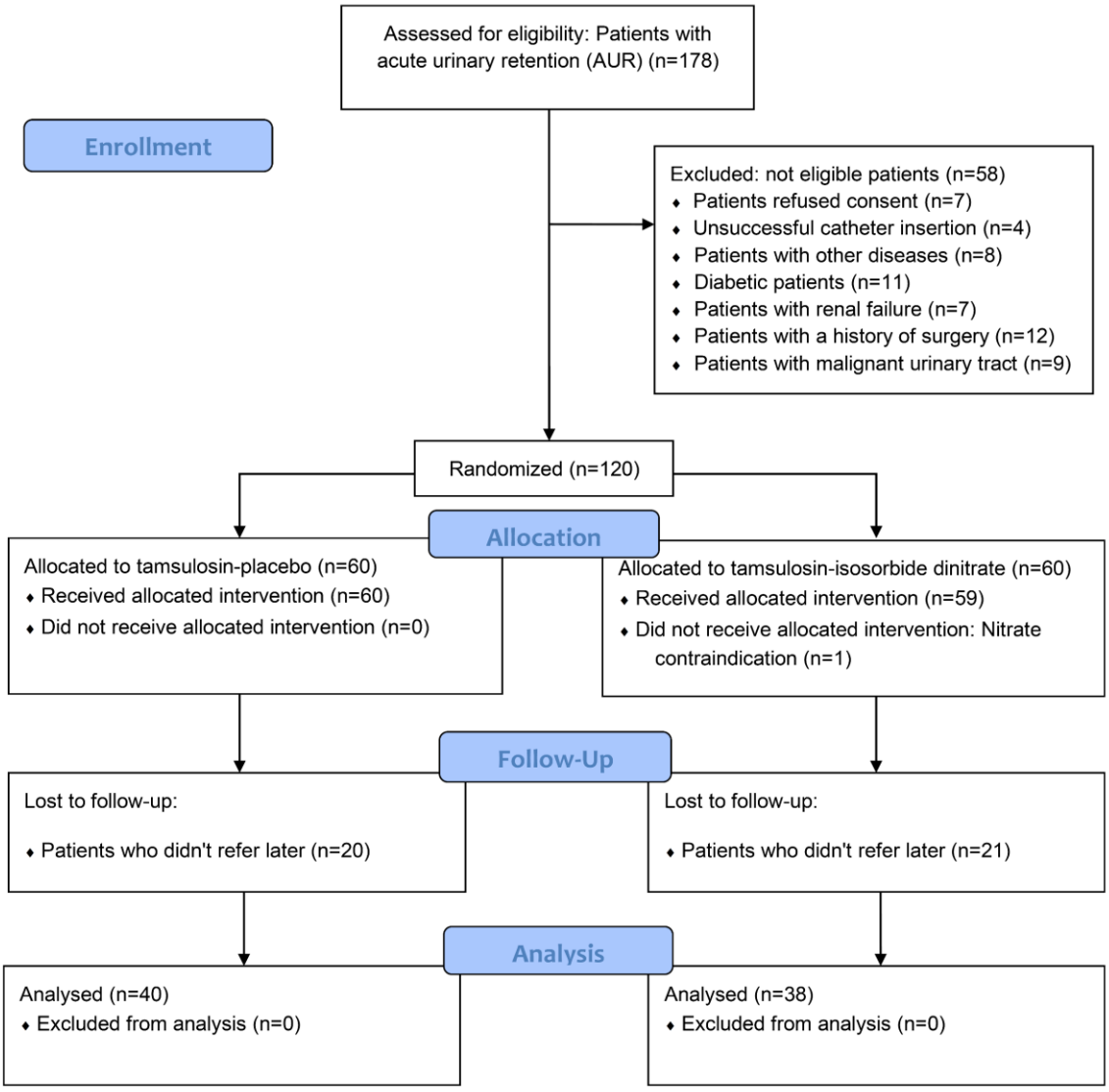

Figure 1: Screening and Enrollment flow diagram

placebo and tamsulosin-ISDN group, respectively (Figure 1).

The patients aged from 55 to 92 in both group and mean age was not significant difference (p=0.624). The positive history of AUC and positive drug history was 20.0% and 40.0% in Tamsulosin-placebo group, 18.4% and 28.9% in Tamsulosin-ISDN group, respectively. The previous history of AUR, drug history, and also renal function, prostate volume and urinary retention volume were not statistically significant difference in two treatment group (p>0.05) (Table 1). All patients in both treatment groups had hypogastric pain, dilated bladder, and a strong feeling of urination. Also, in all patients, the size of the kidneys and bladder was normal.

After 72 hours TWOC in patients with the tamsulosin-ISDN group, was higher than in the tamsulosin-placebo group (81.6% vs 67.5%), but this difference was not statistically significant (p=0.155). But over the course of a month, there was a greater need for urinary re-catheterization in the tamsulosin-placebo group (50.0% vs 39.5%), although, this difference was not statistically significant (p=0.350). The need for urinary re-catheterization in one- and two-week follow-up

Table 1: Baseline characteristics of the patients

Variable	Tamsulosin – placebo (n= 40)	Tamsulosin – Isosorbide dinitrate (n=38)	P-value
Age (year), mean ± SD	71.58 ± 9.95	70.5 ± 9.28	0.624
Serum urea, mean ± SD	45.45 ± 7.66	46.32 ± 6.44	0.592
Serum creatinine, mean ± SD	1.26 ± 0.18	1.28± 0.16	0.576
Retention volume (cc), mean ± SD	287.38 ± 151.63	287.24 ± 145.14	0.997
Prostate volume (cc), mean ± SD	38.45 ± 11.93	37.61 ± 13.50	0.845
Positive history of AUC, n (%)	8 (20.0)	7 (18.4)	0.860
Positive drug history, n (%)	16 (40.0)	11 (28.9)	0.305

Table 2: The age, prostate volume and retention volume difference in successful and failed TWOC patients by treatment group

Variable	Tamsulosin +	Successful TWOC		Failed TWOC		P value*
		Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Age (year)	**Placebo**	70.44 ± 11.25	73 (59, 75)	73.92 ± 6.20	74 (69, 80)	0.317
	ISDN	69.23 ± 9.49	73 (60, 75)	76.14± 5.98	78 (73, 81)	0.076
Prostate volume (cc)	**Placebo**	36.22 ± 12.72	30 (25, 45)	43.08 ± 8.79	45 (40, 50)	0.089
	ISDN	34.48 ± 11.57	30 (25, 45)	51.43 ± 13.45	50 (40, 50)	0.005
Retention volume (cc)	**Placebo**	260.93 ± 150.55	200 (100, 400)	342.31 ± 144.11	400 (150, 450)	0.036
	ISDN	268.87 ± 142.15	200 (150, 400)	368.57 ± 139.33	450 (180, 450)	0.017

ISDN: Isosorbide dinitrate; IQR: Interquartile Range (Q1, Q3); TWOC: Trial Without Catheter
*. P-value based-on Mann–Whitney U test

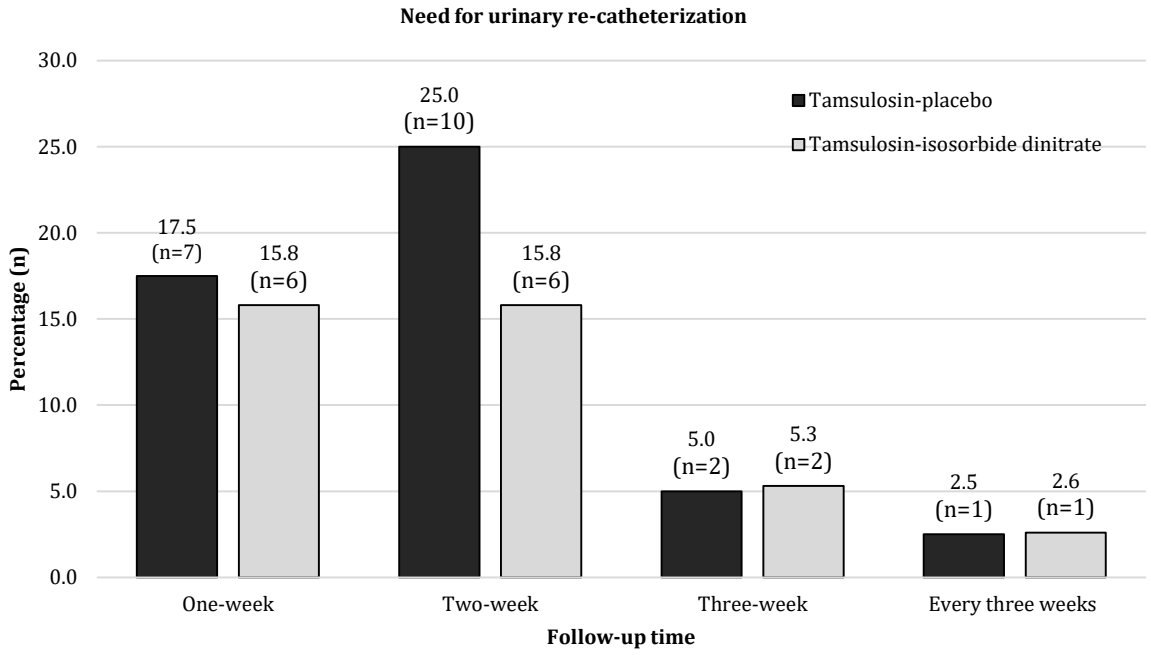

Figure 2: Need for urinary re-catheterization in follow-up time by treatment group

time in tamsulosin-placebo was higher than tamsulosin-ISDN group. Although, this difference was not statistically significant (p>0.05). Also, in each group one patients need for urinary re-catheterization every three weeks (Figure 2).

Patients who had TWOC after 72 hours were younger than those who did not have TWOC in both treatment group, but this difference was not statistically significant (p>0.05). In the tamsulosin-isosorbide denitrite group, patients who had TWOC after 72 hours, prostate volume [Median (IQR): 30 (20) vs 50 (10); p=0.005] and retention volume [Median (IQR): 200 (250) vs 450 (270); p=0.005] were significantly lower than failed TWOC. Also, this difference was obtained in tamsulosin-placebo group (Table 2). The successful TWOC was

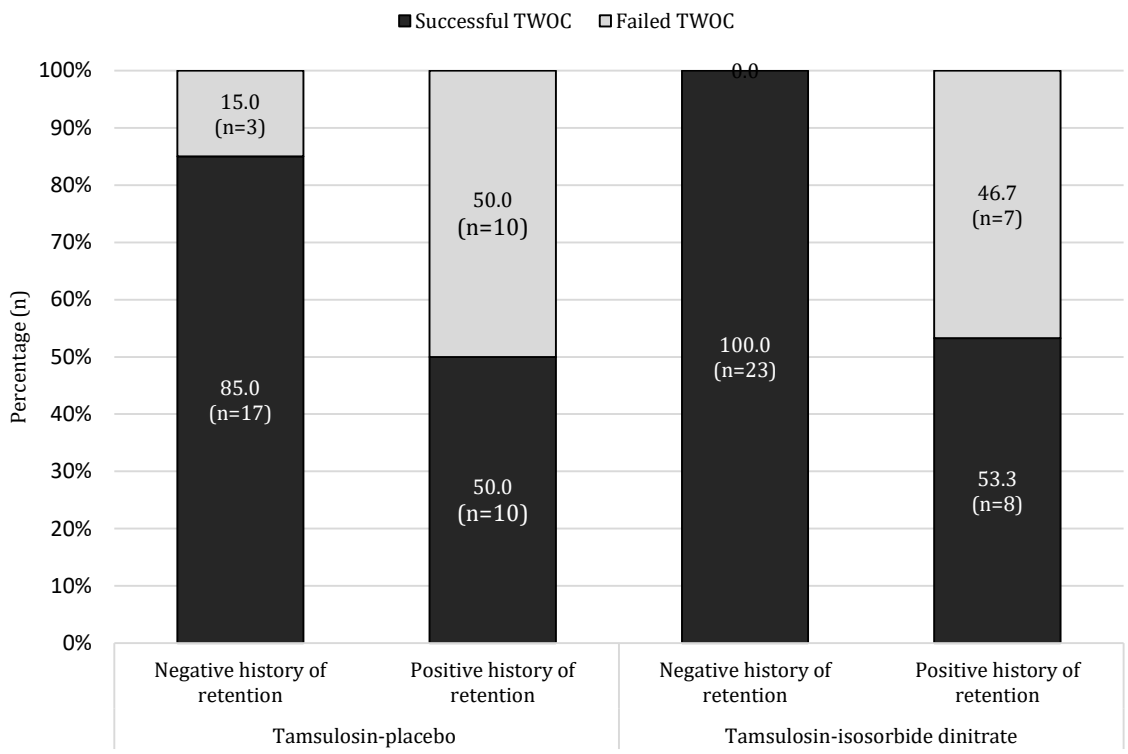

Figure 3: The prevalence of successful TWOC in negative and positive history of retention by treatment group

significantly higher in patients with urinary retention for the first time than in those with a history of acute urinary retention in tamsulosin-ISDN (85% vs 15%, p=0.018) and also in tamsulosin-placebo group (100% vs 0%, p=0.001) (Figure 3).

Discussion

This clinical trial study revealed that adding ISDN to oral tamsulosin in comparison to tamsulosin per se for the treatment of patients with AUR has no effect on TWOC after 72 hours in the two groups. Moreover, one-month follow-up showed no significant differences between the two groups for re-catheterization. The growing success of TWOC by alpha antagonists such as tamsulosin has been approved in many studies (16, 17). However, the effect of using drug combination with tamsulosin such as 5α-reductase inhibitors, Finasteride, is not yet clear in AUR improvement (18). This study also showed that adding nitrate combination to tamsulosin brings about no change in the rate of TWOC among the patients and it was not successful in the treatment of AUR due to BPH. It has been found that some medications such as ISDN can improve urinary parameters like peak urinary flow rate and can be used for AUR (13, 14). Moreover, long-term use of such medications can reduce the proliferation of prostate tissue and prevent BPH progression (12). Similarly, using α-blockers results in the reduction of urine frequency and AUR relapse (19). Those who aged over 65 with a prostate volume of over 35cc had less TWOC level and increased odds of re-catheterization (20). Therefore, in this study age and prostate volume were considered as the effective factors in TWOC. Similar to other studies, this study has also confirmed that a history of lower urinary tract obstruction and excessive urine volume during initial catheterization are directly associated with failed TWOC (21, 22). Although several studies have revealed that retained urine volume has no significant relationship with the success rate of TWOC (21), this study found out that it was significantly higher in the failed TWOC group. Consequently, old age, high prostate volume, excessive urine volume, and history of lower urinary tract symptoms in a patient with AUR due to BPH are indicative of failed TWOC in 72 hours, so the patient should be referred to an urologist for surgery.

Limitations

First of all, the sample size and power of study were low, and although there was a difference in results,

due to the low power and sample size, we probably did not find a significant statistical difference in the study. The other limitation was that most of the patients were old, so they didn't refer for follow-up and they didn't provide us with information about their previous illnesses and medication; this led to problems in sampling. Since this emergency department is the referral center for urology patients all over the province, most of the patients are referred after a failed treatment in other centers; this may cause an error in sampling, too. Finally, aerodynamic parameters were not measured in this study and patients' follow-up and definitive treatment were not investigated. Hence, it is recommended that other studies apply nitrate drugs for a longer period and evaluate aerodynamic criteria in patients with AUR due to BPH.

Conclusions

Short-term use of ISDN along with tamsulosin in patients with BPH does not considerably affect TWOC in comparison to the use of tamsulosin per se. However, factors such as older age, previous history of AUR, increased prostate volume, and retention volume have contributed to the failure of TWOC.

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Authors' contribution

HA and BFK conceived and designed the study, edited the manuscript, and supervised the conduct of the study and data collection. RAS designed and developed the project and collected the data. HA wrote the first and final drafts of the manuscript. MS and FJ were responsible for sample recruitment and data collection. TA were involved in data management and analysis. All authors contributed to the review and revision of the manuscript and approved the final version.

Conflict of interest

None declared.

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