The success of intermittent uroselective alpha-blocker on continuous alpha-blocker respondent BPH patients by Kumlachew Tilahun

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Addis Ababa University College of Health Sciences, Tikur Anbessa Specialized Hospital

Title: The success of intermittent uroselective alpha-blocker on continuous alpha-blocker respondent BPH patients

Principal investigator: Dr Kumlachew Tilahun (Urology resident)

Advisor: Dr Seyfe Bekele (Assistant professor of Urology)

Dr Fitsum Solomon (Assistant professor of Urology)

Name of the principal investigator	Dr Kumlachew Tilahun(Urology resident)
Advisor	Dr Seyfe Bekele (Assistant professor of Urology) Dr Fitsum Solomon(Assistant professor of Urology)
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Address of the principal investigator	Email:tastu211@gmail.com Phone number:+251921580786

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Abbreviations

BPH= benign prostatic hyperplasia

LUTS = lower urinary tract symptoms

IPSS =internal prostatic symptom score

OPD= outpatient department

QOL=quality of life

PVR=post voiding residual

Q-MAX= maximum flow rate

AUR=acute urinary retention

DM= diabetes mellitus

Qave= average flow

Executive summary

Background

Objective: assessing the success of intermittent alpha-blocker in continuous alpha-blocker respondent Benign prostatic hyperplasia patients.

Method: Hospital-based prospective cohort study

Timeline: the study was conducted from April to September 2024 G.C

Keywords: Alpha-antagonist, lower urinary tract symptoms, benign prostatic enlargement, alpha-adrenergic receptors

1 Introduction

1.1 statement of problem

lower urinary tract symptoms (LUTS) are a frequent issue among adult men, significantly affecting their quality of life (QoL) and leading to considerable economic costs(1). The current guidelines provide practical, evidence-based recommendations for assessing and treating men aged 40 and older with various non-neurogenic benign forms of LUTS. The concept of the lower urinary tract (LUT) as a functional unit, along with the recognition of the multifactorial causes of related symptoms, shifts the focus to LUTS itself, rather than the previous emphasis on Benign Prostatic Hyperplasia (BPH)(1).BPH is main cause of LUTS in the age elderly males.

Benign prostatic hyperplasia (BPH) a common benign tumor in men has been attributed to age and male androgen functions(2). Benign prostatic hyperplasia (BPH) is a benign enlargement of the prostate gland that may lead to bladder outlet obstruction, lower urinary tract symptoms (LUTS), and reduced quality of life. BPH is a histologic diagnosis present in 50% of men > 50 years(3). Men with troublesome LUTS/BPH frequently have other age-related health issues, such as sexual dysfunction, heart disease, hypertension, diabetes, and metabolic syndrome, which can make management more complex(4).

BPH is treated primarily with watchful waiting, phytotherapy (herbs), and medical or surgical options(5)

Prior to the 1990s, the treatment of BPH mainly relied on surgery. However, with a growing understanding of alpha-1 adrenergic receptor (α1 AR) stress hormone receptors, a1AR-selective blockers began to be used in the management of LUTS(3). Alpha blockade remains the primary medical treatment for symptomatic bladder outlet obstruction caused by benign prostatic hyperplasia (BPH) because it specifically targets the neural factors involved in the dynamic aspect of BPH. alpha-blockers are predominant receptors in the bladder neck and prostatic stromal tissue(6). Sympathetic stimulation of alpha-adrenergic receptors causes increased tone in the prostatic stroma called dynamic prostatism(6).

Alpha-blockers that are selective for the urinary tract improve symptoms related to the lower urinary tract, increase peak uroflometry, and enhance the quality of life specific to the disease. They also lower the risk of long-term progression of benign prostatic hyperplasia (BPH) overall. These medications are well received by older men, causing minimal side effects related to vasodilation and sexual function, even in those with other health issues. In particular, alfuzosin, a uroselective alpha-blocker, is well tolerated when used in combination with antihypertensive medications and phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction(4). The main objectives of treating men with bothersome lower urinary tract symptoms (LUTS) are to

alleviate symptoms and enhance quality of life. Additionally, when choosing a treatment for benign prostatic hyperplasia (BPH), the individual patient's risk of disease progression and potential serious complications such as acute urinary retention, bladder stones, recurrent urinary tract infections, hematuria, or kidney problems should be taken into account. The benefits and limitations of each treatment option should be assessed and communicated with the patient. Risk factors for the progression of BPH and serious complications include older age, severe LUTS, PSA levels above 1.5 ng/ml, prostate volume over 30 mL, urinary flow rate under 10 ml/sec, and a post-void residual volume greater than 300 ml(4). Other considerations in choosing the most suitable BPH treatment include the patient's comorbid conditions, current medications, and sexual activity/sexual function. For certain patients, the cost of treatment may also be a significant factor(4).

For many patients with LUTS/BPH, first-line medical treatments such as α1-adrenergic antagonists (α1-blockers), 5α-reductase inhibitors (5ARIs), or a combination of α1-blockers and 5ARIs can effectively relieve LUTS with fewer and less severe side effects compared to invasive treatments(4).

Uroselective alpha blocker medications have a rapid onset of action (within a few days for improving LUTS) and are considered the most effective monotherapy for the relief of LUTS, irrespective of prostate size(4). Alfuzosin, doxazosin, tamsulosin, and terazosin demonstrate similar clinical effectiveness (e.g., a 4- to 6-point improvement in the AUA Symptom Index, a 2- to 3-mL/s increase in peak urinary flow rate, and a 1- to 1.5-point improvement in the bother score), though their side-effect profiles vary. The primary side effects of α1-blockers include orthostatic hypotension, dizziness, headache, fatigue, rhinitis, and ejaculatory dysfunction(4). Intermittent uroselective alpha blockers when give for properly selected BPH patients, it has comparable IPSS score and Qmax with daily dose of alpha blockers but has better global satisfaction index than continuous alpha blockers treated patients. Treating patients with intermittent alpha blockers has good patient satisfaction, low drug adverse effect, low patient burden to the treating physicians, and finally low financial burden to the patient and country as a whole.

1.2. Significance of the study

Understanding factors that will contribute to the success and failure of intermittent alpha-blockers in the continuous alpha-blocker respondent is important to increase the quality of life of the patient, lowers the financial burden to the patient, hospital, and the country as a whole, and also lowers patient burden to the treating physician.

2. Literature review

Lower urinary tract symptoms(LUTS) secondary to BPH are common in aging male patients. LUTS symptoms can be obstructive/voiding or storage/irritative symptoms.

The severity of symptoms can be calculated by the international prostatic symptoms score which can be graded from mild to moderate to severe (mild=0-7, moderate 8-19, severe 20-35). those patients with mild symptoms need watchful waiting with behavioral modification. moderate to severe symptoms treated by either medical or surgical treatment based on the patient's need for surgery, response to medical treatment, and presence or absence of complication secondary to BPH-related LUTS. Even though surgery can be done for moderate to severe IPSS BPH patients, it is not without complications. Generally, for patients with moderate to severe LUTS, medical therapy should be the first-line treatment unless the patient has a direct indication for surgery or prefers the surgical treatment. Options of medical therapy can be alpha adrenoreceptor blockers,5 alpha-reductase inhibitors, antimuscarinic, phosphodiesterase 5 inhibitors, B3 agonists, or a combination of drugs depending on the type of predominant symptoms(2).

The smooth muscle of the prostate, bladder neck, prostatic capsule, seminal vesicle, and vas deferens are innervated by alpha adrenoceptors. Sympathetic stimulation of alpha-blockers increases smooth muscle toe which is also called the dynamic component of prostatism and blockage by alpha-blockers relaxes the muscle tone which leads to a reduction in the prostate symptoms and increased Qmax(7).

BPH patients with mild IPSS scores should be followed with watchful waiting since 85% will have stable symptoms for 01 year (8). Alpha-1 adrenoceptor antagonists (a1-blockers) are the first-line pharmacological treatment for male LUTS, because of their rapid onset of action, good efficacy, and low rate of adverse events(9).

All alpha-blockers will decrease the symptoms and increase the flow rate regardless of the prostate volume and patient age when compared with placebo (30 to 45% vs 10 to 20% for symptoms and 5 to 15% vs 20 to 30% for Qmax)(10). However, a1-blockers do not prevent AUR or the need for surgery(9).

Generally treating patients with bothersome LUTS secondary to BPH by alpha-blockers increases the IPSS and quality of life scores of 6 and 2 respectively(11) Treatment of LUTS secondary to BPH improves symptoms in 74% of treated patients(11). Those patients who respond to continuous alpha-blocker have the adverse effect of alpha blockage including dizziness, postural hypotension, asthenia, rhinitis, ejaculatory dysfunction, and peripheral edema and also decreased quality of life because of daily medication intake and a financial burden (6).men who have bothersome LUTS and treated with alpha-blocker can be treated with an intermittent dose of an alpha-blocker with similar efficacy and safety profile(7). A notable therapeutic response is characterized by a 40% reduction in the IPSS and a 30% improvement in Qmax(7).

Before changing alpha blocker to every other day patients were evaluated with baseline IPSS score, Qmax, global satisfaction index, post voiding residual volume after the patient fulfill the inclusion criteria. The inclusion criteria were IPSS score>8, Qmax >5 but <15 ml/sec with voided Volume of 150ml.

The following Patients were excluded like prostatic ca, neurogenic bladder, DM, renal dysfunction, hepatic dysfunction, cardiovascular disease, cerebrovascular disease, neurologic condition, prostatic or urethral surgery(7).111 patients were enrolled for the study and 79 patients who respond to alpha blocker after 3 months of treatment are restartified in to three groups. 27 patients in Group 1 continue with daily dose of alfuzosin, 26 patients in group 2 continue with intermittent alfuzosin and 26 patients in group three discontinued medication and three groups were followed for a period of three months. At 3 and 6 months, the IPSS values were as follows: 7.1 ± 2.9 and 6.5 ± 2.5 for group 1; 6.5 ± 3.2 and 6.7 ± 2.1 for group 2; and 11.4 ± 4.8 and 12.3 ± 4.9 for group 3.

For Qmax, the measurements were 12.7 ± 4.8 and 11.7 ± 5.2 mL/s for group 1; 12.2 ± 3.9 and 11.9 ± 3.7 mL/s for group 2; and 9.7 ± 2.5 and 9.3 ± 2.1 mL/s for group 3 at 3 and 6 months, respectively. Both groups 1 and 2 exhibited similar responses in terms of IPSS scores and Qmax, while group 3 showed no changes in either IPSS or Qmax at 6 months or at baseline. The global satisfaction score at the start of the study was 1.6 ± 1.1. Upon entering the dosing phase, the global satisfaction score increased to 3.9 ± 1.5 for all patients.

At 6 months, global satisfaction was 4.1 ± 1.4 for group 1 and 3.9 ± 1.2 for group 2. In contrast, for group 3, global satisfaction dropped to 1.9 ± 0.7.

In summary, intermittent dosing of alfuzosin has equivalent efficacy to daily dosing but the discontinuation will lead to a reversal of worsening of symptoms(7).

The limitation was the small sample size and intermittent dosing response in every 3rd or 4th day was not studied and answered. any time where alfuzosin discontinuation without reversal of LUTS can occur is not also answered.

Prospective randomized study on Gulhane Military Medical Academy and Medical Facility, Division of Urology, Ankara, Turkey by Erduran, D et al from 2001-2003 to evaluate the effectiveness of intermittent tamsulosin for men with lower urinary tract symptoms secondary to BPH. The study involved 140 patients with LUTS 2ry to BPH and those patients who were eligible for medical treatment were treated for 3 months on daily 0.4 mg tamsulosin. 91 patients were finally selected for the study.17 patients discontinued medication because of lack of response,9 patients discontinued medication of significant side effects (3 retrograde ejaculation and dizziness,6 headache). 65% of respondents (91 patients) regrouped into three groups. Group 1 (31 patients) continued taking 0.4 mg of tamsulosin daily, group 2 (34 patients) took 0.4 mg of tamsulosin every other day, and group 3 (26 patients) stopped the medication. A significant therapeutic response to alpha-blockers is characterized by a 40% reduction in I-PSS, a 25% decrease in residual urine, and a 30% improvement in Qmax(6). At 3 and 6 months, the I-PSS scores were 7.2 ± 2.4 and 7.1 ± 2.0 for group 1, 7.1 ± 2.4 and 7.0 ± 2.1 for group 2, and 11.3 ±

3.4 and 11.8 ± 3.4 for group 3. For Qmax, the values were 11.3 ± 4.0 and 11.1 ± 4.0 ml per second for group 1, 11.3 ± 4.2 and 11.2 ± 3.9 for group 2, and 9.7 ± 3.3 and 8.5 ± 3.1 for group 3, respectively.

Residual urine measurements were 75.1 ± 17.0 and 74.1 ± 16.4 ml in group 1, 70.2 ± 23.2 and 69.0 ± 19.6 in group 2, and 82.3 ± 23.6 and 88.2 ± 26.0 in group 3 at 3 and 6 months, respectively.

No significant differences were found between groups 1 and 2 at 6 months for I-PSS, Qmax, Qave, or residual urine ($p = 0.858, 0.946, 0.635$, and 0.263, respectively). However, differences between groups 1 and 3 were statistically significant for I-PSS, Qmax, Qave, and residual urine ($p < 0.001, 0.010, 0.046$, and 0.011, respectively). Similarly, significant differences were observed between groups 2 and 3 for these parameters at 6 months ($p < 0.001, 0.005, 0.036$, and 0.002, respectively). Tamsulosin, administered at a dose of 0.4 mg once daily or 0.4 mg every other day, leads to similar improvements in urinary flow and symptoms. However, discontinuing the medication resulted in a return of lower urinary tract symptoms to baseline levels(6).

A prospective randomized study was done by the Departments of Urology and Public Health (SK), Gülhane Military Medical Academy, Ankara, Turkey by Goktas et al from January 2001 to December 2004 on 405 patients who are greater than 50 years with LUTS. 30 patients developed abnormal ejaculation out of 405 tamsulosin 0.4mg daily dose respondent patients.

The operational definition of abnormal ejaculation was absent ejaculate, retrograde ejaculation or decreased ejaculate. Abnormal ejaculation was reported as retrograde ejaculation by 18 patients, as decreased volume by 7, and as absent ejaculate by 5 patients. Before starting intermittent treatment, the 30 patients with abnormal ejaculation had a mean I-PSS of 7.6 ± 2.7, a mean Qmax of 11.7 ± 3.1 ml per second, a mean Qave of 5.8 ± 1.9 ml per second, and a mean residual urine volume of 73.9 ± 15.8 ml. At week 6 of the study, these values were 7.5 ± 2.0, 11.6 ± 2.9 ml per second, 5.6 ± 1.8 ml per second, and 72.7 ± 16.2 ml, respectively. The changes in I-PSS, residual urine, Qmax, and Qave were not statistically significant ($p = 0.44, 0.72, 0.16$, and 0.33, respectively). There were no significant statistical changes in I-PSS or residual urine, nor any improvements in Qmax or Qave in patients with abnormal ejaculation before and after intermittent treatment(12).

A prospective, controlled, randomized study conducted by Soliman et al from 2015 to 2017 in the Urology Department, Faculty of Medicine, Tanta University, Tanta, Egypt. The study was conducted on 93 patients who are above 50 years presented with bothersome LUTS secondary to BPH and responded to tamsulosin0.4 mg daily therapy. The study focused on sexually active men who were affected by abnormal ejaculation related to tamsulosin treatment. Patients were divided into three groups: group A (31 patients) received tamsulosin 0.4 mg every other day, group B received a lower dose of 0.2 mg daily, and group C received 0.4 mg daily.

At the study endpoint, 3 months after randomization, various parameters, including IPSS, QoL index, Qmax, and patient-reported ejaculation status (normal or abnormal), were reassessed and compared to baseline values. All groups showed significant improvements in IPSS, Qmax, and QoL compared to baseline. However, while all patients in group C (full daily dose) continued to

experience abnormal ejaculation, only 9.6% (3/31) of patients in group B and 25.8% (8/31) in group A still reported abnormal ejaculation.

When comparing groups, A and B in terms of QoL, group A had a better quality of life, though their Qmax and IPSS scores were similar.

In conclusion, for patients affected by tamsulosin-related abnormal ejaculation, administering 0.4 mg of tamsulosin every other day can significantly improve QoL without compromising the therapeutic goals of the treatment(13).

The prospective study was done by Soliman et al at the Department of Urology, College of Medicine, King Faisal University, Saudi Arabia 2023. The study was done on 25 patients who presented with abnormal ejaculation after a daily dose of 0.4 mg of tamsulosin.

Despite the notable changes in IPSS and PVR resulting from intermittent tamsulosin therapy, the majority of patients exhibit greater overall satisfaction with this treatment approach when contrasted with the standard daily dosage of 0.4 mg(14).

3.Objective

3.1. General Objective:

To determine the effectiveness and safety of using intermittent uroselective alpha-blocker therapy in BPH patients who have shown a good response to continuous alpha-blocker treatment.

3.2 Specific Objectives:

1 Assess if intermittent dosing can maintain improvements in urinary flow and BPH symptoms experienced with continuous therapy.

2 Evaluate if intermittent dosing offers similar or better BPH symptom relief compared to continuous therapy.

3 Investigate the side effect profile of intermittent dosing compared to continuous therapy.

4 Determine if there are any safety concerns associated with switching from continuous to intermittent dosing.

5 Assess if intermittent dosing can reduce the overall amount of medication needed compared to continuous therapy.

6 Evaluate the potential cost-effectiveness of intermittent dosing.

4.Methods and material

4.1. Study setting

Tikur Anbessa Specialized Tertiary Hospital, Addis Ababa University, Addis Ababa, Ethiopia

4.2. study period

From April to September 2024

4.3. Research methodology

Hospital-based prospective cohort study

4.4. Source population

All BPH Patients who visited TASH urology OPD

4.5. Study population

All BPH patients who show a response to uroselective alpha-blockers during follow-up at the TASH urology outpatient department.

4.6. Inclusion and Exclusion Criteria

4.6.1. Inclusion Criteria

All patients who showed a positive response to continuous uroselective alpha-blocker treatment

4.6.2. Exclusion criteria

BPH patients who are in uroselective alpha-blockers and have high post-voiding residual>400 ml

Baseline Q-max <5 ml/sec

Does not respond to alpha-blocker

First-time alpha blocker-treated group

Pelvic/bladder neck or urethral surgery

4.7. Sample size determination

The sample size is determined based on the following assumptions; the confidence level to be 95%, margin of error <0.05 to be significant. Since there is no study done in the African setting or our country the p-value will be 50 % to maximize the representative sample size.

The sample size (n) is calculated according to the following formula (Cochrane formula):

$$n=\frac{z^2 p(1-p)}{d^2}$$

z = 1.96 for a confidence level (α) of 95%,
P = proportion
d = margin of error
z = 1.96, p = 0.5, d= 0.05
n= 384

5% non-respondent
Total sample size =405

4.8. Variables

Age

Ipss score

Uroflowmetry

Post voiding residual

Dizziness, headache, syncope

Abnormal ejaculation (absent /dry ejaculation

4.9. Operational definition

A positive response to alpha-blockers is defined as a 40% reduction in IPSS, a 25% decrease in residual urine, and a 30% improvement in Qmax(6).

Clinical alpha blocker response is defined as 40% decrease in IPSS score.

Radiological response is defined as 25% decrease of post voiding residual.

Urodynamic response is defined as 30% increase in Qmax.

4.10. Data collection

Data was collected from the study population using a kobo toolbox structured data collection tool. The ipss score was scored by direct patient interview, qmax used with voided volume of >125ml ad post voiding residual volume measured using ultrasound.

4.11. Data Analysis

Data were analyzed using SPSS version 26 software.

Descriptive statistics were presented in frequency tables and charts.
Ordinal logistic regression was employed to assess the correlation between dependent and independent variables.

5. Ethical consideration

Ethical approval was granted by the Institutional Research Ethics Committee of the School of Medicine, College of Health Sciences, Addis Ababa University. Once the research proposal passes ethical clearance, a letter of approval to proceed with and support the study was received from the Department of Surgery, Urology Unit

Privacy and confidentiality of collected information was ensured throughout the process.

6.Methods and result of the study

The data is collected by kobo toolbox and analyzed using SPSS version 26. The data distribution is checked using the Shapiro wilke test and histogram curve for the skewness of the data.

The data is not normally distributed so that the data is analyzed using Wilcoxon sign rank test with confidence interval of 95% and level of significance of 0.05.

6.1. The result

The total of 32 patients were enrolled for the study with mean age of 63±9.7 years (45-80) years. Out of 32 patients, 5 patients (15.6%) were excluded because of the following reasons,4 patients had worsening of the symptoms, 1 patient did not come after baseline Q-max and 27 patients completed 3 months follow up. The data were analyzed based on the baseline and 3rd month (IPSS score, Q-max, post voiding residual).

Before the start of intermittent dose for all the patients (27), the mean baseline Q-max was 14.67±6.3, mean baseline PVR was 25±23.45, mean baseline IPSS score is 6.52±3.83.

After 3 months of the follow up the mean Q-max increase to 15±9.3, mean PVR increase to 38.9±39.3, IPSS score increase to 7.63±4.2. statistical analysis of baseline and after 3 months change for the above parameters showed statistically insignificant change with p value >0.05 in all cases (table 10).

The majority of the patients took alfuzosin when compared with tamsulosin (70% vs 30%). out of the 30% who took tamsulosin 75% were potent and 25% were impotent. The side effect of tamsulosin on ejaculation were assessed on patient who are potent and it shows 50 % have low volume ejaculation (low volume/anejaculation) and 50% have no any effect on the ejaculate volume. Out of the patient who develop abnormal ejaculation, all (100%) responded

to intermittent dose of tamsulosin. The adverse effect of the alpha blocker other than ejaculation assessed and it showed 22% developed side effects (syncope, dizziness, headache) the commonest symptom was syncope followed by headache. The patient who develop the side effect of the drug reported either total improvement or some improvement via the intermittent dose of the drug. Comorbidity was assessed and it showed cardiovascular disease and diabetes mellitus has found in 15 % of the patients.

The significance of intermittent uroselective alpha blocker treatment on the continuous uroselective alpha blocker are assessed using Wilcoxon sign rank test. the change in Q-max, IPSS score and post voiding residual were assessed.

The significance of change of Q-max between the baseline (Md=13, n=27) and 3rd month (Md=13, n=27) is not statistically significant between continuous and intermittent uroselective alpha blocker group Z= -0.706, p =0.48, r=0.09.

The change in post voiding residual is also not statistically significant between the continuous (Md=15.3, n=27) and intermittent(Md=32,n=27) uroselective alpha blocker treated patients Z=-1.76, P=0.07, r=0.24.

The change in IPSS score between continuous (Md=6, n=27) and intermittent (Md=6, n=27) uroselective alpha blocker treated patient is not statistically significant Z=-1.69, p=0.09, r=0.23.

The change in global satisfaction between continuous (Md=2, n=3) and intermittent (Md=4, n=3) group in patients who developed abnormal ejaculation is statistically insignificant Z= -1.6, p= 0.109, r=0.65.

The association between variables were checked using ordinal logistic regression. The model fitting information table shows the p value of 0.001 which shows the model is fit for the data. the goodness of fit table shows contains Pearson chi square test and deviance test which show whether the model is fit or not for the data. The model is said to be fit if the p value is>0.005. in our research the Pearson chi square test and deviance test p value are 0.636 and 1.000 respectively. The association between dependent and independent variable shows the association between 3rd month IPSS score and baseline IPSS score, Baseline QMAX and baseline PVR were assessed and the result shows only variable which significantly affect the 3rd month IPSS score is baseline IPSS score with value of (p=0.00, 95% CI of (0.195,0.674) and pseudo R value of 0.467(table12).

Table1: drug type

Drug type	Frequency	Percent
alfuzosin	19	70.4
tamsulosin	8	29.6
Total	27	100

Table 2: Potency from tamsulosin group

Erectile function	Frequency	percentage
Potent	6	75%
Impotent	2	25%
total	8	100%

Table 3: Abnormal ejaculation (tamsulosin group)

Abnormal ejaculation	Frequency	percentage
yes	3	50%
NO	3	50%
total	6	100%

Table 4: Response of abnormal ejaculation after intermittent dose

Positive response	Frequency	percentage
Yes	3	100%
No	0	0%
Total	3	100%

Table 5: adverse effect of drug

Have adverse effect	Frequency	percentage
No	21	77.8%
Yes	6	22,2%
total	27	100%

6: Types of adverse effect

Type of adverse effect	Frequency	percentage
dizziness	1	16.6%
syncope	2	33.3%
Headache	2	33.3%
Dizziness+ syncope	1	16.6%
total	6	100%

Table 7: response after intermittent dose

Response	Frequency	percentage
Yes	6	100%
No	0	0%
total	6	100%

Table 8: Prevalence of comorbidity

comorbidity	Frequency	percentage
NO	19	
DM	4	
Cardiovascular disease	4	
Neurologic/Cerebrovascular disease	0	
total	27	100%

Table 9: Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
baseline_Qmax	.172	27	.040	.891	27	.008
_3rd_month_Qmax	.233	27	.001	.693	27	.000
baseline_PVR	.184	27	.020	.849	27	.001
_3rd_month_PVR	.233	27	.001	.705	27	.000
baseline_IPSS_score	.191	27	.013	.919	27	.036
_3rd_month_IPSS_score	.189	27	.014	.911	27	.024

a. Lilliefors Significance Correction

Table 10: Wilcoxon sign rank test

Test Statistics[a]

	_3rd_month_Qmax - baseline_Qmax	_3rd_month_PVR - baseline_PVR	_3rd_month_IPSS_score - baseline_IPSS_score
Z	-.706[b]	-1.766[c]	-1.694[c]
Asymp. Sig. (2-tailed)	.480	.077	.090

a. Wilcoxon Signed Ranks Test

b. Based on positive ranks.

c. Based on negative ranks.

Table11: global satisfaction

Test Statistics[a]

	Global satisfaction after intermittent dose- global satisfaction on daily dose
Z	-1.604[b]
Asymp. Sig. (2-tailed)	.109

a. Wilcoxon Signed Ranks Test
b. Based on negative ranks.

Table 12: ordinal logistic regression

Model Fitting Information

Model	-2 Log Likelihood	Chi-Square	df	Sig.
Intercept Only	128.748			
Final	111.956	16.792	3	.001

Link function: Logit.

Goodness-of-Fit

	Chi-Square	df	Sig.
Pearson	274.134	283	.636
Deviance	111.956	283	1.000

Link function: Logit.

Pseudo R-Square	
Cox and Snell	.463
Nagelkerke	.467
McFadden	.130

Link function: Logit.

	3rd month IPSS score			
Variables	Estimate	Std error	Significance	95% Confidence interval
Baseline IPSS	0.435	0.122	0.00	{0.195,0.674}
Baseline Qmax	-0.04	0.057	0.483	{-0.152,0.072}
Baseline PVR	0.02	0.015	0.200	{-0.010,0.05}

7. Discussion

The distribution of the data was checked with shapiro wilke test and it is not normally distributed then data analyzed using Wilcoxon sign rank test. The Wilcoxon Signed Ranks Test assessed changes in Q-max, IPSS score, and post-voiding residual from baseline to the 3rd month. The association between dependent and independent variables were checked using ordinal logistic regression and the result shows the only variable which significantly affect the 3rd month IPSS score is baseline IPSS score with p value (p=0.00) with 95% confidence interval of (0.195,0.674) and pseudo R value of 0.467.

The results indicated that none of the measures showed statistically significant differences between continuous and intermittent treatment groups. Specifically, the changes in Q-max ($Z = -0.706$, $p = 0.480$, $r = 0.09$), post-voiding residual ($Z = -1.766$, $p = 0.077$, $r = 0.24$), IPSS score ($Z = -1.69$, $p = 0.09$, $r = 0.23$). The patient baseline IPSS score was assessed by preprepared questionnaire using kobo toolbox and baseline post voiding residual measured using the ultrasound immediately after they void. Those patients with low to moderate symptom score and with post voiding residual volume less than 300 ml are sent for uroflowmetry. Those patients who had low to moderate symptom score and having good baseline PVR<400ml with Q-max>5ml, we put them on intermittent every otherday dose of uroselective alpha blocker and followed them with phone number. Those patients who report worsening of symptoms discontinued the follow up and were taking daily dose of the drug by themselves were four in number. One patient who have baseline PVR, symptom score and Q-max did not come during the follow up. The remaining 27 patients followed over the period of three months. At the 3rd months their PVR, IPSS score and Q-max were rechecked and only one patient with low Q-max were returned to his previous daily dose of alpha blocker and the remaining 26 patient has good response and continued every other day dose of alpha blocker. The study result showed those

patients who were on everyotherday dose of alpha blocker had no any statistically significance difference with baseline symptom score, PVR and Q-max. The result supports the null hypothesis which is making continuous daily dose alpha blocker respondent to everyotherday dose does not change their symptom score, PVR and Q-max. Several studies are done efficacy of the intermittent every other day dose of uroselective alpha blocker on the continuous dose respondent benign prostatic hyperplasia patients.

Kaplan *et al* 1998 studied 79 patients who are respondent to continuous daily dose y categorizing them in to three groups. Group one were 27 in number and continued previous daily dose of alpha blocker, group two were 26 in number and continued everyotherday dose of alpha blocker and group three were 26 in number and discontinued the alpha blocker. The 79 patients were followed for 6 months with IPSS score ad q-max at 3rd and 6th months. The result showed statistically insignificant change in group one and group two($P=0.43$) but the group three when compared with group one and two, it showed statistically significant change ($P<0.02$; $P<0.015$)(7). The above result is similar with our result which is statistically insignificant change between the baseline and 3rd month value($P>0.05$).

Soliman *et al* 2023 studied in 30 patients who were taking daily dose of tamsulosin for LUTS secondary to BPH and complained the ejaculatory dysfunction. Out of the 30 patients, 5 patients were excluded because of worsening of the symptoms and incomplete follow up. 25 patients were followed with baseline and 3rd month IPSS score and PVR and improvement of abnormal ejaculation with global satisfaction. The change in IPSS score and PVR was found to be statistically significant ($P = 0.0001$). The change in the ejaculatory function was 80% which was statistically significant($p=0.0001$). The global stratification index of the patient improved from neutral or unsatisfied to satisfied or very satisfied. Even though the change in symptoms and PVR was statistically significant, patients were satisfied because of the improvement in the side effect(14). This result especially improvement of the ejaculatory function is similar with our result even though statistics of our result is insignificant but those who developed abnormal ejaculation is very small in our case.

Erduran *et al* 2005 studied the efficacy of alpha blocker on continuous alpha blocker respondent 91 patients by classifying them in three group. Group one were 31 patients who continue daily dose of alpha blocker, group two were 34 patients who continue intermittent every other day dose of alpha blocker and group three were 26 patients who discontinued the alpha blocker. All of the patients are followed with IPSS score, Q-max and post voiding residual at the 3rd and 6th months. The differences in IPSS score, Q-max, and PVR between group one and group two at 3 and 6 months were statistically insignificant ($P > 0.05$) but change between group one and three and group two and three are statistically significant ($P<0.05$). They concluded daily and every other day dose of alpha blocker has comparable improvement of urinary symptoms and urinary flow but the discontinuation of the medication leads to return of urinary symptoms(6).This study finding is similar with our study where putting the patient on intermittent every other day dose of alpha blocker has equivalent result on the daily respondent.

Goktas *et al* 2010 studied 30 patients out of 405 patients who developed abnormal ejaculation after start of the daily dose of alpha blocker. the patients baseline IPSS score, Q-max and PVR was assessed and reassessed at the 6th week. The change in IPSS score, Q-max, and PVR was not

found to be statistically significant (P > 0.05). The improvement in retrograde ejaculation was in 63.3% with statistically significant improvement(P=0.02) but the change for decreased and absent ejaculation was not statistically significant (P=0.42, p=0.61) respectively. The study concluded that the change in urinary symptoms, residual volume and urinary flow was insignificant when daily and intermittent dose was compared but the improvement of retrograde ejaculation was statistically significant(12). This study is in line with our study which shows the change in IPSS score, Q-max and PVR between daily and intermittent dose has no any statistically significant change but the side effect was improved on the intermittent group.

Soliman *et al* 2019 studied 93 patients fulfilled the inclusion criteria out of 118 patients who developed abnormal ejaculation from 1,743 men taking tamsulosin were grouped in to three groups. Group one having 31 patients were taking intermittent dose of tamsulosin everyotherday, group two 31 patients were taking low dose of daily tamsulosin and group three 31 patients were taking daily full dose of tamsulosin. patients IPSS score, Q-max and QOL were assessed at the baseline and 3rd month. The change in the score was not statistically significant between three groups(P>0.05). the quality of life change is similar between those taking daily full dose and every other day dose but it was worse on those taking low dose daily. The improvement of the ejaculatory side effect was best improved by low dose daily tamsulosin group followed by everyotherday group but the ejaculatory side effect persisted in those taking full daily dose of the tamsulosin. The conclusion of the study was those patients who are bothered by the ejaculatory side effect of the daily dose of the drug, every other day dose of the tamsulosin has significant improvement in the quality of life without deviating urinary symptom and urinary flow improvement(15).

When this study is compared with our finding, the change in urinary symptoms, urinary flow has no any statistically significant change between daily dose group and intermittent group with improvement in the side effect. This shows intermittent dose of alpha blocker is one choice of treatment on those who has good response to daily dose of alpha blocker or those with side effect but has response to daily dose of alpha blocker.

The uroselective alpha blockers are main stay of medical management of lower urinary tract symptoms secondary to benign prostatic hyperplasia. Tamsulosin and alfuzosins are the predominant drugs prescribed by the treating physicians in our set up. Alfuzosin is α1a and α1b blocker with side effect on the cardiovascular system than tamsulsoin which has α1a and α1d effect with less cardiovascular side effect but higher side effect on the ejaculation because of its retrograde ejaculation effect and its effect on the fibromusculature of seminal vesicle, vas deferens which is dose dependent. The presence of its effect on the α1d receptor makes it better drug for those patients with mixed symptom of both storage and voiding lower urinary symptoms.

This study assessed the effects of intermittent versus continuous treatment with uroselective alpha-blockers, specifically alfuzosin and tamsulosin, in a cohort of 27 patients with a mean age of $63 \pm 9.7\ years$. The findings reveal several important insights into the efficacy and tolerability of these treatments, as well as the side effects experienced by the patients.

The demographic data indicate a predominance of alfuzosin use (70%) over tamsulosin (30%). Among those using tamsulosin, it is noteworthy that a significant proportion (75%) remained potent, suggesting that the majority of patients maintained sexual function while on this medication. However, 50% of those who were potent reported abnormal ejaculation, including low volume or anejaculation. This highlights a critical side effect of tamsulosin that may impact patient adherence and quality of life.

Interestingly, all patients who experienced abnormal ejaculation responded positively to intermittent dosing of tamsulosin, suggesting that this dosing strategy may mitigate some of the adverse effects associated with continuous use. Additionally, 22% of patients reported other side effects, such as syncope, dizziness, and headache, with syncope being the most common. Importantly, those who experienced side effects reported either total or partial improvement with intermittent dosing, indicating that this approach may enhance tolerability.

Comorbidity analysis revealed that cardiovascular disease and diabetes mellitus were present in 15% of patients, underscoring the importance of closely monitoring these populations when prescribing alpha-blockers especially in patients with cardiovascular disease, given their potential cardiovascular implications.

The Wilcoxon Signed Ranks Test was used to evaluate changes in Q-max, quality of life, IPSS score, and post-void residual volume from baseline to the third month. The results showed no statistically significant differences between the continuous and intermittent treatment groups for any of the measures. Specifically, the changes in Q-max ($Z = -0.706$, $p = 0.480$, $r = 0.09$), post-voiding residual ($Z = -1.76$, $p = 0.077$, $r = 0.24$), AUA symptom score ($Z = -1.585$, $p = 0.113$, $r = 0.21$), and quality of life ($Z = -1.706$, $p = 0.088$, $r = 0.23$) suggest that while there were trends toward improvement in the intermittent group, these did not reach statistical significance.

These findings may imply that both treatment strategies offer similar efficacy in managing urinary symptoms, although the intermittent dosing regimen could provide additional benefits in terms of side effect management. Given the trends observed, further studies with larger sample sizes and longer follow-up periods may be warranted to better assess the potential advantages of intermittent dosing of uroselective alpha-blockers. according to above finding, we can conclude that intermittent uroselective alpha blocker has equal effect like continuous uroselective alpha blocker in those patients who responded to continuous dosage of alpha blocker.

8. conclusion

Both continuous and intermittent uroselective alpha-blocker treatments appear to yield comparable outcomes, the latter may enhance patient tolerability and adherence due to its favorable side effect profile with good quality of life.

Intermittent dose treatment is one of choice for those patients who responded with continuous alpha blocker with no statistically significant change in comparable parameters. it will decrease the financial burden to the patient, work load to the treating physician and increase quality of life with decreased side effect of the drug.

9.Limitation

Small sample size

Short duration of follow up

10. Recommendation

Even though the sample is small, still the intermittent every other day treatment can be recommended with low to moderate post continuous treatment baseline IPSS score and moderate to normal Q-max patients and on those with side effect of the drug but it needs close follow up of the patient.

Selection of alpha blocker should be based on the fertility need of the patient, urinary symptom predominance, side effect profile of the patient and comorbidity of the patient.

Further research might be needed on half-life of the drug, drug receptor complex time

11.Annex

Consent: Data was collected from direct patient interviews and investigation

oral consent was taken.

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