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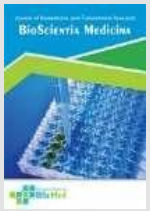

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Effect of Combination of Tamsulosin and Tadalafil in Benign Prostate Hyperplasia Patients on International Prostate Symptom Score

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A B S T R A C T

Background: Benign prostate hyperplasia (BPH) is the most common pathological condition that contributes to lower urinary tract symptoms (LUTS) in men. Alpha1-blockers are recommended as first-line therapy for LUTS due to BPH (LUTS-BPH). Phosphodiesterase 5 (PDE5-I) inhibitors, which have been used as first-line therapy for erectile dysfunction, have also been found to be effective in treating LUTS-BPH. However, the appropriate combination therapy strategy is still unclear until now. **Methods:** This study used an experimental design on 17 BPH patients on medical therapy. The patient was given Tamsulosin 0.4 mg monotherapy for 7 days and then continued combination therapy with Tamsulosin 0.4 mg and Tadalafil 5 mg for the next 7 days. Total IPSS score, obstruction, irritation, and quality of life (QoL) were assessed before treatment, after monotherapy, and after combination therapy. **Results:** The mean age of the research subjects was 62.12 years. Improvements in the total IPSS value, obstruction, irritation, and QoL showed significant changes in both types of therapy compared to the initial value. Combination therapy gave better results than monotherapy, with a mean difference in the decrease in the total IPSS value of 4.41 ($p<0.001$), obstruction of 3.18 ($p<0.001$), irritation of 1.41 ($p<0.001$), and QoL 0.6 ($p<0.001$). **Conclusion:** The combination therapy of Tamsulosin 0.4 mg with Tadalafil 5 mg once a day showed clinically and significantly better results than monotherapy in total IPSS, obstruction, irritation, and QoL values in LUTS-BPH patients.

1. Introduction

Benign prostate hyperplasia (BPH) is the most common and important pathological condition that contributes to lower urinary tract symptoms (LUTS) in men. This condition substantially affects the patient's quality of life.[1,2] Men with BPH may develop LUTS symptoms followed by other conditions such as decreased urine flow rate, increased incidence of urinary tract infections, acute urinary retention, and increased incidence of surgery for BPH. This has a greater unpleasant impact on the patient's quality of life.[1] BPH occurs in about 70% of men over the age of 60. This figure will increase to 90% in men over 80 years old. The exact incidence of BPH in Indonesia has never been studied, but as an illustration of the prevalence at Cipto Mangunkusumo Hospital (RSCM) in 1994-2013 found 3,804 cases with an average age of 66.61 years. Meanwhile, at Hasan Sadikin Hospital, data obtained from 2012-2016 found 718 cases with an average age of 67.9 years.[3] LUTS complaints due to BPH (LUTS-BPH) is a common disorder in elderly men with a significant negative impact on quality of life (QoL).[1,4] One of the widely used scoring systems is the International Prostate Symptom Score (IPSS), which has been developed by the American Urological

Association (AUA) and standardized by the World Health Organization (WHO).[3] Based on the pathophysiological relationship between LUTS-BPH and erectile dysfunction, several studies have confirmed that the two diseases often coexist and have a prevalence that continues to increase with age.[4]

One treatment option for LUTS-BPH is a α1-adrenoceptor (α1-blocker)[3,6] Drugs of this class work to reduce sympathetic tone by α1-adrenergic receptors, subsequently resulting in the relaxation of smooth muscle in the prostate/bladder neck, increased urine, and improvement of LUTS symptoms.[1,3,6] Drugs are Alpha1-blockers available in different formulations. Although this results in different pharmacokinetic and tolerability profiles, the overall difference in clinical efficacy between the different formulations appears to be modest. However, several studies have shown that all α1-blocker drugs have the same effectiveness at the right dose.[7] Tamsulosin is an alpha1-blocker drug that is efficient in improving dysuria and other BPH symptoms by selectively blocking adrenergic receptors in the prostate to relax prostate smooth muscle.[1] Phosphodiesterase 5 (PDE5-I) inhibitors have been used globally as first-line drugs for erectile dysfunction. Drugs of this class have also been found to be proven to treat LUTS-BPH effectively because phosphodiesterase is also expressed and biologically active in the human bladder, urethra, and prostate tissue.[5,6] The mechanism of action of PDE5-I is to increase the concentration and prolong the activity of intracellular cyclic guanosine monophosphate (cGMP), that it can reduce the smooth muscle tone of the detrusor, prostate, and urethra.[6]

Currently, in Indonesia, there are three types of PDE5-I drugs available, namely sildenafil, vardenafil, and tadalafil.[6] To date, only Tadalafil 5 mg has been officially licensed for the treatment of LUTS in men with or without erectile dysfunction. The use of Tadalafil 5 mg once a day can reduce the IPSS value by 22-37%. This significant decrease was felt after one week of use. Gacci et al. (2012) showed that younger men with lower body mass index and more severe LUTS symptoms benefited most from treatment with PDE5-I.[3,7,9] In Indonesia, Tadalafil has not yet been included in the list of drugs covered by national health insurance. Therefore, it is not surprising that the use of Tadalafil for LUTS-BPH is still quite low. European Association of Urology (EAU) guidelines recommend α1-blocker drugs as first-line therapy for LUTS-BPH. PDE5-I, as a first-line therapeutic drug for erectile dysfunction, has also been shown to be effective and safe in treating LUTS-BPH. However, the appropriate combination therapy strategy is still unclear until now.[4] Only Tamsulosin, an alpha1-blocker, is permitted for combination therapy with tadalafil for the treatment of LUTS-BPH. Until now, studies assessing the effectiveness of the combination therapy of Tamsulosin and Tadalafil as a therapy for LUTS-BPH have not been carried out. In Indonesia, data on the effectiveness of using PDE5-I monotherapy or as a combination therapy for LUTS-BPH are still scant. This study aims to assess the effect of giving Tadalafil 5 mg in patients with benign prostate enlargement on Tamsulosin 0.4 mg therapy.

2. Methods

This study is an experimental study with a pre-post test approach with a control group design in order to determine the effect of Tadalafil 5 mg in patients with benign prostate enlargement on Tamsulosin 0.4 mg on the International Prostate Symptom Score (IPSS). The research was conducted at the Dr. M. Djamil General Hospital Padang, Citra Bunda Medical Center Padang Hospital, and Special Surgery Hospital Ropanasuri Padang for three months, starting from March 2022 to May 2022. A total of 17 research subjects participated in this study with inclusion criteria, namely patients with LUTS due to BPH who were given single therapy Tamsulosin 0.4 mg for at least one week and were willing to follow and sign the informed consent. This study was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Universitas Andalas, Padang, Indonesia (No.678/UN.16.2/KEP-FK/2022).

Univariate analysis is used on one variable with the aim of knowing and identifying the characteristics of

that variable. The mean or standard deviation (SD) of the IPSS score will be calculated in combination therapy with Tamsulosin 0.4 mg and Tadalafil 5 mg. Bivariate analysis was used to examine the relationship between the independent variable and the dependent variable. The analysis was carried out using the Repeated ANOVA test. Data analysis was performed using SPSS version 25 software.

3. Results

The mean age of the patients who were the subjects of this study was 62.12 years, with the youngest age being 52 years and the oldest age being 72 years (Table 1).

Table 1. Characteristics of research subjects

Characteristics	Mean	Min-Max	SD
Age (years)	62.12	52-72	± 5.89

Table 2 shows the effectiveness of adding tadalafil to IPSS scores. Table 2 shows the effectiveness of tadalafil against total IPSS, obstructive IPSS, irritant IPSS, and QoL IPSS. Tadalafil administration was able to reduce total IPSS, obstructive IPSS, irritative IPSS, and IPSS QoL better than those who only received tamsulosin and also better than before therapy. There were complaints of side effects that appeared after the addition of Tadalafil 5 mg, namely in 1 patient who complained of having myalgia.

Table 2. Comparison of the effectiveness of IPSS

	IPPS total		p-value
	Mean	SD	
Before therapy	19.76	5.29	<0.001
Tamsulosin	11.12	3.48	
Tamsulosin + Tadalafil	6.88	3.02	
	IPPS obstruction		p-value
	Mean	SD	
Before therapy	13.59	4.12	<0.001
Tamsulosin	7.65	2.67	
Tamsulosin + Tadalafil	4.88	2.32	
	IPPS irritation		p-value
	Mean	SD	
Before therapy	6.47	3, 56	<0.001*
Tamsulosin	3.47	1.66	
Tamsulosin + Tadalafil	1.88	1.22	
	IPPS QoL		p-value
	Mean	SD	
Before therapy	4.12	0.78	<0.001*
Tamsulosin	2.71	0.47	
Tamsulosin + Tadalafil	1, 88	0.69	

4. Discussion

The addition of 5 mg Tadalafil therapy in BPH patients on Tamsulosin 0.4 mg therapy is better in treating LUTS-BPH complaints in general. This is in accordance with studies where the researchers examined a total of 40 patients who were divided into two groups of Tamsulosin 0.4 mg monotherapy and combination therapy Tamsulosin 0.4 with Tadalafil 5 mg and found a significant improvement in the total IPSS value of the combination therapy group when compared to the monotherapy group with a difference in the value of 3, 7 and p-value = 0.01. Another study

showed similar results, in which they studied 140 patients with complaints of LUTS-BPH who were divided into two groups of Tamsulosin 0.4 mg monotherapy and Tamsulosin 0.4 mg combination therapy with Tadalafil 5 mg. The results obtained an improvement in the total IPSS value with a difference of 1.69 and a p-value = 0.01. Another study reported an improvement in the total IPSS score of 1.85 in the combination therapy group. This is due to the synergistic effect of Tadalafil and Tamsulosin, which can improve LUTS-BPH symptoms and erectile function on combination therapy. Tadalafil enhances the inhibitory effect of tamsulosin on the bladder, neck, and prostate. The combination of alpha1-blocker and tadalafil had an additional relaxing effect on the human corpus cavernosum in their in vitro study.[10-14]

There were no serious side effects in this study. The side effects that occurred with the addition of Tadalafil 5 mg were 1 patient (5.88%) complaining of myalgia. Patients who complained of myalgia experienced the same thing within 3 days of the addition of Tadalafil therapy. The percentage of incidence of side effects in this study was relatively high due to the small number of samples. The incidence of a patient suffering from side effects was higher in the combination therapy group. This is in line with studies reporting that myalgia is a common complaint in the combination therapy group. Although the pathophysiological mechanisms leading to back pain and/or myalgia associated with Tadalafil treatment are still unknown, one study reported the incidence of back pain and/or myalgia in subjects in the Tadalafil treatment group indistinguishable from the idiopathic back pain and/or myalgia in the treatment group. The placebo used measurements and laboratory tests used in this study, and these findings identified no serious underlying medical pathology.[15-21]

5. Conclusion

Combination therapy of Tamsulosin 0.4 mg with Tadalafil 5 mg once a day showed clinically and significantly better results than monotherapy on total IPSS, obstruction, irritation, and QoL values in LUTS-BPH patients.

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