CORRELATION OF THE IMPACT OF TAMSULOSIN/DUTASTERIDE COMBINATION THERAPY ON ERECTILE DYSFUNCTION (ED) IN BENIGN PROSTATIC HYPERPLASIA (BPH) IN PKU MUHAMMADIYAH GOMBONG HOSPITAL, KEBUMENSICOVAGINAL FISTULA REPAIR AT TERTIERY HOSPITAL: COHORT STUDY

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ABSTRACT

Objective: *This study assessed the impact of a fixed-dose combination 5α-reductase inhibitor (5-ARI) dutasteride 0.5 mg and the α-blocker (AB) tamsulosin 0.4 mg on erectile dysfunction (ED) using The International Index of Erectile Function-5 (IIEF-5) score and Erectile Hard Score (EHS) in patients with lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH).* ***Material & Methods:*** *This was an analytical cross-sectional with consecutive sampling. We reviewed the medical records of the symptomatic BPH patients. Then we interviewed The International Prostate Symptom Score (IPSS), Quality of Life (QOL), IIEF-5, and EHS scores after administered combination therapy. The data were analyzed with SPSS IBM 21.0 using univariate and then bivariate analysis.* ***Results:*** *Forty (40) patients fulfilled inclusion criteria. The results showed that the frequency of patients at most in the age range of 50-59 years (40%), most of IPSS after therapy showed mild grade 45%, and moderate grade 55%. The QOL average score is 2.08, most of the patients felt pleased (35%). IIEF-5 average score after treatment is 11.6 (moderate ED) and the EHS is 2.48 (grade 2: tumescence with minimal rigidity). The Spearman test showed that there was no correlation between IPSS and IIEF-5, the score is -0.658. Then, the Spearman correlation score between BPH grade after combination treatment and ED grade is 0.739 and had a statistically significant 0.000 ($p<0.001$).* ***Conclusion:*** *This research shows that there is a correlation of the impact of tamsulosin/ dutasteride combination therapy on ED in BPH with secondary LUTS.*

Keywords: *BPH, erectile dysfunction, tamsulosin/dutasteride combination.*

ABSTRAK

Tujuan: *Mengetahui pengaruh kombinasi terapi 5α-reductase inhibitor (5-ARI) dutasteride 0.5 mg dan α-blocker (AB) tamsulosin 0.4 mg pada disfungsi ereksi (DE) menggunakan skor The International Index of Erectile Function-5 (IIEF-5) dan Erectile Hard Score (EHS) pada pasien dengan lower urinary tract symptoms (LUTS) akibat benign prostatic hyperplasia (BPH).* ***Bahan & Cara:*** *Penelitian ini bersifat analitik menggunakan rancangan potong-lintang dengan consecutive sampling. Kami menilai kembali catatan rekam medis pada pasien dengan BPH. Selanjutnya melalukan wawancara menggunakan The International Prostate Symptom Score (IPSS), Quality of Life (QOL), IIEF-5, and skor EHS setelah pemberian terapi kombinasi. Data dianalisis dengan software SPSS IBM 21.0 menggunakan analisis univariate dilanjutkan analisis bivariate.* ***Hasil:*** *Empat puluh pasien memenuhi kriteria inklusi. Didapatkan pasien BPH terbanyak usia 50-59 tahun (40%), skor IPSS setelah terapi menujukkan derajat ringan 45%, dan sedang 55%. Skor rerata QOL adalah 2.08, sebagian besar pasien merasa senang (35%). Skor rerata IIEF-5 setelah terapi adalah 11.6 (DE sedang) dan EHS adalah 2.48 (derajat 2). Hasil uji Spearman menunjukkan tidak ada hubungan antara IPSS dengan IIEF-5, dengan nilai -0.658. Kemudian, nilai korelasi Spearman antara derajat BPH setelah terapi kombinasi dan derajat DE adalah 0.739 dan memiliki signifikansi statistik 0.000 ($p<0.001$).* ***Simpulan:*** *Penelitian ini menunjukkan bahwa ada hubungan pengaruh terapi kombinasi tamsulosin/dutasteride pada DE terhadap pasien BPH dengan LUTS.*

Kata kunci: *BPH, disfungsi ereksi, kombinasi tamsulosin/dutasteride.*

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INTRODUCTION

Benign Prostate Hyperplasia (BPH) is the term for hyperplasia of stromal cells and epithelial cells of the prostate gland. BPH develops in men who are older and have testes that produce testosterone.[1-2] Approximately 50% of men over 50 years have pathological evidence of BPH.[3-4] In Indonesia, the incidence of BPH is still uncertain, because there has not been much research on its incidence. According to data at Hasan Sadikin Hospital (RSHS) from 2012-2016, there were 718 cases with an average age of 67.9 years.[1]

The symptoms of LUTS in BPH are obstruction, post-voiding symptoms, and irritation. To assess the severity of LUTS, urologists create a scoring system that can be filled in by patients in the International Prostate Symptom Score (IPSS). BPH with LUTS is also associated with erectile dysfunction (ED).[4-5]

The treatment of BPH aims to improve the patient's quality of life. Medical therapy is given if the IPSS score > 7, such as (1) 1- blockers (AB) e.g. tamsulosin, (2) 5α- reductase inhibitor (5-ARI) e.g. dutasteride. Combination therapy of AB and 5-ARI are used to obtain a synergistic effect and shows better results in reducing LUTS symptoms. However, combination therapy can also increase the risk of side effects of sexual disorders (ED).[6]

ED or impotence is a persistent inability to achieve or maintain erectile function for satisfactory sexual activity.[7] The prevalence of ED in the world according to the Cologne Male Survey is 19.2%. The Asian population had ED about 15%. Data in Indonesia through a web-based survey estimates that 35.6% suffer from ED.[8]

The International Index of Erectile Function-5 (IIEF-5) and Erectile Hard Score (EHS) questionnaires can be used to diagnose ED.[9] The limitation of the questionnaires are that they cannot differentiate the pathophysiology of ED.[10]

OBJECTIVE

This study can be an initial evaluation of the impact of the side effects of tamsulosin/dutasteride combination therapy on ED in BPH patients so that concurrent management can be carried out.

MATERIAL & METHODS

This study is an analytic study using a cross-sectional design with consecutive sampling. This research was conducted at the urology polyclinic of PKU Muhammadiyah Gombong Hospital, Kebumen from April to May 2021. The sample was BPH patients at the urology polyclinic who met the inclusion criteria and did not meet the exclusion criteria. The sample size is 40 subjects.

The inclusions criteria in this study are: (1) Male patients at the urology polyclinic diagnosed by a urological surgeon as BPH, (2) Patients receiving combination therapy of tamsulosin 0.4 mg and dutasteride 0.5 mg for at least 6 months, (3) Patients aged 40-80 years, (4) Having sexual activity with a partner, and (5) Willing to be included as research subjects. Exclusion criteria in this study are (1) Patients with a history of prostate cancer and surgery, (2) Patients with congenital sexual disorders prior to therapy, and (3) Patients with a history of Phosphodiesterase-5 (PDE-5) inhibitor. The collected data was analyzed with SPSS IBM 21.0 using univariate analysis followed by bivariate analysis.

RESULTS

The data collected were 40 subjects who met the inclusion criteria and did not meet the exclusion criteria. It showed that the age of the respondents ranged from 49-80 years, with an average age of 62.98 years. Based on age group, most BPH patients with tamsulosin/dutasteride combination therapy were aged 50-59 years, 16 respondents (40.0%).

The distribution of the frequency of BPH patients based on the degree of BPH experienced by patients after using tamsulosin/dutasteride combination therapy using the IPSS score shows in Table 1. Table 1 shows that the number of IPSS scores found ranged from 2-17, with an average score of 9.78.

Table 1. Degree of BPH distribution.

Degree of BPH	Total	%
Mild (0-7)	18	45.0
Moderate (8-19)	22	55.0
Severe (=20)	0	0.0
Total	40	100.0
Average	9.78	
Range	2-17	

The frequency distribution of BPH patients with tamsulosin/dutasteride combination therapy who experienced ED was assessed using the IIEF-5 score shown in Table 2.

Table 2. Patients who experienced ED.

Degree of ED	Total	%
Normal (=22)	0	0.0
Mild (17-21)	1	2.5
Mild-Moderate (12-16)	21	52.5
Moderate (8-11)	14	35.0
Severe (5-7)	4	10.0
Total	40	100.0
Average	11.60	
Range	5-20	

Table 2 shows that the number of IIEF-5 scores is between 5-20, with an average score of 11.60. The distribution of the QOL of BPH patients after treatment shown in Table 3.

Table 3. Degree of QOL after treatment.

Degree of QOL	Total	%
Delighted	4	10.0
Pleased	14	35.0
Mostly satisfied	6	15.0
Mixed (equally satisfied and dissatisfied)	9	22.5
Mostly dissatisfied	5	12.5
Unhappy	2	5.0
Terrible	0	0.0
Total	40	100.0
Average	2.08	
Range	0-5	

Table 3 shows that the QOL scores ranged from 0-5, with an average score of 2.08 and the highest QOL level of BPH patients was 35%. The distribution of the frequency of penile tension during erection was assessed by the EHS score shown in Table 4.

Table 4. EHS score after treatment.

Erection Hardness	Total	%
Tofu	4	10.0
Peeled Banana	17	42.5
Unpeeled Banana	15	37.5
Cucumber	4	10.0
Total	40	100.0
Average	2.48	
Range	1-4	

Table 4 shows that the EHS scores found in most is like a peeled banana as many as 17 respondents (42.5%), with an average of 2.48. To see the relationship between the effect of tamsulosin /dutasteride combination therapy on erectile dysfunction in BPH, the Pearson correlation test was used on a parametric test. However, in this study, the data distribution was not normal. Therefore, the data was analyzed using Spearman correlation (Table 5).

Table 5. The results of the Spearman analyzed between BPH patient after treatment and ED.

		Total score IIEF-5
Total score IPSS	R	-0.658**
	P	0.000
	N	40

** Significant correlation at 0.01 (p).

The results of the analysis above show a significance value of 0.000 which concluded that the correlation between the total IPSS score and the total IIEF-5 score was not significant. The Spearman correlation value of -0.658 indicates the strength of the strong correlation and the direction of the correlation is negative, namely the greater the number of IPSS scores, the smaller the number of IIEF-5 scores. The relationship between the degree of BPH after treatment with the degree of ED shows in Table 6.

Table 6. The results of relationship between the degree of after treatment with the degree of ED.

		Degree of ED
Degree of BPH	R	0.739**
	P	0.000
	N	40

** Significant correlation at 0.01 (p)

The results of the above analysis showed a significance value of 0.000 which concluded that the correlation between the degree of BPH after treatment and the degree of ED was statistically significant. The Spearman correlation value of 0.739 indicates the strength of the strong correlation and the direction of the positive correlation, namely the greater the degree of BPH, the greater the degree of ED experienced by the patient.

DISCUSSION

Most of the patients (40%) in this study were 50-59 years old. This is in accordance with the prevalence study of Egan, 2016, that 50% of BPH patients are aged around 50 years and over. The

calculation of the average IPSS score after combination therapy was 9.78, with the criteria being 18% mild and 55% moderate (Table 1). The success rate study for the tamsulosin/dutasteride combination therapy, Zuhirman, 2018 at the Arifin Achmad Hospital showed an improvement of around 18%.[11] Another study, a 2-year observation of combination therapy showed a 25% improvement in IPSS scores. The combination therapy improves voiding and storage symptoms compared to monotherapy.[12-13]

A limitation of our study was that the initial IPSS score before therapy was not calculated. Likewise, for the QOL in this study (Table 3), the mean score was 2.08 and the patients felt happy (35%). Antonio et al., 2016, concluded that the QOL is equivalent to the IPSS score. The IIEF-5 score was used to measure the degree of ED after combination therapy, with a mean score of 11.6 (Table 2), including moderate ED. It can be illustrated that according to the results of the meta-analysis of Zhou et al., 2019, four out of five Randomized Control Trials (RCT) studies involving 4230 respondents showed an increase in the severity of ED after combination therapy.[14]

Combination therapy has effectiveness in reducing symptoms, prostate volume, and risk of surgery.[6] However, this therapy has limitations in the form of sexual adverse events in the form of decreased libido, ED, and ejaculation problems. Furthermore, the occurrence of side effects such as ED was caused by the 5-ARI dutasteride. Roehborn et al., 2010, also reported through a 4-year follow-up analysis, 7% of patients given dutasteride had ED compared with 5% given tamsulosin. Furthermore, 3% of patients given dutasteride experienced decreased libido compared to 2% in the tamsulosin group.[12]

Another study by Erdemir et al., 2008 showed that ED occurred in 3.4-15.8% of patients treated with 5-ARI. The main goal of 5-ARI in prostate therapy is to reduce prostate volume (up to 30%) by preventing the conversion of testosterone to a stronger androgen, namely dihydrotestosterone (DHT) so that there is no stimulation of DNA synthesis in the nucleus and cellular growth. DHT is involved in 70-90% of erectile physiology.[15-16]

In animal model studies, androgen depletion causes deterioration of the dorsal neural structure, endothelial morphology, decreased trabecular smooth muscle, increased intracellular matrix, and penile tissue atrophy. It also increases the incidence of venous leakage and an increase in adipocytes in the subtunica of the corpus cavernosum. Furthermore, there was inhibition of the production of endothelial nitric oxide synthase (eNOS) proteins and enzymes, and neuronal nitric oxide synthase (nNOS) which are mediators of penile erection.[17]

Meanwhile, tamsulosin as a third generation AB which is primarily selective for α-1A receptors in the prostate has side effects of ejaculation problems, namely a decrease in the number of ejaculate and the amount of semen. Prior to orgasm, the pressure in the urethra proximal to the veromontanum peaks. Therefore, the semen flows to the site of lower pressure towards the external urethra. However, due to the uroselective effect of tamsulosin it relaxes the smooth muscle of the bladder neck, reducing pressure proximal to the veromontanum and retrograde ejaculation occurs.[18]

A study of giving tamsulosin 0.4 mg for six months, found 64% (25/39) of patients experienced ejaculation problems and 15% of them experienced complete absence of ejaculate. Although there is still debate, Stojanovic et al., 2015, stated that with the dominance of -1A receptor mRNA in the corpus cavernosum, there was a positive effect on erectile function. The increase in erectile function is directly through the sympathetic activity of the penis and indirectly due to the improvement of LUTS.[19]

Furthermore, penile tension was assessed using the EHS score, it was found that the most tension was like a peeled banana (degree 2) of 42.5% (Table 5). An analysis test was performed with SPSS IBM 21 with a significance of 0.00 ($p<0.01$) Spearman correlation value of -0.658 showed a strong correlation and negative direction, the greater the number of IPSS scores, the smaller the IIEF-5 score (Table 6).

An analysis of the relationship between BPH patients who were given tamsulosin /dutasteride combination therapy with ED was performed, the significance was 0.00 ($p<0.01$), the Spearman correlation value was 0.739, indicating a strong correlation (Table 7). Umul et al., 2014, stated that the association of LUTS with BPH and ED continues to increase, it is important to understand this complex disease. These disturbances have a major impact on quality of life as well as socioeconomic implications and are projected to continue to increase due to changing demographics.[7]

Furthermore, the relationship between LUTS and ED is influenced by: 1) increased activation of Rho-kinase, 2) decreased levels of

NOS, 3) atherosclerosis of the pelvis, and 4) hyperactivity of the autonomic nervous system (ANS).[20] In addition, other potential causes such as free serum and total testosterone profile, lipid profile, blood sugar, blood pressure, body weight and waist circumference.[7] These factors are limitations of our study which were not measured previously. It is hoped that in the future research will be carried out to reveal a clearer relationship between patients after tamsulosin/dutasteride combination therapy and the incidence of ED.

CONCLUSION

The results of this study showed that there was a relationship between BPH and LUTS patients who were treated with the tamsulosin/dutasteride combination with the incidence of ED at PKU Muhammadiyah Gombong. It is hoped that in the future there will be research to explain the causes of ED. Furthermore, modification therapy is needed so that the side effects of combination therapy can be overcome

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