THE EFFECT OF COMBINED α1-ADRENERGIC BLOCKERS AND PDE-5 INHIBITORS THERAPY ON IPSS, IIEF-5, QMAX AND PVR PATIENTS BPH WITH LUTS AND ERECTILE DYSFUNCTION

[1]Muhammad Ridha, [1]Johan Renaldo, [1]Sunaryo Hardjowijoto.

[1]Department of Urology, Faculty of Medicine/Universitas Airlangga, Soetomo General Hospital, Surabaya.

ABSTRACT

Objective: *Assess the efficacy of combined α1-adrenergic blocker (tamsulosin 0.4 mg) and PDE5 inhibitor (tadalafil 5 mg) therapy compared to tadalafil or tamsulosin alone in treating patient Benign Prostate Hyperplasia (BPH) with lower urinary tract symptom (LUTS) and erectile dysfunction (ED).* ***Material & methods:*** *A randomised, double blind experimental study assessed 36 sexually active men with ED and LUTS suggestive of BPH. All patients were randomized to 3 groups: tamsulosin 0.4 mg (n=12), tadalafil 5mg (n=12), and combination of tamsulosin 0.4 mg and tadalafil 5 mg (n= 12), once daily for 6 weeks. Changed in IPSS scores and QoL index, IIEF-5 scores, Qmax, PVR and blood pressure were assessed and compared to baseline. Complication and serious adverse event were also monitored. Outcomes were assessed using ranked analysis of variance (ANOVA) and Kruskall-Wallis depends on data distribution and homogenity.* ***Results:*** *Tamsulosin 0.4 mg once daily for 6 weeks were significantly improved IPSS score, QoL index and Qmax from baseline. Tadalafil 5 mg once daily for 6 weeks were significantly improved IPSS score, QoL index and IIEF-5 index from baseline. Combined tamsulosin and tadalafil therapy were significantly improved IPSS score, QoL index, IIEF-5 index and Qmax from baseline. Significantly better improvement on IIEF-5 dan Qmax from baseline were observed on the combination of tamsulosin and tadalafil compared to monotherapy with tamsulosin or tadalafil after 6 weeks in patients BPH with LUTS and erectile dysfunction. There was no significant decreased in systolic and diastolic blood pressure from combined treatment compared to single treatment.* ***Conclusion:*** *Combined tamsulosin and tadalafil therapy was significantly better in improving IIEF and Qmax, but not significantly better in improving IPSS and PVR compared to monotherapy with tamsulosin or tadalafil alone. Combined therapy was well tolerated without serious adverse effect.*

Keywords: *Benign prostate hyperplasia, lower urinary tract symptom, erectile dysfunction, α1-adrenergic blocker, PDE-5 inhibitor.*

ABSTRAK

Tujuan: *Menilai efikasi kombinasi α1-adrenergic blocker (tamsulosin 0.4 mg) dan terapi PDE5 inhibitor (tadalafil 5 mg) dibandingkan dengan monoterapi tadalafil atau tamsulosin dalam merawat pasien Benign Prostate Hyperplasia (BPH) lower urinary tract symptom (LUTS) dengan disfungsi ereksi.* ***Bahan & cara:*** *Penelitian eksperimental dengan desain penelitian randominasi acak meneliti 36 orang pasien BPH dengan LUTS dan disfungsi ereksi. Semua pasien dibagi kedalam 3 kelompok perlakuan secara random yaitu kelompok tamsulosin 0.4 mg (n=12), kelompok tadalafil 5 mg (n=12) dan kelompok kombinasi tamsulosin 0.4 mg + tadalafil 5 mg (n=12), sekali sehari selama 6 minggu. Perubahan skor IPSS, kualitas hidup (QoL), IIEF-5, Qmax, PVR dan tekanan darah diukur dan dibandingkan dengan baseline. Komplikasi dan efek samping selama penelitian juga dimonitor. Hasil penelitian dianalisa menggunakan uji ANOVA atau Kruskal Wallis sesuai dengan normalitas dan homogenitas sebaran data.* ***Hasil:*** *Pemberian tamsulosin sekali sehari selama 6 minggu mengakibatkan perbaikan skor IPSS, indeks QoL dan Qmax yang bermakna dibanding baseline. Terapi tadalafil sekali sehari selama 6 minggu mengakibatkan perbaikan skor IPSS, indeks QoL dan skor IIEF-5 yang bermakna dibanding sebelum terapi. Kombinasi terapi tamsulosin dan tadalafil menaikkan skor IPSS, QoL, IIEF-5 dan Qmax yang bermakna dibanding sebelum terapi. Terapi kombinasi tamsulosin dan tadalafil selama 6 minggu lebih baik dalam meningkatkan skor IIEF-5 dan Qmax secara signifikan dibandingkan terapi tunggal dengan tamsulosin dan tadalafil saja pada pasien BPH dengan LUTS dan disfungsi ereksi. Tidak terjadi penurunan tekanan darah sistolik dan diastolik yang signifikan dengan kombinasi terapi dibandingkan terapi tunggal.* ***Simpulan:*** *Terapi kombinasi tamsulosin dan tadalafil selama 6 minggu secara signifikan meningkatkan skor IIEF-5 dan Qmax, tetapi tidak lebih baik dalam meningkatkan IPSS dan PVR dibandingkan terapi tunggal tamsulosin atau tadalafil. Terapi kombinasi dapat ditoleransi dengan baik tanpa menyebabkan efek samping serius.*

Kata kunci: *Benign prostate hyperplasia, lower urinary tract symptom, disfungsi ereksi, α1-adrenergic blocker, PDE-5 inhibitor.*

Correspondence: Muhammad Ridha, c/o: Department of Urology, Faculty of Medicine/Universitas Airlangga, Soetomo General Hospital. Jl. Mayjend. Prof. Dr. Moestopo 6-8, Surabaya 60286. Phone: +62 31 5501318; Fax: +62 31 5024971. Mobile phone: 081360479379. Email: dr_ridha1978@yahoo.com.

INTRODUCTION

Benign Prostate Hyperplasia (BPH) is a common condition in elderly people.[1] BPH could be found in about 70% men 60 years old and increased until 90% in men over 80 years. The prevalence of symptomatic BPH in men 40-49 years was almost 15%, and rises with age until 25% in 50-59 years old, and 43% in men 60 years old.[2]

Common symptom in male with BPH were lower urinary tract symptom (LUTS) including voiding symptom or storage symptom which are: frequency, urgency, nocturia, lower stream of urine, intermittency and hesitancy, in the next step becoming urinary retention.[3] The American Urology Association (AUA) has developed an examination system to evaluate lower urinary tract symptom that has been validated internationally and adopted by WHO, called International Prostatic Symptom Score (IPSS).[4]

Standard treatments for BPH/LUTS include watchful waiting, medical treatment with α1-adrenergic blockers and 5α-reductase inhibitor and surgery. The efficacy of these medications remain limited, so that many effort has been raised to find optimal treatment for this condition.[5]

In the 1980s, Lepor and associates recognized that prostatic smooth muscle tension was mediated by α1-adrenoseptor; which led to the development of α-blocker as a treatment for LUTS. There are 4 commonly used α-blockers: doxazosin, terazosin, tamsulosin dan alfuzosin. The European study demonstrated improved total sexual function in patients treated with tamsulosin compared to a placebo. This study provide evidence that treatment of LUTS with α-blocker in men with BPH may in fact improve erectile function.[6]

Erectile dysfunction (ED) according to United States National Institutes of Health and American Urological Association were defined as inability to initiate or maintain adequate erection to reach sexual satisfaction. ED has become sexual health problem in sexually active men that influence to quality of life. The Massachusetts Male Ageing Study (MMAS-7) demonstrated the prevalence of complete ED increased from 5% for men 40 years old to 15% for those 70 years old 13 - 28% male aged 40-80 years suffer from ED.[7] It increases with age and other factors include cardiac disease, hypertension, diabetes mellitus, and low HDL level.[8,9]

PDE5 inhibitor has become first line treatment for erectile dysfunction in the last decade. PDE5 inhibitors are synthesized molecules that block the degradative action of PDE5 on cGMP, thereby elevating intracellular cGMP concentration and promoting relaxation of SMCs needed for normal erection. Relaxation of SMCs mediated by PDE5 inhibitor not only happened in cavernous corporal but also in bladder neck, urethra and prostate. This finding supported the possible use of PDE5 inhibitors to treat LUTS secondary to BPH. Recently there are 3 commonly used PDE5 inhibitor in USA which are sildenafil, tadalafil and vardenafil.[10,11,12] BPH influence sexual activity, erection and ejaculation function in elderly men. The prevalence of ED in men without LUTS was 24.8%, compared with 43.3, 65.8 and 81.9% ED in men with mild, moderate and severe LUTS, respectively.[7] Even though pathophysiology relationship between LUTS and DE not fully understood, several studies indicated that LUTS is a determinant factor for ED.

The association between sexual function and LUTS has become subject of interest. Until recently, it was widely assumed that male sexual dysfunction was a natural consequence of ageing in men. Some evidence for pathophysiological mechanism linking LUTS and ED has been proposed include autonomic hyperactivity, change in nitric oxide/nitric oxide synthase, pelvic ischemia pelvis and other mechanism such as increased Rho-kinase activity in smooth muscle leads to increased sensitivity to calcium, a heightened response to mediators of smooth muscle contraction and tissue changes in prostate, urinary tract and penile smooth muscle. Clinically this would translate into increased bladder neck tone causing LUTS and increased penile muscle tone leading to ED.[6,12-14]

Considering two conditions that occur with relatively high frequency in aging male, optimal treatment toward both disorders could be useful. PDE-5 inhibitors as a treatment for lower urinary tract symptom and α-adrenergic blocker treatment in improving sexual function has become fertile area of research, but combination of both treatment in improving both LUTS and erectile dysfunction has yet reported.

OBJECTIVE

Assess the efficacy of combined α1-adrenergic blocker (tamsulosin 0.4 mg) and PDE5 inhibitor (tadalafil 5 mg) therapy compared to tadalafil or tamsulosin alone in treating patient BPH

with LUTS and ED.

MATERIAL & METHOD

A randomised, double blind experimental study assessed 36 sexually active men with ED and LUTS suggestive of BPH. All patients were randomized to 3 groups: tamsulosin 0.4 mg (n=12), tadalafil 5 mg (n=12), and combination of tamsulosin 0.4 mg and tadalafil 5 mg (n=12), once daily for 6 weeks. Changed in IPSS scores and QoL index, IIEF-5 scores, Qmax, PVR and blood pressure were assessed and compared to baseline. Complication and serious adverse event were also monitored. Outcomes were assessed using ranked analysis of variance (ANOVA) and Kruskall-Wallis depends on data distribution and homogeneity.

RESULTS

A total 36 patients with complete follow up were selected, each group consist of 12 patients. Description of data characteristic could be seen in table 1.

There was improvement in total IPSS score after treatment in each group, with the highest improvement was in group I, as seen in table 2. A little improvement was seen in QoL score in all 3 groups after treatment (table 3).

There was improvement in IIEF-5 score after treatment in each group, with the highest improvement was seen in group III (table 4).

There was improvement in Q max after treatment in group II and III, but no improvement in mean Qmax in group II. The highest improvement was seen in group I (table 5).

Table 1. Data characteristic.

	Group	n	Mean	SD	Min	Max
Age	Tamsulosin	12	65.47	7.48	51	78
	Tadalafil	12	65.33	3.77	60	70
	Combination	12	68.58	7.33	51	78
Prostate Volume	Tamsulosin	12	36.20	7.14	25.20	54.90
	Tadalafil	12	36.12	16.87	25.00	87.40
	Combination	12	32.05	10.31	20.41	59.6
PSA	Tamsulosin	12	1.40[a]	1.08	0.15	1.56
	Tadalafil	12	1.59[a]	1.36	0.01	3.90
	Combination	12	2.63[b]	1.15	0.00	4.00
IPSS	Tamsulosin	12	11	5.309	5	20
	Tadalafil	12	18.08	6.855	9	31
	Combination	12	14.42	7.786	5	33
QoL	Tamsulosin	12	3.92	0.9	2	5
	Tadalafil	12	3.92	0.9	3	5
	Combination	12	3.58	1.084	2	5
IIEF-5	Tamsulosin	12	11.50	4.46	5	20
	Tadalafil	12	14.25	3.86	8	19
	Combination	12	13.92	5.82	3	20
Qmax	Tamsulosin	12	9.73	2.66	4.20	13.90
	Tadalafil	12	11.20	3.35	5.60	14.80
	Combination	12	10.18	2.46	6.20	13.80
PVR	Tamsulosin	12	34.60	25.91	5.00	82.00
	Tadalafil	12	48.29	53.35	8.49	97.00
	Combination	12	36.44	30.29	5.80	77.59
Systolic BP	Tamsulosin	12	134.17	13.95	110	160
	Tadalafil	12	120.00	7.39	110	130
	Combination	12	134.33	12.93	120	150
Diastolic BP	Tamsulosin	12	82.42	62.596	70	90
	Tadalafil	12	71.67	3.89	70	80
	Combination	12	79.33	10.53	60	90

Table 2. Changed in total IPSS score patients with BPH/LUTS and ED at Soetomo Hospital Surabaya in 2014.

Group	Pre		Post		Delta	p
	Mean	SD	Mean	SD		
Tamsulosin	11.00	5.31	6.25	3.31	-4.75	<0.0001
Tadalafil	18.08	6.85	16.58	6.49	-1.50	0.043
Combination	14.42	7.78	10.42	7.86	-4.00	0.002

Table 3. Changed in QoL IPSS score patients with BPH/LUTS and ED at Soetomo Hospital Surabaya in 2014.

Group	Pre		Post		Delta	p
	Mean	SD	Mean	SD		
Tamsulosin	3.92	0.90	2.67	0.78	-1.25	0.007
Tadalafil	3.92	0.90	3.25	1.06	-0.67	0.023
Combination	3.58	1.08	2.67	0.89	-0.92	0.005

Table 4. Changed in IIEF-5 score patients with BPH/LUTS and ED at Soetomo Hospital Surabaya in 2014.

Group	Pre		Post		Delta	p
	Mean	SD	Mean	SD		
Tamsulosin	11.50	4.462	13.42	4.738	1.92	0.015
Tadalafil	14.25	3.864	16.50	3.680	2.25	<0.0001
Combination	13.92	5.823	18.83	4.933	4.92	<0.0001

Table 5. Changed in Qmax uroflowmetri patients with BPH/LUTS and ED at Soetomo Hospital Surabaya in 2014.

Group	Pre		Post		Delta	p
	Mean	SD	Mean	SD		
Tamsulosin	9.73	2.66	13.22	2.35	3.49	<0.0001
Tadalafil	11.20	3.35	10.47	4.53	-1.17	0.474
Combination	10.18	2.47	12.28	2.54	2.09	<0.0001

Table 6. Changed in PVR patients with BPH/LUTS and ED at Soetomo Hospital Surabaya in 2014.

Group	Pre		Post		Delta	p
	Mean	SD	Mean	SD		
Tamsulosin	34.60	25.91	24.81	19.91	-9.80	0.139
Tadalafil	48.29	31.24	35.92	26.10	-12.37	0.374
Combination	36.44	30.29	31.67	26.08	-4.78	0.120

Table 7. Changed in systolic blood pressure patients with BPH/LUTS and ED at Soetomo Hospital Surabaya in 2014.

Group	Pre		Post		Delta	p
	Mean	SD	Mean	SD		
Tamsulosin	134.17	13.95	121.67	9.374	-12.50	
Tadalafil	120.00	7.39	114.17	7.93	-5.83	
Combination	134.33	12.93	125.83	7.93	-8.50	

Table 8. Changed in diastolic blood pressure patients with BPH/LUTS and ED at Soetomo Hospital Surabaya in 2014.

Group	Pre		Post		Delta	p
	Mean	SD	Mean	SD		
Tamsulosin	82.42	6.259	78.33	7.177	-4.08	
	71.67	3.892	74.17	5.149	-2.50	
Combination	79.33	10.526	76.67	6.513	- 2.67	

Improvement in PVR after treatment could be seen in 3 groups, with the highest improvement was in group II (table 6).

Changed in systolic blood pressure after treatment could be seen in all 3 groups, with the highest improvement in group I.

Changed in diastolic blood pressure after treatment was found in all 3 groups (table 8).

DISCUSSION

Age is an important determinant risk factor for LUTS and ED suggestive of BPH. An estimate of LUTS prevalence is that it occurs in greater than 50% of men 50 years old or older. ED prevalence increases with age from 2.3% in men 40 years old to 53% in men over 70 years old, with progressive increase in every decade.[2,15]

Prostate volume does not directly related to the severity of obstruction.[1] Two main component cause bladder outlet obstruction include static and dynamic component. Uroflowmetri examination aim to non-invasively detect lower tract obstructive symptom and could be used to evaluate infra-vesical obstruction before and after treatment. PDE-5 inhibitor and α1-adrenoseptor antagonist can cause hemodynamic interaction that should be consider, so that hemodynamic monitoring should be consider.[2,16,17]

Tamsulosin 0.5 mg or tadalafil 5 mg alone improved IPSS score in patients with LUTS and ED suggestive of BPH. Combined tamsulosin 0.4 mg and tadalafil 5 mg improved IPSS scores in patients with LUTS and DE suggestive of BPH. Improvement in quality of life (QoL) occurred in tamsulosin and tadalfil treatment alone and combined tamsulosin and tadalafil therapy. Combined therapy with tamsulosin and tadalafil did not significantly show better improvement in IPSS scores compared to single therapy with tamsulosin, but better than tadalafil alone. Combined therapy with tamsulosin and tadalafil did not significantly showed better improvement QoL index compared to single therapy with tamsulosin or tadalafil.

Yudanto et al., found significant improvement in total IPSS and QoL index after treatment with tamsulosin + placebo for 8 weeks compared to placebo + placebo.[18] In a systematic review and meta-analysis study Liu et al., identified 5 studied (11RCTs) indicated that PDE-5 inhibitors once daily for 12 weeks significantly improved IPSS score compared to placebo.[19] Porst et al., also reported that tadalafil 5 mg for 12 weeks significantly improved IPSS score compared to placebo (-5.6 compared to -3.6; $p<0.004$). Improvement happened since first week and significant after fourth week.[20]

Oelke et al., found that tadalafil and tamsulosin once daily significantly improved total IPSS score since first week and after 12 weeks, only tadalafil could significantly improve QoL index.[21] In a longer period of study, Reges et al., found that combined tamsulosin 0.4 mg and tadalafil 5 mg for 1 year is more effective in improving total IPSS score and voiding sub score compared to treatment with tamsulosin 0.4 mg alone.[22]

Tamsulosin 0.4 mg or tadalafil 5 mg alone, and combined tamsulosin 0.4 mg and tadalafil 5 mg therapy significantly improved IIEF-5 index in patients with LUTS and DE suggestive of BPH. Combined tamsulosin 0.4 mg and tadalafil 5 mg therapy significantly better in improving IIEF-5 score compared to monotherapy with tamsulosin or tadalafil after 6 weeks for patients with LUTS and DE suggestive of BPH.

Porst et al., found that tadalafil 5 mg once daily (12 weeks) significantly improved IIEF-EF in sexually active patients with LUTS and ED suggestive of BPH.[20] In other studies, Liu et al. and Oelke et al., indicated that short term PDE-5 inhibitors (tadalafil 5 mg for 12 weeks) significantly improved IIEF-EF score compared to placebo.[19,21]

Bechara et al., in their study found that IIEF index were improved in patients treated with combined tamsulosin and tadalafil therapy, but not with tamsulosin alone, combined tamsulosin dan tadalafil therapy were more effective in improving LUTS and ED compared to tamsulosin alone.[10]

Gracci et al., also reported that PDE-5 inhibitors improved IIEF (5.5; $p<0.0001$), while combined PDE-5 inhibitor and α1-blocker therapy can improved IIEF better than α1-blocker alone.[22]

Tamsulosin monotherapy and combined tamsulosin dan tadalafil therapy for 6 weeks significantly improved Qmax. Tadalafil alone did not significantly improved Qmax in LUTS and DE patients suggestive of BPH. Combined tamsulosin 0.4 mg and tadalafil 5 mg therapy can significantly improve Qmax better than therapy with tamsulosin alone during observation.

McVary et al., in their study found that uroflowmetri parameter almost the same between group treated with tadalafil 5 mg once daily for 6 weeks then followed by dosage increasement until 20 mg for 6 weeks compared to placebo.[15] In a

systematic review and meta-analysis, Liu et al., identified 5 studies (11RCTs) indicated that neither PDE-5 inhibitor nor placebo significantly improved Qmax.[19] Porst et al., found that tadalafil did not significantly improved Qmax in patients with BPH LUTS and urinary retention.[4] While Oelke et al., found significant Qmax improvement on treatment with tadalafil (2.4ml/s, $p<0.009$) and tamsulosin (2.2 ml/s, $p<0.014$) compared to placebo (1.2 ml/s).[21]

Gracci et al., in their studied indicated that PDE-5 inhibitor alone did not significantly improved Qmax, combined PDE-5 inhibitor and alpha blocker significantly improved Qmax (1.53 ml/s) compared to treatment with alpha blocker alone.[22] In another study, Lee et al., showed no significant improvement on Qmax in treatment with combined tadalafil 5 mg and alpha blocker for 3 months, but patients with low Qmax at the beginning of study (<10 ml/s) showed significant improvement after 12 weeks from 7.97 ± 1.44 to 8.91 ± 1.6 ml/s ($p<0.012$).[23]

Yudanto et al., indicated that tamsulosin 0.4 mg treatment for 8 weeks did not show significant changes in PVR compared to placebo.[18] Liu et. al., found significant change in PVR on PDE-5 inhibitor treatment for 12 weeks compared to placebo, while Donatucci et al., indicated improvement in mean post void residual urine volume from 61.1–60.4 mL at baseline to 42.2–64.1 mL after treatment with tadalafil 2.5, 5, 10 or 20 mg for 1 year.[19,24]

Tamsulosin or tadalafil monotherapy and combined tamsulosin and tadalafil therapy for 6 weeks did not significantly decrease PVR in patients with LUTS and ED suggestive of BPH. This result consistent with result of other study conducted by Porst et al., that tadalafil once daily for 12 weeks did not decrease PVR compared to placebo in patients with BPH LUTS.[20] McVary et al., also indicated no significant post-void residual volume changes between group treated with tadalafil 5 mg, followed with dosage increasement until 20 mg once daily for 6 weeks and placebo group.[15] Another study conducted by Yudanto et al., indicated that tamsulosin 0.4 mg treatment for 8 weeks did not show significant changes in PVR compared to placebo.[18]

Another study conducted by Liu et al., showed significant changes in PVR on PDE-5 inhibitor treatment for 12 weeks compared to placebo, while Donatucci et al., indicated improvement in mean post void residual urine volume from 61.1–60.4 mL at baseline to 42.2–64.1 mL after treatment with tadalafil 2.5, 5, 10 or 20 mg for 1 year.[19,24]

Tamsulosin treatment alone lowering systolic and diastolic blood pressure. Monotherapy tadalafil, and combined tamsulosin and tadalafil therapy significantly lowering systolic but not diastolic blood pressure. Changes in systolic and diastolic blood pressure in combined tamsulosin and tadalafil treatment were not significantly higher than monotherapy tamsulosin or tadalafil.

Kloner et al., found that tadalafil 10 or 20 mg had little hemodynamic interaction with tamsulosin 0.4 mg. The combination of tamsulosin 0.4 mg and tadalafil 10 mg or 20 mg did not significantly lowering systolic and diastolic blood pressure either on standing or supine position compared to tamsulosin 0.4 mg alone or placebo (mean difference 1.7 and 2.3 mmHg).[25] Reges et al., conclude that combined tamsulosin and tadalafil treatment once daily is safe and more effective compared to tamsulosin alone in treating LUTS secondary to BPH.[26]

CONCLUSION

Combined tamsulosin and tadalafil therapy was significantly better in improving IIEF and Qmax, but not significantly better in improving IPSS and PVR compared to monotherapy with tamsulosin or tadalafil alone. Combined therapy was well tolerated without serious adverse effect.

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