DOXAZOSIN AND MELOXICAM COMBINATION THERAPY FOR BPH TREATMENT WITH LUTS

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ABSTRACT

Objective: *To compare the efficacy of combination therapy of 4 mg doxazosin + 15 mg meloxicam with 4 mg doxazosin single therapy for benign prostate hyperplasia (BPH) patients with lower urinary tract symptoms (LUTS).* ***Materials & Methods:*** *A prospective, randomized and double blind study with total of 22 BPH patients with LUTS were randomized to receive 4 mg doxazosin + placebo once daily for 6 weeks or a combination of 4 mg doxazosin + 15 mg meloxicam once daily for 6 weeks. Inclusion criteria included IPSS ≥ 8, age > 50 years, prostate blood flow grade II. Therapeutic efficacy was assessed by comparing changes in IPSS, maximal urinary flow (Q-max) and changes in prostate blood flow between baseline and immediately after 6 weeks of therapy.* ***Results:*** *There was no significant difference in IPSS change between the two treatment groups (delta IPSS 4 ± 1.1 versus 3.7 ± 1.5, p = 0.630). There was a significant difference in Q-max changes between the two groups (delta Q-max 4 ± 1.5 versus 2.1 ± 0.7, p < 0.001). In group therapied with 4 mg doxazosin + 15 mg meloxicam prostate blood flow decreased from grade II to grade I in 9 of 11 patients (81%). Whereas, in the treatment group of 4 mg doxazosin + placebo no reduction was found in prostate blood flow.* ***Conclusion:*** *Combination therapy of 4 mg doxazosin + 15 mg meloxicam once daily for 6 weeks is better than 4 mg doxazosin therapy alone in improving Q-max and decreasing prostate blood flow in BPH patients with LUTS.*

Keywords: *Benign prostate hyperplasia, inflammation, COX-2 inhibitors.*

ABSTRAK

Tujuan : *Membandingkan efikasi terapi kombinasi doxazosin 4 mg + meloxicam 15 mg dan terapi tunggal doxazosin 4 mg untuk pasien benign prostate hyperplasia (BPH) dengan lower urinary tract symptoms (LUTS).* ***Bahan & Cara:*** *Penelitian prospektif, acak dan double blind dengan 22 pasien BPH dengan LUTS secara acak menerima doxazosin 4 mg + plasebo sekali sehari selama 6 minggu atau kombinasi doxazosin 4 mg + meloxicam 15 mg sekali sehari selama 6 minggu. Kriteria inklusi meliputi IPSS ≥ 8, usia > 50 tahun, aliran darah prostat derajat II. Efikasi terapi dinilai dengan membandingkan perubahan IPSS, pancaran urin maksimal (Q-maks) dan perubahan aliran darah prostat antara data awal dan segera setelah 6 minggu terapi.* ***Hasil:*** *Tidak terdapat perbedaan bermakna dalam perubahan IPSS antara kedua kelompok terapi (delta IPSS 4 ± 1.1 berbanding 3.7 ± 1.5, p = 0.630). Terdapat perbedaan bermakna dalam perubahan Q-maks antara kedua kelompok (delta Q-maks 4 ± 1.5 berbanding 2.1 ± 0.7, p < 0.001). Pada kelompok terapi doxazosin 4 mg + meloxicam 15 mg derajat aliran darah prostat turun dari grade II menjadi grade I pada 9 dari 11 pasien (81%), sedangkan pada kelompok terapi doxazosin 4 mg + plasebo tidak terdapat penurunan grade aliran darah prostat.* ***Simpulan:*** *Terapi kombinasi doxazosin 4 mg + meloxicam 15 mg sekali sehari selama 6 minggu lebih baik daripada terapi doxazosin 4 mg saja dalam peningkatan Q-maks dan penurunan aliran darah prostat pasien BPH dengan LUTS.*

Kata kunci: *Benign prostate hyperplasia, inflamasi, penyakat COX-2.*

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INTRODUCTION

Benign prostate hyperplasia (BPH) is the process of stromal and epithelial proliferation that occurs in prostate transitional zone. It is clinically characterized by symptoms of lower urinary tract symptoms (LUTS).[1] BPH is often accompanied by inflammation, with incidence from 43 – 92%.[2,3]

Patients with inflammatory BPH had a higher risk for the occurrence and progression of acute urinary retention.[4] Prostate tissue of BPH patients with chronic inflammation shown expression of cyclooxygenase-2 (COX-2), B-cell lymphoma 2 (Bcl-2) and vascular endothelial growth factor (VEGF) higher than patients who are not accompanied by inflammatory condition.[5]

Chronic inflammation leads to COX-2 formation through increased prostaglandin E2 (PGE2) and lower E-cadherin protein production that causes loss of adhesion bonds between cells and modulated increasing angiogenic factors that will trigger angiogenesis, cell growth and decreased apoptosis.[6] Color doppler ultrasound examination shows prostate blood flow changes in patients with chronic prostatitis by increasing blood flow to the prostate capsule or parenchyma in 77% of patients with chronic prostatitis.[7] COX-2 inhibitors, a class of non-steroidal anti-inflammatory drugs, work by blocking the action of COX-2 enzyme, causing inhibition in the production of prostaglandins and reduced prostaglandin synthesis in prostate with BPH and inflammation, resulting in decreased cell growth and increased apoptosis activity.[8,9]

Doxazosin is a long acting alpha-1 blocker that works by causing prostatic smooth muscle relaxation and subsequent pressure drop in the prostate, thus improving micturition and alleviate LUTS complaints in BPH.[9] Results of BPH therapy with doxazosin can be observed after treatment for 6 weeks, although symptomatic effects have begun to emerge in the third week.[10]

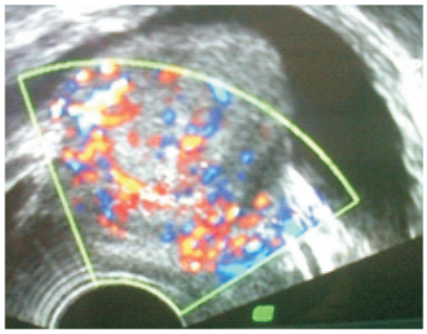
Ozdemir et al. (2009) compared the effectiveness of 4 mg doxazosin and a combination of 4 mg doxazosin + 20 mg tenoxicam for the treatment of BPH patients with LUTS, which resulted in significant reduction of total International Prostatic Symptom Score (IPSS) and IPSS quality of life subscore (IPSS-QoL) in both treatment groups compared with initial data, and maximum urine flow rate (Q-max) increased significantly in both groups. The decrease in IPSS and IPSS-QoL was significantly better in the combination therapy group and an increase in Q-max was also higher in the combined group, although the difference was not statistically significant.[11] Research on effectiveness of combination therapy of alpha blockers and COX-2 inhibitors as well as the side effects are still rarely done. Moreover, similar studies have not been undertaken in Indonesia. The purpose of this study was to compare the efficacy and side effects of combined therapy of doxazosin + meloxicam combination therapy and doxazosin single therapy for BPH patients with LUTS.

MATERIALS & METHODS

From April to August 2012, BPH patients with LUTS who visited Urology Clinic, Dr. Soetomo Hospital, were screened for study enrollment. Inclusion criteria were BPH patients with moderate and severe LUTS (IPSS ≥ 8), age > 50 years, prostate blood flow grade II according to Cho et al. (2000) and willing to fill out and sign an informed consent. Exclusion criteria were: allergy to NSAIDs; history of gastritis based on symptoms such as soreness or burning pain in upper abdomen, nausea, vomiting and bloating; impaired hepatic function, as evidenced by an increase in serum transaminase levels and or serum bilirubin; never had alpha blocker therapy and COX-2 inhibitors in the last 2 weeks; history of severe postural hypotension, diabetes mellitus, evidenced by fasting blood sugar of ≥ 126 mg/dl and 2-hour post prandial glucose of ≥ 200 mg/dl; had prostate surgery; suffering from prostate malignancy based on the results of ten core biopsy; BPH with LUTS complicated by an increase in serum creatinine levels above 1.4 mg/dl, urosepsis, inguinal hernia and lower urinary tract stones, proven by plain abdominal, intravenous pyelography (IVP) or ultrasonography (USG). LUTS complaints was recorded using the IPSS sheet. All patients were also subjected to uroflowmetry to determine maximum emission (Q max), transrectal prostate volume measurements and color doppler ultrasound to determine the appropriate degree of prostate blood flow grading by Cho et al. (2000). The minimum voided urine volume for uroflowmetry result reading was 150 ml.

Degree of prostate blood flow was measured with Doppler color mode transrectal ultrasonography (TRUS) with probe RIC 5-9H 6.5 MHz GE Voluson 730 Pro V. Degree of prostate blood flow was measured in the prostate capsule and parenchyma at level of prostate largest transversal cut. Prostate blood flow measurements was made at the time when prostate color was showing the maximum vascularity. The degree of blood flow to the capsule and parenchyma was divided into 2 grades. Grade 1 means no visible capsule vascularity or rare vascularity in the capsule. Grade 2 means the blood flow existed around the capsule. Grade 1 in prostate parenchyme indicated that the

blood vessels were short and not spreading over the prostate parenchyma. Grade 2 indicated more than one blood vessel spreading over the prostate parenchyma. To obtain the visualization of the selected pulse repetition frequency was 1000 Hz, and color gain was set slightly higher than the noise



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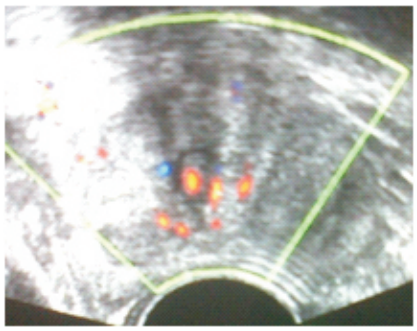

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Figure 1. Degree of prostate blood flow in this study. a). prostate blood flow grade II, b). prostate blood flow grade I.

Patients who met the inclusion criteria and did not meet the exclusion criteria were divided into two groups at random to receive 4 mg doxazosin + placebo or 4 mg doxazosin + 15 mg meloxicam once daily for 6 weeks. In the first week, doxazosin doses given to both groups was 2 mg, then increased to 4 mg at week 2 to week 6. Soon after week 6 of the therapy was completed, IPSS, uroflowmetry and degree of prostate blood flow were re-measured. Then, we carried out a comparative analysis of IPSS, Q-max and the degree of prostate blood flow before and after therapy in each treatment group and a comparative analysis of the changes in IPSS, Q-max and the degree of prostate blood flow between treatment groups.

RESULTS

To obtain 22 patients who met the inclusion criteria, we conducted research from April to August 2012. The 22 patients were enrolled after examining 78 BPH patients with LUTS who were about to have transrectal ultrasonography (TRUS) examination at the Minimally Invasive Urology unit, at Dr. Soetomo Hospital, Surabaya. Of the 78 patients, 56 were excluded. The types of exclusion criteria were diabetes mellitus in 12 patients, urinary tract stones in 8 patients, dyspepsia in 4 patients, serum creatinine levels > 1.2 mg/dL in 6 patients, 4 patients had previous prostate surgery, history of NSAIDs allergy in 2 patients, inguinal hernia in 6 patients, no COX-2 inhibitor therapy within the past 1 week in 2 patients, liver function test abnormalities in 1 patient and grade I prostate blood flow according to Cho et al. (2000) in 11 patients. There were 11 patients in group receiving therapy with 4 mg doxazosin + placebo and 11 patients in the combination therapy group receiving 4 mg doxazosin + 15 mg meloxicam. All patients completed therapy for 6 weeks. No patients dropped out or failed treatment.

The mean age in group with 4 mg doxazosin + placebo therapy (group 1) was 63.6 ± 6.9 years and the mean age in group with 4 mg doxazosin + 15 mg meloxicam therapy (group 2) was 61.8 ± 5.8. The mean prostate volume was 34.7 ± 10.3 ml in group 1 and 40.4 ± 11.9 ml in group 2. The mean IPSS was 18.6 ± 3.7 in group 1 and 17.9 ± 2.4 in group 2. The mean voided volume in group 1 was 193.2 ± 35.4 ml and in group 2 was 178.1 ± 32.8 ml. The mean Q-max in group 1 was 10.4 ± 3.1 ml/sec and the mean Q-max in group 2 was 8.6 ± 1.8 ml/sec. All samples in both groups had a prostate blood flow grade 2 at baseline. Basic characteristics of the two groups according to age, prostate volume, IPSS and Q-max at the start did not differ significantly ($p > 0.05$), as shown in Table 1.

Table 1. Comparison of basic characteristics of the two groups before treatment.

Parameters	Group 1	Group 2	p
Age	63.6 ± 6.9	61.8 ± 5.8	0.513
Prostate volume	34.7 ± 10.3	40.4 ± 11.9	0.244
Early IPSS	18.6 ± 3.7	17.9 ± 2.4	0.590
Early Q-max	10.4 ± 3.1	8.6 ± 1.8	0.119

There was a significant decrease in IPSS after therapy with 4 mg doxazosin + placebo once daily for 6 weeks ($p < 0.001$) and after therapy with 4 mg doxazosin + 15 mg meloxicam once daily for 6 weeks ($p < 0.001$).

There was a significant increase in Q-max after therapy with 4 mg doxazosin + placebo once daily for 6 weeks ($p < 0.001$) and after treatment with 4 mg doxazosin + 15 mg meloxicam once daily for 6 weeks ($p < 0.001$) (Table 2). The mean change in IPSS pre and post therapy was 3.7 ± 1.5 in group receiving 4 mg doxazosin + placebo and 4.0 ± 1.1 in group receiving 4 mg doxazosin + 15 mg meloxicam. There was no significant difference in the magnitude of change in IPSS between the two groups ($p = 0.630$). The mean change in Q-max pre and post treatment was 2.1 ± 0.7 in group receiving 4 mg doxazosin + placebo and 4.2 ± 1.5 in group receiving 4 mg doxazosin + 15 mg meloxicam. There was a significant difference in the magnitude of changes in Q-max between the two groups ($p < 0.001$) (Table 2).

At baseline, all patients in both treatment groups had grade 2 prostate blood flow according to Cho et al. (2000). After six weeks of therapy, prostate blood flow was re-assessed in all patients and found that 9 of 11 patients (81.8%) in the combination therapy group receiving 4 mg doxazosin + 15 mg meloxicam had prostate blood flow changes from grade 2 to grade 1. None of the patients in group receiving 4 mg doxazosin + placebo had changes in prostate blood flow.

Side effects that occurred in the combined therapy with 4 mg doxazosin + 15 mg meloxicam for 6 weeks in patients with BPH with LUTS were dizziness (9%) and dyspepsia (18%). No patients dropped out due to side effects (Table 4).

Table 4. The incidence of side effects.

Side Effects	Total cases (%)	
	Group 1	Group 2
Dyspepsia	-	18
Dizziness	18	9
Tinitus	9	-
Head pain	9	-

DISCUSSION

The effect of 4 mg doxazosin on IPSS in this study was the significant decrease before and after treatment (18.6 ± 3.7 to 14.9 ± 2.9, $p < 0.05$) or a decrease in IPSS in 6 weeks therapy by 3.7 points or

Table 2. Variation of the mean parameters during the study in both groups.

Parameters	Early Data		6 Weeks Post -Therapy		p
	Group 1	Group 2	Group 1	Group 2	
Total sample	11	11	11	11	-
IPSS	18.6 ± 3.7	17.9 ± 2.4	14.9 ± 2.9	13.9 ± 2.3	< 0.001 * < 0.001 + 0.630 ¥
Q-max	10.4 ± 3.1	8.6 ± 1.8	12.5 ± 3.1	12.9 ± 2.6	< 0.001 * < 0.001 + < 0.001 ¥

* 4 mg doxazosin + placebo group pre-therapy vs post-therapy.
\+ 4 mg doxazosin + 15 mg meloxicam group pre- therapy vs. post-therapy.
¥ Difference in value before and after therapy in group receiving 4 mg doxazosin + placebo vs. group receiving 4 mg doxazosin + 15 mg meloxicam

Table 3. Changes in prostate blood flow in each treatment group

Therapy groups	Pre-Therapy		Post-Therapy		Percentage of change (%)
	Grade 1	Grade 2	Grade 1	Grade 2	
4 mg doxazosin + placebo	-	11	-	11	0
4 mg doxazosin + 15 mg meloxicam	-	11	9	2	81

19.9% from baseline IPSS. This result was lower than that of Akan et al (1998) and other studies on the effects of doxazosin on IPSS. Possible causes of the differences from those of Akan et al (1998) was first week doxazosin dose, where Akan et al. directly used 4 mg doxazosin for 6 weeks. The differences from other studies may be due to differences in duration of therapy (Table 5). Differences also appeared on the therapeutic effects of 4 mg doxazosin for Q-max between this study and some other studies (Table 6).

Changes in IPSS pre- and post-treatment in the combination therapy of 4 mg doxazosin + 15 mg meloxicam was different from changes in IPSS pre and post therapy in the treatment group receiving 4 mg doxazosin (4.0 ± 1.1 versus 3.7 ± 1.5, p = 0.630). This means that in this study there was no significant difference in IPSS decrease pre and post treatment of BPH LUTS patients treated with the combination of 4 mg doxazosin + 15 mg meloxicam for 6 weeks from that of BPH LUTS patients treated with 4 mg doxazosinfor 6 weeks (Figure 2).

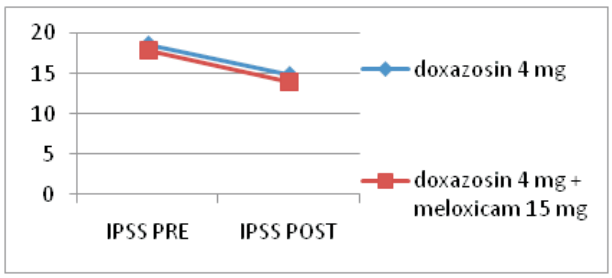

Figure 2. Comparison of IPSS pre and post therapy in groups receiving 4 mg doxazosin and a combination of 4 mg doxazosin + 15 mg meloxicam.

Changes in Q-max pre and post therapy in the combination therapy group receiving 4 mg doxazosin + 15 mg meloxicam was higher than the change in Q-max pre and post therapy in the treatment group receiving 4 mg doxazosin (4.2 ± 1.5 versus 2.1 ± 0.7 p < 0.0001). This means that in this study in patients with BPH LUTS the therapy with 4 mg doxazosin + 15 mg meloxicam for 6 weeks had effect in the increase of Q-max, which was significantly higher than the increase in Q-max that occurs with 4 mg doxazosin therapy for 6 weeks (Fig. 3).

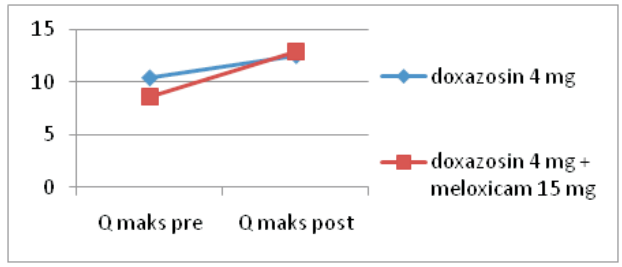

Figure 3. Comparison of Q-max pre and post therapy in group receiving 4 mg doxazosin and a combination of 4 mg doxazosin + 15 mg meloxicam.

Ozdemir et al (2009) found that changes in IPSS before and after the administration of combination therapy of 4 mg doxazosin + 20 mg tenoxicam for 6 weeks was significantly higher than the change in IPSS before and after therapy of 4 mg doxazosin for 6 weeks (delta IPSS 9.4 ± 5.5 vs 5.8 ± 5.8, p = 0.034). While the change in Q-max after combination therapy of 4 mg doxazosin and 20 mg tenoxicam for 6 weeks did not differ significantly from changes in Q-max after 4 mg doxazosin therapy for 6 weeks (delta Q-max 3.4 ± 3.6 vs 2.3 ± 3.5, p > 0.05). Differences in IPSS and Q-max changes between this study and that of Ozdemir et al (2009) may be due to differences in patient inclusion criteria. In the study of Ozdemir et al (2009), it was not determined whether patients receiving combination therapy of 4 mg doxazosin and 20 mg tenoxicam had inflammation or not. All

Table 5. Comparison of therapeutic effect of 4 mg doxazosin on IPSS in several studies.

No	Researchers	No of Subjects	Dose and therapy duration	IPSS Change
1	Fawzy et al.1995	100	4 or 8 mg for 12 - 52 weeks	5.7
2	Andersen et al. 2000	795	4 or 8 mg for12 - 52 weeks	8.4 ± 0.3
3	McConnell et al. 2003	3047	4 or 8 mg more than 52 weeks	6.6
4	Kirby et al. 2003	1095	4 or 8 mg for 52 weeks	8.3 ± 0.4
5	Ozdemir et al. 2009	28	4 mg for 6 weeks	5.8 ± 5.8
6	Suarsana et al . 2012	22	Titrated dosing, 2 mg for 1 week continued at 4 mg for 5 weeks	3.7 ± 1.5

Table 6. Comparison of therapeutic effect of 4 mg doxazosin on Q-max reported.

No	Researchers	Number of Subjects	Dose and therapy duration	IPSS Change
1	Fawzy et al. 1995	100	4 or 8 mg for 12 - 52 weeks	5.7
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4	Kirby et al. 2003	1095	4 or 8 mg for 52 weeks	8.3 ± 0.4
5	Ozdemir et al. 2009	28	4 mg for 6 weeks	5.8 ± 5.8
6	Suarsana et al. 2012	22	Titration dose 2 mg for 1 weeks followed with 4 mg for 5 weeks	3.7 ± 1.5

BPH patients with LUTS were enrolled as research sample.

In this study we also found changes in prostate blood flow from grade 2 to grade 1 in 81.8% of BPH patients with LUTS who received combination therapy of 4 mg doxazosin + 15 mg meloxicam for 6 weeks. The decrease of the degree of prostate blood flow may contribute to changes in Q-max that occurred in this patient group through the effect of decreasing inflammation resulting from COX-2 by 15 mg meloxicam. The decrease in COX-2 may lead to decreased production of VEGF, which will cause a decrease in blood flow of the prostate. In addition, a decrease of COX-2 also leads to reduced cell proliferation due to inflammation of the prostate.[6]

CONCLUSION

Combination therapy of 4 mg doxazosin + 15 mg meloxicam once daily for 6 weeks is superior to 4 mg doxazosin therapy alone in improving Q-max and decreasing prostate blood flow in BPH patients with LUTS.

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