COMPARATIVE EFFICACY OF INTERMITTENT AND DAILY DOXAZOSIN THERAPY FOR LUTS ASSOCIATED WITH BPH

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ABSTRACT

Objective: *To investigate the efficacy of intermittent doxazosin therapy on LUTS associated BPH.* ***Material & Method:*** *This study was performed between January to April 2010 enrolling 20 patients with LUTS associated BPH. Study subjects were randomly allocated to 2 therapeutic groups. The first group was assigned daily doxazosin therapy (11 patients), while the second group was assigned intermittent doxazosin therapy (9 patients). Initially all subjects were given doxazosin 2 mg daily for 2 weeks. Subsequently group I received doxazosin 2 mg daily therapy, while group II received doxazosin 2 mg every other day. All medications were taken up to 12 weeks. Outcomes were evaluated prior to therapy, and after 2, 4, 8, and 12 weeks of therapy. Efficacy of doxazosin therapy was measured by International Prostate Symptom Score (IPSS), peak urinary flow rate (Q max), and residual urine volume. Statistical analysis was performed to evaluate difference in efficacy between the treatment groups.* ***Results:*** *Daily doxazosin therapy for 2 weeks resulted in significant improvement of Q max and IPSS. After 4, 8, and 12 weeks significant improvement was maintained in both daily and intermittent groups, as measured by Q max, residual urine volume and IPSS. There were no significant differences in Q max, residual urine volume, and IPSS between the daily and intermittent groups at 4, 8, and 12 groups.* ***Conclusion:*** *There were significant improvements of Q max, residual urine and IPSS at 2 to 12 weeks in daily as well as intermittent doxazosin therapy groups. There were no significant differences in efficacy between daily and intermittent therapy groups.*

Keywords: *Benign prostatic hyperplasia, intermittent alpha blocker therapy.*

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a benign prostate enlargement in adult males.[1,2] Changes in prostate volume occur variably at each age. Several cross sectional studies of prostate volume by age indicate that prostate volume increases to 25 ml in men aged 30 years and 35 - 45 ml in men age 70 years.[3] The relationship between BPH with LUTS is complex, in which not all patients with BPH are complaining about micturition disorder. Conversely, not all micturition complaints are caused by BPH.[4-6]

American Urological Association (AUA) BPH Guidelines Committee recommends initial evaluation of adult males with LUTS symptoms. Initial evaluation includes a diagnosis, physical examination, laboratory tests, radiological examination, and other supporting examinations.[7] Investigations include uroflowmetry, residual urine, and pressure-flow urodynamic studies. Those examinations are required to evaluate patients with BPH LUTS.[7]

BPH treatment options were based on the severity of complaints or symptoms experienced by patients, including watchful waiting, lifestyle changes, pharmacologic agents, and surgery. Medical management of BPH includes treatment with alpha blockers, 5 alpha reductase inhibitors, or a combination of alpha blockers with 5 alpha reductase inhibitors. Alpha blocker therapy in BPH serves to relax the bladder neck smooth muscle, so the micturition process becomes more smooth.[8]

Some researchers have advocated the use of alpha blockers on a daily basis, but some patients discontinue therapy after the symptoms reduced and patients felt better. The results of a study by Teruhiko Yokoyama (2007) stated that in BPH patients with relatively small prostate volume and improvement of flow rates after daily therapy, intermittent alpha blockers can be administered as subsequent therapy.[9] Intermittent alpha blocker therapy is an appropriate strategy for patients with LUTS due to BPH. Charnow (2009) reported the results of research by Muhammad A and Bulbul from the surgical department of the American University of Beirut in Lebanon on alpha blocker intermittent therapy in 84 patients with BPH LUTS. The alpha blockers used for therapy were doxazosin, alfuzosin or tamsulosin. After 2 weeks of therapy there was improvement of LUTS symptoms, and then patients were asked to take medications intermittently according to complaints. Results showed that BPH LUTS patients who received alpha blockers therapy for 3 months, 34 (40%) felt no longer require continued therapy, whereas 50 patients (60%) still required continued therapy with alpha blockers in an interval between 1 to 24 days after stopping the last drug. The intermittent alpha-blocker therapy has been recommended for therapy in patients with BPH LUTS. The result of the study could influence costs for medical therapy in patients with BPH LUTS, especially in developing countries.[10]

In patients who have a good response to short term alfuzosin therapy, alternating-day (intermittent) alfuzosin therapy is likely to be a therapeutic option for patients with BPH LUTS.[11] Research by Kaplan et al (1998) on alfuzosin therapy against BPH LUTS proved that intermittent alfuzosin therapy has the same effectiveness with daily alfuzosin therapy.[12] Yanardag et al (2005) used tamsulosin as intermittent BPH LUTS therapy for 3 months. The study showed that there was no significant difference in the effectiveness of intermittent therapy compared to daily therapy.[13] Alfuzosin, doxazosin, tamsulosin, and terazosin are appropriate treatment options for LUTS caused by BPH. Although there is little difference between those drugs, but some researchers believe that each drug has a comparable clinical effectiveness.[14]

Intermittent alpha blocker therapy is a new strategy for the management of BPH patients with LUTS. The use of alpha blockers on a daily basis or continuous will increase the side effects and require a high cost. Therefore, BPH LUTS management strategies with intermittent alpha blockers therapy should be tested.

OBJECTIVE

To prove the difference between therapeutic efficacy of intermittent and daily alpha blockers (doxazosin) therapy in BPH patients with LUTS.

MATERIAL & METHOD

The study was quasi-experimental research studies (quasi-experimental), conducted from January to April 2010.

BPH patients with LUTS who came to the outpatient clinic of Soetomo Hospital and Ramelan Hospital, Surabaya, were selected according to inclusion and exclusion criteria. Criteria for inclusion in this study were LUTS patients caused by BPH and age more than 50 years.

Total study sample was 27 patients, consisting of 20 patients who fulfilled the inclusion criteria, while 7 patients dropped out. The whole study sample were divided into 2 groups. Daily doxazosin therapy group consisted of 11 patients, while intermittent doxazosin therapy group consisted of 9 patients. Seven patients dropped out because they were not willing to continue doxazosin therapy. Six patients refused further therapy because they felt cured and 1 patient underwent TURP. All samples were subjected to initial evaluation, including the assessment of IPSS, Q max, and residual urine before receiving doxazosin therapy to obtain preliminary data on voiding function in BPH LUTS patients included in the study. In the first phase, all patients with BPH LUTS were given initial therapy of doxazosin 2 mg once daily for 2 weeks. After 2 weeks of doxazosin therapy, IPSS, Q max and residual urine were assessed then patients were randomly allocated into 2 groups, daily doxazosin therapy (group I) and intermittent doxazosin therapy group (group II). In the second stage, patients in group I resumed daily doxazosin

therapy (every day) until 12 weeks, whereas group II continued intermittent doxazosin therapy (every 2 days) until 12 weeks. Evaluation was performed after 4, 8, and 12 weeks. Evaluation aimed to prove efficacy of doxazosin therapy by assessing the IPSS, Q max, and residual urine. Difference in therapeutic efficacy between the two groups was subjected to statistical tests.

The data were analyzed descriptively and analytically. The data had normal distribution. Therefore, the statistical tests used were parametric tests. The parametric statistical tests chosen in this study were paired t test and independent t test.

RESULTS

Most patients were in the age group 60 - 69 years, as many as 13 people or 65%. Age 70 - 79 years and more than 80 years totaled as many as 3 persons each or 15%. Patient aged less than 60 years was only 1 person or 5%.

Mean prostate volume in the daily group was 45,1 grams, while in the intermittent group was 33,8 grams. In the daily group the lowest prostate volume was 30,5 grams and the highest prostate volume was 72,9 grams. In the intermittent group, the lowest prostate volume was 20,9 grams and highest prostate volume was 48,5 grams.

Characteristics of the study sample consisted of Q max, residual urine and IPSS before administration of doxazosin therapy, in which the mean Q max was 9,0 ml/sec; 88,6 ml of residual urine and IPSS 14,5; while in intermittent group the mean Q max was 9,6 ml/sec; 80,3 ml of residual urine and IPSS 12,1.

Side effects of therapy were only found in 2 patients in the form of postural hypotension, which was temporary in the first 2 weeks of doxazosin therapy.

Normality test for all data in both groups showed that the data on Q max, residual urine and IPSS had normal distribution with significance value of more than 0,05. Variance homogeneity test in all groups in week 4, 8, and 12 showed that all variables in daily and intermittent groups had homogeneous variance, with significance value of F test (Levene) higher than 0,05.

There was no significant difference in the improvement of Q max, residual urine, and IPSS at 4 weeks between daily and intermittent group, with significance value higher than 0,05.

Table 1. Comparison of change in Q max, residual urine, and IPSS between daily and intermittent groups after 4 weeks therapy.

	Daily therapy (n = 11)	Intermittent therapy (n = 9)	Comp. Test	Notes
Q max (ml/dt)				
- Mean pre-therapy	9,0	9,6	t: -0,55	No significant
- Mean post-therapy	11,7	12,8	Sig: 0,52	different
- Δ Mean	2,7	3,2		
Residual urine (ml)				
- Mean pre-therapy	88,6	80,3	t: -0,02	No significant
- Mean post-therapy	55,0	55,2	Sig; 0,98	different
-Δ Mean	33,6	25,1		
IPSS				
- Mean pre-therapy	14,5	12,1	t: 1,42	No significant
- Mean post-therapy	10,1	8,0	Sig: 0,172	different
-Δ Mean	4,4	4,1		

Table 2. Comparison of change in Q max, residual urine, and IPSS between the daily and intermittent groups after 8 weeks of therapy.

	Daily therapy (n = 11)	Intermittent therapy (n = 9)	Comp.Test	Notes
Q max (ml/dt)				
- Mean pre-therapy	9,0	9,6	t: -0,25	No significant
- Mean post-therapy	13,0	13,4	Sig: 0,802	different
- Δ Mean	4	3,8		
Residual urine (ml)				
- Mean pre-therapy	88,6	80,3	t: -0,41	No significant
- Mean post-therapy	45,0	48,0	Sig; 0,687	different
- Δ Mean	43,6	32,3		
IPSS				
- Mean pre-therapy	14,5	12,1	t: 0,68	No significant
- Mean post-therapy	8,7	7,6	Sig: 0,507	different
- Δ Mean	5,8	4,5		

Table 3. Comparison of change in Q max, residual urine, and and IPSS between daily and intermittent groups after 12 weeks of therapy.

	Daily therapy (n = 11)	Intermittent therapy (n = 9)	Comp.Test	Notes
Q max (ml/dt)				
- Mean pre-therapy	9,0	9,6	t: -1,01	No significant
- Mean post-therapy	13,2	15,1	Sig: 0,327	different
- Δ Mean	4,2	5,5		
Residual urine (ml)				
- Mean pre-therapy	88,6	80,3	t: 0,35	No significant
- Mean post-therapy	33,0	30,0	Sig: 0,733	different
- Δ Mean	55,6	50,3		
IPSS				
- Mean pre-therapy	14,5	12,1	t: -0,15	No significant
- Mean post-therapy	7,3	7,6	Sig: 0,881	different
- Δ Mean	7,2	5,5		

There was no significant difference in the improvement of Q max, residual urine, and IPSS post 8 weeks of therapy between daily group and intermittent group, with significance value higher than 0,05.

There was no significant difference in improvement of Q max, residual urine, and IPSS post 12 weeks of therapy between daily and intermittent groups, with significance values higher than 0,05.

Overall improvement in means of Q max, residual urine and IPSS in daily and intermittent groups from pre treatment to 12 weeks of therapy are presented in Figures 1, 2, and 3.

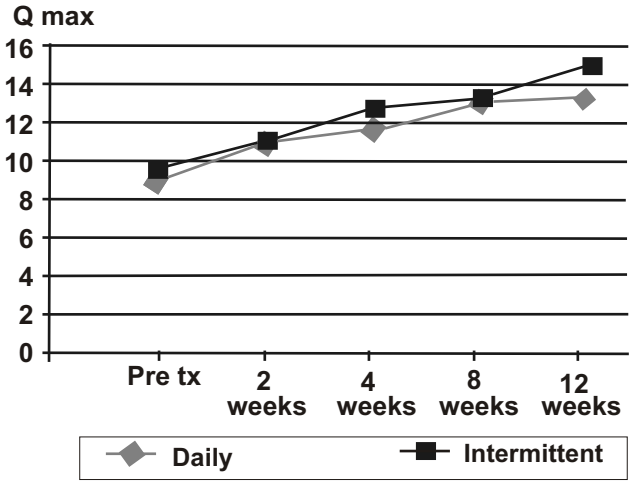

Figure 1. Mean values of Q max in daily and intermittent groups from pre treatment to 12 weeks of therapy.

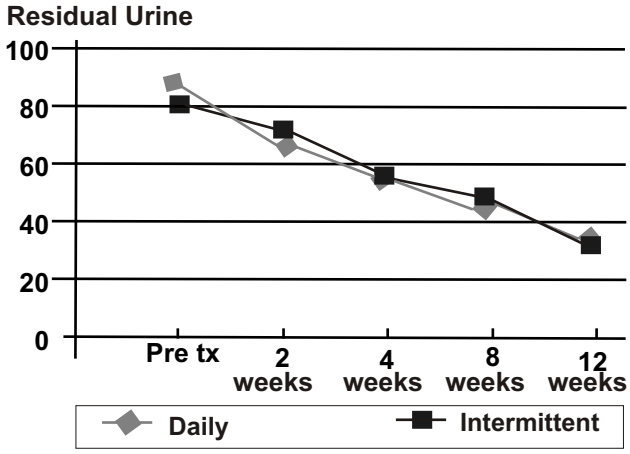

Figure 2. Means of residual urine in daily and intermittent groups from pre treatment to 12 weeks of therapy.

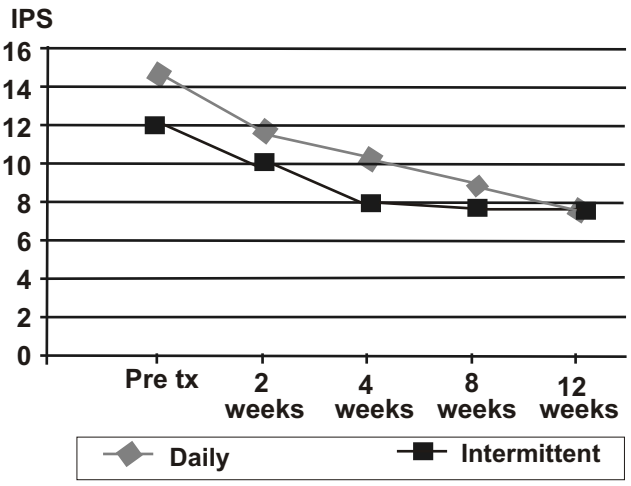

Figure 3. Mean IPSS scores in daily and intermittent groups from pre treatment to 12 weeks of therapy.

DISCUSSION

Samples included in this study were BPH patients aged more than 50 years, which was in accordance with the statement that gradual enlargement of prostate occurs after age 50 years or older. After age 70, about 8 out of 10 men have an enlarged prostate.[15]

Mean prostate volume in daily group reached 45,1 grams, while in the intermittent group it was 33,8 grams. In the daily group the smallest prostate volume was 30,5 grams and the largest was 72,9 grams. In intermittent group, the smallest prostate volume was 20,9 grams and the largest was 48,5 grams. Prostate size was not related to the degree of obstruction.[4,5]

In daily group the mean Q max was 9,0 ml/sec, the residual urine was 88,6 ml, and IPSS 14,5. While in the intermittent group mean Q max was 9,6 ml /sec, the residual urine was 80,3 ml, and IPSS was 12,1. The assessment of Q max, residual urine and IPSS before and after therapy was intended to assess response to therapy in patients with BPH LUTS. This was consistent with the statement that in order to assess response to therapy or progression of LUTS during the evaluation period (follow-up period) it requires IPSS assessment and additional investigation, including uroflowmetry, residual urine, and pressure-flow urodynamic studies.[7,16,17]

Side effects of temporary postural hypotension therapy were found only in 2 research subjects in two weeks of therapy, whereas other side effects were not encountered. Postural hypotension was not a contraindication of doxazosin and did not result in treatment discontinuation. Previous research on doxazosin side effects in 665 patients during 85 days of treatment showed an incidence of less than 1%.[18]

Q max improvement in the study was consistent with previous research, which stated that doxazosin therapy increased Q max in a statistically significant value up to 3 ml/sec.[18-20]

Overall results from pre treatment to 12 weeks of therapy in this study proved that there was significant improvement in LUTS symptoms that included Q max, residual urine and IPSS in daily and intermittent groups. Meanwhile, comparative test using independent t tests proved that the improvement of LUTS symptoms among daily group compared to intermittent group did not differ significantly.

Elimination half-life of doxazosin (22 hours), which is longer than that of the other alpha blockers, has wider therapeutic effects, thus it is considered for intermittent administration once every two days. Intermittent doxazosin therapy is given after 1 to 2 weeks of daily therapy, in which doxazosin plasma concentrations had reached steady state levels. In this study, the intermittent therapy group was started on doxazosin daily for 2 weeks followed by intermittent therapy. After 4 weeks of therapy there was no significant difference in Q max between daily and

intermittent therapy group. This is consistent with the statement that after 2 weeks of therapy there would be improved LUTS symptoms, and intermittent therapy may be continued in accordance with the complaints. Previous research by the Bulbul on 84 BPH LUTS patients who received therapy of alpha blockers for 3 months showed that 34 patients (40%) felt no longer require continued therapy, whereas 50 patients (60%) still felt need for further intermittent alpha blocker therapy.[10]

The relationship between BPH and LUTS is complex, not all patients with BPH complained of micturition disorder, while not all micturition complaints are caused by BPH. The symptoms are caused by three components, i.e., static, dynamic, and detrusor.[4-6]

This study showed that significant improvement of Q max and IPSS began to appear after 2 weeks of doxazosin therapy. Whereas, the residual urine decreased significantly after 4 weeks of therapy in either in daily or intermittent therapy groups.

Significant improvement of Q max, residual urine and IPSS after 4 weeks and 12 weeks of therapy was also found in both groups. Symptom improvement or efficacy in the two groups showed no significant difference. This is consistent with Mohammed A and Bulbul's research reported by Charnow (2009) on intermittent alpha blockers therapy for 3 months in 84 patients with BPH LUTS. The results stated that there was equal efficacy between daily therapy and intermittent therapy. Intermittent alpha blocker therapy is recommended for treatment of BPH with LUTS.[10] Kaplan et al (1998) conducted research on alfuzosin therapy for BPH LUTS, where intermittent alfuzosin therapy had similar efficacy to daily alfuzosin therapy.[12] Whereas Yanardag et al (2005) used tamsulosin as BPH LUTS intermittent therapy for 3 months. The study also showed that there was no significant difference in efficacy of intermittent therapy compared to daily therapy.[13] Alfuzosin, doxazosin, tamsulosin, and terazosin are appropriate treatment options for LUTS caused by BPH. Although there is little difference between those drugs, but some researchers believe that each drug has comparable clinical effectiveness.[14] Overall results from several studies have demonstrated that intermittent alpha-blocker therapy had similar efficacy to daily alpha blocker therapy. Choice of intermittent alpha-blocker therapy is expected to save costs in medical therapy for patients with BPH LUTS, especially in developing countries.[10]

CONCLUSION

Q max, residual urine and IPSS after 12 weeks of therapy improves significantly both in group receiving daily therapy and intermittent therapy. Difference in improvement or efficacy between both groups was not significant.

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