Tamsulosin Efficiency in Treatment of Benign Prostatic Hyperplasia Evaluated by Determining Bladder Weight

Snjezana Milicevic
Urologic Clinic, Clinical Center Banja Luka, Banja Luka, Bosnia and Herzegovina

Introduction/Goal: Bladder wall thickness and bladder mass are higher in patients with subvesical obstruction caused by benign prostate enlargement (BPE) in compensated stage of the disease. The goal of the study was to determine changes of bladder detrusor in patients suffering from benign prostatic hyperplasia (BPH) during tamsulosin treatment. The study was open, prospective and multi-centric.

Material and methods: The material in this study was composed of 20 patients, aged > 45 years, with the present lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia, who had not been treated for the previous 3 months. The inclusive criteria also included the value of International Prostate Symptom Score (IPSS) ≥ 8 points, post-void residual urine volume (PVR) < 100 ml and prostate specific antigen (PSA) < 4 ng/ml. After the end of the trials that were necessary for the introduction of the patients in the study, the patients started taking tamsulosin in a daily dosage of 0.4 mg, and the evaluation parameters during the research were measured at time intervals of 4, 12 and 24 weeks. The evaluation parameters were primary and secondary. The primary parameter included ultrasound estimated bladder weight (UEWB), while the secondary included determination of the blood pressure values (RR) and pulse frequency (PF), of total International Prostate Symptom Score (T-IPSS), a part of IPSS that related to the storage symptoms (I-PSS), a part that related to the voiding symptoms (O-IPSS), quality of life determination (IPSS-QoL), ultrasound estimation of prostate volume (VP) and the quantity of post-void residual urine volume (PVR), along with the determination of the number and strength of adverse reactions.

Results: During the introduction of the patients in the trial, the arithmetic mean of UEWB was 65 g, of PVR 43 ml, VP 35 ml, of total T-IPSS 15.6 points, of I-IPSS 6.9 points, of O-IPSS 8.7 points, and of IPSS-QoL 3.6 points. During the four-week, twelve-week and twenty-four-week checkups, the values were the following: the arithmetic mean of UEWB 36, 39 and 28 grams, of PVR 26, 29 and 21 ml, of T-IPSS 8.3, 6.4 and 5.0 points, of I-IPSS 6.9 points, of O-IPSS 7.9 points, and of IPSS-QoL 3.6 points. During the four-week, twelve-week and twenty-four-week checkups, the values were the following: the arithmetic mean of UEWB 36, 39 and 28 grams, of PVR 26, 29 and 21 ml, of T-IPSS 8.3, 6.4 and 5.0 points, of I-IPSS 3.8, 3.0 and 2.4 points, of O-IPSS 4.6, 3.4 and 2.6 points, of IPSS-QoL 1.7, 1.1 and 1.0 points and of VP 34 ml during the last control. The obtained results of this trial were processed by descriptive statistics (arithmetic mean and standard deviation) and analytical statistics by way of Student’s t-test for dependant (paired) samples, with the comparison made between the obtained results with the zero checkup and four-week checkup, and subsequently the comparison between four-week and twelve-week checkup, twelve-week and twenty-four week checkup, and the zero checkup and the twenty-four week checkup. Adverse drug reactions (libido and ejaculation problems 5% and headache 5%) were mild and tolerant and did not require the interruption of the therapy.

Conclusion: During a 24-week treatment of benign prostatic hyperplasia with tamsulosin, the same showed clinical efficiency in the sense of improvement of LUTS and a decrease of bladder outlet obstruction (BOO), without the influence on prostate volume or showing statistically significant vasodilatory effect. The same affected a significant decrease of ultrasound estimated bladder weight (from 65 g to 28 g). Key words: benign prostatic hyperplasia, urinary bladder, tamsulosin, ultrasonography, bladder wall thickness, ultrasound estimated bladder weight

1. INTRODUCTION

Benign prostatic hyperplasia (BPH) is a chronic disease, the incidence and prevalence of which grows with age. Very frequently, BPH causes lower urinary tract symptoms (LUTS), although it is not the only cause of its occurrence (1). According to the literature data, 50% of patients with LUTS do not have benign prostate enlargement (BPE), i.e. 50% of patients with BPE do not have LUTS (2).

In general, pathophysiology of LUTS and bladder outlet obstruction (BOO) associated with BPH has been considered to consist of two components, a static or anatomic component related to the enlargement of the prostate gland...
and a dynamic or functional component related to variations in prostatic smooth muscle tone (3,4). Although anatomic enlargement of the prostate is a major contributing factor, much attention has been focused on the role of the sympathetic nervous system, especially alpha1 adrenocorticotropin stimulation in the dynamic component, leading to clinical studies of alpha 1 adrenoreceptor antagonists as an agent to relieve LUTS and BOO (5).

Biomolecular research also shows that there are three types of postsynaptic 1-adrenoreceptors, i.e.: α1A, α1B, and α1D (6-8). α1A adrenoreceptors are predominant in the prostate (70%) compared to α1D adrenoreceptors. α1D adrenoreceptors are predominant in bladder detrusor (66%) compared to α1A (34%). α1A adrenoreceptors are the most probable cause underlying the obstruction caused by benign prostatic hyperplasia, with the consequential occurrence of voiding symptoms such as difficult start of micturition, weak urinary flow with terminal dribbling, prolonged urination with incomplete emptying. α1D adrenoreceptors in the bladder are responsible for bladder instability and the consequential storage symptoms such as frequency, nocturia, urgency, urge incontinence, and dysuria.

During its evolution, BPH, being a progressive disease, may lead to the occurrence of numerous complications. The parameters of BPH progression risk include the prostate volume (VP) and prostate specific antigen (PSA). The other factors, such as the bladder weight and the bladder wall thickness are also important (9, 10). Namely, infravesical obstruction caused by benign prostatic hyperplasia is well known to lead to detrusor hypertrophy and an increase in bladder mass. In 1966, Kojima et al. proposed ultrasound estimation of bladder weight from its thickness and the volume in patients with BPH in quantitative estimation of hypertrophy degree (11).

BPH treatment algorithm was also defined in the latest guidelines of the European Association of Urology (EAU), while alpha 1-blockers are frequently considered a first-choice therapy for moderate to severe LUTS, caused by BPE (12). In general, patients with no significant obstruction but has bothersome symptoms may benefit from medical treatment; that is, alpha blockers, for relief of symptoms and 5 alpha reductase inhibitors (5ARI), if VP > 40 ml (13). Tamsulosin represents uroselective α1A/α1D antagonist of the said adrenoreceptors.

2. GOAL

The goal of the study is to determine the changes of bladder detrusors in patients suffering from benign prostatic hyperplasia during treatment with tamsulosin. The study was open-labeled, prospective and multicentric.

3. MATERIALS AND METHODS

The material in the study represented 20 patients, > 45 years of age, with the present lower urinary tract symptoms caused by benign prostatic hyperplasia, who had not been treated for the past 3 months, that is to say, who were treated as outpatients at the Urologic Clinic of Banja Luka Clinical Center, during the conducted trial. The inclusive criteria also included the value of IPSS ≥8 points, residual urine (RU) <100 ml and PSA <4 ng/ml. After the end of the trials that were necessary for inclusion of the patients in the study, they started taking tamsulosin in a daily dose of 0.4 mg, following which, during a continuous therapy with the same, the evaluation parameters during research were measured at 4-, 12- and 24-week intervals. The primary parameter included ultrasound estimation of bladder weight, while the secondary parameters included determination of blood pressure values and the pulse frequency, total (T-total) IPSS, a part of IPSS related to the storage symptoms, a part of IPSS relating to the voiding symptoms, determination of the quality of life, ultrasound determination of prostate volume and post-void residual urine volume, along with the determination of the number and strength of adverse reactions.

In order to achieve the primary goal we used the method described by Kojima et al in 1996. Based on their research, bladder weight is estimated by ultrasound measurement of detrusor volume and bladder volume, according to the following formula:

\[ \text{UBBW} = + \frac{4\pi}{3} \left( \frac{V}{4\pi} + D \right)^{3} - V \]

Detrusor thickness was measured with 6-10 MHz linear multi-frequency probe in all the patients in the supine position, on the anterior side in medial line, with at least three measurements done at the distance of 1 cm each between them, whereby the mean value was taken as an indicator, at the approximately same urine volume in the bladder during each control at the said time intervals.

In order to accomplish the secondary goal, quantification of subjective symptoms, the International Prostate Symptom Score (IPSS) was used, which contains 7 questions relating to the voiding symptoms (questions no. 1, 3, 5 and 6), as well as storage symptoms (questions no. 2, 4 and 7), while the answers were expressed in six categories depending on a degree of expressed symptomatology. We designated the total IPSS as T-IPSS, while a part of the score relating to the voiding symptoms was designated as O-IPSS, and a part of the score relating to storage symptoms as I-IPSS. The quality of life, as a consequence of urinary symptoms, was estimated based on the eighth IPSS question. Ultrasound determination of prostate volume and of the post-void residual urine volume was done by transabdominal access using 3.5 MHz probe.

4. RESULTS

The measured evaluation parameters during the study were marked as the first, the second, the third and the fourth examination (checkup), with a note that the first examination implied the indicators during the introduction of the patients into the trial, the second examination implied certain parameters after 4 weeks, the third certain parameters after 12 weeks and the fourth parameters after 24 weeks.

Testing the difference of arithmetic means of all the above parameters (primary and secondary) was done by way of t-test for dependent (paired) samples.

During the introduction of the patients into the study, the mean RR value...
was 153/92 mmHg, during the second examination 149/88, the third 145/86 and the fourth 145/88 mmHg (figure 1).

The mean value of pulse frequency during the first examination was 77/min, during the second 78/min., the third 77/min. and the fourth 78/min. (figure 2).

Testing the difference of arithmetic means of all the above parameters (primary and secondary, the third and the fourth examination) with a note that the first examination was a statistically high significant difference (p < 0.01) in the values of T-IPSS, and a part of IPSS that related to the voiding symptoms (O-IPSS), i.e. storage symptoms (I-IPSS) during the second examination compared to the first, and the third compared to the second, and the fourth compared to the first, as well as statistically significant differences (p < 0.05) during the fourth examination compared to the third, in the sense of alleviation of the symptoms.

With regards to the quality of life, as a consequence of urinary symptoms, its mean value (IPSS-QoL) was 3.6 points, 1.7 points, 1.1 points and 1.0 points during the first, the second, the third and the fourth examination, respectively (figure 4).

Speaking of a part of IPSS relating to the storage symptoms, I-IPSS, with questions 2, 4 and 7 in IPSS, the mean value of I-IPPS was 6.9, 3.8, 3.0 and 2.4 points during the first, the second, the third and the fourth examination, respectively (figure 4).

Concerning a part of IPSS that related to the voiding symptoms, O-IPSS, with the questions 1, 3, 5 and 6 in IPSS, the mean value of O-IPSS was 8.7, 4.6, 3.4 and 2.6 points during the first, the second, the third and the fourth examination, respectively (figure 5).

Figure 3, 4 and 5 show that there was a statistically high significant difference (p < 0.01) of PVR value during the second examination compared to the first and the fourth examination compared to the first, and which showed that there was no statistically significant difference (p > 0.05) during the third examination compared to the second and the fourth compared to the third.

The mean value of ultrasound estimated bladder weight was 65 grams, 36 grams, 39 grams and 28 grams during the first, the second, the third and the fourth examination (figure 9). Figure 9 shows that there was a statistically high significant difference (p < 0.01) in the values of ultrasound estimated bladder weight in the sense of its decrease during the second examination compared to the first and the fourth compared to the first, that there was statistically significant difference (p < 0.05) in the val-

![Fig. 1. Blood pressure values](image1)

![Fig. 2. Pulse frequency values](image2)

![Fig. 3. Total IPSS values](image3)

![Fig. 4. IPSS values – irritative symptoms](image4)

![Fig. 5. IPSS values – obstructive symptoms](image5)
The mean value of the prostate volume during the first examination was 35 grams, and significant difference (p > 0.05).

Second examination compared to the first and the fourth examination compared to the first, and questions 1, 3, 5 and 6 in IPSS, the mean value of O-IPSS was 8.7, 4.6, 3.4 and 2.6 points during alleviation of the symptoms.

Differences (p < 0.05) during the fourth examination compared to the third, in the sense of compared to the second, and the fourth compared to the first, as well as statistically significant (IPSS-QoL) was 3.6 points, 1.7 points, 1.1 points and 1.0 points during the first, the second, the third and the fourth examination, respectively (figure 6), which means that the quality of life increase during the fourth compared to the third examination, and that there was no statistically significant difference (p > 0.05) in the values during the third examination compared to the second.

5. DISCUSSION

Bladder wall thickness or the bladder mass is known to be significantly higher in patients with subvesical obstruction caused by benign prostatic hyperplasia in compensated stage of the disease (10, 14, 15). Hypertrophic changes of bladder detrusors in patients with infravesical obstruction have been for years evaluated endoscopically (urethrocytostoscopy) or radiologically (intravenous urography with descendant cystography or retrograde cystography) for the presence of bladder wall trabeculation, cellule formation and diverticula. (16). However, during the past decades, the changes of the bladder mass have been relatively easily determined by ultrasonographic measurement of the bladder wall thickness. The measurement techniques developed during the implementation of the studies which showed the results and experiences of different measurement methods. Oelke et al measured the bladder wall thickness using a transabdominal method and presented the results of the connection of BOO in men and the increase of the bladder wall thickness. This study included the measurement of bladder detrusor thickness at the maximum cistometric capacity, based on the indicators that after refilling of the bladder, i.e. > 50% of its capacity, the detrusor thickness remains unchanged (17). Ulucak et al estimated the detrusor thickness in 244 healthy subjects of school age population, of the average age of 11 years (18). Their measurements were done at the mean bladder volume value of 256 ml on anterior, posterior and lateral walls. The data that they presented showed that there was a connection (correlation) between the age and the thickness of anterior and posterior wall, however not of the lateral walls. They also presented the data about the similar relation in terms of positive correlation between the body mass index, anterior and posterior wall, but not between the measured results of the bladder lateral wall. Blatt et al estimated the relation between detrusor thickness and BOO. They measured the detrusor thickness by transabdominal method in two positions on anterior wall with the bladder volume of 200 ml (19). In that study, in which a group of men and women with „non-neurogenic voiding dysfunction” were a testing sample, the authors presented a data according to which there was no statistically significant difference between the patients with DO (detrusor overactivity), BOO and normal urodynamic studies. Generally speaking, all the previous studies dealing with the measurement of the detrusor thickness describe different methods with transabdominal or transrectal/transvaginal access, being the only techniques that are valid according to the available information. The latest studies that were carried out, applying the transabdominal approach, underlined the importance of taking three measurements on the anterior wall, with the insufficiently of taking the measurements from the trigonum area using the same approach (19, 20). Speaking of the calculation of the bladder mass, it is necessary to make a calculation with the bladder volume. Volume determination was described by Hakenberg, who measured the volume as „bladder height x bladder width x bladder depth x 0,6”, as well as by Kojima et al., who added the voided and post-void residual urine, determined by ultrasound or by catheterization, as alternative methods with equivalent results (10,15). In a study that comprised 65 men with benign prostatic hyperplasia, carried out in 1996, Kojima et al determined the detrusor thickness with transabdominal ultrasonography, i.e. a high frequency probe of 7.5 MHz, on the anterior wall at three different places at a distance of 1 cm each. They used the mean value of detrusor thickness and of bladder volume to calculate the bladder mass. They found a significant correlation of ultrasound estimated bladder weight and the present obstruction, and took, as a limit value of ultrasound estimated bladder weight, based on the results of the study group, the value of 35 grams (11, 21).
In our trial we used ultrasound estimated bladder weight using the method described by Kojima et al in 1996. The bladder mass determined by ultrasound (from 65 g to 28 g). Tamsulosin therapy did not affect prostate volume and urodynamic findings in elderly male volunteers without and with BPH and in patients with LUTS suggestive of benign prostatic hyperplasia. Urol. 2001; 58: 966-971.

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