Ultrasound Estimated Bladder Weight During the Treatment of Benign Prostatic Hyperplasia with Tamsulosin

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SUMMARY
The aim of study is to investigate influence of tamsulosin on detrusor in patients with BPH. This is multi-centre, prospective and open study. Our analysis covers 20 patients above 45 y., with IPSS≥8, RU<100 ml, PSA<4 ng/ml and last 3 months no LUTS treatment. At the end of screening with inclusion criteria, patients were treated with tamsulosin 0.4 mg o.d. for 3 month. We measured parameters for evaluation after 4 and 12 weeks of active treatment period: a. Primary: ultrasound estimated bladder weight /UEWB/ according to the techniques already described by Kojima et al. B&K Medical and Digital Communications developed software for linking the data obtained by measuring the bladder wall thickness with PC for calculating the UEWB. The bladder wall thickness was measured by using a linear probe 6-10 MHz by scans of the anterior wall at three points with a distance of about 1 cm between them; b. Secondary: pulse and blood pressure, T-IPSS, I-IPSS, O-IPSS, quality of life, US-residual urine, prostate volume and side effects of tamsulosin treatment. At screening, average value of UEWB was 64 gr., RU 47 ml, T-IPSS 15.4 points, I-IPSS 7.1 points, O-IPSS 8.4, IPSS Q&L 3.6. After 4 and 12 weeks of active treatment period we measured average value of UEWB 40 and 37gr., RU 30 and 23 ml, T-IPSS 7.4 and 5.2, I-IPSS 3.5 and 2.8, O-IPSS 3.9 and 2.5, IPSS Q&L 1.5 and 0.9. Side effects of tamsulosin treatment (ejaculation and libido problems 5%, headache 10%) were infrequent and mild and not a single patient stopped the treatment. Statistical analysis used comparison between results at the screening, 4 and 12 active treatment period with paired samples t test. We concluded that during 12-week tamsulosin treatment, all components of LUTS, measured with IPSS, improved significantly and residual urine decreased. With increased time of treatment, effect of tamsulosin statistically increased. Treatment did not influence pulse rate or blood pressure. After 12 weeks of treatment we measured significant reduction of ultrasound estimated bladder weight.

Key words: urinary bladder, benign prostate hyperplasia, tamsulosin, bladder wall thickness, ultrasound estimated bladder weight

1. INTRODUCTION
Benign prostatic hyperplasia is the most common cause of symptoms appearing in the lower part of urinary tract in men, although any increase in prostate does not lead to the appearance of symptoms in lower urinary tract, or, all men with symptoms of lower urinary tract does not have increase of prostate (1,2,3,4,5).

It is well known that infravesicular obstruction, caused by benign prostate hyperplasia, consequently leads to hypertrophy o detrusor of urinary bladder. Hypertrophy of urinary bladder detrusor can be objectified with tubercular look of the bladder, appearance of cellule or diverticulums by cystography or cystoscopy. Both tests cannot precisely define the degree of hypertrophy quantity. Kojima and colleagues in 1996 suggested ultrasonic determination of urinary bladder weight by its thickness and volume, in patients with BPH, in quantitative estimation of hypertrophy degree.

Enlarged prostate causes two types of obstruction: a dynamic and mechanical. Functional obstruction (dynamic factor) stems from contractile smooth muscles of the prostate and the urinary bladder neck, which are innervated from autonomous nervous system. Mechanical obstruction (static factor) occurs with massive prostate gland enlargement and it is caused with the deformation of posterior urethra.

Adrenoreceptos have a crucial importance in occurrence of symptoms in the lower part of urinary tract caused by benign prostate hyperplasia. There are three types of postsynaptic α-1 adrenoreceptors α 1A, α 1B and α 1D. in the prostate gland most dominant are α 1A (70%) adrenoreceptors compared to α 1D adrenoreceptors, in detrusor of the urinary bladder most dominant are α 1D adrenoreceptors (66%) compared to α 1A (34%). α 1A adrenoreceptors are most probable cause for obstruction occurrence due to benign prostate hyperplasia, with consequential occurrence of urination symptoms, such as more difficult onset of miction, poor flow with terminal drops, prolonged urination, more difficult urination. α 1D adrenoreceptors are responsible for the instability of the bladder and consequential filling symptoms, such as more frequent urge for urination, nocturia, urgency and urgent incontinence.

Medicament therapy of benign prostatic hyperplasia have clearly defined indication area, and initial area, whether it is a case of mono or combined therapy, represent antagonist of alpha adrenergic receptors (6,7,8). Because tamsulosin is urology selective α 1A/1D antagonist, which reduce obstructive and irritation symptoms, or symptoms of urination and symptoms of filling.

2. GOAL
The aim of study was to investigate influence of treatment in patients with benign prostate hyperplasia BPH during treatment with tamsulosin trough evaluation of ultrasound estimated bladder weight.
3. MATERIAL AN METHODOLOGY

Material for this research is consisted of 20 patients older than 45 years, with symptoms in lower part of urinary tract due to BPH, and which last for more than 3 months, than value of IPSS≥8, RU<100 ml, PSA<4 ng/ml and without treatment for at least 3 months due to urinary problems. At the end of screening which was necessary for inclusion of the patients in the study, patients were treated with tamsulosin 0.4 mg per day. We measured parameters for evaluation after 4 and 12 weeks of active treatment period:

Primary: ultrasound estimated bladder weight,

To achieve primary goal which was determination of urinary bladder weigh, we used method already described by Kojima et al. in 1986. Based on their research urinary bladder weight is estimated with ultrasonic measurement of detrusor thickness and bladder volume according to following formula:

$$\text{UEBW} = \frac{4\pi}{3} \left( \frac{3V}{4\pi} + D \right)^3 - V$$

The bladder wall thickness was measured with linear multi frequency probe 6-10 MHz in all cases by scans of the anterior wall at three points on medi- al line with a distance of about 1 cm between them in at least 3 measurements and mean as indicator, with the approximately same quantity of urine in the bladder, during each control in above mentioned time periods.

4. RESULTS

For easier comprehension of the results, measured parameters for the assessment for testing will be mark as first, second and third review, with a note that the first review includes indicators on inclusion of patients in the study, the second review of certain parameters after 4 weeks and the third after 12 weeks.

During inclusion of patients in the study mean value of blood pressure was 153/93 mmHg, during second review 151/89, and third 147/87 mmHg.

Mean value of pulse during all reviews was 77/ min. Mean value of IPSS was during first review 15.4 points, second 7.4, and third 5.2 points.

Irritation symptoms (filling symptoms) in IPSS-I are present in questions 2, 4 and 7. Mean value of IPPS-I (irritation symptoms) was during first review 7.1 points, second 3.5, and third 2.8. Obstructive symptoms (urinating symptoms) in IPSS-O were present according to questions 1, 3, 5 and 6. Mean value of IPSS-O obstructive symptoms) was during first review 8.4 points, second 3.9 and third 2.5 points.

Mean value of life quality was during the first review 3.6 points, second 1.5 and third 0.9 points.

Mean value of residual urine was during the first review 47 ml, second 30 and third 23 ml.

Mean value of ultrasound measured urinary bladder weight was during first review 64 grams, second 40 and third 37 grams.

Testing of differences between means all of the above parameters (primary and secondary) are done using t-test for dependent (paired) samples. Tables 1-9 show the number of tested differences between the means of results in zero examinations, the first

$$V_1 \text{ RRS: } V_2 \text{ RRS } 1.198 \quad 0.246 \quad p>0.05$$

$$V_2 \text{ RRS: } V_3 \text{ RRS } 2.070 \quad 0.152 \quad p>0.05$$

Table 1. Testing results of systolic blood pressure values

$$V_1 \text{ RRD: } V_2 \text{ RRD } 1.524 \quad 0.144 \quad p>0.05$$

$$V_2 \text{ RRD: } V_3 \text{ RRD } 0.842 \quad 0.410 \quad p>0.05$$

Table 2. Testing results of diastolic blood pressure values

$$V_1 \text{ IPPS: } V_2 \text{ IPPS } 6.767 \quad 0.000 \quad p<0.01$$

$$V_2 \text{ IPPS: } V_3 \text{ IPPS } 4.951 \quad 0.000 \quad p<0.01$$

Table 4. Testing results of total IPSS values
and second control. Labels of used variables in these tables are as follows:
- V1- first examination,
- V2- second examination (after 4 weeks of tamsulosin therapy),
- V3- third examination (after 12 weeks of tamsulosin therapy),
- UEBW- ultrasound estimation of bladder weight.

Table 5. Testing of difference in IPSS value–questions 1, 3 and 5.

<table>
<thead>
<tr>
<th>Variables</th>
<th>t</th>
<th>p</th>
<th>conclusion</th>
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<tr>
<td>V1 IPSS-O: V2 IPSS-O</td>
<td>5.955</td>
<td>0.000</td>
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<td>V2 IPSS-O: V3 IPSS-O</td>
<td>4.188</td>
<td>0.000</td>
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Table 6. Testing of difference in IPSS value–questions 2, 4 and 7.

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<td>V1 IPSS-I: V2 IPSS-I</td>
<td>6.249</td>
<td>0.000</td>
<td>p&lt;0.01</td>
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<td>V2 IPSS-I: V3 IPSS-I</td>
<td>3.135</td>
<td>0.005</td>
<td>p&lt;0.01</td>
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Table 7. Testing differences of life quality results

- V3- third examination (after 12 weeks of tamsulosin therapy),
- UEBW- ultrasound estimation of bladder weight.

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<td>V1 RU: V2 RU</td>
<td>3.483</td>
<td>0.002</td>
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<td>V2 RU: V3 RU</td>
<td>0.256</td>
<td>0.801</td>
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Table 8. Testing of differences in residual urine results

- IPSS-I–(answers in IPSS on questions 2, 4 and 7, irritation symptoms),
- IPSS-O–(answers in IPSS on questions 1, 3, 5 and 6, obstructive symptoms),
- IPSS– total IPSS,

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<td>V1 UEBW: V2 UEBW</td>
<td>5.879</td>
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<td>V2 UEBW: V3 UEBW</td>
<td>0.597</td>
<td>0.557</td>
<td>p&gt;0.05</td>
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Table 9. Testing of difference of ultrasound estimated urinary bladder mass

- IPSS Q&L- quality of life,
- RRS- value of systolic blood pressure,
- RRD- values of diastolic blood pressure,
- PUL- pulse frequency,
- RU- residual urine.

Tables 1, 2 and 3 shows that between values of systolic and diastolic blood pressure and pulse frequency there was no statistically significant difference during all examinations.

Tables 4, 5 and 6 indicates that there was a statistically significant difference in values of IPSS, and part of IPSS which refers to obstructive, or irritation problems during second examination compared to the first one, and third compared to the second one. 

Table 7 shows that the quality of life statistically significantly changed in terms of improvement during second examination compared to the first, as well as during third compared to second one.

Testing of difference in residual urine showed that there was a statically significant difference in RU values in terms of reduction during second examination compared to the first, as well as during third compared to second one.

Table 9 shows that there was a high statistically significant difference in values of estimated mass of urinar bladder by ultrasound in terms of reduction during second examination compared to the first, and that there was not statically significant difference in values during third compared to second one.

5. DISCUSSION

For many years, hypertrophic changes in urinary bladder detrusor, in patients with infravesical obstruction are evaluated with endoscopic methods (uretrocystoscopy) or radiographic (intravenous urography with descendent cystography or retrograde cystography) in relation to presence of trabeculcy look of urinary bladder wall, cellule and diverticulum (9). Use of transabdominal ultrasonography shows the presence of hypertrophy signs in urinary bladder detrusor with infravesical obstruction (10,11,12,13,14). Ultrasound evaluation of the lower part of urinary tract originally was normally used in pediatric urology since 1982. Thus in case of infravesical obstruction caused by valvules of urethra, urinary bladder ultrasound is interpreted with significantly thicker bladder wall. Maizels and colleagues were in 1987 offered results of the study in which they among 16% of children with problems urinating, and 17% of children with urinary infection, detected ultrasound changes in detrusor of urinary bladder thickness (11,12). Matthews and colleagues in 1982 and Cascione et.al. 1987 concluded in their studies that in patients with other prostatic signs, ultrasound of lower urinary tract can detect hypertrophy of detrusor as well as excretory urogram (13,14).

However, all these studies in addition to subjective assessments of detrusor thickness not offered quantitative assessment. In the original studies ultrasound examinations were done with conventional transabdominal transducer of low frequency (3.5 MHz), which is now known to give much weaker possibility of a clear assessment of urinary bladder wall in relation to the high frequency transducer (7.5 MHz). Transabdominal ultrasound transducer of low frequency can detect developed hypertrophy of detrusor, but in cases of mild or moderate hypertrophy this method is less sensitive.

In order to have clear quantitative estimates of detrusor hypertrophy detrusor Kojima and col-
leagues were in 1996 proposed determination of urinary bladder weight using measurements of detrusor hypertrophy (15,16). They are in the study, which included 65 men with prostate benign hyperplasia determined detrusor thickness using transabdominal ultrasound transducer of high frequency 7.5 MHz, at the anterior wall at three different places, at distance of 1 cm. Mean value of detrusor thickness and volume of the urinary bladder were used to calculate the mass of the bladder. They find significant correlation of ultrasound estimated urinary bladder weight and presence of obstruction, and as a border value of ultrasound estimated urinary bladder weight, based on the results of the study group, took the value of 35 grams.

In our research, we used the ultrasound determination of the urinary bladder weight using methods that are described by Kojima and associates in 1996. Ultrasound estimated urinary bladder weight during the 12-weeks treatment of BPH with tamsulosin has reduced the average 64 grams to 37 grams, which is a statistically highly significant difference, and a significant positive therapeutic effect which eliminated obstructive component.

We wish to emphasize that, bearing in mind the pathomorphologic changes in detrusor, hypertrophy of detrusor can be fully reversible only if the history of benign hyperplasia did not lasted too long, or in case of excessive length of obstruction caused by BPH leads to irreversibility or partial reversibility of detrusor hypertrophy (17). In our sample significant reduction, with all of the patients in which urinary bladder weight is estimated by ultrasound, as quantitative indicators of detrusor hypertrophy presence, confirmed that all respondents had short history of present symptoms in lower urinary tract caused by benign prostate hyperplasia due reversibility of detrusor hypertrophy.

Antagonists of $\alpha_1$ adrenergic receptors reduce symptoms in lower urinary tract which are result of the present benign prostate gland hyperplasia with mechanism of blockade of these receptors, primarily in the bladder neck, prostate and prostatic urethra, resulting in a reduction of urethra resistance. However, some patients have persistent irritation symptoms or filling symptoms even after removing obstructive factor or BPH tissue with prostatectomy method, which points to the other mechanisms present outside of the prostate at the emergence of irritation symptoms in lower urinary tract (18-24). According to opinion of Schvinn and his associates, $\alpha_1A$ adrenergic receptors in the prostate are responsible for obstructive symptoms and $\alpha_1D$ adrenergic receptors for irritation symptoms in lower urinary tract caused by benign prostate hyperplasia.

Bearing in mind the distribution of alpha adrenergic receptors ($\alpha_1A$ dominantly in the prostate, urethra and trigonum and $\alpha_1D$ dominantly in detrusor) on one side, and urology selectivity of tamsulosin for $\alpha_1A$ and D adrenergic receptors on the other side, the relaxation of $\alpha_1A$ receptors under the influence of tamsulosin reduced the obstructive symptoms from the average of 8.4 points to 2.5, which represents a statistically highly significant difference, and relaxation of $\alpha_1D$ adrenergic receptors reduced the irritation symptoms from the average of 7.1 points to 2.8, which is also highly significant difference.

From this it is a clear advantage tamsulosin as uroselective antagonist of $\alpha_1A$/D adrenergic receptors in relation to nonselective antagonists of $\alpha_1A$ adrenergic receptors, which are considerably less effective in reducing irritation symptoms in lower urinary tract (18-24).

6. CONCLUSIONS

During 12 weeks treatment of benign prostatic hyperplasia with tamsulosin, all components of lower part of urinary system, quantified by IPSS, showed significant improvement.

With the longer duration of treatment (4-12 weeks) positive therapeutic effect of tamsulosin significantly grow. After 12-week of BPH treatment with tamsulosin there was a significant reduction in ultrasound estimated bladder mass (from 64 grams to 37 grams). Residual urine significantly reduced. Tamsulosin did not affected values of blood pressure and pulse frequency.

Figure 1. Testing of detrusor mass
REFERENCES


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