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Optimizing individual treatment outcomes in men with lower urinary tract symptoms using storage subscale score/total International Prostate Symptom Score (IPSS) as a new IPSS ratio

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Background/aim: To evaluate the effects of the storage/total International Prostate Symptom Score (s/T) ratio on the selection and success of medical therapy in men with lower urinary tract symptoms (LUTS).

Materials and methods: A total of 54 men (>45 years of age) with moderate or severe LUTS were divided into 2 groups according to the s/T ratio: Group 1 at <0.43 and Group 2 at >0.43. Tamsulosin (0.4 mg to Group 1) and tolterodine ER (4 mg to Group 2) were administered. Patients were evaluated during the 1st and 3rd months of follow-up treatment.

Results: Thirty-seven (68.5%) and 17 (31.5%) patients were in Groups 1 and 2, respectively. The mean s/T ratios in Groups 1 and 2 increased to 0.38 ± 0.19 from 0.33 ± 0.08 ($P = 0.03$) and decreased to 0.54 ± 0.18 from 0.59 ± 0.1 ($P = 0.17$) during the 3rd month of follow-up, respectively. The treatment success rates of Groups 1 and 2 were 88.4% and 75.7%, respectively. Nine unsuccessful cases were treated with combination therapy and the treatment success was 86.6% at follow-up.

Conclusion: The s/T ratio is effective to determine symptom dominance in men with LUTS and can guide medical treatment selection through better identification of symptoms.

Key words: Lower urinary tract symptoms, medical therapy, storage symptoms, antimuscarinics, α -blockers, treatment success, International Prostate Symptom Score

1. Introduction

Lower urinary tract symptoms (LUTS) indicate the pathologies of storage, voiding, and the postmicturition phases of urination (1). The results of a large prevalence study showed that storage symptoms such as urine frequency, nocturia, urgency, and urge incontinence were more prevalent (51.3%) than other LUTS in men (2). In recent years, the paradigm shifted from the prostate to the bladder for understanding, diagnosis, and treatment strategies of LUTS in men. Accordingly, detrusor overactivity (DO) and bladder outlet obstruction (BOO) play integral roles in men with LUTS (3). Overactive bladder (OAB) symptoms have more deteriorating effects on health-related quality of life (QoL) than other LUTS (4,5). Furthermore, recent studies have emphasized that combination therapy (ComRx) with α -blockers and antimuscarinics had better results in men with BOO who had mixed symptoms (6). In contrast, LUTS in men are often still treated with therapies targeting the prostate even if they have OAB symptoms (1).

Although DO and OAB symptoms may develop secondary to BOO in men, they also may occur independently (7,8). Determination of the dominating pathology in the clinical scenario of patients with LUTS is a major concern in opting for medical therapy.

The International Prostate Symptom Score (IPSS) is the most relevant tool to assess the severity of LUTS (9). Three of the 7 questions evaluate storage symptoms and 1 evaluates QoL. The major disadvantage of the IPSS total score is its inability to determine potential etiologies. Urodynamic evaluation is the gold standard but it is an invasive method. There is no widely accepted noninvasive diagnostic test to identify dominant symptoms of storage or voiding in LUTS. Recently, the importance of the IPSS has become well recognized and some authors have published data that constitute different IPSS ratios (10,11). The objective of the present study was to evaluate the effect of the storage/total IPSS ratio (s/T) as a new tool to individualize medical therapy in men with LUTS.

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2. Materials and methods

2.1. Patient selection

A total of 54 men (>45 years of age) with moderate or severe LUTS on the IPSS were prospectively included in this study. Exclusion criteria were the diagnoses of any lower urinary tract condition other than prostatic enlargement (prostate cancer, surgery, infection, stones, strictures, neurological diseases, etc.), previous prostatic surgery, and medication for BOO and/or DO. The institutional review board and ethics committee approved the study protocol. Prostate-specific antigen (PSA), IPSS, uroflowmetry, prostate volume, postvoiding residual urine volume (PVR), and pressure flow study (PFS) were measured in all patients.

All patients were further divided into 2 groups according to the s/T ratio obtained by dividing the total score of all questions examining storage function in the IPSS (2nd, 4th, and 7th) by the total score of all questions (15/35 = 0.43). Patients were grouped by s/T cut-off value of 0.43 (Group 1 at <0.43 and Group 2 at >0.43). Tamsulosin (0.4 mg, once daily per os) was administered in Group 1, while tolterodine ER (TER; 4 mg, once daily per os) was administered in Group 2. Patients were evaluated during the 1st and 3rd months of follow-up treatment. Treatment success was defined as symptom improvement by IPSS of ≥4 points on 2 consecutive visits, 1 point improvement of QoL score, and/or any rise of maximum flow rate (Qmax) (12,13). A treatment algorithm according to the design of the study is shown in Figure 1. ComRx was administered in case of treatment failure during the 1st month of follow-up treatment. Treatment success of ComRx was evaluated 1 month after starting the ComRx treatment as stated above. If a patient's Qmax was <8 mL/s and PVR was >200 mL after initial treatment, transurethral resection of the

prostate (TURP) was performed and these patients were excluded from the study.

2.2. Pressure flow studies

All patients underwent PFS, and the bladder outlet obstruction index (BOOI) and bladder contractility index (BCI) were calculated using the following formulas:

BOOI: detrusor pressure at maximum flow rate (PdetQmax) - 2 × maximum flow rate (Qmax).

BCI: PdetQmax + 5 × Qmax.

Patients were categorized into 3 groups with reference to the BOOI score: obstructed (BOOI of >20), equivocal (BOOI = 20–40), or unobstructed (BOOI of <20). Using BCI, patients were categorized into groups with strong (BCI of >100), normal (BCI = 100–150), and weak (BCI of <100) contractility.

2.3. Statistical analysis

Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The Mann–Whitney U test and chi-squared test were used to compare the 2 groups. The Wilcoxon rank test and logistic regression analysis were performed to determine treatment success. P < 0.05 was accepted as statistically significant.

3. Results

The mean age of the patients was 62.1 ± 8 years. There were 37 (68.5%) patients in Group 1 and 17 (31.5%) in Group 2. The mean s/T ratios of Groups 1 and 2 were 0.33 ± 0.08 and 0.59 ± 0.1, respectively. No statistically significant difference was found in the pretreatment variables between the groups for the s/T ratios (Table 1). Five (13.5%) patients in Group 1 and 8 (47%) in Group 2 had statistically significant differences in urge urinary incontinence (P = 0.01). When we compared the pretreatment variables

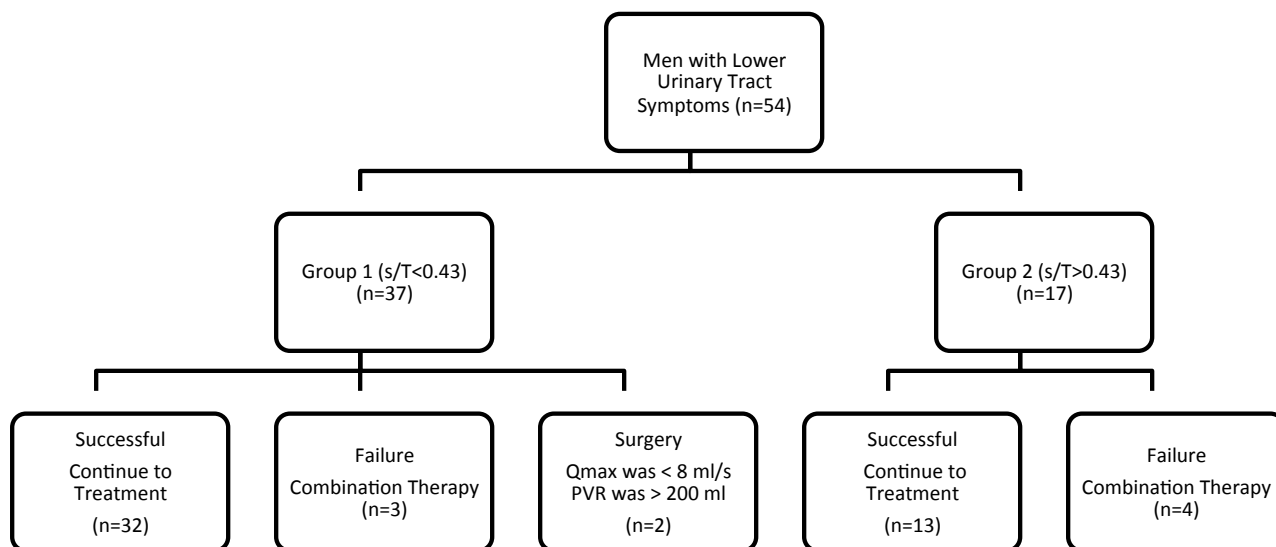


Figure 1. Treatment algorithm according to design of the study.

Table 1. Comparison of patient pretreatment variables according to s/T ratio.

	Group 1 (s/T ratio of <0.43) (n = 37) (mean ± SD)	Group 2 (s/T ratio of >0.43) (n = 17) (mean ± SD)	P-value
Age	61 ± 7.59	60.9 ± 8.8	0.96
Total IPSS	17.8 ± 5.84	16.2 ± 8.14	0.44
QoL score	3.52 ± 1.1	3.53 ± 1.3	0.92
Total PSA (ng/mL)	1.5 ± 1.06	1.62 ± 1.33	0.744
Prostate volume (cm ³)	32.9 ± 16.5	32 ± 15.5	0.859
Maximum cystometric capacity (mL)	381.14 ± 77.4	262.8 ± 143.3	0.006
Qmax (mL/s)	11.9 ± 3.77	15.1 ± 6.18	0.08
Maximum detrusor pressure during voiding phase	69 ± 27.4	62.7 ± 16	0.47
Maximum detrusor pressure during maximum flow	50.9 ± 25	46.8 ± 12.1	0.6
Voiding volume (mL)	282 ± 135.8	276 ± 141.8	0.891
Residual volume (mL)	50.3 ± 41.9	44.7 ± 57	0.7

between the 2 groups, only the maximum cystometric capacity was higher in Group 1 ($P < 0.001$) (Table 1).

Treatment success of Groups 1 and 2 was 88.4% and 75.7%, respectively. The data from the baseline and the 1st and 3rd months' follow-up variables in Groups 1 and 2 are shown in Figures 2 and 3, respectively. The mean s/T ratios in Groups 1 and 2 changed from 0.33 ± 0.08 to 0.38 ± 0.19 ($P = 0.03$) and from 0.59 ± 0.1 to 0.54 ± 0.18 ($P = 0.17$) in

the 3rd month of follow-up treatment, respectively. When we compared the data from each group in terms of total IPSS, storage and voiding scores, QoL score, and Qmax (mL/s) in the follow-up periods, all parameters were statistically different from baseline values, except for Qmax in the 1st month of follow-up for Group 2 (Figures 2 and 3). Significant decreases were found in total IPSS (-7.6), along with an improvement in QoL score (-1.6), a slightly

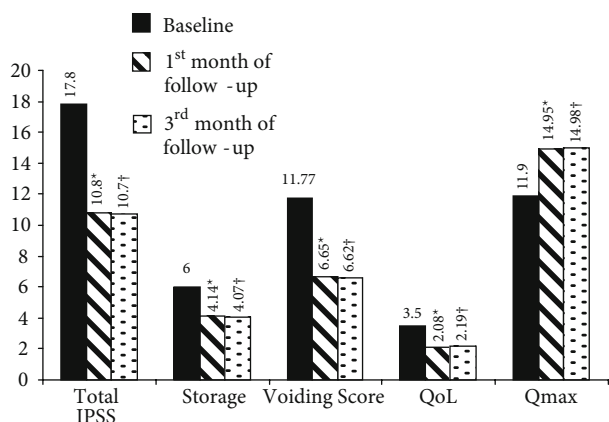


Figure 2. Mean values of IPSS, storage and voiding subscale scores, QoL, and Qmax (mL/s) in Group 1 during the follow-up period.

*: Statistically significant difference was found when comparing 1st month follow-up values with baseline values.

†: Statistically significant difference was found when comparing 3rd month follow-up values with baseline values.

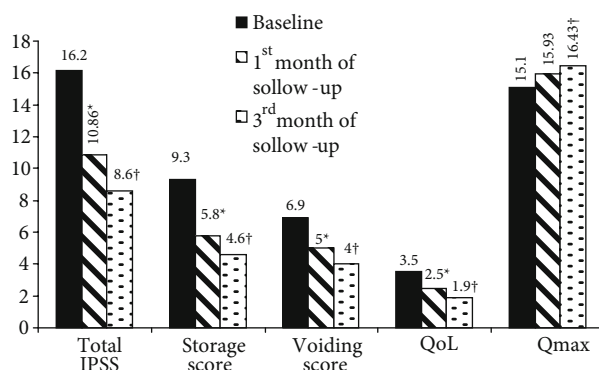


Figure 3. Mean values of IPSS, storage and voiding subscale scores, QoL, and Qmax (mL/s) in Group 2 during the follow-up period.

*: Statistically significant difference was found when comparing 1st month follow-up values with baseline values.

†: Statistically significant difference was found when comparing 3rd month follow-up values with baseline values.

increased Qmax (+1.33 mL/s), and a minimally decreased PVR (-22.6 mL) in Group 2 during the 3rd month of follow-up. The PVR of unsuccessful cases in the 1st month of follow-up treatment (95 ± 65 mL) was significantly higher than in the successful counterparts (42 ± 36.2 mL) in Group 1 (P = 0.007). The multivariate analysis showed that only PVR was identified as an independent predictive factor affecting treatment success in Group 1 (P = 0.004; odds ratio = 1.05, range: 1.01–1.07). There was no increase in the PVR of Group 2 during the 1st and 3rd months of follow-up treatment (P > 0.05).

The calculated BOOI and BCI values of Groups 1 and 2 according to PFS are shown in Table 2. Regarding the baseline PFS, BOOI and BCI values of the patients did not show any significant difference between the groups (P = 0.324, P = 0.153; data not shown in Table 2).

Five patients in Group 1 and 4 patients in Group 2 did not respond to first-line treatments. TURP was performed in 2 of 5 patients in Group 1. Seven of 9 nonresponsive patients received ComRx and the treatment success rate was 86.6% (6 of 7 patients) during the 1st month of follow-up treatment. The mean s/T ratio was 0.47 in the ComRx group. There was a decrease of 7.8 in IPSS and 1.88 in QoL, and an increase of 3.03 mL/s in Qmax with ComRx.

The most common adverse event was mild xerostomia, reported by 18% of the patients (3 of 17) receiving antimuscarinics. No serious adverse event was reported to prompt drug withdrawal and no urinary retention was observed in either group.

4. Discussion

Epidemiological studies have shown that 60% of men in the general population complained about at least 1 type of LUTS, whereas 48.4% of men with LUTS had only OAB symptoms and 35.2% had mixed symptoms, including voiding, storage, and postmicturition symptoms

(2). Although treating the prostate gland has been an accepted method in LUTS management, the presence and predominance of OAB symptoms in bothersome LUTS seems to be an important issue. The determination of predominant symptoms of LUTS in the clinical scenario with noninvasive diagnostic tools is challenging.

α-Blockers are widely accepted as the first-line treatment for men with LUTS suggestive of BOO. Although there are controversies concerning treatment success criteria of α-blockers in the literature, studies have reported that 56%–80% of patients had improved symptoms using α-blockers (12,14). In the present study, treatment success with tamsulosin monotherapy was 88.4%, which was higher than in previous studies. We think that our success rate was related to the selection of appropriate patients who would likely benefit from tamsulosin monotherapy. Additionally, a significant increase in the mean s/T ratio (0.33 to 0.38) indicated that tamsulosin improved voiding symptoms rather than storage symptoms.

Although antimuscarinics reduce DO and are indicated for the treatment of OAB, until recently, many men have been only prescribed antimuscarinics for persistent OAB symptoms following prostatic surgery (8). Antimuscarinic therapy in men with LUTS has traditionally been avoided due to an increased risk of acute urinary retention in BOO cases. However, primary studies (15,16) and post hoc analyses (17,18) suggested that antimuscarinics were not associated with an increased incidence of urinary retention and substantial increase of PVR in men with OAB with or without other LUTS. Kaplan et al. (16) evaluated the effectiveness of TER monotherapy in men with LUTS who did not respond to initial α-blocker treatment and found significant changes in total IPSS (-6.1), peak urinary flow rate (+1.9 mL/s), and PVR (-22 mL) after 6 months of TER monotherapy. They also reported that the storage and voiding scores

Table 2. Comparisons of the BOO and BC indexes of patients in Groups 1 and 2 according to success of the treatments at 3rd month of follow-up.

	BOOI subgroups	BOO index, n (%)	P-value*	BCI subgroups	BC index, n (%)	P-value*
Group 1 (n = 37)	<20	15 (40.5)	0.101	<100	34 (45.3)	0.050
	20–40	18 (24)		100–150	36 (48)	
	>40	27 (36)		>150	5 (6.7)	
Group 2 (n = 17)	<20	21 (63.6)	0.143	<100	3 (9.1)	0.247
	20–40	9 (27.2)		100–150	27 (81.8)	
	>40	3 (9.2)		>150	3 (9.1)	

*: P-values indicate the comparison of each index in each group according to success of treatment.

of patients significantly decreased after treatment and concluded that TER is an effective and well-tolerated therapy and can be used initially or after failed treatment with α -blockers. Similarly, we found a significant decrease in total IPSS (-7.6), an improvement in QoL score (-1.6), a slightly increased Qmax (+1.33 mL/s), and a minimally decreased PVR (-22.6 mL) in Group 2 during the 3rd month of follow-up. Additionally, the s/T ratio decreased from 0.59 to 0.54. Treatment success of this group was 75.7% with TER monotherapy. Acute urinary retention and an increase in PVR were not detected. Hence, TER monotherapy seems to be safe, at least over a 12-week period, in patients with BOO and DO.

Recently, several groups have evaluated the efficacy and tolerability of ComRx in men with OAB and BOO. A multicenter randomized trial was conducted to investigate the implications of TER and tamsulosin (TIMES study) in men with LUTS (15), whereas others performed subgroup analyses using PSA, prostate size, and IPSS (6,19,20). Treatment success was defined as the patients' perceptions of treatment benefit and was reported as 61.7% in placebo, 65.1% in TER, 70.8% in tamsulosin, and 80% in ComRx therapies. The s/T ratios of their groups were 0.51, 0.5, 0.51, and 0.5, respectively. Improved bothersome symptoms with ComRx, rather than tamsulosin monotherapy, might be explained by the dominance of storage symptoms in that group. In contrast, the authors reported unsuccessful treatment results with TER monotherapy compared with a placebo, but the greater treatment success obtained in our study appeared to be related to the higher s/T ratio (0.59) in Group 2 than in the TER group of the TIMES study. Chapple et al. (21) evaluated the effectiveness of added TER to previous unsuccessful α -blocker treatment in men with prominent storage symptoms suggestive of OAB and found that additional TER caused significant improvements in diary variables, IPSS storage scores, and bothersome symptoms. The s/T ratios of the placebo and TER groups were 0.5 and 0.49, respectively. Regarding this ratio, their study group had predominant storage symptoms and, with respect to our hypothesis, additional TER treatment was successful as expected.

A prospective randomized study evaluated the efficacy and safety of propiverine combined with doxazosin in urodynamically confirmed BOO patients with OAB symptoms and concluded that ComRx was more effective than doxazosin monotherapy (12). The calculated s/T ratio was 0.41 in the doxazosin group and 0.43 in the ComRx

group; the patient groups had nearly equal voiding and storage symptoms according to our s/T cut-off value and 2/3 of the patients had simultaneous BOO after urodynamic studies. Therefore, successful therapy was anticipated with doxazosin. Better results with ComRx might be explained by the presence of OAB symptoms. According to the s/T ratio, the treatment success rates in the present study were 88.4%, 75.7%, and 86.6%, respectively, for tamsulosin, TER, and ComRx. In other words, we successfully treated 84.2% of 54 patients who were admitted to our clinic with first-line therapy. The success rate reached 96.2% when the ComRx results were added. Our results indicated that most patients were successfully treated with any kind of medical therapy after the 1st month of follow-up using the s/T ratio. We suggest that ComRx should be initially prescribed in men with mixed symptoms.

Song et al. evaluated voiding and storage functions with respect to bladder outlet obstruction grade and contractility in 232 patients treated with alfuzosin. They did not find any correlation between treatment success and the indexes (BOOI and BCI) (22). Similarly, neither the obstruction grade nor the contractility status in Groups 1 and 2 impacted the treatment success in our study ($P = 0.311$ and 0.466 , respectively; data not shown in a table). These data show that urodynamic parameters do not predict the baseline symptom severity and improvement after treatment.

The major limitation of the present study was an inadequate cohort number to determine a definitive s/T cut-off value and the lack of a placebo group. Although the underlying pathologies of LUTS are complex, the s/T ratio can predict the underlying pathology and it allows determination of the patients who would benefit from antimuscarinic administration. On the other hand, we suggest that different cut-off values should be defined for selecting first-line medical treatment including α -blockers, antimuscarinics, or ComRx. The other shortcoming of our study was the lack of using a specific validated OAB questionnaire in the evaluation of the patients.

In conclusion, the s/T ratio may affect selection of medical treatment by better identifying storage or voiding symptoms and may improve success rates by preventing over- or underutilization of medications. We suggest initially administering antimuscarinic monotherapy in men with LUTS using the s/T ratio. However, the s/T cut-off value for medical treatment selection should be confirmed in a large prospective randomized study.

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