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The change of IPSS 7 (nocturia) score has the maximum influence on the change of Qol score in patients with lower urinary tract symptoms

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Abstract

Purpose This study evaluated the factors affecting lower urinary tract symptom (LUTS)-related quality-of-life (Qol) scores and the change in the Qol scores following treatment.

Methods This pooled data analysis study collected the international prostate symptom score (IPSS) with Qol score from five studies which evaluated the change in the IPSS after medication for LUTS. Post-treatment IPSS with Qol scores were measured at 3 months after the initiation of medication.

Results The mean age of 444 men was 62.5 ± 8.5 years. The mean IPSS total and Qol score at baseline were 18.6 ± 6.7 points and 4.0 ± 0.9 points, respectively. Each IPSS item score, except IPSS 3, was found to be an independent factor that had an influence on baseline Qol scores, with IPSS 7 (nocturia) showing the most significant correlation. After 3 months' medication, IPSS total and Qol score were significantly decreased to 11.7 ± 6.4 ($p < 0.001$) and 2.9 ± 1.2 points ($p < 0.001$), respectively. On multivariate analysis, the improvements in IPSS item 2, 4, 5, and 7 scores were found to be independent factors that had an influence on the improvement in Qol scores. The improvement in IPSS 7 had maximum influence on the improvement in Qol score. Among men with a decrease in total IPSS score by 5 or more points but without improvement in nocturia, Qol was not improved in one-third of them.

Conclusions Storage symptoms had a greater influence on QoL scores than voiding symptoms. The improvement in nocturia after treatment was the most important factor for the improvement in Qol.

Keywords Lower urinary tract symptoms · Prostate · Quality of life

Introduction

LUTS/BPH is highly prevalent in the general population [1, 2]. The IPSS questionnaire is the most widely used, validated questionnaire for evaluating LUTS/BPH [3, 4]. The

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IPSS questionnaire consists of seven items related to symptoms and one item related to QoL [5]. Among these eight items, the Qol item is an essential item for the evaluation of bother caused by LUTS/BPH [6].

The QoL item of IPSS is an independent and unsubstitutable item, because the symptom severity does not always account for the bothersomeness and its negative impact on QoL [7, 8]. Some men might show high Qol score in spite of having only mild LUTS, and some men might show low Qol score, although they have severe LUTS [9]. This discrepancy between symptom severity and Qol score is also observed in response to treatment of LUTS/BPH. Some men show improved Qol score proportional to the improvement in LUTS; however, some men show constant or worse Qol score in spite of improvement in LUTS after treatment [10]. To date, there is no reliable explanation for this discrepancy in a subset of patients.

The aim of this study was to evaluate the symptoms or factors which affect the Qol score at baseline and the change in Qol score after treatment. Numerous studies have been performed to evaluate the efficacy of medical treatment for LUTS and most of these studies obtained sufficient data for analyzing the Qol score and the change in Qol score. This study used combined data of previously performed studies with the investigator's agreement about providing data. This was more efficient and ethical, because it allowed avoiding unnecessary performance of a new study.

Patients and methods

This study was approved by the Institutional Review Board of Konkuk University Hospital (KUH 1130052). This study collected pre-treatment and post-treatment IPSS data and LUTS/BPH-related profiles from five previously performed studies. Flowchart of study selection is presented in Fig. 1. To search for studies that evaluate the effect of treatment for LUTS/BPH, a list of studies that used an alpha blocker for primary treatment of LUTS/BPH was requested from pharmaceutical companies that manufacture the alpha blocker. One pharmaceutical company (Astellas) responded, and 30 trials were included. Disagreement about providing data to the investigator via individual contact, lack of sufficient IPSS
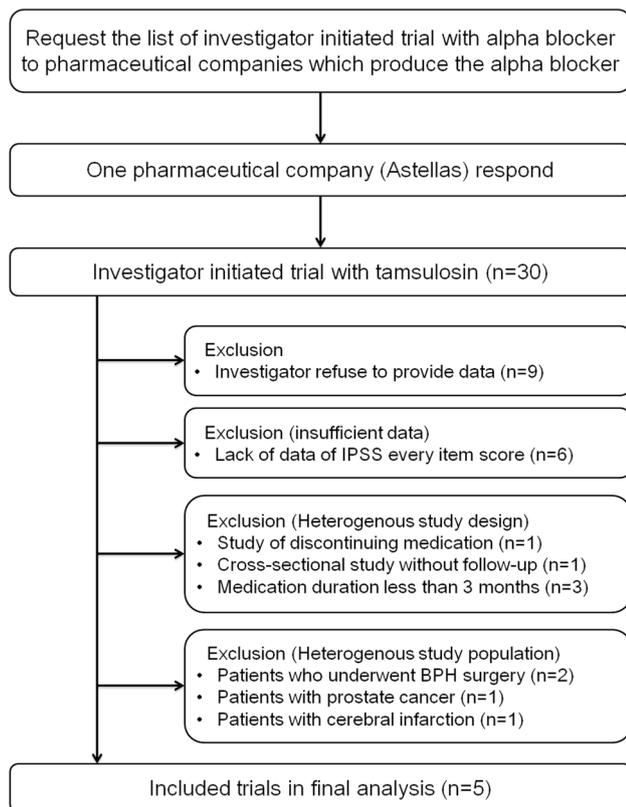
data, and unsuitable study design or participant for analysis were the reasons for exclusion. Detailed information about the selected studies is presented in Supplementary Table 1.

Data collection

All received data did not contain personally identifiable information or treatment related information. Because the aim of this study was not to evaluate the effect of medication, but to evaluate the influence of symptom or symptom change on Qol, data about the drug which the patients had received were not included in our dataset. It included data contained demographic details (age, height, and weight) and past medical history. Baseline IPSS score and baseline BPH profile including PSA, prostate volume, maximum flow rate, and PVR on Uroflowmetry were collected. Post-treatment IPSS score, Qmax, and PVR following 3 months' treatment were also collected. Among patients in included study, men without IPSS data at 3 months due to lost to follow-up were excluded in final analysis.

Analysis of factors that had an influence on baseline Qol scores

To evaluate the influence of each symptom on baseline Qol scores, demographic details, BPH profile, and each IPSS score were included in the analysis. Multivariate analysis using linear regression analysis was performed with variables that were significant in univariate analysis.

Analysis of factors that had an influence on the change in Qol

Changes in Qol and each IPSS item were calculated as "baseline scores—post-treatment scores". A positive value indicates a decrease in values and improvement in symptom scores. Change in each IPSS item and change in uroflowmetry parameter were evaluated as possible factors that could have an influence on the change in Qol scores. Baseline Qol score was also included, because it was directly correlated to the change in Qol scores. Multivariate analysis using linear regression analysis was performed with variables that were significant in univariate analysis.

Subgroup analysis according to the change in nocturia

Based on the result of factors that had an influence on Qol or change in Qol scores, IPSS item 7 (nocturia) had the maximum influence on the Qol score among all IPSS items. To evaluate the impact of the change in IPSS item 7, subgroup analysis was performed. Among men in whom the frequency of nocturia was 2 or more at baseline, those who

Fig. 1 Flowchart of study selection

showed improvement in IPSS total score of 5 or more points was selected. The patients were allocated to the following groups according to the change in nocturia: Aggravation group (change in nocturia < 0); Stationary group (change in nocturia = 0); Improvement group 1 (change in nocturia = 1); Improvement group 2 (change in nocturia ≥ 2). Qol score improvement was defined as a decrease in score by 1 or more points. The proportion of Qol score improvement was compared group-by-group and p for trend was calculated.

Statistical analysis

All statistical analyses were performed using PASW statistics version 17.0 (SPSS, Chicago, IL, USA). Data are presented as mean ± standard deviation. The Chi-square test was used to compare categorical data, and the independent t test was used to compare numeric parameters. All hypotheses were evaluated in a two-sided manner, and $p < 0.05$ was considered statistically significant. To evaluate the influence of parameters on QoL at baseline or change in Qol, linear regression analysis was performed. p for trend was used in subgroup analysis.

Results

A total of 748 patients were identified from five included studies. After exclusion of 304 patients due to lost to follow-up, 444 men were included in final analysis. Baseline characteristics of the study population are presented in Table 1. The mean age of the patients was 62.5 ± 8.5 years. Baseline total IPSS score and Qol score were 18.6 ± 6.7 points and 4.0 ± 0.9 points, respectively. At 3 months' post-treatment, the total IPSS score and Qol score were significantly decreased to 11.7 ± 6.4 points ($p < 0.001$) and 2.9 ± 1.2 points ($p < 0.001$), respectively.

Factors that had an influence on baseline Qol scores

The presence of hypertension or diabetes was negatively related to Qol scores (Table 2). All baseline IPSS item scores were correlated to baseline Qol scores. However, BPH profile including PSA, prostate volume, and uroflowmetry parameters were not significant factors that had an influence on Qol scores. Multivariate regression analysis showed that IPSS item 1 (RU sense), item 2 (frequency), item 4 (urgency), item 5 (weak stream), item 6 (hesitancy),

Table 1 Baseline characteristics and changes after medication for 3 months

Variables	Baseline	3M follow-up	p value
Age (year)	62.5 ± 8.5		
Height (cm)	167.7 ± 6.3		
Weight (kg)	68.3 ± 8.3		
Body mass index (kg/m^2)	24.3 ± 2.4		
Medical disease			
Hypertension	98 (22.1%)		
Diabetes	45 (10.1%)		
Serum PSA (ng/dl)	1.7 ± 1.9		
Prostate volume (cc)	32.7 ± 12.6		
IPSS scores			
IPSS item 1	2.8 ± 1.7	1.7 ± 1.4	< 0.001
IPSS item 2	3.0 ± 1.5	1.9 ± 1.3	< 0.001
IPSS item 3	2.8 ± 1.7	1.9 ± 1.6	< 0.001
IPSS item 4	2.5 ± 1.6	1.3 ± 1.3	< 0.001
IPSS item 5	3.1 ± 1.6	2.1 ± 1.5	< 0.001
IPSS item 6	2.0 ± 1.6	1.3 ± 1.3	< 0.001
IPSS item 7	2.3 ± 1.2	1.6 ± 1.1	< 0.001
QoL	4.0 ± 0.9	2.9 ± 1.2	< 0.001
Voiding symptom sum	10.8 ± 4.8	7.0 ± 4.4	< 0.001
Storage symptom sum	7.8 ± 3.2	4.8 ± 2.7	< 0.001
Total IPSS scores	18.6 ± 6.7	11.7 ± 6.4	< 0.001
Uroflowmetry			
Maximum flow rate (ml/s)	12.5 ± 5.8	15.2 ± 7.1	< 0.001
Voided volume (ml)	201.3 ± 108.6	226.8 ± 126.1	0.005
Post-void residual urine volume (ml)	32.3 ± 34.9	29.3 ± 37.1	0.061

Table 2 Factors that were related to the baseline QoL score

Variables	Univariate			Multivariate		
	B	95% CI	p	B	95% CI	p
Age	−0.009	−0.020 to 0.001	0.074			
Height	−0.013	−0.031 to 0.004	0.143			
Weight	0.002	−0.009 to 0.013	0.756			
BMI	−0.010	−0.057 to 0.037	0.678			
Hypertension	−0.234	−0.442 to −0.026	0.027	−0.178	−0.361 to 0.004	0.055
Diabetes	−0.356	−0.642 to −0.071	0.015	−0.115	−0.364 to 0.134	0.363
PSA	−0.027	−0.08 to 0.025	0.309			
Prostate volume	−0.005	−0.013 to 0.003	0.193			
Baseline IPSS item 1	0.197	0.148–0.246	<0.001	0.070	0.018–0.121	0.009
Baseline IPSS item 2	0.222	0.167–0.278	<0.001	0.058	0.001–0.115	0.047
Baseline IPSS item 3	0.115	0.064–0.166	<0.001	−0.014	−0.064 to 0.037	0.598
Baseline IPSS item 4	0.215	0.164–0.266	<0.001	0.106	0.055–0.158	<0.001
Baseline IPSS item 5	0.215	0.165–0.265	<0.001	0.096	0.044–0.147	<0.001
Baseline IPSS item 6	0.171	0.120–0.222	<0.001	0.073	0.021–0.125	0.006
Baseline IPSS item 7	0.273	0.208–0.338	<0.001	0.179	0.118–0.24	<0.001
Maximum flow rate	0.007	−0.009–0.022	0.388			
Voided volume	0.000	−0.001–0.001	0.988			
PVR volume	−0.002	−0.004–0.001	0.155			

and item 7 (nocturia) were significant factors that had an influence on Qol scores. Among them, IPSS item 7 had the maximum impact on Qol scores (B = 0.179, 95% CI 0.118–0.240, p < 0.001).

Factors that had an influence on the change in Qol scores

Multivariate analysis results for factors that had an influence on change in Qol scores are presented in Table 3. Change

Table 3 Factors that were related to the improvement in QoL score after medication

Variables	Univariate			Multivariate		
	B	95% CI	p	B	95% CI	p
Age	0.003	−0.011 to 0.017	0.664			
Height	−0.008	−0.033 to 0.016	0.495			
Weight	0.002	−0.013 to 0.017	0.777			
BMI	0.039	−0.026 to 0.104	0.234			
Hypertension	0.020	−0.263 to 0.303	0.888			
Diabetes	−0.052	−0.440 to 0.337	0.793			
PSA	0.012	−0.060 to 0.084	0.742			
Prostate volume	0.009	−0.002 to 0.020	0.127			
Change in IPSS item 1[a]	0.230	0.162–0.298	<0.001	0.036	−0.029 to 0.102	0.276
Change in IPSS item 2[a]	0.319	0.248–0.391	<0.001	0.140	0.071 to 0.21	<0.001
Change in IPSS item 3[a]	0.196	0.124–0.268	<0.001	0.04	−0.027 to 0.108	0.238
Change in IPSS item 4[a]	0.318	0.252–0.383	<0.001	0.148	0.081–0.214	<0.001
Change in IPSS item 5[a]	0.273	0.205–0.341	<0.001	0.125	0.06–0.19	<0.001
Change in IPSS item 6[a]	0.181	0.104–0.258	<0.001	0.047	−0.023 to 0.116	0.188
Change in IPSS item 7[a]	0.358	0.254–0.463	<0.001	0.171	0.079–0.263	<0.001
Baseline Qol score	0.514	0.397–0.631	<0.001	0.328	0.222–0.433	<0.001
Change in Maximum flow rate[a]	−0.015	−0.033 to 0.003	0.104			
Change in Voided volume[a]	0.000	−0.001 to 0.001	0.841			
Change in PVR volume[a]	−0.001	−0.004 to 0.002	0.655			

[a]Values were calculated as baseline values—follow-up values

in IPSS item 2 (frequency), item 4 (urgency), item 5 (weak stream), item 7 (nocturia), and baseline Qol score were independent factors that had an influence on the change in Qol scores after treatment. Except for baseline Qol score, which was directly correlated with the change in Qol score, change in IPSS item 7 (nocturia) had the maximum influence on Qol scores. As the score of IPSS item 7 decreased by one point, the Qol score decreased to 0.171 points (95% CI 0.079–0.263, $p < 0.001$).

Qol improvement according to the change in nocturia

Among men who had a decrease in the IPSS score by 5 or more points after treatment, the proportion of men with improvement in Qol scores increased as subgroups with more improvement in nocturia (p for trend < 0.001) (Table 4). Baseline total IPSS, IPSS item 7, and Qol scores of the subgroup were 21.4 ± 6.7, 4.2 ± 0.9, and 4.2 ± 0.9 points, respectively. At 3 months' post-treatment, the total IPSS, IPSS item 7, and Qol scores decreased to 11.0 ± 5.9, 1.5 ± 1.1, and 1.3 ± 0.9 points, respectively. Even though IPSS scores were decreased by five or more points, Qol scores were not improved in 33.3% of patients when nocturia was not improved. In contrast, 95% of the patients showed improvement in Qol scores when the frequency of nocturia was decreased by 2 or more.

Discussion

This study showed that certain symptoms had more impact on Qol scores and change in Qol scores. The QoL score of IPSS is an independent and important item among the eight items of IPSS, because it reflects subjective bother and the patient's need for treatment. Furthermore, Qol score is an

Table 4 Improvement in Qol score according to improvement in nocturia among patients who had pre-treatment nocturia frequency of 2 or more and showed improvement in IPSS total score of five or more points

Group according to the change in nocturia	Stationary Qol score	Improved Qol score[a]
Aggravation group	1 (50%)	1 (50%)
Stationary group	9 (32%)	19 (68%)
Improvement group 1	24 (23%)	80 (77%)
Improvement group 2	4 (5%)	76 (95%)
p for trend	< 0.001	

[a]Qol score improvement was defined as a decrease in score of 1 or more points; group A, aggravation of nocturia; group B, no change in nocturia; group C, nocturia score decrease by 1 point; group D, nocturia score decrease by 2 or more points

important item for post-treatment evaluation. If Qol scores were not decreased, even though LUTS were improved, it means that there was no improvement in the degree of bother in the patient. Numerous studies have shown improvement in Qol scores after treatment; however, only a few studies have shown the factors which had an influence on the improvement in Qol scores [10].

In this study, storage symptoms had more impact on Qol scores than voiding symptoms. This result was in contrast to that of a previous study which analyzed the IPSS data of a healthy population. In that study, voiding symptoms had a greater influence on Qol scores than storage symptoms [11]. In addition, IPSS item 1 (incomplete emptying) score had the maximum impact on Qol scores. Median total IPSS score was 6.4 points and mean Qol score was 1.5 points. This different result can be interpreted as follows: men with mild LUTS feel bothered by voiding symptoms; however, when the symptoms were aggravated, bother from storage symptoms increased.

Although LUTS can be divided into storage, voiding, and post-voiding symptoms, most of the patients report a combination of these symptoms. When patients have multiple symptoms, the degree of bother from each individual symptom varies [12]. Some LUTS are more often associated with higher levels of bother and more often lead to treatment seeking behavior [13].

The previous studies in LUTS patients also supported the claim that storage symptoms affect the quality of life more than voiding symptoms [10, 14]. A study with tamsulosin and tolterodine in patients with overactive bladder (TIMES study) suggested that the higher baseline IPSS score appears to be largely driven by the storage subscale [14]. A structural equation modeling analysis demonstrated that bothersomeness and Qol score are influenced twofold by three IPSS questions on storage symptoms compared to four questions on voiding symptoms [10]. The study also showed that a decrease in storage symptoms following treatment of LUTS can more accurately predict Qol improvement than a decrease in total IPSS score.

Numerous studies have reported that nocturia affects Qol [15]. An observational study has shown that increasing number of night-time voids was associated with deterioration of health related QoL [16]. Especially, significant differences in health related Qol scores were observed between 0–1 and ≥ 2 voids. Bother from nocturnal voiding was reported as the most relevant component of LUTS responsible for medical consultations in German men [17]. A cross-sectional study with 373 men aged > 50 years from a community setting reported that nocturia and frequency were the only symptoms associated with poorer QoL, with nocturia showing a stronger association [18]. However, there are no studies which show that improvement in nocturia had the maximum influence on the improvement in Qol score. In

this study, when nocturia was not improved, in most men, bothersomeness was not changed, although other symptoms were improved.

In this study, age had a negative correlation with Qol scores, but it was not significant. In addition, the presence of hypertension was also related to lower baseline Qol scores. It was significant in the univariate analysis, but it was not significant in the multivariate analysis. This trend could be interpreted as follows: aged men or men with a co-morbidity adapted to the symptoms and endured bother from the symptoms well. Qol changes in longitudinal studies supported the hypothesis [19–21]. The Krimpen study and the Olmsted County study showed that the total IPSS score increased with passage of time; however, there was little or no changes in IPSS Qol scores with passage of time, which was fairly consistent across age groups [19, 20]. Furthermore, in a longitudinal study in Japan, Qol scores were decreased with passage of time [21].

This study had several limitations. First of all, the small number of patients included in this pooled analysis was the main limitation of this study. More than 6000 patients from 30 studies were screened; however, only 444 patients from five studies were included after strict exclusion. Especially, because some studies with a large number of patients collected only voiding symptom sum score, storage symptom sum scores, total IPSS scores, and Qol scores without each detailed item score, these studies were excluded. Second, the studies included in this pooled analysis provided unpublished data. Some studies are still being published. Some studies did not identify any new finding from the previously reported data. However, the IPSS data of the studies were real-practice data, and we confirmed that the data quality of studies was well controlled. Third, among several alpha adrenoceptor antagonists, only tamsulosin was included in this study, because only one pharmaceutical company responds our request to provide data. In spite of the limitations, we thought that the influence of change in each IPSS score on Qol scores and change in Qol was a meaningful finding of this study.

Conclusion

In this pooled data analysis, baseline Qol score of patients in the IPSS was affected by almost each item score of IPSS. Among the seven items of the IPSS, IPSS item 7 (nocturia) had the maximum influence on Qol scores. After treatment for LUTS/BPH, total IPSS score, and Qol score were decreased. The improvement in IPSS items 2, 4, 5, and 7 had an influence on the improvement in Qol scores. Among them, the change in IPSS 7 (nocturia) had the maximum impact on the change in Qol scores. When nocturia was not improved, a large proportion of men replied that Qol was not improved, even though other symptoms were improved.

Compliance with ethical standards

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