FACTORS ASSOCIATED WITH A BETTER THERAPEUTIC EFFECT OF SOLIFENACIN IN PATIENTS WITH OVERACTIVE BLADDER SYNDROME

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ABSTRACT

Aims: To analyze the predictors of therapeutic success after solifenacin treatment. Methods: Between January 2010 and December 2013, all patients with overactive bladder syndrome (OAB) who consecutively visited the urologic outpatient clinics at Institute of Kidney Diseases were prospectively enrolled. All enrolled patients received 5mg solifenacin once a day for 12 weeks. Results: Overall, 648 patients, 332 men, and 316 women, completed the 12-week study. The overall success rate was 48.8%. The success rate for female patients was superior to that for male patients (55.4% vs. 42.5%, $P < 0.001$). The urgency severity scale (USS) score, daytime frequency, nocturia, voided volume, and bladder capacity were all improved after 12 weeks' treatment. Multivariate logistic regression analysis revealed that female gender, high USS score, high maximum flow rate (Qmax), and low post void residual volume (PVR) were all significant predictive factors for success after antimuscarinic treatment. USS score ¼ 4 and Qmax _ 12 ml/sec were the most strongly predictive cutoff values for success, with receiver operating characteristic curve (ROC) areas of 0.70 (sensitivity ¼ 66.8%, specificity ¼ 66.0%) and 0.63 (sensitivity ¼ 80.7%, specificity ¼ 43.1%), respectively. PVR _70 ml was the most predictive cutoff value for failure, with a ROC area of 0.58 (sensitivity ¼ 18.2%, specificity ¼ 93.7%). Conclusions: Female gender, high USS score, high Qmax, and low PVR were associated with better therapeutic efficacy. These findings could serve as an initial guide or assist in consultation regarding the treatment of OAB patients with antimuscarinics.

INTRODUCTION

Overactive bladder syndrome (OAB), with or without incontinence, is characterized by urinary urgency, frequency, and nocturia. Muscarinic receptor antagonists are the first-line pharmacotherapeutic agents for OAB. At present, several anti-muscarinic drugs are marketed for the treatment of OAB. Each has demonstrated efficacy in the treatment of OAB symptoms, though their pharmacokinetic and adverse effect profiles vary.[1] However, some OAB patients are refractory to anti-muscarinic treatment.[2, 3] If we could predict which patients would fail to respond to anti-muscarinic treatment, then we could avoid giving these patients ineffective medication and exposing them to potential drug-related adverse effects. Unfortunately, the question of whether one can predict which patients will fail to benefit from anti-muscarinic treatment remains unanswered. [4]

Thus, the aim of this study was to perform a posthoc analysis of a large, open-label, observational post-marketing study in order to determine the predictors of success after solifenacin treatment. Besides, we were also interested in the evolution of the treatment response over 12 weeks.

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MATERIALS AND METHODS

Between January 2010 and December 2013, consecutive OAB patients who visited the urologic outpatient clinics at Institute of Kidney Diseases, Hayatabad Medical Complex, for treatment were prospectively enrolled in this post-marketing study. To be included in the study, patients had to be at least 18 years of age, with at least a 1-month history of OAB symptoms, including urinary frequency and urgency with or without incontinence. Patients with predominant symptoms of stress urinary incontinence, previous bladder or urethral surgery or possible neurogenic lesions were excluded, as were those with any active urinary tract infection. The study was approved by the Research Ethics Committees of the hospital. Written informed consent was obtained from all subjects enrolled.

The screening visit was designated as visit 0. Eligibility was determined at visit 1 (baseline, 2 weeks after visit '0' using the results recorded in the 3-day voiding diary prior to visit 1. Patients received 5mg solifenacin once a day for 12 weeks.

Patients were followed up at week 1 (visit 2), week 4 (visit 3), and week 12 (visit 4). In addition, adverse events were evaluated at each visit for all patients who received at least one dose of the study medication.

The enrolled patients were requested to complete a three-day voiding diary and the indevus urgency severity scale (USS) questionnaires.[5] We simply requested patients to record the daytime and nighttime voiding frequency; the episodes of urgency or urge urinary incontinence (UUI) per day were not included

in the voiding diary. In addition, we used the USS to represent the severity of urgency and UUI. Patients were carefully trained in the USS classification and reported their global perception of USS during the 3 days before each visit. Urgency severity as measured by the USS was rated by circling 0, 1, 2, or 3, which were defined as none, mild, moderate, and severe urgency, respectively. In addition to the scores of 0–3, we defined urgency with urinary incontinence as a score of 4.[5] The efficacy of the treatment was evaluated on the basis of changes in the USS scores and parameters from the 3-day voiding diaries, including daytime frequency and nocturia. The uroflowmetry and measurement of post-void residual volume (PVR) were also performed at each visit. The voided volume was derived from the uroflowmetry. PVR was measured by trans-abdominal ultrasound at each visit to the outpatient clinic. Bladder capacity was derived from voided volume plus PVR. The therapeutic effect was considered successful if there was a reduction in USS of 2 from baseline, or the USS value was 0 at visit 4.[6] The success rate was defined as the number of patients with successful therapeutic effects divided by the number of patients who completed 12 weeks treatment.

STATA software (Version 11.0; Stata Corporation, College Station, TX) was used for the statistical analysis. The Wilcoxon signed-rank test, univariate and multivariate logistic regression analysis were used where appropriate. Univariate logistic regression analysis was performed on all data in order to identify significant variables. Backward stepwise multivariate logistic regression analysis was then performed on all variables to analyze any association between these variables and therapeutic success as defined above.[7] A P-value <0.05 was considered an indication of statistical significance. Receiver operating characteristic (ROC) curve analysis was performed to identify the optimal cutoff value for differentiating the success group from the failure group. The optimal cutoff value was determined by the point on the ROC curve closest to the upper left-hand corner.

RESULTS

Overall, 648 patients, 316 women, and 332 men, completed the 12-week study. The overall success rate was 48.8% (95% confidence interval [CI] ¼ 44.9–52.6%). The success rate for female patients was superior to that for male patients (55.4%, 95% CI ¼ 49.4 to 60.9% vs. 42.5%, 95% CI ¼ 37.1 to 47.8%; $P < 0.001$, Chi-square test). The USS score, daytime frequency, nocturia, voided volume, and bladder capacity were all improved after 12 weeks treatment (Table 1). Therapeutic effects appeared after 1 week and improved steadily up to 12 weeks (Fig. 1a–d), all $P <0.001$, Friedman one-way ANOVA test; all treatment effects except voided volumes at 1 week are statistically significant versus baseline at the level $P <0.001$).

However, maximum flow rate (Qmax) and PVR did not change after treatment (Table 1).

A further analysis of gender differences showed that female patients had a greater improvement in USS (coefficient¼_0.3) and voided volume (coefficient ¼ 14.5), but a lesser improvement in nocturia (coefficient ¼ 0.3) than male patients (Table 1).

Univariate logistic regression analysis found that female gender, USS, Qmax, and PVR were significant factors associated with success. Multivariate backward stepwise logistic regression analysis revealed that female gender, high USS score, high Qmax, and low PVR were all significant factors associated with success after Solifenacin treatment (Table 2).

Based on the ROC analysis, the following optimum cutoff values were determined: (1) USS score ¼ 4, with the area under the ROC curve being 0.70 (95% CI ¼ 0.66 to 0.73; sensitivity ¼ 66.8%, specificity ¼ 66.0%, (Fig. 1e). (2) Qmax ¼ 12 ml/s, with the area under the ROC curve being 0.63 (95% CI ¼ 0.58–0.68; sensitivity ¼ 80.7%, specificity ¼ 43.1%). (3) PVR ¼ 70 ml, with the area under the ROC curve being 0.58 (95% CI ¼ 0.53–0.63; sensitivity ¼ 18.2%, specificity ¼ 93.7%).

The common adverse effects of Solifenacin at visit 4 (week 12) included dry mouth (9%), constipation (4%), dry eyes (3%), blurred vision (2%), dysuria (2%) and dizziness (1%).

DISCUSSION

It had been reported that gender does not affect the efficacy of antimuscarinic.[8] Contrarily, Schneider et al.[9] reported that younger age and female gender were associated with a better response to antimuscarinic treatment. In our study, although female gender was associated with higher therapeutic efficacy, age did not emerge as a significant factor. This discrepancy may be related to the different sample sizes (n ¼ 3,766 in the Schneider et al. study [9] vs. n ¼ 648 in our study). In any case, the effect of age on therapeutic efficacy according to Schneider et al.[9] appeared to be small (odds ratio ¼ 0.978 per year) and may be clinically insignificant.

We found that high Qmax and low PVR were independent predictors of therapeutic success. In clinical terms, patients with high Qmax and low PVR should have good voiding function with little bladder outlet obstruction. Low Qmax in male patients may be associated with benign prostate hyperplasia; in patients with this condition OAB may have a poor response to antimuscarinic alone and an additional alpha blocker may be necessary to improve efficacy.[10,11] High Qmax has also been reported in female patients who underwent urethral dilatation for drug-resistant OAB and voiding dysfunction, where a higher Qmax was associated with an improvement in the OAB.[12] In addition, an increase in Qmax was found in female patients undergoing anterior vaginal wall prolapse repair and was associated with resolution of the OAB.[13] The

Table 1: PVR, post-void residual volume; Qmax, maximum flow rate; USS, urgency severity scale. Values are given as mean _ standard deviation, or number (percentage).

Variables	Baseline	3 months	Difference	P-value[a]	Coefficient of gender	P-value[b]
Female gender	316(45.8%)			-		
Male gender	332(52.2%)			-		
Age	63.5+15.2			-		
USS	3.2+1	1.7 + 1.1	-1.5 +1.2	<0.001	-0.3	0.004
Daytime frequency	11.4+ 3.6	8.2 + 2.5	-3.3 + 3.1	<0.001	-0.4	0.08
Nocturia	3.4+ 1.8	2 + 1.5	1.4 + 1.6	<0.001	0.3	0.02
Qmax(ml/s)	15.9+ 8.2	15.8 + 6.7	0.0 + 4.7	0.15	2.2	<0.001
PVR (ml.)	36.6 + 46.4	38.5 + 53.0	2.2 + 51.5	0.21	-2.1	0.67
Voided vol.(ml)	202.9 + 91.2	239.3 + 95.6	39.2 + 76.3	<0.001	14.5	0.045
Bladder capacity (ml)	234+ 100.2	277 + 106.6	43.5 + 93.9	<.0.001	15.9	0.08

[a]By Wilcoxon sign-rank test.

[b]Differences are subtraction of pre-treatment values from post-treatment values of data. The coefficient of gender (female ¼ 1; male ¼ 0) is derived from linear regression analysis of the difference in each variable adjusted for age.

Table 2: Univariate and Multivariate Logistic Regression Analyses of Predictors for Success among 648 Patients With Overactive Bladder Syndrome.

Variables	Therapeutic Outcome		Univariate Analysis		Multivariate Analysis a	
	Success	Failure	OR (95%CI)	p-value	PR (95%)	p- value
Female gender	175 (55.4%)	141(44.6)				
Age (years)	62.9+ 14.2	64.1 + 16.1	0.99	0.32	-	-
USS	3.6+ 0.7	2.9+ 1.0	2.46	<0.001	2.20	<0.001
Daytime frequency	11.6+ 3.5	11.3+ 3.6	1.02	0.33	-	-
Nocturia	3.4+ 1.9	3.3 + 1.8	1.08	0.50	-	-
Qmax (ml/s)	17.7 + 8.2	14.0+ 7.8	1.06	<0.001	1.03	0.02
PVR (ml)	30.4+ 33.2	42.9 + 56.1	0.993	0.003	0.993	0.03
Voided volume (ml)	199.4 + 75.6	206.7 + 113.9	0.999	0.25	-	-
Bladder capacity (ml)	229.9+ 84.3	239.5 + 114.8	0.999	0.25	-	-

CI, confidence interval; OR, odds ratio; other abbreviations as in Table I. Values are given as mean standard deviation, number (percentage) or odds ratio (95% confidence interval).

[a]Backward stepwise multivariate logistic regression analysis was performed including all variables from the univariate analysis.

above findings may partially explain our finding that a high Qmax was associated with a higher efficacy of antimuscarinic therapy. However, Oelke et al.[14] reported that Qmax did not affect the efficacy of extended-release propiverine, which combines antimuscarinic properties with calcium influx inhibition.

In this study, we used USS to represent the severity of urgency and UUI. Patients were carefully trained in the classification of USS and reported their global perception of USS during the 3 days before each visit. Urinary urgency is a subjective symptom experienced by the patient. Previous clinical studies measured the episodes of urgency or UUI in order to evaluate the treatment effect of OAB. However, OAB patients might modify their drinking or voiding behaviors to avoid the occurrence of urgency or UUI. Therefore, the urgency episodes might be under-reported in the voiding diary

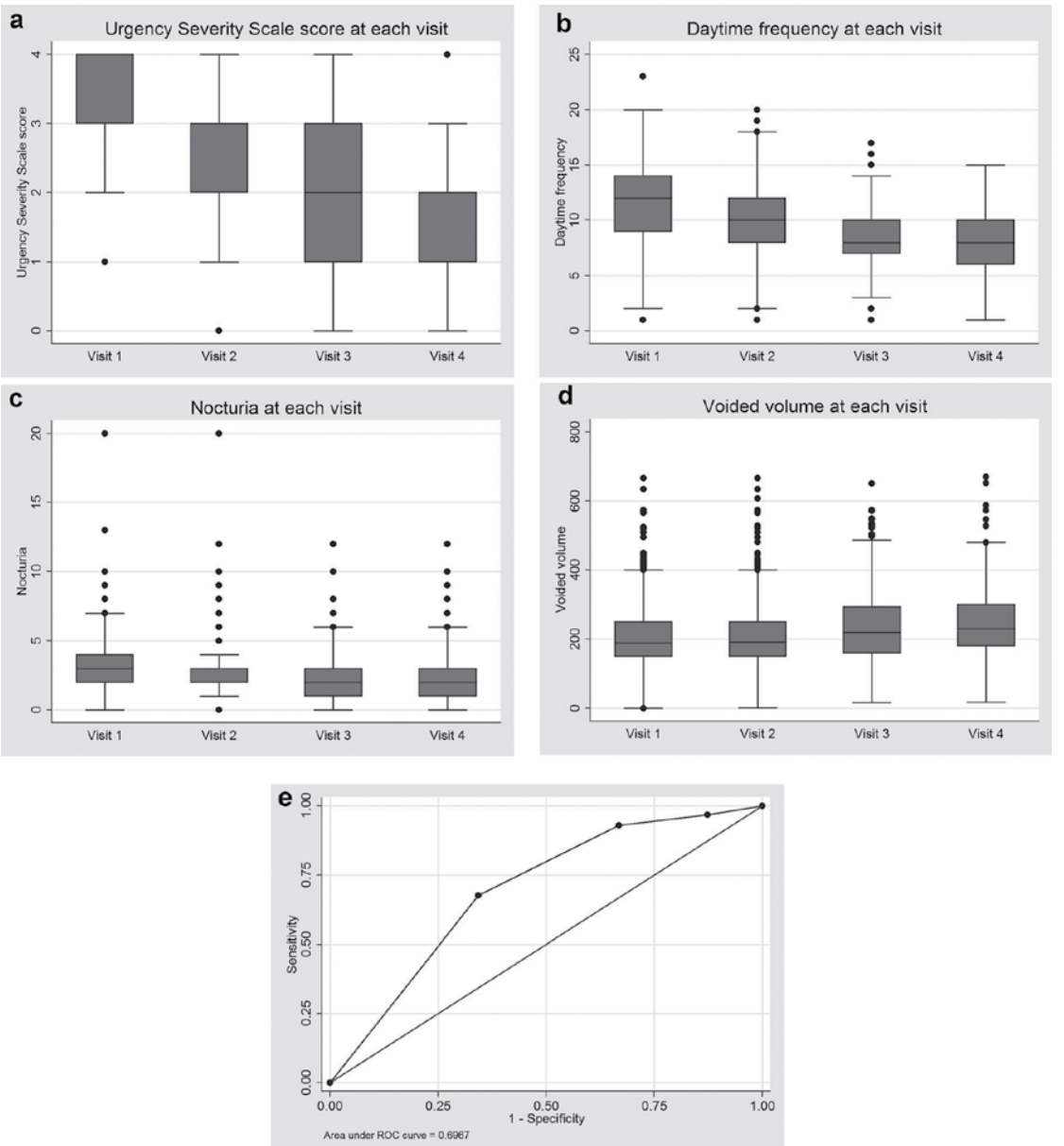

Figure 1: Efficacy of muscarinic medication in overactive bladder patients. The box plots of (a) urgency severity scale scores, (b) episodes of daytime frequency, (c) episodes of nocturia, (d) voided volumes at each visit, and (e) the area under the receiver operating characteristic (ROC) curve for Urgency Severity Scale scores as a diagnostic test for the success group. Some points are not within the largest and smallest observations in the box plots, and may be considered as outliers.

and might not reflect the real severity of OAB in daily life. Our previous study has demonstrated that a high USS recorded in a voiding diary is strongly correlated with the urodynamic DO. Well instructed and reported USS and voiding diary recording provides direct evidence of urodynamic DO, which enables us to treat patients without an invasive urodynamic study.[15] The finding of this study that a higher USS (such as USS ¼ 4) is associated with a higher success rate as a result of antimuscarinic treatment is quite logical.

According to the AUA/SUFU OAB guideline, the first-line treatment for patients with OAB symptoms is behavioral therapies (e.g., bladder training, pelvic floor muscle training, fluid management).[16] However, including a behavioral therapy might interfere with the interpretation of drug effects and thus change the predictors of success. Therefore, we did not routinely recommend behavioral therapies for each enrolled patient before solifenacin treatment.

This study had some limitations. First, the predictors of the success of solifenacin treatment were derived from a post-hoc analysis of our prospective post-marketing study, and this may have biased the results. Second, this study failed to address the placebo effect. A significant placebo effect had been reported from OAB patients treated with solifenacin.[17,18] Third, this study was not a randomized trial, thus the real therapeutic efficacy and adverse effects of solifenacin may have been overestimated. Finally, although a USS score of 4, Qmax of 12 ml/s , and PVR of 70 ml. or less, were found to be the best cutoff values for predicting therapeutic efficacy, the clinical implications of these cutoff values are limited by their small areas under the ROC curve, and their low sensitivities and specificities.

CONCLUSIONS

Female gender, a high USS score, high Qmax, and low PVR were associated with a better therapeutic efficacy of solifenacin. These findings may serve as an initial guide or assist in consultation regarding the treatment of OAB patients with solifenacin.

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