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Original scientific paper

The Efficacy and Safety of Solifenacin in Patients with Overactive Bladder Syndrome

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A B S T R A C T

The aim of the randomised, double blind, placebo controlled study was to evaluate the efficacy, tolerability and safety of solifenacin, a once-daily M3 selective receptor antagonist, in patients with overactive bladder syndrome. Following a single blind 2-week placebo run in period, patients who complained from symptoms of OAB for at least 6 months, were randomized to 4 weeks of solifenacin in 5 mg once daily doses or placebo. 171 patients were enrolled in the study and 157 patients completed the study. Patients with solifenacin had significantly improved micturitions per 24 hours after first week of treatment (1.75±0.63 vs. *2.64±0.48, p<0.001), and after four weeks (1.56±0.58* vs. *2.71±0.45, p<0.001)compared to placebo group. The mean number of urgency episodes per 24 hours had significantly decreased in patients with solifenacin compared to placebo after first week (5.75±1.43* vs. *6.65±0.65, p<0.001), and after four weeks of treatment (5.77± 1.33* vs. *6.54±0.50, p<0.001). Solifenacin was also significantly more effective than placebo in reducing the mean number of episodes of severe urgency from baseline to end point (5.83±1.16* vs. *6.48±0.50, p<0.001). Compared with changes obtained with placebo, episodes of urinary frequency were significanlty reduced after first week (0.3* vs. *–0.5, p<0.001) and four weeks check up periods in patients treated with solifenacin (0.19* vs. *–0.15, p<0.001). Episodes of nocturia was significantly reduced in patients treated with solifenacin after first week (0.3* vs. *–0.5, p<0.001), and after four weeks treatment period (0.45* vs. *–0.50, p<0.001). The number of incontinence episodes was also significantly decreased in solifenacin group compared to placebo group after first week (1.06±0.57* vs. *2.74±0.47, p<0.001) and four weeks check up (0.96±0.57* vs. *2.75±0.43, p<0.001). The most common adverse effects with solifenacin were dry mouth and constipation. Adverse effects were mild or moderate severity. The discontinuation rate owing to adverse effects was 4.5%–6.7% with solifenacin and 3.8%–6.1% with placebo, respectively. According to subjective estimation, significant improvement was achieved in 71 (92.21%) of patients treated with solifenacin and in 68(85%) patients treated with placebo there was no change in OAB symptoms compared to baseline values. UDI score was significantly improved after solifenacin (22.26± 5.91* vs. *29.61±8.45, p<0.001) compared to placebo. IIQ score was significantly decreased in patients with solifenacin (36.25±10.34* vs. *46.86±6.81, p<0.001) compared to placebo. In conclusion, solifenacin is a safe and effective treatment alternative for patients with overactive bladder symptoms.*

Key words: *solifenacin, overactive bladder syndrom*

Introduction

Overactive bladder syndrome (OAB) has been defined by the International Continence Society as a complex cascade of symptoms that includes urinary urgency, with or without urge incontinence, usually accompanied by urinary frequency and nocturia[1]. These symptoms are associated with significant morbidity and often have a profound impact on patient quality of life[2–5]. Antimuscarinic therapy represents the most common treatment for patients with OAB[6–7]. They have been proven to be the most effective agents in supressing premature detrusor contractions, enhacing bladder storage, and relieving symptoms. Several antimuscarinic agents are currently available for the treatment of OAB in adults, including oxybutynin, tolterodine, trospium chloride, darifenacin and solifenacin[1,5–9]. Although all are deemed to be effective in improving the bothersome symptoms of OAB,

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they differ in their molecular properties, metabolism, and tolerability/side effect profile. Solifenacin is new specific antimuscarinic drug which compared with oxybutynin and tolterodine have more favourable side effects profile which enhance tolerability and patient compliance. In recent clinical trials solifenacin has shown superiority to placebo and equal efficacy as oxybutynin and tolterodine[1–5]. The aim of the study is to evaluate the efficacy, tolerability and safety of solifenacin, a once-daily M3 selective receptor antagonist in patients with overactive bladder syndrome.

Material and Methods

Following a single blind 2-week placebo run in period, patients were randomized to 4 weeks of solifenacin in 5 mg once daily doses or placebo. 171 patients were enrolled in the study and 157 patients completed the study. Patients who complained from symptoms of OAB for at least 6 months were included in the randomised, double-blind, placebo controlled study. Inclusion criterias are urge incontinence (at least but no more than 50 episodes per week), frequency of micturition (at least eight voids per 24 hours) and urgency (a strong desire to void at least once per day). Patients were excluded from the study if they had contraindications for the use of antimuscarinic drugs (e.g. uncontrolled narrow-angle glaucoma, urinary or gastric retention), clinically significant stress urinary incontinence (more than one episode per week), clinically significant bladder outlet obstruction and /or a post-void residual volume more than 200 mL, genitourinary condition that could cause urinary symptoms, recent urogenital surgery or hepatic disease. Treatment efficacy was evaluated after one and four weeks treatment periods according to subjective assesment using data recorded in patient diaries in the one and four week periods preceding the scheduled clinical visits. The objective assesment of treatment efficacy was determined by Urinary incontinence-specific quality of life (QOL) instruments included the Urinary Distress Inventory (UDI) and Incontinence Impact Questionnaire (IIQ). Higher UDI and IIQ scale scores reflect increasing symptom bother and greater impact on daily activities. The primary endpoint for this 12 week trial was the mean change from baseline in the mean number of micturition episodes, urgency, nocturia, and incontinence episodes per 24 hours. Safety and tolerability of solifenacin were secondary study objectives. Tolerability and safety data were collected at each visit, and at other times if volunteered by the patient. All observed or volunteered adverse events were evaluated by the investigator and the patient in terms of severity, seriousness and potential relationship to treatment were also evaluated by the investigator. Treatment discontinuations were also assessed for potential relationship to study treatment. The Ethical Committee of Department for Gynecology and Obstetrics Medical School University of Zagreb approved the study protocol and consent forms. Written informed consent was obtained from each patient. Statistical analysis was performed using PASW for Windows, 17.02. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity. Numerical variables were tested for the normality of distribution using Kolmogorov-Smirnov test. Normally distributed variables were presented as means±standard deviations and Student's t-test was used for comparissons between the groups. Data that were not normally distributed were presented as medians and Mann-Whitney U-test was used to evaluate differences between the groups. Data from different time periods was tested for statistical significance with the repeated measures ANOVA or Friedman test as appropriate with further analysis carried out with the paired t-test or Wilcoxon signed rank test. Categorical data are expressed as numbers and frequences. The differences between more than 2 groups for categorical data were analysed using Pearson's chi square, and Fisher exact test. A P value<0.05 (two sided tests) was considered to be significant.

Results

From a total of 171 women randomised to solifenacin or placebo, data from 157 patients were available for the analysis of efficacy and safety of solifenacin. Baseline characteristics of OAB patients are summarised in Table 1 and were similar among two treatment groups. At baseline, there was no difference in voiding parameters among placebo and solifenacin group ($p>0.05$). Patients with solifenacin had significantly improved micturitions per 24 hours after first week of treatment (1.75±0.63 *vs*.

TABLE 1
BASELINE CHARACTERISTICS OF OAB PATIENTS ENTERED THE STUDY

Variables (X±SD)	Solifenacin	Placebo
Age (years)	56.77±10.16	57.03±10.05
BMI (body mass index)	29.18±4.06	29.64±4.08
Parity	1.90±1.05	1.95±1.10

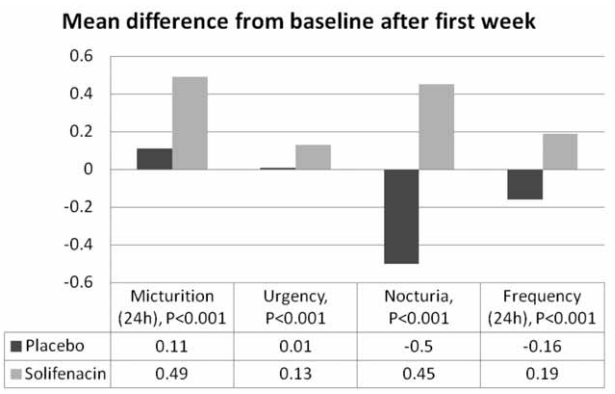
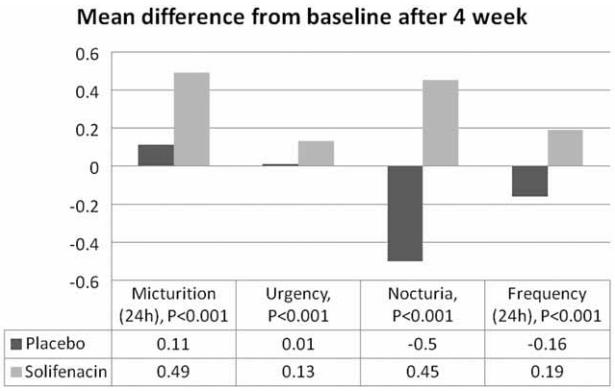


Fig. 1. Mean differences in urinary frequency, nocturia, urgency and micturition per 24 hours from baseline after first week of treatment.



	Micturition (24h), P<0.001	Urgency, P<0.001	Nocturia, P<0.001	Frequency (24h), P<0.001
Placebo	0.11	0.01	-0.5	-0.16
Solifenacin	0.49	0.13	0.45	0.19

Fig. 2. Mean differences in urinary frequency, nocturia, urgency and micturition per 24 hours from baseline after four weeks of treatment.

2.64±0.48, p<0.001), and four weeks compared to placebo group (1.56±0.58 *vs.* 2.71±0.45, p<0.001) (Figure 1,2). The mean number of urgency episodes per 24 hours had significantly decreased in patients with solifenacin compared to placebo after first week (5.75±1.43 *vs*. 6.65± 0.65, p<0.001), and after four weeks of treatment (5.77± 1.33 *vs*. 6.54±0.50, p<0.001) (Figure 1,2). Solifenacin was also significantly more effective than placebo in reducing the mean number of episodes of severe urgency from baseline to end point (5.83±1.16 *vs*. 6.48±0.50, p<0.001).

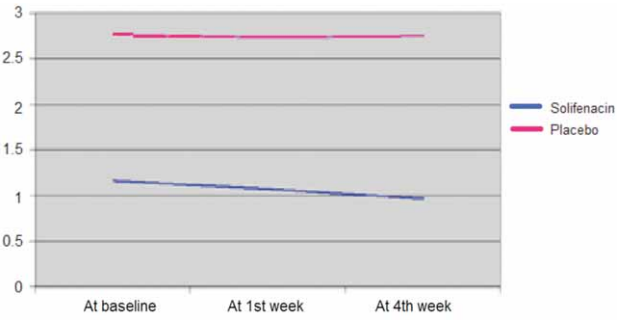


Fig. 3. Incontinence episodes per 24h.

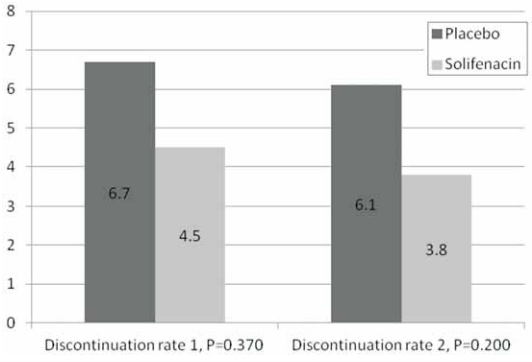
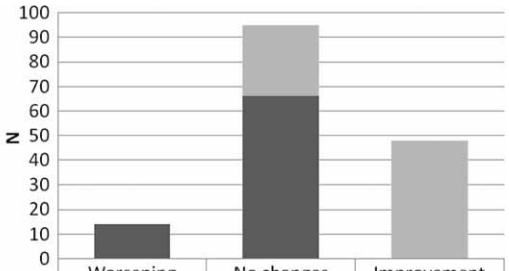


Fig. 4. Incidence of discontinuation rate between solifenacin and placebo group. Discontinuation rate 1-at baseline, discontinuation rate 2-after treatment.

Compared with changes obtained with placebo, episodes of urinary frequency were significanlty reduced after first week (0.3 *vs*. –0.5, p<0.001) and four weeks check up periods in patients treated with solifenacin (0.19 *vs*. –0.15, p<0.001) (Figure 1,2). Episodes of nocturia were significantly reduced in patients treated with solifenacin after first week (0.3 *vs*. –0.5, p<0.001), and after four weeks treatment period (0.45 *vs*. –0.50, p<0.001) (Figure 1,2). The number of incontinence episodes was also significantly decreased in solifenacin group compared to placebo group after first week (1.06±0.57 *vs*. 2.74±0.47, p<0.001) and four weeks check up (0.96±0.57 *vs*. 2.75± 0.43, p<0.001) (Figure 3). The most common adverse effects with solifenacin were dry mouth and constipation (Table 2). Adverse effects were mild or moderate severity. The discontinuation rate owing to adverse effects was 4.5–6.7% with solifenacin and 3.8–6.1% with placebo, respectively (Figure 4). After first week in 48 (62.34%) patients with solifenacin was subjectively estimated im-



	Worsening	No changes	Improvement
Solifenacin		29	48
Placebo	14	66	

Fig. 5. Subjective evaluation of treatment outcome after first week, p<0.001.

TABLE 2
INCIDENCE RATES OF ADVERSE EVENTS AFTER SOLIFENACIN

	Frequency	Percent (%)
Increase eye pressure	3	3.8
Dry mouth and opstipation	3	3.8
Intestinal disturbances	2	2.6
Dry mouth	2	2.6
Intestinal disturbances and i blurred vision	1	1.3
Dry mouth and decreased concentration	1	1.3
Dry mouth, tremor	1	1.3
Dry mouth, opstipation, intestinal disturbances	1	1.3
Dry mouth,opstipation, blurred vision	1	1.3
Opstipation and intestinal disturbances	1	1.3
Dizziness	1	1.3
Dizziness, blurred vision	1	1.3

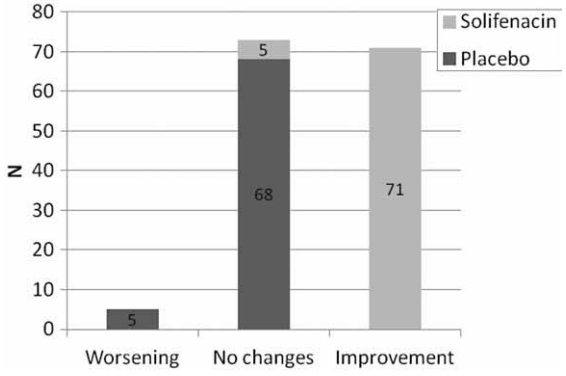


*Fig. 6. Subjective evaluation of treatment outcome after four weeks, *p<0.001.*

provement compared to 66 (82.50%) patients on placebo who presented no change in micturition problems compared to baseline (p<0.001) (Figure 5). After four weeks statistically significant improvement was achieved in 71(92.21%) patients with solifenacin compared to 68

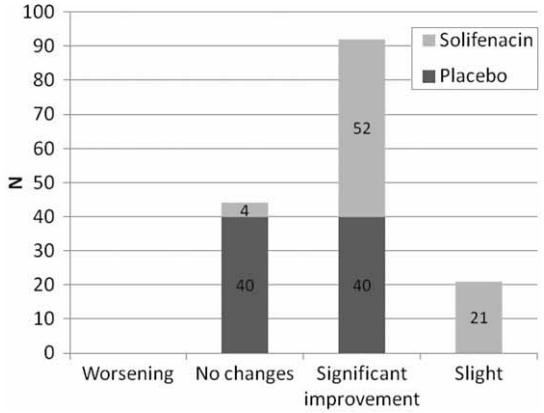


Fig. 7. Subjective evaluation of treatment outcome after three months.

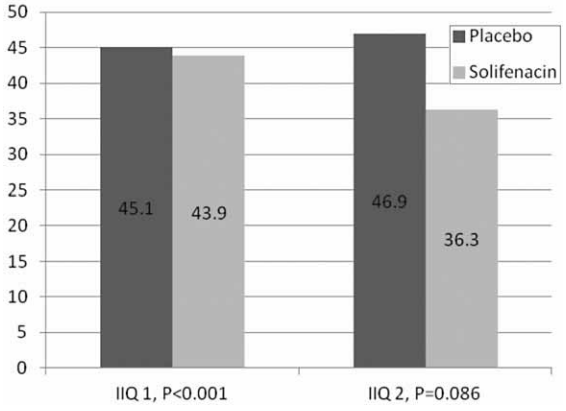


Fig. 8. Comparison of urinary distress inventory before and after treatment with solifenacin and placebo. UDI 1-urinary distress inventory at baseline, UDI 2-urinary distress inventory after treatment.

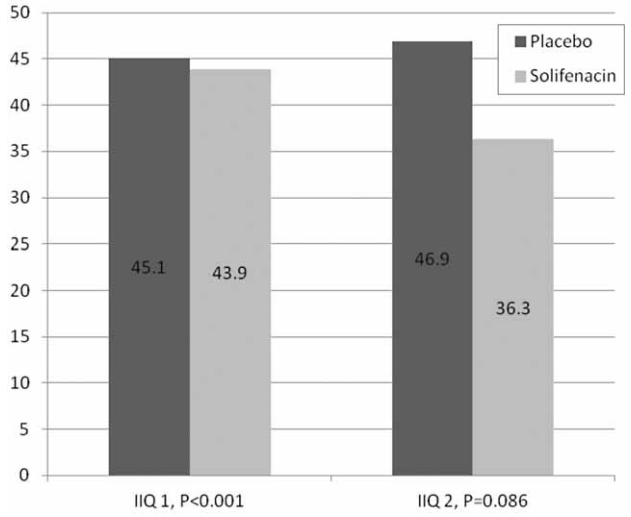


Fig. 9. Comparison of incontinence impact questionnaire at baseline and after treatment with solifenacin and placebo. IIQ 1-incontinence impact questionnaire at baseline, IIQ 2-incontinence impact questionnare after treatment.

(85.00%) patients with placebo who determined no changes in micturition pattern (Figure 6). According to subjective estimation, significant improvement was achieved in 71 (92.21%) of patients treated with solifenacin and in 68 (85.00%) patients treated with placebo there was no change in OAB symptoms compared to baseline values after three months as shown in Figure 7. UDI score was significantly improved after solifenacin (22.26±5.91 *vs*. 29.61±8.45, p<0.001) compared to placebo as presented in Figure 8. IIQ score was significantly decreased in patients with solifenacin (36.25±10.34 *vs*. 46.86±6.81, p< 0.001) compared to placebo (Figure 9).

Discussion and Conclusion

Overactive bladder is a common condition which has an adverse effect on quality of life. The most commonly used pharmacologic agents for the treatment of overactive bladder disturbances are the muscarinic receptor antagonists. These included oxybutynin, tolterodine, and three agents that have recently been approved for the use i.e. trospium, darifenacin, and solifenacin[9,10]. Their action resulted in less uninhibited bladder contractions, thereby allowing improved bladder filling and reduced urgency as well as other symptoms of overactive bladder. The ideal antimuscarinic drug should effectively relieve the symptoms of OAB with the minimum of side effects. Furthermore, it should be available as a once-daily sustained release formulation and in dosage strenght that allows easy dose titration for the majority of patients. Solifenacin has been shown in both short and long term clinical trials to fulfill these criterias. In multiple clinical trials, solifenacin treatment has been associated with statistically significant reductions in all key symptoms of OAB (urinary frequency, urgency and incontinence) as

well as increase in volume voided[1–10]. In particular, it produces a significant decrease in urgency episodes, which is the principal symptom of OAB[11]. Our study confirmed the efficacy of solifenacin in reducing the number of urgency episodes in patients with OAB. It was effective as early as day seven of treatment. The mean number of micturition episodes per 24 hours was also decreased in patients treated with solifenacin compared to placebo. The results of our study correlated with results of Cardozo et al who also confirmed solifenacin efficacy in reducing the micturition per 24 hours in double blind placebo controlled study[9]. Diurnal and nocturnal urinary frequency are common signs of overactive bladder. Our data demonstrated the efficacy of solifenacin in 5 mg once daily doses in reducing diurnal and particularly nocturnal frequency. One of the major findings of this study was the significant reduction in nocturia episodes in patients taking a 5 mg dose of solifenacin compared to study of Cardozo et al who demonstrated equal effect but with solifenacin in 10 mg dosage[1]. Our study confirmed results of Chapple et al who found a significant decrease of incontinence episodes in patients with solifenacin[12]. The possible explanation of these benefit is suppresing of premature detrusor contractions and enhacing of bladder storage and maximal cystometric capacity. Despite potential benefits, primary care clinicians may avoid using antimuscarinic drugs in women with OAB because of safety concerns. Oxybutynin, tolterodine, darifenacin, solifenacin, and trospium antagonize the effects of acetylcholine at muscarinic receptors on the detrusor muscle and are known as antimuscarinic agents. These agents potently and selectively bind to the M_3 receptor subtype more than other muscarinic receptor subtypes, with the exception of tolterodine, which has demonstrated no specificity for any subtype. Solifenacin has demonstrated greater tissue selectivity for inhibition of detrusor contraction over salivation, offering an advantage over other agents by reducing adverse effects and improving compliance. In our study, treatment with solifenacin was well tolerated. Dry mouth and opstipation were the most common adverse effects with solifenacin. Adverse effects were mild or moderate severity. The discontinuation rate owing to adverse effects was 4.5–6.7% with solifenacin and was similar to withdrawal rate in patients treated with placebo. Urinary incontinence-specific quality of life (QOL) instruments included the Urinary Distress Inventory (UDI) and Incontinence Impact Questionnaire (IIQ). Higher UDI and IIQ scale scores reflect increasing symptom bother and greater impact on daily activities[13,14]. Both, UDI and IIQ were significantly improved in our patients treated with solifenacin confirming efficacy in patients with overactive bladder symptoms. In conclusion, solifenacin is a well tolerata and effective treatment modality for patients with overactive bladder.

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UČINKOVITOST I SIGURNOST SOLIFENACINA U LIJEČENJU BOLESNICA S PREKOMJERNO AKTIVNIM MOKRAĆNIM MJEHUROM

SAŽETAK

Cilj randomizirane, dvostruko slijepe placebo kontrolirane studije je procjeniti učinkovitost, podnošljivost i sigurnost solifenacina, selektivnog M3 antagonista u bolesnica s prekomjerno aktivnim mokraćnim mjehurom. Nakon jednostruko slijepog dvotjednog »run in« perioda, bolesnice sa smetnjama prekomjerno aktivnog mokraćnog mjehura u trajanju od najmanje šest mjeseci randomizirane su na primjenu 5 mg solifenacina ili placeba u trajanju od četiri tjedna.

Od 171 pacijentica uključenih u studiju, njih 157 je završilo istraživanje. Bolesnice liječene solifenacinom imaju značajno bolje mikcijske parametre u usporedbi sa pacijenticama tretiranim placebom. Bolesnice liječene solifenacinom imaju značajno smanjen broj epizoda mikcije na 24 sata nakon prvog tjedna studije (1,75±0,63 *vs.* 2,64±0,48, p<0,001), te nakon četiri tjedna studije (1,56±0,58 *vs*. 2,71±0,45, p<0,001) u usporedbi s placebom. Prosječan broj epizoda urgencije u 24 sata značajno je manji u žena korisnica solifenacina nakon prvog tjedna ispitivanja (5,75±1,43 vs. 6,65±0,65, p<0,001) i nakon četiri tjedna (5,77±1,33 *vs*. 6,54±0,50, p<0,001) u usporedbi s placebom. Solifenacin je značajno učinkovitiji u smanjenju epizoda teške urgencije u usporedbi s placebom (5,83±1,16 *vs*. 6,48±0,50, p<0,001). U usporedbi s placebom, značajno je manji broj epizoda urinarne frekvencije u žena korisnica solifenacina nakon prvog tjedna (0,3 *vs*. –0,5, p<0,001) i nakon četvrtog tjedna liječenja (0,19 *vs*. –0,15, p<0,001). Broj epizoda nikturije značajno je manji u žena koje su liječene solifenacinom nakon prvog tjedna liječenja (0,3 *vs*. –0,5, p<0,001) i nakon četvrtog tjedna liječenja (0,45 *vs*. –0,50, p<0,001). Broj epizoda inkontinencije značajno je smanjen u žena korisnica solifenacina u usporedbi s placebom nakon prvog tjedna liječenja 1,06±0,57 *vs*. 2,74±0,47, p<0,001) i nakon četvrtog tjedna liječenja (0,96±0,57 *vs*. 2,75±0,43, p<0,001). Najčešće nuspojave u žena koje su liječene solifenacinom su bile suha usta i opstipacija. Stopa prekida liječenja zbog nuspojava iznosila je 4,5%–6,7% za solifenacin i 3,8%–6.1% za placebo. Na temelju subjektivne procjene, značajno poboljšanje je postignuto u 71 (92,21%) pacijentica korisnica solifenacina, a u 68 (85%) pacijentica liječenih placebom nisu uočene promjene u simptomima prekomjerno aktivnog mokraćnog mjehura u odnosu na početne vrijednosti. UDI skor je značajno poboljšan u žena liječenih solifenacinom (22,26±5,91 *vs*. 29,61±8,45, p<0,001) u usporedbi s placebom. U usporedbi s placebom, IIQ skor je značajno manji u bolesnica koje su primjenjivale solifenacin 36,25±10,34 *vs*. 46,86±6,81, p<0,001). U zaključku, solifenacin predstavlja sigurnu i učinkovitu terapijsku alternativu u liječenju bolesnica s prekomjerno aktivnim mokraćnim mjehurom.