



Comparison of the Effects of Solifenacin Succinate for the Treatment of Overactive Bladder with Extended Release Tolterodine

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Conflicts of interest: None

Abstract:

Objective: To compare the therapeutic effects of solifenacin succinate with extended release tolterodine for the treatment of overactive bladder (OAB) in Bangladeshi patients.

Methods: A prospective, randomized, single-blind, two-arm, parallel-group, clinical trial was conducted in the department of Urology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from January 2013 to June 2014. A total of 65 patients with OAB were treated with solifenacin succinate 5 mg (experimental group, n=33) and extended release tolterodine 4 mg (control group, n=32), both at night daily for 12 weeks. Efficacy and safety variables were assessed and compared with baseline and at 12 weeks treatment in between the two groups.

Results: At week 12, solifenacin succinate and extended release tolterodine demonstrated reduction in the mean number of micturition (50% vs. 51%), urgency (87% vs. 73%), urge incontinence (89% vs. 71%), nocturia (89% vs. 74%), usage of pads (90% vs. 71%) per 24 hours. There was increased in the mean voided volume of each micturition in both the groups without any difference in between them. The incidence of major adverse events were dry mouth (15.2% vs. 9.4%), constipation (9.1% vs. 15.6%), and blurred vision (6.1% vs. 3.1%) respectively.

Keywords: Sol group, Solifenacin group, ER tol group, Extended Release tolterodine group, Over Active Bladder (OAB)

Conclusions: Solifenacin succinate had greater efficacy to extended release tolterodine in treating overactive bladder. There were no significant treatment difference between the two groups in decreasing the number of micturition and increasing the voided volume of each micturition and the incidence of major adverse events. All the adverse effects were mild and transient in nature and discontinuation of medication due to adverse effects were low.

Introduction:

Overactive bladder (OAB) has been defined by the International Continence Society as a syndrome comprising the symptoms of urgency, with or without urge incontinence, usually accompanied by increased micturition frequency and nocturia, in the absence of another identifiable metabolic or pathological process affecting the lower urinary tract.² Overactive bladder

(OAB) syndrome is a common symptom complex that affects millions of people worldwide, with an increasing prevalence with increased age.² This chronic prevalent condition affects both men and women, with slightly more prevalence in women (12.8% versus 10.8%, respectively, based in a population based survey of patients in five countries.³ In addition to its high prevalence rate, OAB adversely affects quality of life

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and is associated with an increased risk of urinary tract infection, skin infection, and fall Injury [4, 5 & 6]. Treatment approaches for OAB include behavioral, pharmacological and surgical therapy. Among these, antimuscarinic agents remain the mainstay of treatment.⁷

There are five subtypes of muscarinic receptors (M1-M5) throughout the human body. In the urinary bladder, although M2 receptors (75%) predominate in number, normal bladder contraction is mainly mediated by stimulation of M3 receptors (25%).⁸ By blocking the muscarinic receptors, antimuscarinic agents inhibit the abnormal bladder contractions (detrusor overactivity) and subsequently reduce OAB symptoms. However, antimuscarinic agents also act on other muscarinic receptors throughout the body and therefore cause adverse effects, including dry mouth, constipation, and blurred vision. In recent decades, several new antimuscarinic agents have been developed to reduce these unfavourable adverse effects. Extended release Tolterodine was the first agent introduced for this purpose. It is bladder-selective and has been shown in animal studies to have a greater affinity in the bladder than in the salivary glands [9]. Extended release Tolterodine was first introduced in 2000, and it became available from 2001 as a 4mg once-daily formulation to improve the tolerability and compliance of patients with OAB.¹⁰

A newer antimuscarinic agent, solifenacin succinate, has also proved to be bladder-selective and M3-receptor-selective. It is a long-acting muscarinic receptor antagonist and is metabolized by the cytochrome P450 system.¹¹ It was first introduced in 2004 and in recent years, it was also became available as a 5mg once-daily formulation in the treatment of OAB. The aim of this study is to see the effects of solifenacin succinate and extended release tolterodine in the treatment of overactive bladder (OAB).

Study Methods:

This randomized clinical trial was conducted in the department of urology, BSMMU, Dhaka from January 2013 to June 2014 after receiving approval from Institutional Review Board (IRB). The study population was selected on the basis of selection criteria from the patients attended in the out patient department of Urology, BSMMU, Dhaka.

The study commenced with the initial screening visit during which a complete medical and drug history was taken along with a physical examination with special

attention to uro-genital and nervous system. Laboratory screening for Hb% and clinical chemistry (blood sugar, serum creatinine) and urine for routine examination and culture and sensitivity was performed to exclude urinary tract infection (UTI). Ultrasonography of the KUB region was done to exclude any obstructive uropathy. Plain x-ray KUB region was done to exclude urinary stone disease and any lesion in vertebral column.

After completion of baseline clinical evaluation and investigations, those meeting the inclusion criteria were selected for the present study. The aims and objectives of the study along with its procedure, risks and benefits of this study was explained to the study population in an easily understandable local language.

A total of 76 patients were recruited and divided into two groups (Solifenacin group and Tolterodine group) by randomization. Half of the patients were enrolled in each group. Solifenacin group was experimental group and Tolterodine group was control group. Cases of Solifenacin group were given single dose of solifenacin succinate 5 mg and Tolterodine group were also given single dose of Extended Release tolterodine 4 mg, both at night daily for 12 weeks.

Patients were supplied with a Bengali version micturition diary form and instructed to complete a 3-days voiding diary prior to medication and each follow up scheduled visit at the end of 4, 8 and 12 weeks of treatment to record- the number of micturitions, urgency, urge incontinence, nocturia, the number of pads used, and the voided volume of each micturition / 24 hours over 3 consecutive days. Patients were also evaluated the adverse effects during the medication like dry mouth, constipation, and blurred vision.

At last, a final evaluation and comparison was made of those patients who strictly adhered to the study and was taken the drugs for at least 12 weeks without any interruption. After compilation, the data were presented in the form of tables and figures, as necessary. Statistical analysis of the results were done by using the computer based Statistical Package for Social Sciences (SPSS) software, version 16. Results were described as mean \pm standard deviation (SD) and compared by using two sample Z-test for quantitative data and Chi-square (χ^2) test for qualitative data. A 'P' value of < 0.05 was considered statistically significant.

Results and observation:

A total of 76 patients with OAB were randomized into two groups initially: first participant was selected by lottery method then rest of the participants were enrolled alternatively dividing into two groups. Throughout the study, Solifenacin group 3 (3.9%) and Tolterodine group 3 (3.9%) patients discontinued from the study medication due to adverse events or insufficient therapeutic response. On the other hand, Solifenacin group 2 (2.6%) and Tolterodine group 3 (3.9%) patients were lost or not communicate during follow up for any reason. Then ultimately 33 cases of Solifenacin group and 32 cases of Tolterodine group (total of 65 patients) with OAB were included in the present study. The results of the study were as follows: Improvement of micturition frequency in each follow-up was significant in both groups. But, there was no

significant difference of mean micturition frequency at end point (12 week) follow-up visit between the groups ($P>0.05$). The mean micturition frequency of both groups were equally reduced.

Improvement of urgency in each follow-up was significant in both groups. There was significant difference of mean urgency at end point (12 week) follow-up visit between the groups ($P<0.05$). The mean urgency of Solifenacin group was more reduced than the Tolterodine group.

Improvement of urge incontinence was seen in each follow up significant of both groups. There was significant difference of mean urge incontinence at end point (12 week) follow up visit between the groups ($P<0.05$). The mean urge incontinence of Solifenacin group was more reduced than the Tolterodine group.

Table-I : Distribution of the patients according to micturition frequency (N=65)

Frequency before intervention (Mean±SD)	Intervention	Frequency after intervention			P value
		4 week Mean±SD	8 week Mean±SD	12 week Mean±SD	
14.75±2.24	Solifenacin (n=33)	11.54±1.77	9.03±1.63	7.36±1.88	0.0001
15.56±2.66	ER tolterodine (n=32)	12.06±2.03	9.65±2.03	7.65±1.94	0.0001

Two sample Z-test, # Two sample Z-test was used to measure the level of significance

Table-II: Distribution of the patients according to urgency in two groups (N=65)

Urgency before intervention (Mean±SD)	Intervention	Urgency after intervention			P value
		4 week Mean±SD	8 week Mean±SD	12 week Mean±SD	
5.00±1.87	Solifenacin (n=33)	2.94±1.03	1.76±0.71	0.64±0.65	0.0001
4.81±2.07	ER tolterodine (n=32)	3.09±1.80	1.94±1.54	1.31±1.65	0.0001

Two sample Z-test, # Two sample Z-test was used to measure the level of significance

Table-III : Distribution of the patients according to urge incontinence (N=65)

Urge incontinence before intervention (Mean±SD)	Intervention	Urge incontinence after intervention			P value
		4 week Mean±SD	8 week Mean±SD	12 week Mean±SD	
2.7±0.66	Solifenacin (n=33)	1.6±0.50	0.7±0.57	0.3±0.57	0.0001
2.43±0.65	ER tolterodine (n=32)	1.43±0.51	0.79±0.80	0.71±0.72	0.0001

Two sample Z-test, # Two sample Z-test was used to measure the level of significance

Table-IV : Distribution of the patients according to nocturia in two groups (N=65)

Nocturia before intervention (Mean±SD)	Intervention	Nocturia after intervention			P value
		4 week Mean±SD	8 week Mean±SD	12 week Mean±SD	
2.94±1.20	Solifenacin (n=33)	1.79±0.82	0.91±0.68	0.33±0.54	0.0001
2.87±1.04	ER tolterodine (n=32)	1.78±1.04	1.00±1.02	0.75±1.01	0.0001

Two sample Z-test, # Two sample Z-test was used to measure the level of significance

Table-V : Distribution of the patients according to pad usage in two groups (N=65)

Pad usage before intervention (Mean±SD)	Intervention	Pad usage after intervention			P value
		4 week Mean±SD	8 week Mean±SD	12 week Mean±SD	
2.50±0.52	Solifenacin (n=16)	1.44±0.51	0.56±0.51	0.25±0.45	0.0001
2.62±0.52	ER tolterodine (n=8)	1.50±0.53	0.75±0.46	0.75±0.46	0.0001

Two sample Z-test, # Two sample Z-test was used to measure the level of significance

Table VI: Distribution of the patients according to adverse events (N=65)

Adverse events	Experimental group (Solifenacin group, n=33)		Control group (Tolterodine group, n=32)		P value
	No	Percentage	No	Percentage	
Dry mouth	5	15.2	3	9.4	0.527
Constipation	3	9.1	5	15.6	
Blurred vision	2	6.1	1	3.1	

$\chi^2 = 1.280$, $df=2$, # Chi-square test was used to measure the level of significance

Improvement of nocturia in each follow-up was significant in both groups. There was significant difference of mean nocturia at end point (12 week) follow up visit between the groups ($P < 0.05$). The mean nocturia of Solifenacin group was more reduced than the Tolterodine group.

Reduction of pad usage was seen in each follow up significant of both groups. There was significant difference of mean pad usage at end point (12 week) follow up visit between the groups ($P < 0.05$). The mean pad usage of Solifenacin group was more reduced than the Tolterodine group.

Table VI shows the distribution of the patients according to adverse events in two groups. In Solifenacin group, dry mouth, constipation and blurred vision were 5(15.2%), 3(9.1%) and 2(6.1%) respectively. In Tolterodine group, dry mouth, constipation and

blurred vision were 3 (9.4%), 5 (15.6%) and 1(3.1%) respectively. There was no significant difference of adverse events between the two groups ($P > 0.05$).

Discussion:

In the current study, the patients were separated into five groups 18-30 years (38.5%), 31-40 years (35.4%), 41-50 years (12.3%), 51-60 years (7.7%), and >60 years (6.1%) respectively and most of the sufferer were less than forty years of age (48, 73.9%). The mean age of patients was 37.30 years. Stewart et al. (2001) reported increasing number of patients with increased age.² The mean age of patients was 52.86 years.¹²

The condition was frequently encountered by both adult male and female, and was more common in male, as noted in the present study. Male patients were 36 (55.4%) and female patients were 29 (44.6%). The male and female ratio was=1:0.80. Chapple et al. (2004)

reported female and male ratio was=3:1.¹³ In Bangladesh most of the people are muslims and conservative family, women are not forward as like western country. As men are easily expressed his problem to the physicians whether women are not. They have tendency to hide their personal problems.

In the present study, a significant reduction of mean micturition frequency was found after 12 weeks of treatment in both Solifenacin and Tolterodine groups. There was no significant difference of mean micturition frequency at end point (12 week) follow-up visit between the groups ($P>0.05$). Similar reduction was observed (Ho et al., 2010) in the mean micturition numbers per 24 hours from baseline to the end point (12 week) and were not significantly different between the Solifenacin and Tolterodine groups ($P=0.58$).¹⁴

In the present study, the mean urgency of both treatment groups was significantly reduced, but Solifenacin group was more reduced than the Tolterodine group. There was significant difference of mean urgency at end point (12 week) follow-up visit between the groups ($P<0.05$). Chapple et al. (2005) studied the mean number of urgency episodes per 24 hours was significantly decreased in patients treated with solifenacin ($P=0.035$) compared with patients receiving ER tolterodine.¹⁵

In the current study, the mean urge incontinence was significantly reduced in both treatment groups, but Solifenacin group was statistically more significant reduced than the Tolterodine group ($P<0.05$). This observation was consistent with the study (Chapple et al., 2004), which showed that 65% (-1.41) reduced in the number of urge incontinence episodes in patients treated with solifenacin compared with 58% (-0.91) of ER tolterodine treated patients ($P=0.002$).¹³

The mean nocturia episodes was significantly reduced in both treatment groups, but Solifenacin group was statistically more significant reduced than the Tolterodine group ($P<0.05$). Chapple et al. (2005) observed that solifenacin treated patients benefited from a larger reduction in nocturia episodes from baseline to end point (-0.71) compared with (-0.63) ER tolterodine treated patients, although the between-treatment difference was not statistically significant ($P=0.730$).¹⁵

In the present study, the mean pad usage was significantly reduced in both treatment groups, but Solifenacin group was statistically more significant

reduced than the Tolterodine group ($P<0.05$). Chapple et al. (2005) reported that the number of pads used by patients reduced for both treatment groups, but there was a significantly greater reduction for those patients treated with solifenacin ($P=0.002$).¹⁵

In the present study, the incidence of dry mouth, constipation, and blurred vision were 15.15% versus 9.37%, 9.09% versus 15.62%, and 6.06% versus 3.12% with treated solifenacin and ER tolterodine respectively. The incidence of adverse events was not significantly different between the two groups ($P>0.05$). All the adverse effects were mild and transient in nature. Similar study was reported (Choo et al., 2008) in the incidence of dry mouth, constipation, and blurred vision were 19.49% vs. 18.64%, 6.78% vs. 2.54%, and 13.56% vs. 10.17% for the Solifenacin and Tolterodine groups respectively and there was not statistically different between the two groups ($P>0.05$).¹²

Conclusions:

Solifenacin succinate has greater efficacy to extended release tolterodine in treating overactive bladder. There are no significant treatment difference between the two groups in decreasing the number of micturition and increasing the voided volume of each micturition and the incidence of major adverse events. All the adverse effects are mild and transient in nature and discontinuation of medication due to adverse effects are low.

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