Original Article

Outcome of Solifenacin Monotherapy and Combined Solifenacin and Mirabegron Therapy in Patient with Overactive Bladder

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Abstract:

Background: Overactive bladder has a profound detrimental effect on quality of life. In the vast majority of the patients, the management plan entails behavioral modification and the anti-muscarinic drug solifenacin, which has considerable side effects and lower patients satisfaction rate. Mirabegron, a β3-adrenoceptor agonist, significantly improves OAB symptoms and plays an important role in the management algorithm. Objectives: This study examined the effectiveness and safety of solifenacinmonotherapy versus mirabegron and solifenacin combination therapy in the treatment of OAB. **Methods:** This study was conducted as a quasi-experimental model. A total of 90 patients were included in the study through purposive sampling and divided into two comparison groups: Group A (control group) receiving Solifenacin (5 mg) once daily at night for 12 weeks, and Group B (experimental group) receiving a combination of Solifenacin (5 mg) and Mirabegron (25 mg) nightly for the same period. Follow-up visits were conducted at 4, 8, and 12 weeks to track the number of micturitions, urgency, urge incontinence, nocturia, and voided volume over 24 hours. Data analysis was conducted using SPSS version 22, and the chi-square test was used to compare percentages of different outcome variables. A p-value of less than 0.05 was considered statistically significant. **Results:** Solifenacin (5 mg) monotherapy and combined miragraben (25 mg) and solifenacin (5 mg) showed comparable efficacy in alleviating symptoms of OAB, but greater improvement with regard to frequency of micturition, urgency, and urge incontinence were showed in the combined therapy group. **Conclusion:** The combination of Solifenacin and Mirabegron provides a more effective treatment for overactive bladder compared to Solifenacin alone. Although the combined treatment group experienced more adverse effects, these differences were not statistically significant between the two groups. Since the adverse effects were generally mild and temporary, the combined therapy remains a viable option for managing overactive bladder.

Key words: Overactive bladder (OAB), Urgency, Urge incontinence, Solifenacin, Mirabegron, Anti-muscarinic, β3-adrenoceptor

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Introduction:

Overactive bladder (OAB) is defined by the conjoint effort of the International Uro-gynecological Association (IUGA) and the and the International Continence Society (ICS) as "a syndrome characterized by urinary urgency, usually with urinary daytime frequency and nocturia in the absence of an underlying metabolic or pathological condition and may or may not be accompanied by urge incontinence".[1] It is a heterogenous symptom complex that has significant impact on the psycho-social wellbeing; social (restricting travel because of frequent urination, social withdrawal), psychological (poor self-esteem, depression, and stress associated with incontinence), and occupational (decreased produ ctivity).[2] OAB is a chronic incapacitatingillness that affects both male and female populations somewhat around 10–15%. Though risk increases with advancing age and particularly after 40 years. has slightly higher predilection for elderly females; it may affect children and young populations as well. Its prevalence also shows some regional variations, reportedly 20.8% in Asia and 11.8% in western countries.[3]

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Overactive bladder (OAB) is predominantly presented asan array of symptoms affecting the control and quality of micturition in the lower urinary tract. Itaffects members of both genders and is associated with significant bother and impact on quality of life (Agarwal et al., 2014).[4] In a good number of cases, no apparent cause is found, and OAB is regarded as 'idiopathic'.

The prevalence of overactive bladder is high, with 12–16% of adults in Europe, USA, and Japan (Homma et al., 2005; Milsom et al., 2001)[5]. The prevalence of OAB worldwide is estimated to be greater in women (Irwin et al. 2011).[6] Treatment approaches for overactive bladder include lifestyle modification, medical management, and operative interventions. Lifestyle changes include bladder drill, bladder management (use of relaxed and double voiding techniques) or instrumentation, pelvic floor muscle strengthening, and control of fluid intake, moderation of intake of caffeine, alcohol fluid management (Hubbard et al., 2017)[7]. Among these, oral pharmaco logical products, antimuscarinics (e.g., solifenacin), and mirabegron, the β3-adrenoceptor agonist, remain the mainstay of treatment. Both classes of drugs show comparable clinical efficacy (Andersson, 2004)[8], although mirabegron is not associated with anticholinergic adverse effects (e.g., incidence of dry mouth).[9] Antimuscarinicdrugs such as Solifenacin is the first-line agent for the management of overactive bladder symptoms. But many patients showed poor adequate symptom control on antimuscarinics, and increasing the antimuscarinic dose may result in intolerable adverse drug reactions such as dry mouth and constipation (Benner et al., 2010; Chapple et al., 2008) that result in discontinuation of the drug.[10,11] During 2012, β3 adrenergics were effectively introduced as an substitute to antimuscarinics for OAB management. The clinical efficacy of β3 adrenergics has been shown, and they havepromised a superior tolerability profile that differs from that of antimuscarinics (Maman et al., 2014) Mirabegron, the extensivelyprescribed β3 adrenergic drug, has thus achieved widespread acceptance in clinical setting.

Combination therapy with an antimuscarinic with β3 agonist appears to be the best possible alternative in the stepwisealgorithm for the treatment of OAB when either class drug monotherapy showedpoor perfor mance, provided an precise diagnosis has been established (Apostolidis et al., 2017)[12] Antimuscarinics and β3 adrenoreceptor agonists are believed to mediate detrusor relaxation via two disparate cellular pathways.There are five subtypes of muscarinic receptors (M1–M5) function throughout the human body. Although M2 receptors (75%) are most abundant in the urinary bladder, normal bladder contraction is predominantly executed by stimulation of M3 receptors (25%)(Hegde and Elgin, 1999).

Today, a number of antimuscarinic agents are available, namely tolterodine, solifenacin, darifenacin, trospium, etc. Among several antimuscarinics, solifenacin shows much greater inclination and responsiveness for the muscarinic M3 subtype. By prohibiting the receptor binding of acetylcholine, solifenacin inhibits detrusor muscle contractility, allowing the bladder to hold greater amount of urine and lessening the frequency of micturition, urgency, and urge incontinence incidents.13Mirabegron, a β3 adrenoreceptor agonists may inhibit Aδ and C-fiber activity during urinary bladder filling as well asdampenautonomous contractile activity[14] (Andersson et al., 2013). Theoretically, therefore, aintegrated effort of β3 adrenoreceptor priming and muscarinic receptor pre-occupation could have a mutually reinforcing effect to successfully unwind the bladder.The aim of this study is to analyze the outcome of Solifenacin monotherapy and combined Solifenacin and Mirabegron in the management of overactive bladder.

Method:

This quasi-experimental study was conductedat the outpatient department of urology at the National Institute of Kidney Diseases & Urology in Dhaka from January 2018 to March 2019. Men and women aged 18 to 65 with overactive bladder (OAB) symptoms persisting for three months or more were included using purposive sampling. Each participant underwent an initial screening, which included a comprehensive medical and drug history review, a physical examination with emphasis on the uro-genital and nervous systems, and a digital rectal exam (DRE) to rule out bladder outlet obstruction (BOO) due to pelvic pathology. A detailed neurological assessment (perianal sensation, anal tone, bulbocavernosus reflex) was also performed to exclude neuropathic bladder. Blood tests, including blood sugar and serum creatinine levels, along with urine analysis (routine, microscopic, and culture & sensitivity), were conducted to rule out urinary tract infections (UTI). Ultrasonography of the kidneys, ureters, and bladder (KUB) was performed to exclude conditions such as kidney stones, cystitis, bladder masses, enlarged prostate, and postvoid residual urine. Additionally, a plain X-ray of the KUB region was requested to rule

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out urinary stones and vertebral column abnormalities. After completing the baseline clinical evaluations and tests, participants who met the inclusion criteria were selected for the study.

A total of 90 patients were included in the study and divided into two comparison groups: Group A (control group) with 45 patients receiving Solifenacin (5 mg) once daily at night for 12 weeks, and Group B (experimental group) with 45 patients receiving a combination of Solifenacin (5 mg) and Mirabegron (25 mg) nightly for the same period. Patients were provided with a clear medication guide and instructed to complete a 3-day voiding diary before starting treatment. Follow-up visits were conducted at 4, 8, and 12 weeks to track the number of micturitions, urgency, urge incontinence, nocturia, and voided volume over 24 hours. All data were recorded in a pre-designed collection sheet, and patient confidentiality was strictly maintained.Qualitative data were presented as frequency distributions and percentages, while quantitative data were expressed as means and standard deviations. Data analysis was conducted using SPSS version 22, and the chi-square test was used to compare percentages of different outcome variables. A p-value of less than 0.05 was considered statistically significant.

Results:

A total of 90 patients were initially recruited for the study through purposive sampling. However, 10 patients from Group A and 3 from Group B were lost to follow-up at various stages. Consequently, the final analysis included 77 patients, with 35 in the control group (receiving Solifenacin) and 42 in the experimental group (receiving the combination of Solifenacin and Mirabegron).

Table-I: Comparison of age between two groups (n=77)

Age in years	Group A(n=35)		Group B (n=42)		*p* value
	No	%	No	%	
18-30	6	17.1	4	9.5	
31-40	3	8.6	9	21.4	
41-50	7	20.0	10	23.8	
51-60	16	45.7	17	40.5	
>60	3	8.6	2	4.8	
Mean± SD Range	45.62±12.39 18 – 65		46.28±8.79 24 – 64		0.787^{ns}

The table compares the age distribution between two groups (Group A with 35 patients and Group B with 42 patients). The age range in both groups is similar, with Group A ranging from 18 to 65 years and Group B from 24 to 64 years. The largest proportion of patients in both groups is in the 51–60 age range (45.7% in Group A and 40.5% in Group B). The mean age is 45.62±12.39 years for Group A and 46.28±8.79 years for Group B, with no significant difference between the groups (p = 0.787).

Table-II: Distribution of the patients by gender in two groups (n=77)

Sex	Group A (n=35)		Group B (n=42)		*p* value
	No	%	No	%	
Male	16	45.7	16	38.1	0.499^{ns}
Female	19	54.3	26	61.9	
Total	35	100.0	42	100.0	

The table presents the gender distribution between Group A (n=35) and Group B (n=42). In Group A, 45.7% of patients are male, and 54.3% are female. In Group B, 38.1% are male, and 61.9% are female.

A statistical analysis was performed to compare the gender distribution between the two groups, and the p-value is 0.499, indicating that there is no statistically significant difference in gender distribution between Group A and Group B (p > 0.05). This suggests that gender is well-balanced between the groups and unlikely to influence the study outcome.

Table-III: Comparison of micturition frequency between two groups (n=77)

Frequency of Micturition	Group A(n=35) Mean±SD	Group B(n=42) Mean±SD	p value
Before intervention	12.71±1.72	12.74±1.58	0.950^{ns}
After 4 weeks	9.97±1.20	8.83±0.79	$<0.001^{s}$
After 8 weeks	8.34±0.73	7.60±0.59	$<0.001^{s}$
After 12 weeks	7.46±0.78	7.05±0.70	0.017^{s}

The table compares the mean micturition frequency between Group A and Group B at different time points. Before the intervention, both groups had similar frequencies (p = 0.950). After 4, 8, and 12 weeks, both groups showed significant reductions in micturition frequency, with Group B consistently showing a greater improvement than Group A. The differences between the groups were statistically significant at 4, 8, and 12 weeks, with p-values <0.001 and 0.017, respectively.

Table-IV: Comparison of urgency of micturition between two groups (n=77)

Urgency of Micturition	Group A (n=35) Mean±SD	Group B (n=42) Mean±SD	p value
Before intervention	5.06±1.33	4.71±0.77	0.162^{ns}
After 4 weeks	3.09±0.51	2.55±0.77	0.001^{s}
After 8 weeks	2.11±0.47	1.76±0.69	0.013^{s}
After 12 weeks	1.00±0.49	0.62±0.49	0.001^{s}

The table compares the urgency of micturition between Group A and Group B at various time points. Before the intervention, there was no significant difference in urgency between the two groups (p = 0.162). After 4 weeks, both groups showed a reduction in urgency, with Group B improving more significantly (p = 0.001). This trend continued after 8 weeks, with Group B still showing a greater reduction (p = 0.013). By 12 weeks, both groups had further improvements, but Group B had a significantly lower urgency level than Group A (p = 0.001). Group B consistently exhibited more significant improvements across all time points.

Table-V: Comparison of urge incontinence of micturition between two groups (n=77)

Urge incontinence of Micturition	Group A (n=35) Mean±SD	Group B (n=42) Mean±SD	p value
Before intervention	2.60±1.06	2.24±0.88	0.106^{ns}
After 4 weeks	1.86±0.49	1.52±0.51	0.005^{s}
After 8 weeks	0.83±0.66	0.29±0.46	<0.001^{s}
After 12 weeks	0.46±0.51	0.14±0.35	0.002^{s}

The table compares urge incontinence between Group A and Group B at different time points. Before the intervention, there was no significant difference between the groups (p = 0.106). After 4, 8, and 12 weeks, both groups showed improvements, with Group B consistently showing a greater reduction in urge incontinence. The differences were statistically significant at each follow-up point, with p-values of 0.005, <0.001, and 0.002, respectively. Group B demonstrated a more substantial improvement compared to Group A throughout the study.

Table VI: Comparison of nocturia between two groups (n=77)

Nocturia	Group A(n=35) Mean±SD	Group B(n=42) Mean±SD	p value
Before intervention	3.03±0.89	2.74±0.73	0.121^{ns}
After 4 weeks	1.89±0.58	1.79±0.68	0.496^{ns}
After 8 weeks	0.97±0.30	0.81±0.45	0.074^{ns}
After 12 weeks	0.60±0.50	0.38±0.49	0.064^{ns}

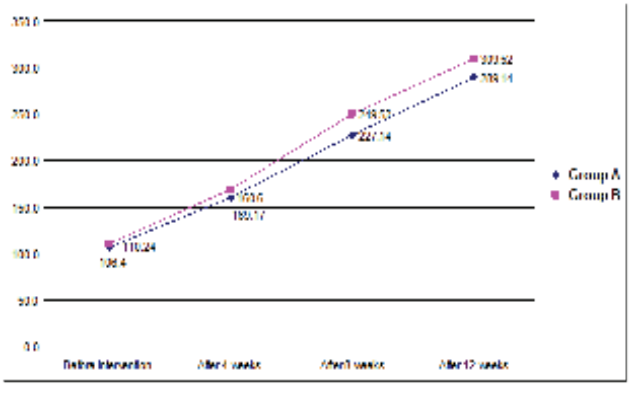
The table compares nocturia between Group A and Group B at various time points. Before the intervention, there was no significant difference between the groups (p = 0.121). After 4, 8, and 12 weeks, both groups showed reductions in nocturia, but the differences between them were not statistically significant, with p-values of 0.496, 0.074, and 0.064, respectively. Overall, both groups improved similarly over time.

Table-VII: Comparison of voided volume of each micturition between two groups (n=77)

Voided volume	Group A(n=35) Mean±SD	Group B(n=42) Mean±SD	p value
Before intervention	106.43±16.16	110.24±14.81	0.286^{ns}
After 4 weeks	160.57±17.52	169.17±13.06	0.016^{s}
After 8 weeks	227.14±27.07	249.52±21.63	<0.001^{s}
After 12 weeks	289.14±25.48	309.52±29.46	0.002^{s}

The table compares the voided volume per micturition between Group A and Group B. Before the intervention, there was no significant difference between the groups (p = 0.286). After 4, 8, and 12 weeks, both groups showed increased voided volumes, with Group B consistently having a higher volume. The differences were statistically significant at each time point, with p-values of 0.016, <0.001, and 0.002, respectively, indicating a greater improvement in Group B.

Improvement of voided volume of each micturition



Comparison of mean voided volume of each micturition (ml) before and after intervention

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Group A- Solifenacin group.
Group B—Combined Solifenacin and Mirabegron.

Figure 1 illustrates the mean voided volume per micturition for Group A (Solifenacin) and Group B (Combined Solifenacin and Mirabegron) before and after the intervention. Both groups showed increases in voided volume over time. However, Group B consistently had higher voided volumes compared to Group A. The improvements were more pronounced in Group B at each follow-up point, reflecting a more significant enhancement in micturition volume with the combined treatment. The diagram highlights the superior effectiveness of the combined treatment in increasing voided

Table-VIII: Distribution of the patients according to adverse events (n=77)

Adverse effects	Group A(n=35)		Group B(n=42)		p value
	No.	%	No.	%	
Dry mouth	5	14.3	9	21.4	0.418 ^{ns}
Constipation	3	8.6	10	23.8	0.076 ^{ns}
Blurred vision	1	2.9	5	11.9	0.140 ^{ns}
Headche	1	2.9	4	9.5	0.237 ^{ns}
Post void residual	2	5.7	3	7.1	0.800 ^{ns}
Hypertension	0	0.0	4	11.9	0.061 ^{ns}

The table summarizes the distribution of adverse events between Group A (n=35) and Group B (n=42). For dry mouth, 14.3% of Group A and 21.4% of Group B experienced it, with no significant difference (p = 0.418). Constipation was reported by 8.6% of Group A and 23.8% of Group B (p = 0.076), while blurred vision was noted in 2.9% of Group A and 11.9% of Group B (p = 0.140). Headache affected 2.9% of Group A and 9.5% of Group B (p = 0.237). Post-void residual was seen in 5.7% of Group A and 7.1% of Group B (p = 0.800). Hypertension was reported in 11.9% of Group B but none in Group A (p = 0.061). Overall, none of the adverse events showed statistically significant differences between the two groups.

Discussion:
This prospective study compared the effects of solifenacin succinate alone aganist a combination of solifenacin succinate and mirabegron in treating overactive bladder. Overactive bladder symptoms have cruial impact on quality of life, affecting psychosocial, physical, and occupational health aspects. Antimuscarinic agents are commonly used to manage these symptoms, aiming to enhance quality of life by alleviating issues such as frequent urination, urgency, urge incontinence, and nocturia, thus reducing the burden on patients and their families. However, despite their effectiveness, these medications may have tolerability issues due to side effects, including dry mouth, constipation, and blurred vision.

In this study, 35 patients received solifenacin succinate 5 mg daily, while 42 patients were treated with a combination of solifenacin 5 mg and mirabegron 25 mg daily. The patients were followed up at 4, 8, and 12 weeks to assess the efficacy and safety of the treatments and compare the outcomes between the two groups. The patients were categorized into five age groups, with the highest proportions in both Group A and Group B being over 40 years old (45.7% and 40.5%, respectively). The mean ages were 45.62±12.39 years for Group A and 46.28±8.79 years for Group B, with no significant age difference between the groups. Previous studies, such as Stewart et al. (2001), have noted an increase in the number of patients with age, and Choo et al. (2008) reported a mean patient age of 52.86 years.[15,16]

The condition was commonly seen in both adult males and females, with a higher prevalence in females, as observed in this study. Specifically, 32 males (41.6%) and 45 females (58.4%) participated, giving a male-to-female ratio of 1 :1.4. Chapple et al. (2004) reported a male-to-female ratio of 1:3.[17] In the Solifenacingroup, the mean micturition frequency decreased from 12.71±1.72 at baseline to 7.46±0.78 after 12 weeks. In the combined group, it decreased from 12.74±1.58 to 7.05±0.70 over the same period. Both groups experienced a significant reduction in micturition frequency after 12 weeks, with a notable difference between the groups at this endpoint (p = 0.017). A similar reduction was reported by Herschorn et al. (2017), who found significant differences in mean micturition frequency between the Solifenacin and combined groups at the 12-week endpoint (p = 0.04).18In the present study, the mean urgency score for the Solifenacin group decreased from 5.06±1.33 at baseline to 1.00±0.49 after 12 weeks. For the combined group, the mean urgency score dropped from 4.71±0.77 to 0.62±0.49 over the same period. Both groups experienced significant reductions in urgency, but the combined treatment resulted in a greater reduction. The difference in mean urgency between the groups at the 12-week follow-up was statistically significant (p = 0.001). Yankai et al. (2017) also

reported a significant decrease in urgency episodes per 24 hours with the combined treatment compared to solifenacin alone ($p = 0.0001$).[19]

Regarding urge incontinence, the mean score in the Solifenacin group reduced from 2.60±1.06 at baseline to 0.46±0.51 at the 12-week follow-up, representing an 82.7% reduction. In the combined group, the mean score decreased from 2.24±0.88 to 0.14±0.35, a 93.8% reduction. Both treatments significantly reduced urge incontinence, but the combined treatment showed a more pronounced reduction ($p = 0.002$). This finding aligns with Drake et al. (2016), who observed a greater reduction in urge incontinence episodes with the combined treatment compared to solifenacin alone (-1.82 vs. -1.54 episodes/24 hours, $p = 0.003$).20In the Solifenacin group, the mean number of nocturia episodes decreased from 3.03±0.89 at baseline to 0.60±0.50 after 12 weeks, reflecting an 80.2% reduction. In the combined group, the mean nocturia episodes dropped from 2.74±0.73 to 0.38±0.49, an 86.1% reduction. Although both groups showed significant reductions, the combined group did not have a statistically more significant reduction in nocturia compared to the Solifenacin group ($p = 0.064$). Drake et al. (2016) found that combined therapy resulted in a slightly greater reduction in nocturia episodes compared to solifenacin alone, but the difference was not statistically significant ($p = 0.174$).[20] Regarding voided volume per micturition, the Solifenacin group increased from 106.43±16.16 ml at baseline to 289.14±25.48 ml at 12 weeks, while the combined group increased from 110.24±14.81 ml to 309.52±29.46 ml. There was a significant difference between the groups at the 12-week follow-up ($p = 0.002$), with the combined group showing a more notable increase.[16]. Yankai et al. (2017) also reported a significant increase in mean voided volume per micturition in the combined group compared to the Solifenacin group ($p < 0.001$).[19]

In terms of adverse effects, the incidence of dry mouth, constipation, blurred vision, headache, post-void residual, and hypertension were 5 (14.3%) vs. 9 (21.4%), 3 (8.6%) vs. 10 (23.8%), 1 (2.9%) vs. 5 (11.9%), 1 (2.9%) vs. 4 (9.5%), 2 (5.7%) vs. 3 (7.1%), and 0% vs. 4 (11.9%) for the Solifenacin and combined groups, respectively. Although the combined group had higher rates of adverse effects, the differences were not statistically significant ($p > 0.05$). All adverse effects were mild and transient. This aligns with findings from Herschorn et al. (2017) and Yankai et al. (2017), which reported a higher incidence of dry mouth, constipation, and blurred vision in the combined Solifenacin and mirabegron group compared to the Solifenacin group.[18,19]

Conclusion:

The combination of Solifenacin and Mirabegron provides a more effective treatment for overactive bladder compared to Solifenacin alone. Although the combined treatment group experienced more adverse effects, these differences were not statistically significant between the two groups. Since the adverse effects were generally mild and temporary, the combined therapy remains a viable option for managing overactive bladder.

Limitations of the study:

The present study had several limitations:

- It was conducted at a single center in Dhaka city, which may not fully represent the broader population.
- The sample size was relatively small.
- The study was not double-blinded, which means the results were dependent on baseline values and might not be entirely accurate.
- Urodynamic testing was not performed due to a lack of available facilities.

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