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Comparative Study of Solifenecin Alone Versus Solifenecin with Duloxetine in Patients of Overactive Bladder

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***Abstract*- Aims and Objective-** Present study was undertaken to see and compare the effect of solifenacine alone and solifenacine with duloxetine therapy in patients with overactive bladder.

Material Methods:- The study was done on the patients with overactive bladder. The patients were diagnosed clinically by the physician and urologists. Before enrolling in the study each patient was asked to give a written consent. The outcome measures were evaluated in form of reducing the frequency, urgency and other clinical symptoms. Simultaneously we also measured the quality of life of the patients using accepted scale.

Results and Conclusion:- Present study showed that addition of duloxetine with solifenasin has definitely produced better clinical improvement in patients as well as the quality of life was also imporved. Though minor side effects increased by this addition but overall quality of life was better in patients on combination therapy as compared to the single solifenasin treatment.

***Index Terms*-** Overactive bladder, Quality of life, Duloxetine, Solifenasin

I. INTRODUCTION

Overactive bladder (OAB) is defined as a "symptom syndrome suggestive of lower urinary tract dysfunction" characterized by "urgency, with or without urge incontinence, usually with frequency and nocturia (Wein AJ. et al., 2002; Abrams P, et al. 2002) [1,2]. Typically occurring without a recognizable underlying etiologic factor, OAB is a diagnosis of exclusion, intuitively considered to be related to detrusor overactivity (DO). OAB has significant negative impact on the quality of life (QOL). As such, QOL issues encompass physical, psychological and social functioning, overall life satisfaction, perception of health status, and pain (Liberman JN.et al., 2001; Chancellor M. B., et al. 2008; Abrams P, et al. 2000) [3,4,5]. The World Health Organization (WHO) estimated that urinary incontinence affects nearly 200 million people worldwide (Stewart WF.et al., 2003)[6]. OAB is a common condition that affects millions of people worldwide and OAB-associated urge urinary incontinence (UUI, 'wet' OAB) is especially prevalent in older women (Rovner and Wein 2002)[7]. OAB occurs as a result of abnormal and involuntary contractions of the detrusor muscle in the bladder, which is embedded by muscarinic receptors (M_2 and M_3 subtypes). Stimulation of M_2 and M_3 receptors by acetylcholine causes bladder contractions that lead to urination (Chu FM.et al., 2006; Erdem N.et al., 2006)[8,9]. Normally, the detrusor muscle remains at rest as the bladder is filled by urine (filling phase). However, it contracts during the filling phase in patients with OAB. Therefore, muscarinic receptor antagonists (antimuscarinic agents) are considered the mainstay of pharmacologic treatment for OAB.

Solifenacin belongs to a class of medications called anticholinergics. It is a bladder-selective, muscarinic (M_1 and M_3) receptor antagonist. Solifenacin works by relaxing the bladder muscles to prevent urgent, frequent, or uncontrolled urination, by competitively inhibiting acetylcholine from binding to cholinergic receptors. It reduces smooth muscle tone in the bladder, allowing the bladder to retain larger volumes of urine and reducing the number of micturition, urgency and incontinence episodes. As it is highly receptor (M_3) specific, it has lesser incidence of side effects like dry mouth and constipation (Cardozo L.et al., 2004; Smulders RA.et al., 2004; Ohtake A.et al., 2004) [10,11,12].

Duloxetine, the dual serotonin (5-HT)/ nor epinephrine (NE) reuptake inhibitor, modulates lower urinary tract function through selective inhibition of 5-HT and NE reuptake sites. It works centrally at Onuf's nucleus to increase activity of the pudendal nerve. It facilitates sphincter activity during urine storage but not during voiding, maintaining the bladder-sphincter synergy (Norton PA.et al., 2004) [13]. Treatment planning for patients with OAB must be based on clinical evidence of efficacy for the drugs chosen, individual patient psychological illness, and an assessment of the probable benefits of treatment versus its associated adverse effects. The present study aimed at evaluating better treatment with more efficacy, better safety profile and positive impact in quality of life in patients of OAB. The objective of this study was to assess and compare the effects of solifenacin alone versus solifenacin with duloxetine in patients suffering from over active bladder.

II. MATERIALS AND METHODS

Study design

This was an open, parallel, prospective and randomized study and was carried out in outpatient in the department of medicine of Era's Lucknow Medical College and Hospital (ELMC&H), Lucknow and department of urology of Chatrapati Shahuji Maharaj Medical university (CSMMU) Lucknow, to compare the effect, quality of life and safety profile in patients suffering from over active bladder treated with Solifenacin alone versus Solifenacin with Duloxetine. The total duration of the study was 18 months (Fig. 1).

Eligibility of patients

The clinical criteria for the diagnosis of over active bladder were accordingly as recommended by Wein and Abrams (Abrams P.et al., 2003) [14].. Possibility of OAB due to other causes was excluded by clinical history, clinical examination and investigations of the patients.

Parameters of study

(A) OAB-V8 Questionnaire asks about how much patient have been bothered by selected bladder symptoms during the past 4 weeks with 8 questions (OAB-V8 Questionnaire). Scoring was given from 0 to 5 where 0 indicates no symptom at all and 5 indicates a very great deal of symptom (Coyne K.et al., 2002); (**B) OAB-q short form symptom bother** includes questions which assess the effect of OAB on quality of life and interference with daily activities. It uses 13 items to assess interference with activities of daily life (OAB-q short form symptom bother). Each question uses a 6-point interference scoring from 1 to 6 where 0 indicating no interference and 6 indicating complete interference). After completing all the questions we took the mean of all the parameters by adding the score and dividing them by 13. This mean score of OAB-q short form symptom bother was later on used for statistical comparisons (Coyne K.et al., 2002) '[15]and (**C) Safety assessment study noted** all the adverse events in each treatment group. Safety of treatment was assessed by using list of adverse events in both the treatment groups.

Initial evaluation

The patients were included in the study after proper diagnosis and fulfilling the inclusion/exclusion criteria with informed consent. A standardized initial evaluation, which included a complete clinical history, clinical examination, investigations were done at initial screening visit and assessment of OAB and assessment of QOL was done at the time of 1st visit (day0).

Treatment groups with drugs studied

Eligible patients fulfilling the mentioned criteria were randomized by card method into two treatment groups (Groups A and B) depending on the drugs prescribed. In Group A, eligible 35 patients (20 males and 15 females) were given tablet solifenacin, 5 mg available as tablet Solitan, manufactured by Ranbaxy Pharmaceuticals, once daily after breakfast for 8 weeks. In Group B, eligible 37 patients (20 males and 17 females) were given tablet solifenacin, 5mg once daily after breakfast and duloxetine 40 mg available as capsule Duzela, manufactured Sun Pharmaceuticals, twice daily after breakfast and after meal at night for 8 weeks.

Follow-ups for clinical assessment

Patients were requested to come after 4 weeks and again the same assessment of OAB and QOL were done at the IInd visit. Adverse events in each treatment group were noted at the IInd visit. Repetition of the same work was done after 8 weeks at the IIIrd visit.

Outcome measures

Comparison of responses obtained by group A (solifenacin) and group B (solifenacin + duloxetine) on day 0, after 4 weeks and after 8 weeks were done within the groups and in between the groups. There were two types of comparisons:

1- Intra group's comparison (within A and B groups): Visit I (day 0) versus Visit II (after 4 weeks); Visit I (day 0) versus Visit III (after 8 weeks); Visit II (4 weeks) versus Visit III (after 8 weeks).

2-Inter group's comparison (in between A and B groups): Visit I (solifenacin) versus Visit I (solifenacin + Duloxetine); Visit II (solifenacin) versus Visit II (solifenacin + Duloxetine); Visit III (solifenacin) versus Visit III (solifenacin + Duloxetine).

Statistical methods

Data were summarized as Mean ± SD. Groups were compared by using two factor repeated measures analysis of variance (RMANOVA) and the significance of mean difference within and between the groups was done by Newman-Keuls post hoc test. Discrete (categorical) data were subjected with χ^2 test. A two-tailed (α=2) probability $p<0.05$ was considered to be statistically significant. All analyses were performed on STATISTCA (version 6.0) while graphs were done on Graph Pad Prism (version 3.0). For each treatment, a percent mean change (from initial to final or final to initial) was also calculated as:

$$\% \text{ change} = \frac{\text{Mean}_1 - \text{Mean}_2}{\text{Mean}_1} \times 100$$

where, $\text{Mean}_1 > \text{Mean}_2$ and Mean_1 = Mean of I[st] group; Mean_2 = Mean of II[nd] group.

III. Results

All 72 eligible patients (40 males and 32 females) aged ≥18 were divided into two groups, Group A with 35 patients (20 males and 15 females) were given tablet solifenacin 5 mg once daily after breakfast for 8 weeks and Group B with 37 patients (20 males and

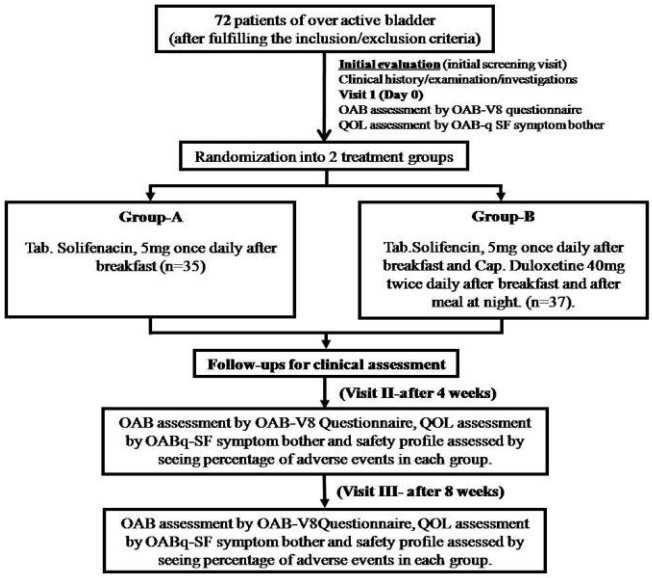

Fig. 1: Flow Chart of the study

17 females) were given tablet solifenacin, 5mg once daily after breakfast and duloxetine 40 mg twice daily after breakfast and after meal at night for 8 weeks. In the patients of OAB three main assessments were done in each group:-

A. Assessment of OAB by OAB-V8 questionnaire

OAB-V8 questionnaires in patients of two treated groups over the periods showing comparison of scores of all the 8 conditions (i. frequent urination during day time hrs?; ii. an uncomfortable urge to urinate?; iii. a sudden urge to urinate with little or no warning?; iv. accidental loss of small amount of urine?; v. night time urination?; vi. waking up at night to urinate?; vii. an uncorrelated urge to urinate? and; viii. urine loss associated with a strong desire to urinate?). On the basis of above scores the total (overall) scores of OAB-V8 questionnaires in patients of two treated groups over the periods were summarized. In both the treatments, the mean scores of total OAB-V8 questionnaires decreases with the time (wks) and the decrease (improvement) was evident more in patients those who received the Duloxetine + Solifenacin (64.2%) than those who received the Solifenacin (37.4%) (Table 1 & Fig. 2). In other words, the effect size of Duloxetine + Solifenacin was 1.7 times higher than the Solifenacin alone.

Table 1: OAB-V8 questionnaire scores summary (Mean ± SD) of two groups

Treatment groups	Periods			% mean change (day 0 - 8 wks)
	day 0	4 wks	8 wks	
Solifenacin (n=35)	4.41 ±0.29	3.49 ±0.34	2.76 ±0.29	37.4%
Duloxetine + Solifenacin (n=37)	4.45 ±0.30	2.51 ±0.47	1.59 ±0.24	64.2%

n= number of patients

For each treatment, comparing the mean scores of OAB-V8 questionnaires between the periods (within groups), the mean scores of OAB-V8 questionnaires decreased significantly ($p<0.05$ or $p<0.01$) in both the treatments at 4 wks and 8 wks as compared to day 0. Further, in both the treatments, the means of OAB-V8 questionnaire also decreased significantly ($p<0.05$) at 8 wks as compared to 4 wks. Similarly, for each period, comparing the mean scores of OAB-V8 questionnaires between the treatments (between groups), the mean scores of OAB-V8 questionnaires in two treatments did not differed ($p>0.05$) at day 0 while differed ($p<0.05$ or $p<0.01$) at both 4 wks and 8 wks. In other words, the mean scores of OAB-V8 questionnaire at both 4 wks and 8 wks lowered more in subjects those who received the Duloxetine + Solifenacin than those who received the Solifenacin. Improvement (reduction in OAB scores ≥2) in each individual questions asked in OAB-V8 questionnaire is seen in two groups from beginning to end of treatment. The data obtained is assessed and comparison is done in between the two groups. This shows that improvement in questions 4, 7 and 8 does not show much difference in between the two groups as compared to other questions.

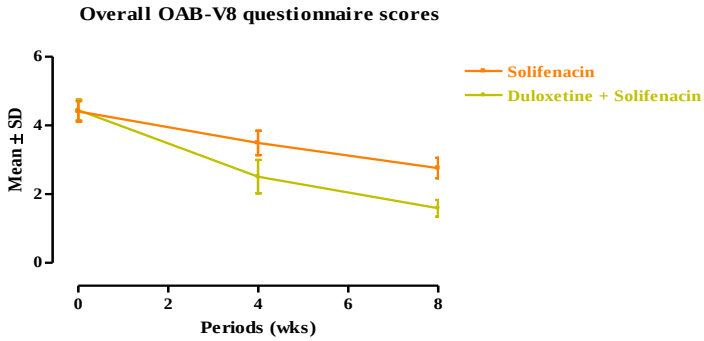

Fig. 2: Mean (± SD) scores of OAB-V8 questionnaires over the periods in patients treated with Solifenacin and Duloxetine + Solifenacin.

B. Assessment of Overall Quality of Life by OAB-q short form symptom bother

In both the treatments, the overall quailty of life (QOL) scores improves (decrease) with the time (wks) and the improvement was evident more in patients those who received the Duloxetine + Solifenacin (69.5%) than those who received the Solifenacin (49.4%). In other words, for improvement in overall QOL, the Duloxetine + Solifenacin was 1.4 times more better than the Solifenacin. For each treatment, comparing the mean QOL scores between the periods (within groups), the overall QOL scores improved significantly ($p<0.05$ or $p<0.01$) in both the treatments at both 4 and 8 wks as compared to day 0. Further, in both the treatments, the overall QOL scores also improved significantly ($p<0.05$ or $p<0.01$) at 8 wks as compared to 4 wks. Similarly, for each period, comparing the mean QOL scores between the treatments (between groups), the overall QOL scores in two treatments did not differed ($p>0.05$) at day 0 while differed ($p<0.01$) at both 4 wks and 8 wks. In other words, the overall QOL scores at both 4 wks and 8 wks improved more in subjects those who received the Duloxetine + Solifenacin than those who received the Solifenacin.

C. Assessment of safety by using list of adverse events

At 4th week and 8th week, the adverse events in patients of two groups were assessed and summarised. In both the groups, the adverse events especially, metabolism and nutrition disorder, skin and subcutaneous tissue disorder, immune system disorders, respiratory disorder and vascular disorder were negligible. However, both the groups showed adverse events such as gastrointestinal disorders, genitourinary disorders, nervous system disorders, eye disorders and psychiatric disorders and were evident higher in patients those who received the Duloxetine + Solifenacin than those who received the Solifenacin. As compared to 8th week, adverse events were evident higher at 4th week in Duloxetine + Solifenacin. However on comparing the adverse events, the proportions of its in two groups were found to be the same i.e. did not differed significantly ($p>0.05$).

IV. Discussion

The present study aimed at evaluating better treatment with more efficacy, better safety profile and positive impact in quality of life in patients of OAB. The objective of this study was to assess and compare the effects of solifenacin alone versus solifenacin with duloxetine in patients suffering from over active bladder.

For the assessment of OAB, Group A (solifenacin) having baseline mean OAB score 4.41±0.29. Significant improvements ($p<0.05$ or $p<0.01$) in overall OAB scores were observed in all patients at 4th and 8th week (20.9% and 37.4% improvement - table 9) in the form of reduction in frequency (21.9% and 34.8%), urgency (21.8% and 34.2%), urinary incontinence (22.5% and 47.1%) and nocturia (19.18% and 33.6%), respectively when compared with baseline scores. While the previous studies showed improvements in OAB scores were 9Gittelman, et al. (2003) [16]comparing solifenacin with placebo in large number of patients of OAB (n=850-1050). This study shows that solifenacin 5 or 10mg once daily significantly reduced the mean number of voids per 24 hours versus placebo. Across study, there was 2.19–2.81 (with solifenacin) and 1.2–1.59 (with placebo) fewer voids per 24 hours than at baseline (baseline mean values 11–12). There were significantly greater reductions from baseline in the daily incidence of incontinence (47–67% vs. 28–41%, $p < 0.001$) or urge incontinence (58–66% vs. 35–43%, $p < 0.05$) for recipients of solifenacin 5 or 10mg once daily versus placebo recipients. Solifenacin 5 or 10mg once daily significantly increased the volume of urine voided per micturition versus placebo (by 25–30% vs. 4–11%, $p <0.01$–0.001). Solifenacin 10 mg/day (but not 5 mg/day) significantly decreased the number of episodes of nocturia per 24 hours compared with placebo. There were 0.71 fewer nocturnal voids per 24 hours (a reduction of 39%) shown. Some differences in results of present study compared to these studies appeared to be clinically important and the power of the analysis to detect differences was limited both by small sample size of present study and by the variability of the measures used in the studies. Group B patients for the assessment of OAB treated with solifenacin + duloxetine the baseline mean OAB scores in this group of patients was 4.45±0.30. Significant improvements ($p<0.05$ or $p<0.01$) in overall OAB scores were observed in all patients at 4th and 8th week (43.6% and 64.2% improvement) in the form of reduction in frequency (43.4% and 62.0%), urgency (42.1% and 65.6%), urinary incontinence (41.3% and 59.9%) and nocturia (40.8% and 71.3%), respectively when compared with baseline scores. While the previous studies showing the similar positive efficacy . Thor K B, et al. (1995)[17]. In a 12 weeks study conducted by Steers WD, et al. (2007)[18] on 306 women patients efficacy of duloxetine (80-mg/day for 4 weeks increased to 120-mg/day for 8 weeks) was compared with placebo shows significant improvement over those randomized to placebo. There is decrease in voiding episodes (16.8% vs. 5.9%VE/24hrs) and UI episodes (43.5% vs. 9.7%IE/24hrs) and increase in the daytime voiding interval (25.9% vs. 5.4%VI/24hrs). In a study conducted by K. B. Thor, et al. (2007)[19] duloxetine compared with placebo for treating women with symptoms of overactive bladder shows that it is a suitable compound for the treatment of OAB as incontinence, depression and pain share common biochemical imbalances. Mulcahy JJ, et al. (1996) [20], in a study showed no treatment differences between duloxetine 20 mg/day (nine patients) and placebo (eight) in patients with urge UI, after 3 weeks of treatment. A second study compared duloxetine (30 or 40 mg/day) and placebo (16 patients each) treatments for 1 week in patients with neurogenic and non-neurogenic DOA. This study showed no significant differences in the Detrusor Activity Index from an ambulatory urodynamic study at 1 week. The final study (total 68 patients) compared duloxetine (30 or 40 mg/day), oxybutynin (7.5 or 10 mg/day) and placebo treatments for 4 weeks in patients in a crossover design study. There were no significant treatment differences between active treatment and placebo after 4 weeks. The lack of response to duloxetine in these studies was probably the result of the low doses used, and guided the selection of higher doses in subsequent studies.

For the assessment of QOL in group A patients treated by solifenacin alone were having baseline mean QOL scores 5.13±0.23. Significant improvements ($p<0.05$ or $p<0.01$) in overall QOL scores were observed in all patients at 4th and 8th week (27.3% and 49.4% improvement), respectively. While previous studies showing the similar positive impact on QOL of patients of OAB were Haab F, et al. (2005); Cardozo Kelleher CJ, et al. (2005) [21,22]. These studies show the improved quality of life experienced by patients with OAB who received solifenacin 5 or 10mg once daily for 12 weeks was maintained and even further improved during the extension study conducted by. This shows that with 52 weeks of treatment with solifenacin, the quality of life of patients receiving solifenacin improved by 35–48% from baseline in almost all domains. In Group B patients for the assessment of QOL treated with (solifenacin +duloxetine) the baseline mean QOL scores in this group of patients was 5.21±0.29. Significant improvements ($p<0.05$ or $p<0.01$) in overall QOL scores were observed in all patients at 4th and 8th week (38.9 and 69.5% improvement), respectively. While earlier study showing the similar positive impact on QOL of patients of OAB is Steers WD, et al. (2007). It is a 12 weeks study on 306 women patients. In it, efficacy of duloxetine (80-mg/day for 4 weeks increased to 120-mg/day for 8 weeks) and its effect on QOL of OAB patients was compared with placebo.

Which shows significant improvement over those randomized to placebo in I-QOL scores (14.7%) at both doses of duloxetine.

For the assessment of Safety in Group A patients treated with solifenacin the adverse effects observed were mainly dry mouth (5.7%), constipation (5.7%) and dry eyes (5.7%). Similar adverse effects were observed by earlier 12 weeks studies showing the tolerability profile of solifenacin 5 or 10mg once daily.). These studies show that solifenacin was generally well tolerated. The most frequently reported adverse events with 5 and/or 10mg administered once daily in short term study and long term study conducted by were dry mouth, constipation and blurred vision, which were mostly of mild or moderate intensity. The incidence of adverse events is numerically greater with solifenacin 10mg once daily than with 5mg once daily in short- or long-term studis. Dry mouth was reported 10%-21% of patients receiving solifenacin 5 or 10 mg once daily, numerically higher incidence in 10 mg group, constipation occurred in 10% and blurred vision in 7% of patients. In Group B for the assessment of safety patients treated with solifenacin + duloxetine the adverse effects observed in this group were mainly dry mouth (18.9%), nausea (21.6%)). constipation (10.8%), dizziness (10.8%), vision blurred (8.1%), and dry eyes (8.1%). The safety profile of duloxetine in this study is nearly identical to the safety profile established in women with SUI shown in a study conducted by Hurley DJ, et al. (2006)[23].

Some differences in percentage of adverse events as compared to present study may be due to combination therapy with solifenacin, small sample size and by the variability of the measures used in the studies. On comparing individually each symptom of OAB in OAB-V8 questionnaire, the improvement in scores ≥ 2 in patients taking solifenacin alone versus patients taking duloxetine + solifencin from day 0 to 8^{th} week shows that 4^{th} (accidental loss of small amount of urine), 7^{th} (An uncorrelated urge to urinate) and 8^{th} (urine loss associated with a strong desire to urinate) symptoms does not show much variation between the two groups. Will adding some other drug instead of duloxetine show much more improvement in these symptoms? Other drugs can be further studied either alone or in combination with solifenacin which may show much more improvement in above symptoms of OAB.

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