Efficacy and safety of mirabegron plus vitamin D_3 vs mirabegron alone in the treatment of adult patients of overactive bladder: a randomized controlled trial.

Abstract

Introduction: Overactive bladder (OAB) is a syndrome of complex etiology affecting millions of patients worldwide. Both pharmacological and non-pharmacological treatment options have been tried for resolution of its symptoms with limited option in pharmacotherapy of OAB. β_3 receptor agonists like mirabegron are now mainstay of treatment.

Material and methods: This open labelled, randomized controlled study was conducted with 99 patients divided into 3 groups based on their vitamin D levels and evaluation of OAB symptoms was done at baseline, 4 weeks, 8 weeks and 12 weeks using urgency severity score (USS), overactive bladder symptoms severity score (OABSS) and three days voiding diary.

Result: At each follow-up visit severity of symptoms reduced gradually and difference was statistically significant in all the parameters. There was significant difference between group B and group C at the end of study.

Conclusion: This study concluded that severity of the symptoms was higher in Vitamin D insufficient patients and reduction in symptoms was higher in group C suggesting that vitamin D supplementation may be helpful in reducing the symptoms of OAB.

Keywords: OAB, USS, OABSS, Vitamin D.

Introduction

Overactive bladder (OAB) is a syndrome of complex etiology affecting millions of patients worldwide. Both pharmacological and non-pharmacological treatment options have been tried for resolution of its symptoms. [1,2] In pharmacotherapy of OAB, β_3 receptor agonists like mirabegron are now mainstay of treatment. Due to its action on β_3 receptors, it helps in relaxation of detrusor muscle leading to decreased overactivity and leads to

reduction in symptoms of OAB. But some patients may present with headache, increase in basal heart rate, and increase in blood pressure (BP) as side effects.[3]

Recently, many studies have pointed that vitamin D deficiency is one of the causative factors in pathophysiology of various diseases including OAB. This may be due to the role of vitamin D in calcium homeostasis leading to hypercontractile detrusor muscle.[4,5,6] As there are limited studies researching the impact of vitamin D on OAB patients and the side effects associated with β_3 agonists, this study was planned to assess the role of vitamin D as an adjuvant therapy to mirabegron in reducing the symptoms of OAB.[7]

Material and methods

This was an open labelled, randomised clinical study, conducted in a rural tertiary care hospital after Institutional ethics committee (IEC) review and in accordance with the principles of good clinical practice (ICH-GCP) and declaration of Helsinki. A written informed consent was obtained from all the subjects before enrolling in this study.

SELECTION CRITERIA

Patients with clinically diagnosed OAB having age ≥18 years of either sex with symptoms for a duration of ≥1 month and having USS scale severity grade of 2 & 3 were enrolled in the study. Subjects with severe deficiency of Vitamin D (Serum Vitamin D levels <10ng/ml), PVR ≥150 ml, history suggestive of UTI, catheterized subjects, subjects with obstructive symptoms, history suggestive of hypertension, diabetes mellitus, diabetes insipidus, renal disease and nervous system disorders, glaucoma, stress urinary incontinence and neurogenic bladder, already taking treatment for OAB, having history of hypersensitivity to drugs to be used in study, pregnant and lactating females were excluded from the study.

Total 108 patients with clinical symptoms of OAB were enrolled in the study & underwent serum Vitamin D estimation which were further divided into three groups on the basis of their vitamin D levels. Group A had vitamin D (>30 ng/ml) sufficient patients and patients with vitamin D insufficiency (10-30 ng/ml) were further randomly divided into two groups i.e. B & C. All the patients were assessed at baseline and each follow-up visit using Urgency

severity score (USS), Overactive bladder symptoms severity score (OABSS) and Three-Day Voiding Diary. Assessment of USS and OABSS was also done at 4 weeks, 8 weeks and 12 weeks follow-up visit and three-day voiding diary assessment was done at 8 weeks and 12 weeks follow-up visit. For safety assessment, detailed history was taken from each patient at each follow-up visit.

Scales used for efficacy assessment were:

USS: The USS is scored as 0 (no feeling of urgency), 1 (mild urgency), 2 (moderate urgency), 3 (severe urgency), or 4 (inability to hold urine). Subjects were explained meaning of urgency in his/her language and were asked to fill the response based on severity of urgency which is best suited according to his experience.[8]

OABSS: The OABSS is a symptom assessment questionnaire designed to quantify OAB symptoms into a single score. The questionnaire consists of 4 questions on OAB symptoms with maximum scores ranging from 2 to 5: daytime frequency (2 points), night-time frequency (3 points), urgency (5 points), and urinary urgency incontinence (UUI (5 points)). The total score ranges from 0 to 15 points, with higher scores indicating higher symptom severity.[9]

Three Day Voiding Diary: Subjects were asked to maintain micturition diary for three days prior to their scheduled visit for follow up. In this diary, subjects were asked to record the total number of micturition/24hrs, total number of urgency episode, total nocturnal voiding and incontinence episode in the daily diary.[10]

RESULT AND DISCUSSION

At baseline, routine investigations such as routine urine examination, renal function test, USG, PVR, electrocardiogram (ECG), lipid profile and random blood sugar (RBS) levels were recorded in all the patients of either group before drug administration.

There was no statistically significant difference (p-value> 0.05) in any of the baseline parameters among groups thereby showing that the study outcomes were not affected by any of the parameters. Both the groups were also comparable in age, gender, marital status, and primary and secondary endpoints at baseline and the difference was statistically not significant.

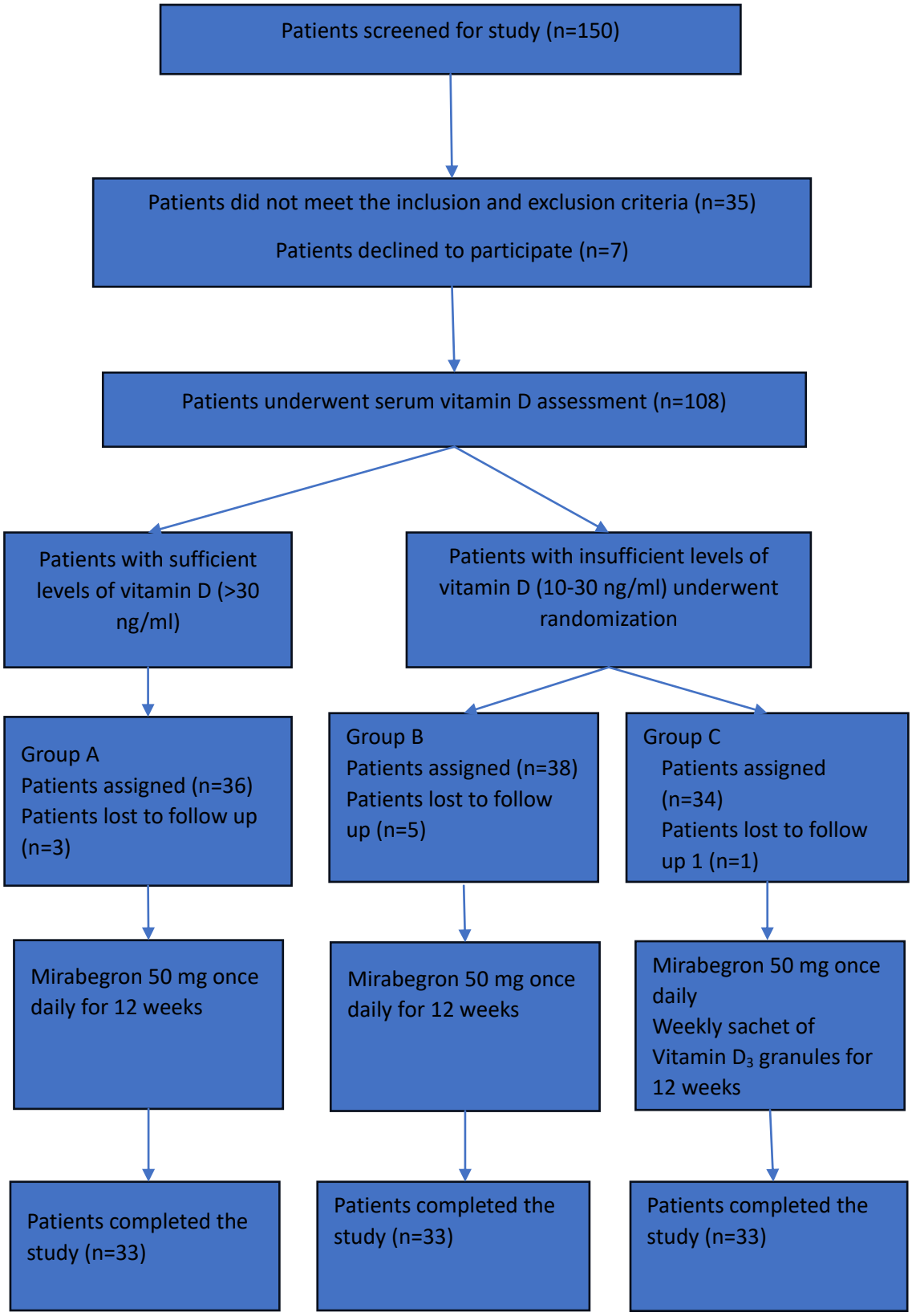
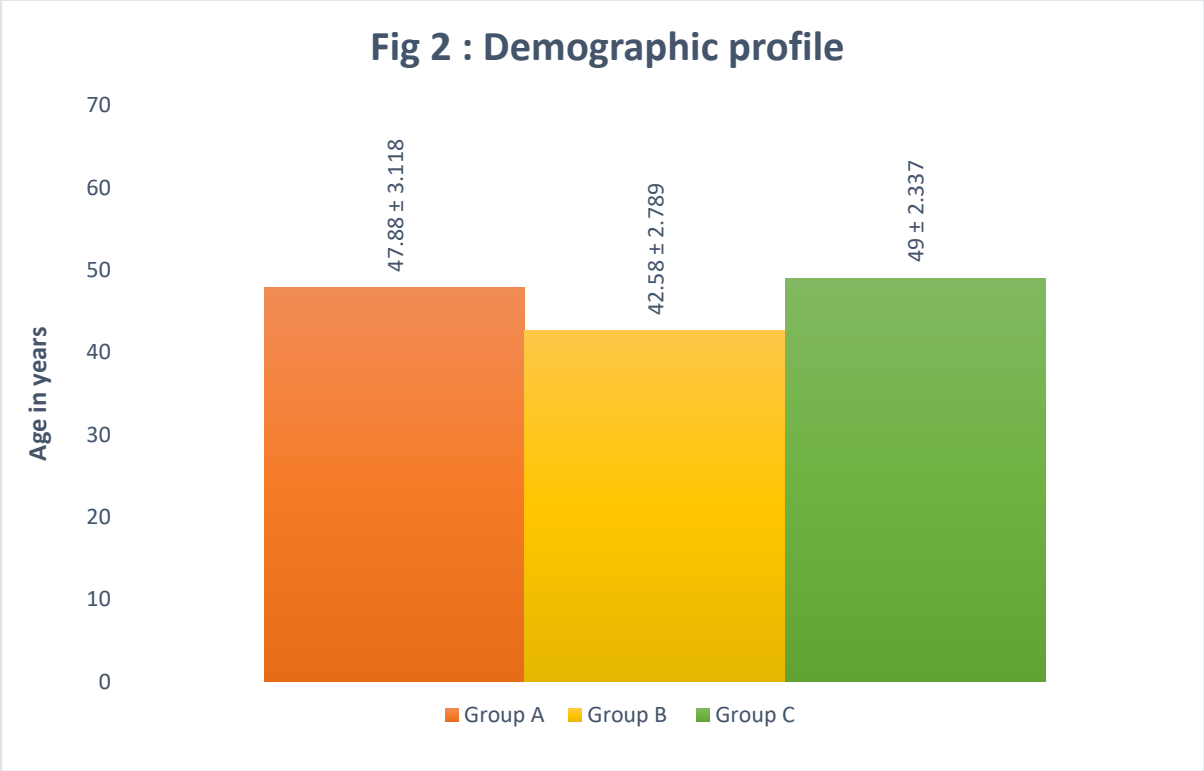


Fig 1: Flowchart of the study

The demographic profile and sex distribution in all groups are shown in figure 2 & 3 respectively.



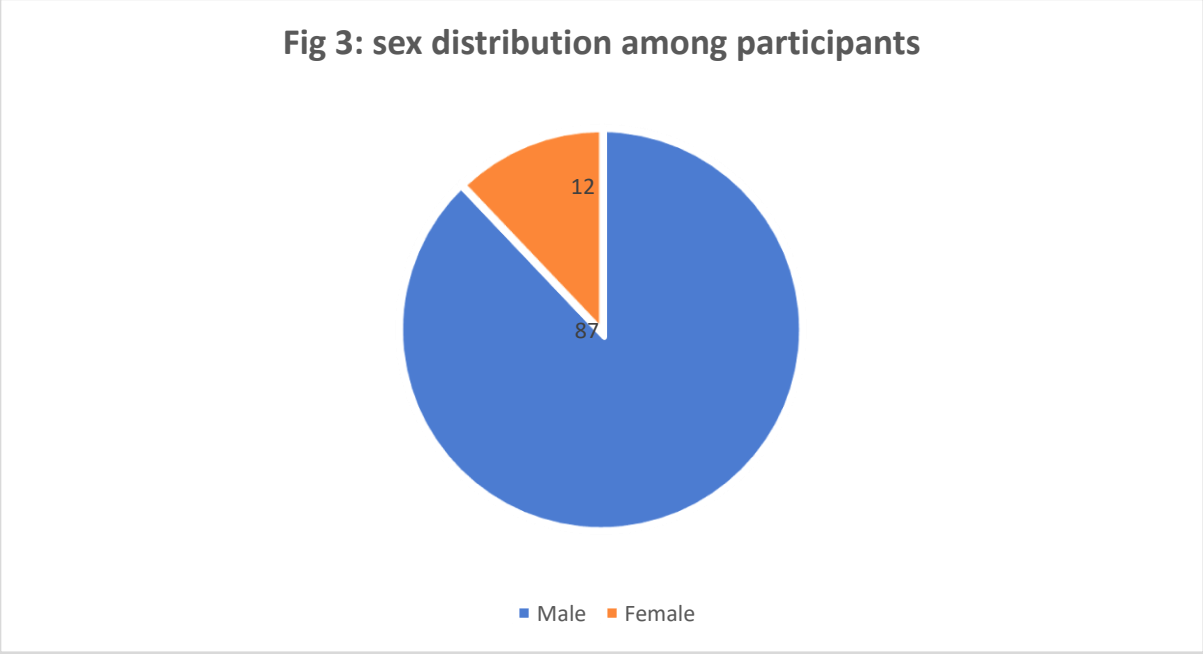


Table 1: Vitamin D Estimation

Group	Baseline	12 weeks	p value
A	33.09	32.97	0.39
B	19.76	20.45	0.52
C	18.65	26.95	0.000**

Patients were given treatment as follows:

Group A: Patients (>30 ng/ml) were prescribed Tab. Mirabegron 50 mg OD for 12 weeks.
Group B: Patients (10-30 ng/ml) were prescribed Tab. Mirabegron 50 mg OD for 12 weeks.
Group C: Patients (10-30 ng/ml) were prescribed Tab. Mirabegron 50 mg OD for 12 weeks along with once weekly supplementation of vitamin D_3 granule sachet for 12 weeks.

For assessment of severity of OAB symptoms, following scales were used i.e. urgency severity scale (USS), overactive bladder symptoms severity score (OABSS) and 3-days voiding diary. USS and OABSS were assessed at baseline and each follow-up visit at 4 weeks, 8 weeks and 12 weeks. At each follow-up visit, all the participants were asked to maintain a 3-days voiding diary and its score were assessed at 8 weeks and 12 weeks.

USS: All three groups showed gradual decline in the score at each follow-up visit.

Intragroup analysis

Statistically significant ($p \leq 0.05$) results were found at 4 weeks and highly significant ($p \leq 0.001$) at 8 and 12 weeks as compared to baseline as shown in Fig 4.

Intergroup analysis

At 4 weeks result showed statistically significant ($p \leq 0.05$) difference between group A and B but difference was not statistically significant ($p \geq 0.05$) between group A & C and Group B & C scores. At 8 weeks statistically significant ($p \leq 0.05$) results were seen between group A & B and B & C but statistically non-significant ($p \geq 0.05$) between group A & C. At 12 weeks follow up, results between group A & B and group B & C were highly significant statistically ($p \leq 0.001$) and non-significant between group A & C ($p \geq 0.05$).

On post hoc analysis, at 4 weeks, difference was statistically highly significant ($p \leq 0.001$) between group A & B and A & C but was statistically non-significant ($p \geq 0.05$) between B & C. Difference was statistically significant at 8 weeks ($p \leq 0.05$) and highly significant at 12 weeks ($p \leq 0.001$) between A & B and B & C but were statistically non-significant ($p \geq 0.05$) between A & C.

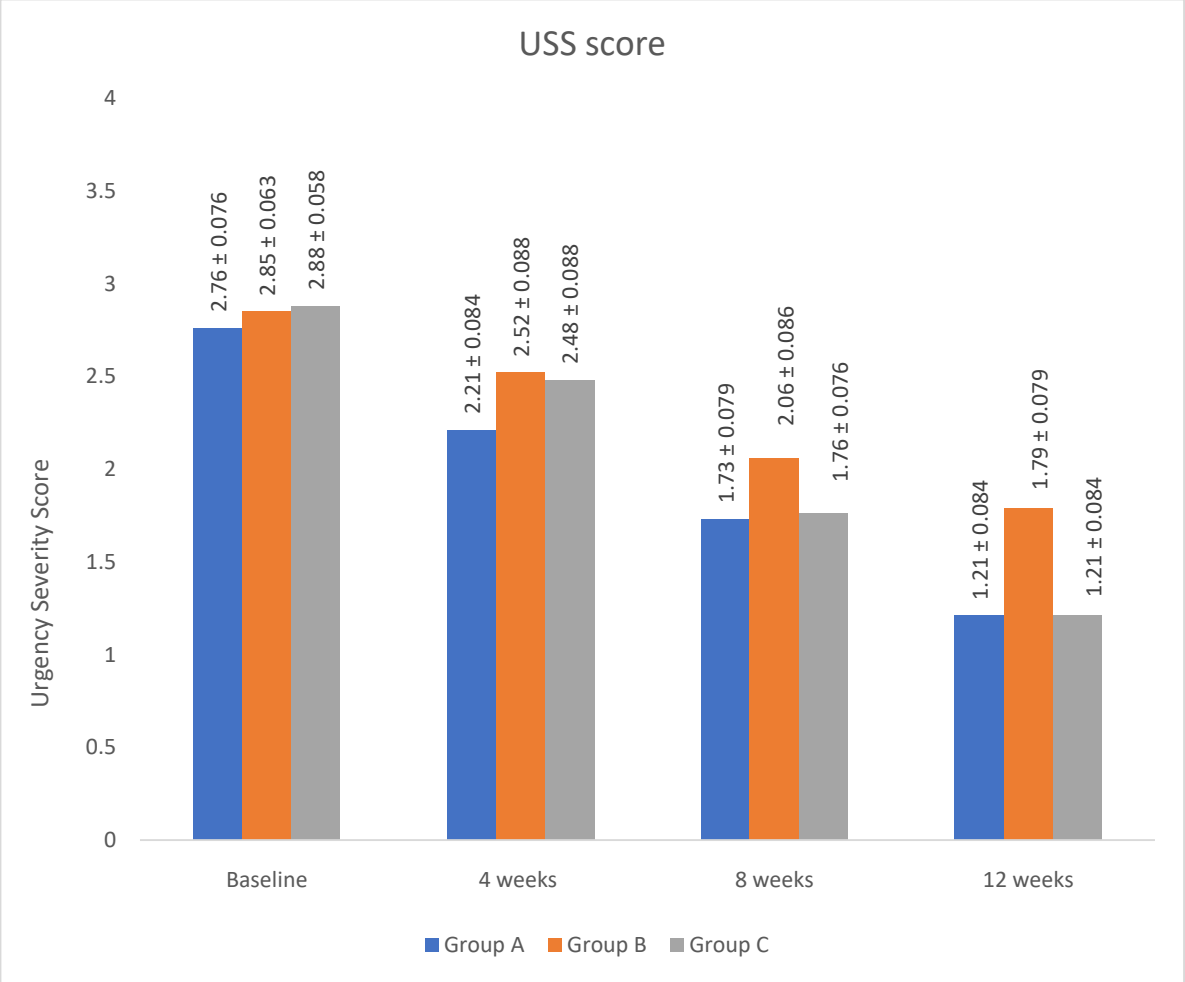


Figure 4: USS score among groups

In 2012, Digesu et al conducted a study on the effects of elocalcitol on women with OAB and idiopathic detrusor overactivity with 257 eligible patients randomized into three groups which showed no significant difference between the placebo and elocalcitol groups.[11] Markland et al's study in 2002 with women over the age of 55 yrs found no association between vitamin D_3 supplementation and urinary incontinence in older women, a finding inconsistent with our study which could be due to difference in demographic characteristics of both studies as only post-menopausal females were enrolled in their study.[12]

OABSS:

Intragroup analysis

Similarly at baseline, OABSS scores among group A, Group B and Group C were not statistically significant($p \geq 0.05$) but difference was statistically highly significant ($p \leq 0.001$) at 4 weeks, 8 weeks and 12 weeks as compared to baseline as shown in figure 5.

Intergroup analysis

At baseline, OABSS scores among group A, Group B and Group C were not statistically significant but difference was statistically highly significant at 4 weeks, 8 weeks and 12 weeks.

On post hoc analysis at 4 weeks, difference was statistically highly significant ($p \leq 0.001$) between group A & B and A & C but was statistically non-significant ($p \geq 0.05$) between B & C. At 8 weeks and 12 weeks follow-up, results were statistically highly significant ($p \leq 0.001$) between A & B and B & C but were statistically non-significant ($p \geq 0.05$) between A & C.

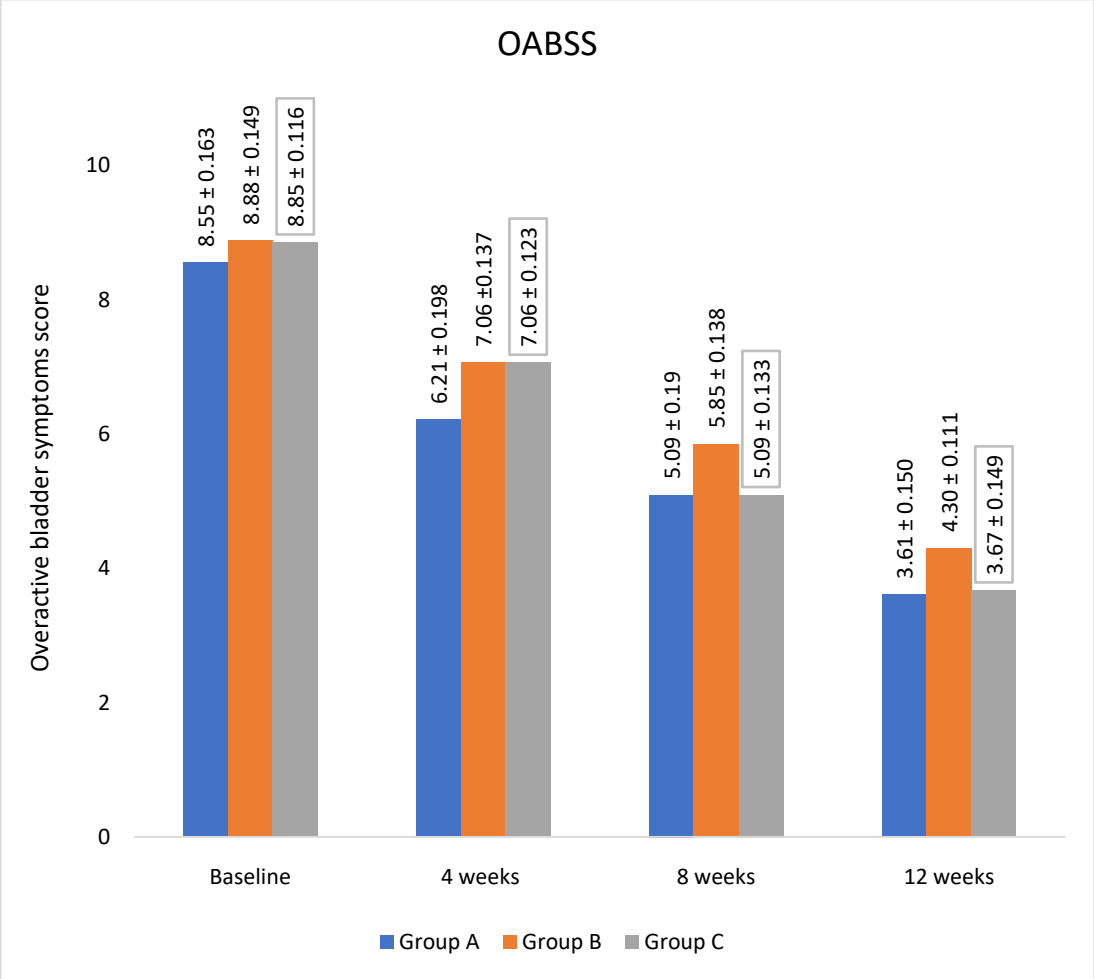


Fig-5 OABSS among all groups.

Yoo et al.'s 2018 study found that vitamin D deficiency in male patients increased during winter, leading to an increase in OABSS. However, vitamin D_3 supplementation significantly reduced OABSS, a finding that is consistent with our study.[13]

3-days voiding Diary:

Intragroup analysis

Difference between all three groups was statistically significant at 4 weeks, highly significant ($p \leq 0.001$) at 8 weeks and significant at 12 weeks when compared to baseline as shown by figure 6.

Intergroup analysis

At 4 weeks, difference was statistically significant (p≤0.05) between group A & B and A & C but was statistically non-significant (p≥0.05) between B & C. At 8 weeks and 12 weeks follow-up, results were statistically significant (p≤0.05) between A & B and B & C but were non-significant (p≥0.05) between A & C.

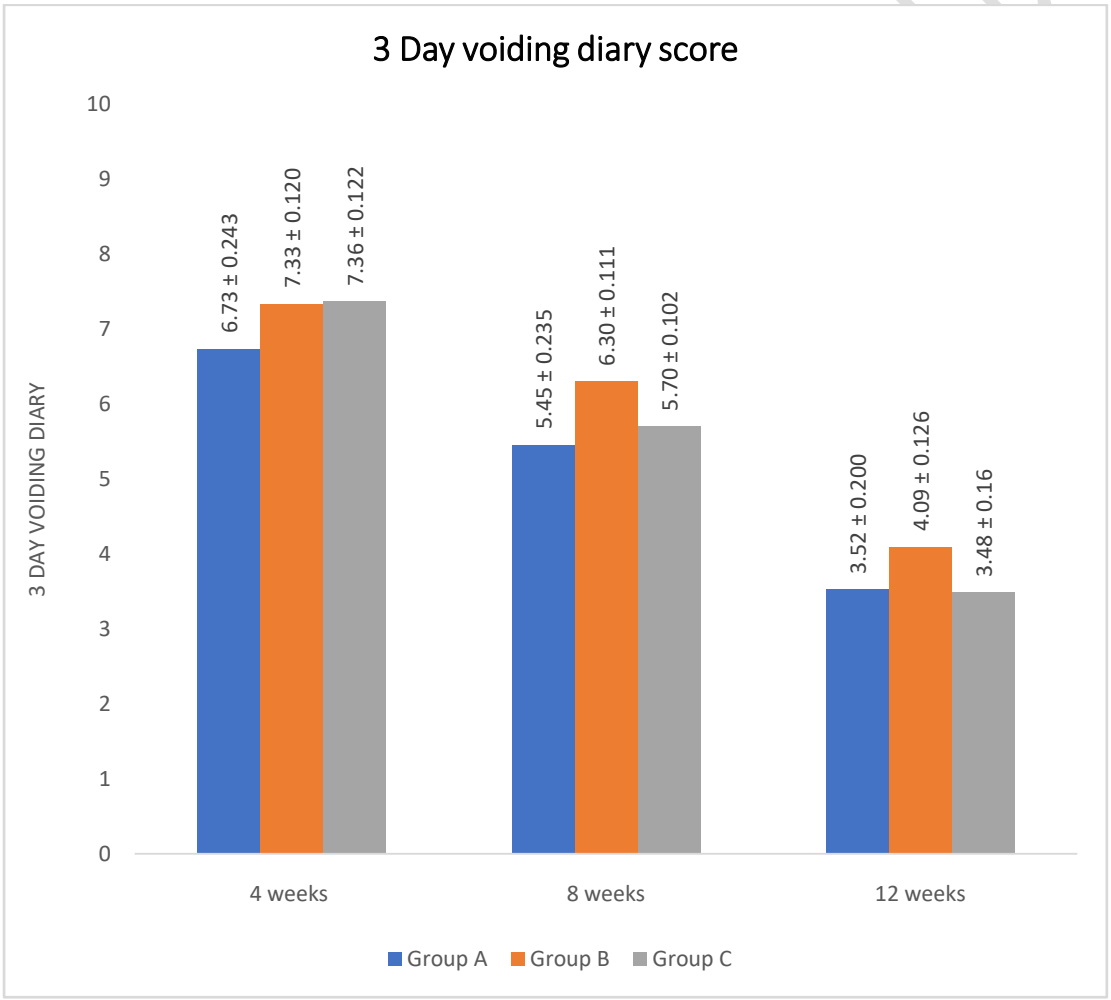


Fig 6: 3-Days voiding diary score among groups

In a randomised trial by Digesu et al, there was no statistically significant difference from baseline in 3-day voiding diary which differs from the findings in the present study. This

may be attributed to difference in number of patients (308 vs 99) and lower dose of vitamin D supplementation (150 µg daily vs 1500 µg weekly) in the aforementioned trial.[11]

In our study, there is a statistically significant difference in all the parameters at 12 weeks from baseline after vitamin D_3 supplementation as an add-on therapy to mirabegron. This decrease in symptoms can be explained by widespread presence of vitamin D_3 receptors on various tissues, including the bladder, which suggests that vitamin D3 may play a role in regulating bladder function. Vitamin D3 has also been shown to affect immunological function, which might lessen underlying inflammation and help explain the reported clinical improvement. Furthermore, vitamin D has a proven role in increasing absorption of calcium, its deficiency may be responsible for hypocalcaemia in detrusor muscle cells in turn leading to its hyperactivity. When supplemented for 12 weeks, there was a significant increase in serum vitamin D levels in group C patients. This increase in vitamin D_3 levels can be corelated with the increase in intracellular calcium leading to reduction in hyperactivity and a resultant decrease in symptoms of OAB in group C patients. Vitamin D_3 may thus strengthen the therapeutic benefits and promote patient outcomes when combined with mirabegron.

Conclusion: The present study shows the beneficial role of Vitamin D_3 supplementation with Mirabegron in reducing the symptoms of OAB, suggesting that vitamin D_3 supplementation may be useful in OAB patients. Vitamin D_3 may have greater significance in the pathophysiology of OAB than previously believed, given the extensive distribution of vitamin D receptors and their crucial function in serum calcium regulation. Also, no new side effects were observed in any of the study groups throughout the study and both monotherapy with mirabegron and add-on therapy with mirabegron plus vitamin D were well tolerated by all the study participants.

Limitations: Due to decreased reporting of this medical condition because of social stigma associated with it in rural India, the sample size is limited. Demographic, ethnical and regional variations need to be considered in larger randomized controlled trials for better evaluation of the impact of Vitamin D_3 supplementation in resolution of symptoms of OAB.

Conflict of interest: The authors report no professional or personal conflict of interest.

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