Efficacy and safety of tamsulosin versus its combination with mirabegron in the management of benign prostatic Hyperplasia (BPH) with predominantly coexisting overactive bladder symptoms (OABS) - An open label randomised controlled clinical study.

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Abstract

PURPOSE: We aim to do an efficacy-safety analysis of Mirabegron-Tamsulosin combination therapy versus tamsulosin-placebo monotherapy in a select subset of medication virgin BPH patients with coexisting predominantly overactive bladder symptoms (OABS). METHODS: After prior written informed consent and institutional ethics clearance, 80 patients of uncomplicated BPH with coexisting OABS and IPSS of >7 were computer randomized and allocated to receive therapy with either [50mg Mirabegronplus Tamsulosin 0.4 mg (Intervention arm)]or [Tamsulosin 0.4 mg plus capsule lactobacillus (Comparator arm)] once daily for a period of 8 weeks. Efficacy was evaluated using the OABS Score (OABSS), mean change in the frequency of nocturnal voiding, post void residue (PVR) and international prostate symptom score (IPSS) while safety was assessed by recording treatment emergent adverse events (TEAE). The protocol was registered prospectively with the clinical trials registry of India (CTRI/2018/12/016541). RESULTS: Significant improvements were visualised in the primary endpoint total OABS subscore (OABSS-ss) at the end of 8 weeks in the combination group (mean difference -5.62 vs -2.22p< 0.001).Similar significant improvements were seen with most of the secondary parameters such as the mean change in voiding episode/night, IPSS, IPSS-ss,OABS-ss, voided volume/micturition, Qmax, and Quality of Life (QOL) indices (p<0.001). No significant increase in PVR was observed in the Mirabegron arm and no patient developed urinary retention. The TEAE were minor, self-limiting and were managed symptomatically without any treatment discontinuity. CONCLUSION: Mirabegron was significantly efficacious and safe in ameliorating OABS induced by BPH versus placebo. This efficacy can be safely enhanced by initiating Mirabegron-Tamsulosin combination therapy from the start in medication virgin patients as opposed to the usual add on therapy protocol. This combination appeared to be superior in terms of overall safety, minimal side effects, better compliance and tolerability versus Tamsulosin monotherapy particularly in the select subset of patients of with BPH coexisting/predominant OABS.

TITLE

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RUNNING TITLE

Tamsulosin versus mirabegron combination de-novo therapy for BPH with predominantly coexisting OABS.

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ABSTRACT

PURPOSE: Numerous therapeutic options exist in the management of lower urinarytract symptoms (LUTS)due to benign prostatic hyperplasia. The efficacy and safety ofBeta-3 agonists (Mirabegron 50 mg) has been sparingly assessed in the published English literature. We aim to do an efficacy-safety analysis of Mirabegron-Tamsulosin combination therapy versus tamsulosin-placebo monotherapy in a select subset of medication virginBPH patients with coexisting predominantly overactive bladder symptoms (OABS).

METHODS: After prior written informed consent and institutional ethics clearance, 80 patients of uncomplicated BPH with coexisting OABS and IPSS of >7 without medical contraindications to the planned drug therapy were computer randomized and allocated to receive therapy with either[50mg Mirabegronplus Tamsulosin 0.4 mg (Intervention arm)]or [Tamsulosin 0.4 mg plus capsule lactobacillus (Comparator arm)] once daily for a period of 8 weeks. Efficacy was evaluated usingthe OABS Score (OABSS), mean change in the frequency ofnocturnal voiding, post void residue (PVR) andinternational prostate symptom score (IPSS) while safety was assessed by recording treatment emergent adverse events (TEAE). Follow up visits were done at 2^{nd}, 4^{th} and 8^{th}weeks post therapy and data was analysed using the SPSS vr23$^{(IBM\ Corp)}$ as per protocol. The protocol was registered prospectively with the clinical trials registry of India (CTRI/2018/12/016541).

RESULTS: Patients in both groups were comparable on basis of their demographic data, preoperative renal function, prostate specific antigen (PSA), prostate volume and baseline efficacy parameters with the exception of nocturnal frequency and IPSS storage sub score(IPSS-ss). Significant improvements were visualised in the primary endpoint total OABSsubscore (OABSS-ss) at the end of 8 weeks in the combination group (mean difference -5.62 vs -2.22p< 0.001).Similar significant improvements were seen with most of the secondary parameters such as the mean change in voiding episode/night, IPSS, IPSS-ss, OABS-ss, voided volume/micturition, Qmax, and Quality of Life (QOL) indices (p<0.001). No significant increase in PVR was observed in the Mirabegron arm and no patient developed urinary retention. The TEAE were minor, self-limiting and were managed symptomatically without any treatment discontinuity.

CONCLUSION: Mirabegron was significantly efficacious and safe in ameliorating OABS induced by BPH versus placebo. This efficacy can be safely enhanced by initiating Mirabegron-Tamsulosin combination therapy from the start in medication virgin patients as opposed to the usual 'add on therapy' protocol. This combination appeared to be superior in terms of overall safety, minimal side effects, better compliance and tolerability versus Tamsulosin monotherapy particularly in the select subset of patients of with BPH coexisting/predominant OABS.

KEY WORDS : Mirabegron, Tamsulosin, Benign Prostate Hyperplasia, Overactive Bladder Symptoms.

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Authors' contributions – IS was the responsible faculty consultant surgeon/urologist who supervised this study, designed the protocol of this study and was also in-charge of the overall care of the patients enrolled in this study and approved the final draft of the manuscript. DPB collected patient data. IS & DPB wrote the first draft of the manuscript. ATK and DPB were involved in day to day patient care and follow up. SG co-supervised the study and co-approved the final draft of this manuscript.

What's already known about this topic?

1. The shining limelight is on mirabegron, a novel beta-3 agonist approved for the management of OABS owing to its unique mechanism of action and lack of the troublesome adverse effect profile of the frequently utilized anti-cholinergic drugs.

2. The efficacy of mirabegron as an add on therapy for the management of residual storage symptoms in patients of BPH with associated OABS after the initial run in therapy with alpha blockers is already documented reasonably well in the published English literature**.**

What does this article add to?

1. This manuscript attempts to establish the efficacy and safety of mirabegron-tamsulosin combination therapy versus the routinely used tamsulosin alpha blocker monotherapy in a subset of Indian population with 'symptomatic BPH with predominantly coexisting OABS' as a De-novo therapeutic measure.

This article is novel for its unique de-novo utility of using mirabegron-tamsulosin combination therapy initially from the start in medicine naive virgin select patients of 'LUTS due to BPH with OABS' as opposed to the majority of published research utilising mirabegron mainly in an add on therapy fashion to manage residual BPH-OAB symptoms post alpha blocker therapy.

2. This manuscript also especially focuses closely on investigating whether there was of any occurrence of rising PVR and urinary retention, associatied specifically with the concomitant use of initial mirabegron –tamsulosin combination therapy for 'LUTS due to BPH with OABS' without the add on therapy protocol as the current literature regarding mirabegron and its effect on PVR is ambiguous about the same.
3. The current results of this research adds to the clarity in the literature and strengthens the notion of utilizing mirabegron combination therapy as a start-up therapy without the apparent fear of inducing any rise in the incidence of PVR and urinary retention as opposed to the usually employed add on protocol in majority of patients of 'LUTS due to BPH with OABS'. This measure in itself is novel attempt to change the global perception of practicing urologists towards mirabegron's utility in the medical management of symptomatic patients of BPH with OABS.

INTRODUCTION

International continence society had divided OABS into storage, voiding and post micturition symptoms based on their aetiological factors in which overactive bladder symptoms (OABS) was defined as urgency with or without urge incontinence usually with increased frequency and nocturia without any proven infection or obvious pathology. OABS frequently overlap with storage LUTS induced by similar patho-physiological causes[1] . In older men, BPH with LUTS and chronic obstruction induces changes in detrusor muscle culminating in detrusor over activity and inappropriate detrusor contractions during the storage phase of the micturition producing OABS[2] . Around 50-75% of elderly male patients of BPH with LUTS appear to have predominant/coexisting OABS[3] . Thus there exists a common unifying factor amongst BPH, LUTS and OABS with the common denominator being an inability to accommodate progressively increased bladder filling and sensation inducing secondary OABS.

Traditionally antimuscarinic drugs were the main stay of therapy for 'BPH induced OABS' albeit accompanied by bothersome adverse events like dry mouth, constipation and urinary retention leading to significant drug discontinuity[4] . Mirabegron is a newer selective beta-3 agonist that has been tried in combination with α-1 blockers for alleviating 'BPH induced OABS' that act by relaxing the bladder detrusor in the storage phase thereby increasing its storage capacity and ameliorating OABS[5, 6] . Some studies have documented the efficacy of Mirabegron as an add on (post alpha blocker therapy) managing residual storage LUTS in BPH patients with co-existing residual OABS[8,9] . Herein we attempt to analyse the efficacy and safety of combination therapy (Mirabegron 50mg + tamsulosin0.4mg) in de novo select patients of BPH with predominantly coexisting OABS without prior alpha blockers run in therapy.

MATERIALS AND METHODS

A prospective randomised control study was performed on 80 eligible and consenting patients of BPH with predominantly OABS with the primary intent to treat, as per protocol inclusion criteria (newly diagnosed uncomplicated BPH of any size with predominant OABS and an IPSS >7 without any medical contraindications to the planned drug therapy or any absolute indication for surgery). Patients with prior history of anaphylaxis/hypersensitivity, drug therapy with metabolic interference to administered medication, prostatic/urethral surgery andother concomitant prostate diseases or neurogenic bladder were excluded from this study. Patients were computer randomised and allocated to either the intervention group (I) (Tamsulosin 0.4 mg plus 50mg Mirabegron tablet) or the comparator group (II) (Tamsulosin 0.4 mg plus capsule lactobacillus 1 capsules) with the medications administered at bedtime after meals for study period of two months (considering rapid onset of action of drugs in both the arms and their major side effects if any would be exhibited within this study time frame). Patients were evaluated as per protocol with (hemogram, LFT, KFT and urine routine, culture, ECG, ultrasound KUB+PVR and uroflow) during the initial visit (D0) prior to initiation of therapy. The efficacy outcome measure was evaluated by estimating the OABSS(primary

outcome parameter)followed by the mean change nocturnal voiding frequency, PVR and IPSS (secondary efficacy parameters).Safety was assessed by monitoring for post therapy TEAE with follow up visits at the 2^{nd}, 4^{th} and 8^{th} week post initiation of therapy. Fig-1 depicts flow of the current study protocol.

Statistical Analysis: Statistical analysis was performed using Statistical Package for the Social Sciences version 23.0 IBM, New York, USA. The data was recorded in the MS Excel worksheet. Continuous data was analysed by unpaired Student's t test while the Chi-square test and Repeated measure ANOVA was used to analyse the categorical data. $P < .05$ was considered statistically significant.

Power factor &sample size calculation: Based on a similar published comparative study by Ichihara et al[7] in which 94 patients were randomised (76 completed the study) considering a standard deviation (SD) in the peak flow rate of 12.33 ± 1.22 in tamsulosin group and 10.5 ± 1.79 in the Mirabegron group with Power = 90% and $\alpha = 5\%$ hence, to estimate this difference in mean value, the requisite sample size for significance was about 20 per group. We incorporated a study sample size of 80 (40 subjects in each group).

RESULTS

Salient demographic patient pre- and post-treatment parameters are depicted in Table 1(a) and 1(b) respectively, the pre-treatment data was comparable in most parameters with the exception of nocturia ($p<0.001$) and IPSS (SS), $p = 0.001$. In terms of the post treatment data (Table 1b) that there was statistically significant improvement of the OABS score (primary outcome parameter) in the intervention group (Mean difference -5.62 vs -2.22$p< 0.001$). Similar improvements were seen in most secondary outcome parameters [mean change in voiding episode/night, IPSS, IPSS-S, OABS-SS, voided volume/micturition, Qmax and QOL ($p<0.001$)]. As opposed to other published studies depicting acute urinary retention (AUR) as a major complication of Mirabegron intake, our study did not reveal any significant increase in PVR ($p=0.136$) nor any Acute Urinary Retention (AUR)in the intervention arm.Three of 80(3.8%), 2 and 1 in groups I and II respectively) had TEAE (tachycardia/headache) which were minor self-limiting and managed symptomatically without drug discontinuity. There was complete compliance to the administered therapy.

DISCUSSION

In present study, combination therapy of Mirabegron with Tamsulosin was superior to Tamsulosin monotherapy with respect to improvement in OABSS and IPSS including the storage sub score (IPSS-S) as per higher improvements in the IPSS-S (-9.40±2.57 vs-4.60±2.35) and nocturnal frequency (-5.05±1.78 vs-1.57±1.38) was observed in the intervention arm. TEAE/side effects were minor and without any study disruption. Mirabegron-tamsulosin combination therapy could be considered efficacious and safe versus tamsulosin monotherapy in improving BPH induced OABS without the need of an initial run in alpha blocker therapy (the desirable lack of increase in PVR/AUR possibly could be attributed to this).Table-2 depicts a summary review of salient features of similar studies published in the English literature.

Ichihara et al[7] demonstrated the efficacy and safety of 50mg Mirabegron as an add-on treatment for residual OABS after 0.2mg of Tamsulosin therapy in symptomatic BPH patients. These authors demonstrated a significant difference in the mean change in the overall OABSS by -0.87 and -2.21 in the Tamsulosin monotherapy and combination group respectively over an eight week period($p=0.012$) along with similar significant improvements in the IPSS-S and QOL index in the Mirabegron add-on group which was in line with the present study.

Kakizaki et al[8] in another randomized placebo-controlled study demonstrated that Mirabegron (50mg) was effective and safe in controlling OABS as an add-on treatment to after 4 weeks of initial tamsulosin(0.2mg) monotherapy. They demonstrated a significant difference in the mean change in micturition episodes/24hrs by -1.27 and -0.75 in the Mirabegron add-on and (Tamsulosin+placebo) groups respectively ($p<0.001$). The authors also established a significant difference in the mean change in OABSS and the total IPSSof -2.78/ -2.13 and -2.13/ -4.25 respectively in the (Mirabegron addon and Tamsulosin+placebo) groups respectively which was in harmony with the present study.

In a meta-analysis and systemic review of three RCTs comprising 1317 patients conducted by Shunye et al[10]

the authors calculated a significant difference in the mean difference of total OABSS with a 95% CIof -0.69 (-1.00 to -0.38) betweenthe combination (Mirabegron + Tamsulosin) and (Tamsulosin + placebo) groups respectively ($p < 0.001$)and concluded that Mirabegron was an effective treatment for BPH induced OABS.

In another prospective study by Matsuo et al[11] on 50 men with LUTS(>65 years with persistent OABS post 12 weeks α1 blocker therapy)stratified into younger (65-74 years) and the older groups (75-84 years)prior to alocating Mirabegron (50mg) additional therapy. These authors demonstrated that the total OABS score pre/post therapy was 6.5±2.7/4.4±1.6 ($p= 0.004$) and 5.6±1.3/4.2±1.2 ($p<0.001$) for younger and older age groupsrespectively with significant improvement in storage subscore of IPSS in both the groups.

Wada et al[12] in another prospective study conducted on 26 Japanese men with persistent OABSpost 8 weeks Tamsulosin therapy,too demostrated a significant improvement in theirOABSS from 8.5±2.3 to 4.7±2.5 with Mirabegron add-on therapy ($p< 0.001$) with concomitant similar improvement in the IPSS and IPSS-S.

In the present study there was significant improvement in the OABSS, total IPSS and IPSS-S, on the basis of which it appeared that the initial combination therapy could be considered efficacious for the management of BPH with predominant/co-existing OABS versus tamsulosin monotherapy. However in the present study the voiding sub score (IPSS-V) was unaffected by Mirabegron versus placebo which was in harmony with other similar studies[8,11] . This could be explained and attributed to the fact that Mirabegron actions on detrusor smooth muscle and voiding dysfunctions are mainly due to bladder outlet obstruction/urethral abnormalities. The significant change observed within groups in the IPSS-V in the present study could be explained by the mechanism of action of Tamsulosin[13] .Tables 3(a-b) briefly depicts the salient outcome parameters (OABSS/IPSS) in various RCTs on mirabegron published in the literature.

Based on the search of literature the present study is the first such RCT to compare the efficacy of Mirabegron combination with tamsulosin-placebo (without using add on therapy protocol for post tamsulosin residual symptoms) in improving the nocturnal frequency in patients of BPH which appears to be the core bothersome symptom in about 30% males with LUTS[14] . In the current study the mean change ± SD in nocturnal frequency with was -5.05±1.78 and -1.57±1.38 in groups I and II respectively. In the present study statistically greater improvement with Mirabegron was enhanced by the worse baseline nocturnal frequency observed in the intervention group versus the tamsulosin arm (5.75±2.03 vs 3.90±1.35) which appeared to suggest that improvement in nocturnal frequency may be a better determinant versus nocturia score for deciding the severity of OABS.

In another randomized placebo-controlled study by Kuo et al[15] conducted on 1126 OABS patients the authors demonstrated an adjusted mean difference of -0.13(-0.33, 0.00) and -0.01(-0.18, 0.21) for Mirabegron vs placebo and Tolterodine vs placebo respectively and these researchers independently observed a significant decrease in the nocturnal frequency with Mirabegron versus the placebo.

Effect on PVR/AUR: Various past studies on Mirabegron have demonstrated ambiguous results regardingits effect on PVR in men with BPH-LUTS (Table 2c). In a study by Wada et al[12] on 26 men with post tamsulosin residual OABS the authors demonstrated that Mirabegron was not associated with any significant increase in PVR ($p=0.23$) which was similar to our study with non-significant numerical decrease in PVR with Mirabegron therapy. The mean change ±SD in PVR in our study was -7.20±42.66 / 30.2789.62 in the Mirabegron /Tamsulosin combination and Tamsulosin/ placebo groups respectively.

The combination of Mirabegron and antimuscarinic agents has been used synergistically for managing OABS which does not appear to adversely impact the rate of complications related to reduced bladder contractility like increasing PVR/voiding symptoms/AUR. The mechanism of as to why this synergistic combination fails to act in unison remains to be elucidated[16] . This confusion is further compounded by fact that biased inclusion criteria in many such studies which had recruited several patients with higher baseline PVR of [?] 200ml and the lack of long term studies on antimuscarinic drugs in OABS either as monotherapy or in combination and such void in data has resulted in physicians using Mirabegron-antimuscarinics with caution especially in high risk symptomatic patients aged [?] 75 years with an initial PVR >200ml[17] .

Lack of significant rise in the PVR/AUR in the currents study could possibly be explained by the mutual antagonistic action of both drugs/combination on bladder emptying[18].Tamsulosin serves as a bladder neck relaxant and acts on the voiding component preventing urine/ PVR accumulation, thereby acting in positive antagonism to Mirabegron's effect on bladder contractility. The merit of this combination therapy is further enhanced by the long term available scarce data depicting no increase in AUR with long term alpha blocker therapy in contrast to antimuscarinics[19-22].In an experimental study by Alexandre et al[23]the authors investigated on the effects of mirabegron in the mouse urethral smooth muscle and concluded that the mirabegron result was attributed to β_3 -adrenoceptor agonism in combination with α1A and α1D -adrenoceptor antagonism. Though Tamsulosin has been used in combination with other drugs like (tadalafil) in BPH patients with predominant storage LUTS it, however merits further evaluation with larger trials[24,25] .

In the present study significant improvement was also demonstrated in uroflowmetry parameters like voided volume/micturition (VV/micturition) and maximum flow (Q_{max}) in Mirabegron add on group. The mean change ±SD in VV/micturition was 129.40±149.24 (Mirabegron + Tamsulosin) and 86.92±288.99 (Tamsulosin +placebo). Kakizaki et al[8] demonstrated similar results in terms of voided volume in their study. The mean change in the Q_{max} in our study was -4.04±4.35 for the combination group and -0.72±3.51 for the (Tamsulosin + placebo) group, which was significant and similar to the study conducted by Ichihara et al[7] .

Effect on QOL: In the present study the mean change in QOL index in both groups was -3.05±0.55 and -2.38±1.00 respectively and the overall QOL had improved significantly ($p<0.001$) in the combination group. Similarly, Ichihara et al[7] , in their study observed significant improvement in QOL index in combination group (p-0.020).

TEAE: In the present study, two patients in the Mirabegron + Tamsulosin group (headache and tachycardia) and one patient from the Tamsulosin + placebo group (headache) developed adverse reactions which were self-limiting and were managed symptomatically without any drug discontinuity. Mirabegron appeared to score high on its safety aspect in the select group of BPH-LUTS patients with predominantly co-existing OABS.

Limitations: Despite the adequate power and sample size of this study we admit to certain limitations. An age stratified sample size was omitted which could have made this study more robust. Dose escalation was omitted in this study due to protocol restrictions and patient safety concerns. Size stratification of the prostate at presentation was not considered in this study bearing in mind that bothersome LUTS are usually largely independent of prostate size. Considering the longer duration (12 weeks) of other published trials[26, 27] on Mirabegron, one could question our shorter duration of study. For reasons described previously the present eight 8 week follow up was done in this protocol considering the fact that both drugs in the study had rapid onset of action and majority of their usually observed side effects if any would be exhibited well within this frame. This study did not evaluate the long term adverse events if any as due to protocol restrictions. However a longer duration of study could have enhanced this void in data on the long term safety/efficacy/AUR/PVR elevation if any with prolonged Mirabegron therapy. Nevertheless, the major findings of this study would still hold relevance albeit excluding the absence of long term adverse effect monitoring data. Considering this area of research to be relatively recent, we expect in future trials of larger sizes and longer durations to further validate our safety data.

There was no attempt to establish the role of Mirabegron as an add on therapy for post tamsulosin residual OABS if any, as the conventional initial run in tamsulosin therapy was omitted. Another limitation observed in the study was the relative minor mismatch in baseline comparability between both groups in the IPSS-ss/NF. However this was negated by the fact that the combination group showed greater improvements in the above mentioned parameters at the end of the study (NF -2.20±0.65 vs -0.70±0.56 $p<0.001$, IPSS-S -9.40±2.57 vs -4.60±2.35 $p<0.001$) despite inferior baseline parameter values (NF 5.75±2.03 vs 3.90±1.35 and IPSS-S 12.68±2.71 vs 10.97±3.02) versus the comparator group. We feel that the aberration of baseline comparability was minor which could have been minimised by inclusion of a larger age stratified sample size of patients. As a result of scarcity of studies of similar nature, future studies of the same nature on a larger scale may be required to support the findings of the present study.

We did not attempt examine the effect of Mirabegron in patients of OABS without BPH in this study, however in a post marketing study by Takahashi et al[26] using Mirabegron 12 weeks therapy for OABS patients [with/without BPH on 4540 (3176 diagnosed with BPH)] in which the occurrences of AUR and the concomitant use of α1-blockers were specifically investigated, the authors concluded that Mirabegron was well-tolerated and effective for majority of their patients with OABS with or without concomitant BPH. In a multicentre, randomized, double-blind, placebo-controlled, parallel comparison phase IV study on Mirabegron conducted exclusively on 464 males with OABS by Shin et al[27] the authors concluded that mirabegron therapy was well tolerated for 26 weeks, without additional adverse effects compared to placebo. Finally no comparison of mirabegron combination therapy with anti-cholinergics (darifenacin) for BPH induced OABS was done in this study; as this has been previously examined and reported that initial combination therapy with tamsulosin/darifenacin was safe and effective in select patients of BPH with accompanying OABS[28] .

Conclusions: In summary despite these limitations we can confidently conclude that mirabegron combination therapy was safe and effective in ameliorating BPH induced OABS versus tamsulosin monotherapy in majority of our patients with minimal side effects and good tolerability. This efficacy could be further potentiated by the utility of Mirabegron with Tamsulosin combination as a potential viable start-up therapeutic option for select patients of BPH with predominantly coexisting OABS without the ill confounded fear of a potential rise in the post void residue culminating in any urinary retention.

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ABBREVIATIONS

BPH – Benign Prostatic Hyperplasia; OABS – Over Active Bladder Symptoms ; LUTS – Lower Urinary Tract Symptoms; UTI – Urinary Tract Infection; PVR – Post Void Residue; IPSS – International Prostate Symptom Score; IPSS –S – IPSS storage subscore; IPSS-V – IPSS voiding subscore; PSA – Prostate Specific Antigen; QOL – Quality Of Life Index; AUR – Acute Urinary Retention.

DISCLOSURE: The authors further declare that we have nothing to disclose and have no direct or indirect commercial and or financial incentive associated with this research.

INFORMED CONSENT STATEMENT : The authors also certify that informed consent was obtained from all the human participants in this study as per its protocol registered with the Clinical Trials Registry of India.

ETHICAL STATEMENT: The authors declare that the above manuscript is in compliance with Ethical Standards for research in human participants and have no potential sources of conflict of interest associated with its publication.

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LEGENDS FOR FIG & TABLES :

Fig 1: Figure depicting the flow of the current study protocol

Table 1 (a-b): Table 1a depicting the baseline and demographic features of the patient parameters and Table 1b depicting the post treatment parameters of the same in the two groups.

Table 2: Depicting a summary of mirabegron comparative studies on BPH induced OABS. Table 3 (a-c): Table 3 depicting a comparison previous similar study designs with the present studywith respect to OABSS total score improvement (Table3a); IPSS-ss score improvement (Table 3b) and change in the PVR (Table 3c) in both the patient groups.

Table-1

TABLE 1a *DEMOGRAPHIC AND BASELINE CHARACTERISTICS*

PARAMETERS	**GROUP I (Mean±S.D)**	**GROUP II (Mean±S.D)**	**P Value**
Age(Years)	62.27±10.01	62.60±10.13	0.886
Prostatomegaly Grade 1	8 (20%) 25 (62.5%) 7	12 (30%) 22 (55%) 6	0.586
Grade 2 Grade 3	(17.5%)	(15%)	
Sr. Creatinine(mg/dl)	1.39±3.20	0.97±0.23	0.210
Sr. PSA(ng/ml)	1.83±1.08	1.53±0.79	0.290
Baseline LUTS	7.95±2.80 5.75±2.03	6.75±2.08 3.90±1.35	0.056 **<0.001*** 0.171
parameters OABSS NF	18.45±6.12 5.88±5.09	16.55±6.19 5.88±4.81	0.850 **<0.001*** 0.392
IPSS IPSS voiding sub	12.68±2.71 4.88±0.52	10.97±3.02 5.03±0.92	0·667 0.443 0.954 0.292
score IPSS Storage sub	58.38±68.79 7.94±4.03	79.35±119.39	
score QOL PVR(ml)	3.89±1.78	10.03±8.03 4.72±3.80	
UROFLOWMETRY	236.90±120.12	249.40±114.03	
Q_{max} (ml/sec) AFR			
(ml/sec) VV (ml)			

Sr – Serum, PSA – prostate-specific antigen, LUTS – Lower urinary tract symptoms, IPSS – international prostate symptom score, OABSS- Over Active Bladder Symptom Score, NF- Nocturia Frequency, QOL – Quality of life, PVR – post void residual urine, Q_{max}– maximum flow rate, AFR- Average Flow Rate, VV- Voided Volume, S.D – standard deviation. *- Significant.

Sr – Serum, PSA – prostate-specific antigen, LUTS – Lower urinary tract symptoms, IPSS – international prostate symptom score, OABSS- Over Active Bladder Symptom Score, NF- Nocturia Frequency, QOL – Quality of life, PVR – post void residual urine, Q_{max}– maximum flow rate, AFR- Average Flow Rate, VV- Voided Volume, S.D – standard deviation. *- Significant.

Sr – Serum, PSA – prostate-specific antigen, LUTS – Lower urinary tract symptoms, IPSS – international prostate symptom score, OABSS- Over Active Bladder Symptom Score, NF- Nocturia Frequency, QOL – Quality of life, PVR – post void residual urine, Q_{max}– maximum flow rate, AFR- Average Flow Rate, VV- Voided Volume, S.D – standard deviation. *- Significant.

Sr – Serum, PSA – prostate-specific antigen, LUTS – Lower urinary tract symptoms, IPSS – international prostate symptom score, OABSS- Over Active Bladder Symptom Score, NF- Nocturia Frequency, QOL – Quality of life, PVR – post void residual urine, Q_{max}– maximum flow rate, AFR- Average Flow Rate, VV- Voided Volume, S.D – standard deviation. *- Significant.

TABLE 1b POST TREATMENT DATA COMPARISON BETWEEN GROUPS

PARAMETERS Efficacy parameters	**GROUP I MIRABEGRON + TAMSULOSIN Mean ±SD**	**GROUP I MIRABEGRON + TAMSULOSIN Mean Change FB**	**GROUP II TAMSULOSIN + PLACEBO Mean ±SD**	**GROUP II TAMSULOSIN + PLACEBO Mean change FB**	**GROUP II TAMSULOSIN + PLACEBO P-value**
Total OABSS Baseline Endpoint	7.95±2.80 2.33±1.82	-5.68±1.85	6.75±2.08 4.53±1.88	-2.23±1.59	<0.001
Day frequency Baseline Endpoint	1±0.64 0.08±0.27	-0.92±0.68	0.80±0.65 0.10±0.30	-0.70±0.56	0.103
Nocturia Baseline Endpoint	2.95±0.50 0.75±0.67	-2.20±0.65	2.73±0.45 2.02±o.73	-0.70±0.56	<0.001
Urgency Baseline Endpoint	3.05±1.52 1.07±0.94	-1.98±1.14	2.80±1.47 1.88±1.16	-0.92±1.12	<0.001
Urge incontinence Baseline Endpoint	1.10±1.46 0.40±0.74	-0.70±1.04	0.42±0.98 0.32±0.73	-0.10±0.38	<0.001
Nocturia frequency Baseline Endpoint	5.75±2.03 0.70±0.69	-5.05±1.78	3.90±1.35 2.33±1.29	-1.57±1.38	<0.001
Total IPSS Baseline Endpoint	18.45±6.12 5.72±3.46	-12.72±4.19	16.55±6.19 9.07±3.81	-7.47±4.27	<0.001

IPSS-V Baseline Endpoint	5.85±5.09 2.48±2.84	-3.40±3.12	5.88±4.81 2.88±2.90	-3.00±3.08	0.752
IPSS-S Baseline Endpoint	12.68±2.71 3.27±1.26	-9.40±2.57	10.97±3.02 6.38±2.16	-4.60±2.35	<0.001
Q_{max} Baseline Endpoint	7.94±4.03 11.98±3.98	4.04±4.35	10.03±8.03 10.75±7.02	0.72±3,51	<0.001
VV Baseline Endpoint	236.90±120.12 366.30±164.29	129.40±149.24	249.40±114.03 336.32±323.64	86.92±288.99	<0.001
PVR Baseline Endpoint	58.38±68.79 51.17±51.32	-7.20±42.66	79.35±119.39 49.08±70.07	-30.27±89.62	0.136
QOL index Baseline Endpoint	4.88±0.52 1.82±0.55	-3.05±0.55	5.03±0.92 2.65±0.95	-2.38±1.00	<0.001
FB-From baseline, OABSS-overactive bladder symptom score, IPSS-international prostate symptom score,IPSS-V: IPSS voiding sub score, IPSS-S: IPSS storage sub score, QOL: Quality of life	FB-From baseline, OABSS-overactive bladder symptom score, IPSS-international prostate symptom score,IPSS-V: IPSS voiding sub score, IPSS-S: IPSS storage sub score, QOL: Quality of life	FB-From baseline, OABSS-overactive bladder symptom score, IPSS-international prostate symptom score,IPSS-V: IPSS voiding sub score, IPSS-S: IPSS storage sub score, QOL: Quality of life	FB-From baseline, OABSS-overactive bladder symptom score, IPSS-international prostate symptom score,IPSS-V: IPSS voiding sub score, IPSS-S: IPSS storage sub score, QOL: Quality of life	FB-From baseline, OABSS-overactive bladder symptom score, IPSS-international prostate symptom score,IPSS-V: IPSS voiding sub score, IPSS-S: IPSS storage sub score, QOL: Quality of life	FB-From baseline, OABSS-overactive bladder symptom score, IPSS-international prostate symptom score,IPSS-V: IPSS voiding sub score, IPSS-S: IPSS storage sub score, QOL: Quality of life

TABLE-2 SUMMARY OF MIRABEGRON COMPARATIVE STUDIES ON BPH INDUCED OABS

AUTHORS	**STUDY**	**NOS**	**ARMS OF THE STUDY**	**CONCLUSIONS**
Ichihara et al (7)	RC	76	Tamsulosin 0.2mg + Mirabegron 50mg vs Tamsulosin 0.2mg **(8 weeks)**	Combination therapy with tamsulosin& mirabegron was effective in BPH with residual OABS postinitiation of tamsulosin

Kakizaki et al (8)	RC	568	Tamsulosin 0.2mg + Mirabegron 50mg Vs Tamsulosin 0.2mg+placebo **(12 weeks)**	Mirabegron add-on therapy to tamsulosin for 12wk in men with LUTS & OABS demonstrated superior efficacy to placebo with good tolerance
Kaplan et al (9)	RC	676	Tamsulosin 0.4mg + Mirabegron 50mg Vs Tamsulosin 0.4mg + placebo **(12 weeks)**	Mirabegron add on therapy was statistically significant in reducing OABS in comparison to placebo
Shunye Su et al (10)	MA	1317	Mirabegron + tamsulosin vs Tamsulosin **(8-12 weeks)**	Mirabegron was effective and safe treatment for OABS induced by BPH in men receiving tamsulosin therapy with a low occurrence of side effects.
Matsuo et al (11)	PA	50	Analysis of Mirabegron (50mg) add on therapy to α1 adrenergic blocker. **(12 weeks)**	Mirabegron add on therapy was effective in persistent OABS after α1 blockers in men with BPH.
Wada et al (12)	PA	26	Analysis of Mirabegron (50mg) add on therapy to pre-existing tamsulosin. **(8 weeks)**	Mirabegron add on treatment with tamsulosin was efficacious/safe in improving OABS without impairing bladder contractility in men with OAB.
Present Study	RC	100	Tamsulosin 0.4mg + Mirabegron 50mg vs Tamsulosin 0.4mg+Placebo**(8 weeks)**	Mirabegron & tamsulosin combination therapy was significantly efficacious and safe versus Tamsulosin monotherapy for BPH induced OABS without an increase in PVR/AUR.

PA-Prospective Analysis, MA-Metanalysis, RC- Randomised controlled study, AUR-Acute urinary retention, PVR-Post void residue, OABS-Overactive bladder symptoms	PA-Prospective Analysis, MA-Metanalysis, RC- Randomised controlled study, AUR-Acute urinary retention, PVR-Post void residue, OABS-Overactive bladder symptoms	PA-Prospective Analysis, MA-Metanalysis, RC- Randomised controlled study, AUR-Acute urinary retention, PVR-Post void residue, OABS-Overactive bladder symptoms	PA-Prospective Analysis, MA-Metanalysis, RC- Randomised controlled study, AUR-Acute urinary retention, PVR-Post void residue, OABS-Overactive bladder symptoms	PA-Prospective Analysis, MA-Metanalysis, RC- Randomised controlled study, AUR-Acute urinary retention, PVR-Post void residue, OABS-Overactive bladder symptoms

TABLE 3a COMPARISION PREVIOUS SIMILAR STUDY DESIGNS WITH THE PRESENT STUDY WITH RESPECT TO OABSS TOTAL SCORE IMPROVEMENT

AUTHOR	**STUDY GROUP (mean change from baseline)**	**CONTROL GROUP(S) (mean change from base line)**	**P-VALUE**
Ichihara et al(7) (2013)	Mirabegron(50mg) -2.21 + Tamsulosin(0.2mg)	Tamsulosin(0.2mg) -0.87	P - 0.012
Kakizaki(8) (2017)	Mirabegron(50mg) -2.78 + Tamsulosin(0.2mg)	Tamsulosin (0.2mg) -2.13 + placebo	P - 0.001
Present study	7.95±2.80 2.33±1.18	6.75±2.08 4.53±1.88	$P < 0.001$
Baseline(mean ± S.D)	-5.62	-2.22	
End point(mean ± S.D)			
Mean difference			
OABSS – Overactive bladder symptom score, S.D – Standard deviation.	OABSS – Overactive bladder symptom score, S.D – Standard deviation.	OABSS – Overactive bladder symptom score, S.D – Standard deviation.	OABSS – Overactive bladder symptom score, S.D – Standard deviation.

TABLE 3b

COMPARISION PREVIOUS SIMILAR STUDY DESIGNS WITH THE PRESENT STUDY WITH RESPECT TO IPSS-S SCORE IMPROVEMENT

TABLE 3b

COMPARISION PREVIOUS SIMILAR STUDY DESIGNS WITH THE PRESENT STUDY WITH RESPECT TO IPSS-S SCORE IMPROVEMENT

COMPARISION PREVIOUS SIMILAR STUDY DESIGNS WITH THE PRESENT STUDY WITH RESPECT TO IPSS-S SCORE IMPROVEMENT

TABLE 3b

COMPARISION PREVIOUS SIMILAR STUDY DESIGNS WITH THE PRESENT STUDY WITH RESPECT TO IPSS-S SCORE IMPROVEMENT

AUTHOR	**STUDY GROUP (mean change from baseline)**	**CONTROL GROUP(S) (mean change from base line)**	**P-VALUE**
Ichihara et al(7) (2013)	Mirabegron(50mg) -2.03 + Tamsulosin(0.2mg)	Tamsulosin(0.2mg) -0.42	P - 0.006
Kakizaki(8) (2017)	Mirabegron(50mg) -2.29 + Tamsulosin(0.2mg)	Tamsulosin (0.2mg) -1.51 + placebo	$P < 0.001$
Present study	12.68±2.71 3.27±1.26	10.97±3.02 6.38±2.16	$P < 0.001$
Baseline(mean ± S.D)	-9.40	-7.48	
End point(mean ± S.D)			
Mean difference			
IPSS-S: IPSS storage subscore, S.D – Standard deviation.	IPSS-S: IPSS storage subscore, S.D – Standard deviation.	IPSS-S: IPSS storage subscore, S.D – Standard deviation.	IPSS-S: IPSS storage subscore, S.D – Standard deviation.

TABLE 3c

COMPARISION OF SIMILAR STUDIES WITH THE PRESENT STUDY WITH RESPECT TO CHANGE IN PVR

TABLE 3c

COMPARISION OF SIMILAR STUDIES WITH THE PRESENT STUDY WITH RESPECT TO CHANGE IN PVR

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COMPARISION OF SIMILAR STUDIES WITH THE PRESENT STUDY WITH RESPECT TO CHANGE IN PVR

COMPARISION OF SIMILAR STUDIES WITH THE PRESENT STUDY WITH RESPECT TO CHANGE IN PVR

AUTHOR	**STUDY GROUP (mean change from baseline)**	**CONTROL GROUP(S) (mean change from the baseline)**	**P-VALUE**
Ichihara et al(7) (2013)	Mirabegron(50mg) 37.3 + Tamsulosin(0.2mg)	Tamsulosin(0.2mg) 3.9	P – 0.020
Kakizaki et al (8) (2017)	Mirabegron(50mg) 2.72 + Tamsulosin(0.2mg)	Tamsulosin (0.2mg) -0.97 + placebo	P - 0.059
Present study	58.38±68.79 51.17±51.32 -7.20	79.35±119.39 49.08±70.07 -30.27	P – 0.136
Baseline(mean ± S.D)			
End point(mean ± S.D)			
Mean difference			
PVR- Post void residual urine, S.D – Standard deviation.	PVR- Post void residual urine, S.D – Standard deviation.	PVR- Post void residual urine, S.D – Standard deviation.	PVR- Post void residual urine, S.D – Standard deviation.

FLOW OF STUDY

Key: UTI - urinary tract infection, IPSS – International prostate symptom score, PVR – Post void residual urine,OABSS-

Figure 1: Flow chart depicting the present study protocol process.