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EFFICACY OF MIRABEGRON ADD-ON THERAPY TO SILODOSIN FOR THE TREATMENT OF PERSISTENT STORAGE SYMPTOMS IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA

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Abstract

Introduction: BPH associated lower urinary symptoms (LUTS) represent one of the most common bothersome condition in day to day urological practice and having negative impact on patient's quality of life (QoL). Silodosin alone fails to alleviate moderate to severe storage symptoms and thus requiring additional therapeutic approach. The present study was aimed to evaluate the efficacy of Mirabegron addition in BPH patients on silodosin complaining of persistent storage LUTS.

Materials & methods: A total no of 130 patients of BPH on silodosin 8 mg with persistent storage LUTS who had attended urology OPD, Regional Institute of Medical Sciences (RIMS), Imphal were randomized into two groups and prospectively evaluated for 8 weeks. Group-A continued to use silodosin 8 mg only whereas mirabegron 25 mg was added with silodosin in group-B and statistically evaluated.

Results: After completion of 8 weeks group-B showed statistically significant improvement in respect to total IPSS (*p*-0.04); IPSS storage (*p*-0.002) and QoL (*p*- 0.006) score. However no statistically significant difference was noted in term of Q-max and residual urine volume measurement between both the groups.

Conclusion: Mirabegron, a potent B3 adrenoreceptor agonist improves compliance by relaxation of bladder smooth muscle. Add-on therapy is more effective than monotherapy for improvement of quality of life improvement and alleviation of persistent storage symptoms in BPH patients.

Keywords-Benign prostatic hyperplasia, Lower urinary tract symptoms, International prostate symptom score, Silodosin, Mirabegron

Introduction

Benign prostatic hyperplasia (BPH) is a common condition in elderly men and represent substantial diseae burden. BPH affects about 50 percent of men between the ages of 51to 60 and upto 90 percent of men older than 80. [**1**] Nearly 28 % of men more than 50 years of age experience troublesome lower urinary symptoms(LUTS), especially storage due to BPH. **[2]** Storage symptoms consist of frequency, urgency, urge incontinence and nocturia. Most commonly used medication to treat BPH related LUTS is adrenoreceptor blocker (A1B). Silodosin is a selective A1B and appears to be effective for both storage and voiding LUTS. **[3]** However even after adequate treatment with silodosin monotherapy many patients present with persistent storage symptms. According to European urologic association guideline antimuscarnic or beta-3 adrenoreceptor agonist (B3A) is recommended to administer in combination with A1B to relief moderate to severe LUTS predominantly storage. [**4]** Mirabegron is a potent B3A, which increases cyclic adenosine monophosphate concentration in bladder tissue and leading to relaxation of bladder smooth muscle. **[5]** A daily dose of 25 mg is effective and safe in elderly patient and dose escalation upto 50 mg is safe. [**6**] There are paucity of studies comparing efficacy of mirabegron add-on therapy in BPH patients complaining of persistent storage symptoms and being treated with alpha 1A blocker. [**7**] Thus the present study was aimed to evaluate the changes in storage LUTS after mirabegron Add – on to Silodosin.

Materials and methods

This was a prospective randomized study conducted between January 2020 to December 2022 at Department of Urology, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur. Data were collected and analysed, in accordance with laws/regulations and ethical principals that have their original in the decleration of Helsinki. Patients with known case of BPH with persistent storage symptoms after being treated with silodosin for a period of two weeks were included in the study.

A total number of 130 patients was enrolled and assigned into two groups by use of a random number generator and followed up for a period of 8 weeks. Group A (65 patients) were continued further with silodosin 8 mg only whereas in Group B (65 patients) Mirabegron 25 mg was added with Silodosin 8 mg. Both the groups were evaluated in respect to age, prostate specific antigen (PSA), total prostate volume (TPV), International prostate symptom score (IPSS), IPSS storage subscore, maximum flow rate (Qmax), post void residual urine (PVRU) and quality of life (QoL) at baseline and endpoint (8 weeks).

Patients treated with 5-alpha reductase inhibitors, antimuscarinic agents within three months, patients with predominant obstructive LUTS, PVRU more than 100 ml, deranged renal function, known case of diabetis mellitus and orthotopic hypotension were excluded from the study. Variables were compared using paired t-test and a p-value <0.05 was considered statistically significant.

Results

Table-1 Baseline characterstics of patients in both groups

Characterstics	Group A (Silodosin only, n-65)	Group B (Mirabegron Add-on, n-65)	*p*-value
Age (years)	68.2±7.2	66.5±7.8	0.19
PSA (ng/ml)	2.3±2.5	1.9±1.8	0.29
TPV(ml)	32.5±11.0	29.3±9.5	0.07
Total IPSS	18.7±6.5	21.0±8.4	0.08
IPSS storage	9.3±3.7	8.7±4.9	0.43
QoL	4.2±1.3	3.9±2.0	0.31
Q-Max	14.3±6.8	15.6±7.0	0.28
PVRU (ml)	21.9±19.5	28.3±23.0	0.08

n-Number, PSA-Prostate specific antigen, TPV-Total prostate volume, IPSS-International prostate symptom score, QoL-Quality of life, Q-max-Maximum flow rate, PVRU-Post void residual urine

Table-2 Baseline & endpoint characterstics evaluation between groups and statistical significance

Characterstics	Group A (Silodosin only, n-65)			Group B (Mirabegron Add-on, n-65)		
	Baseline	Endpoint	*p*-value	Baseline	Endpoint	*p*-value
Total IPSS	18.7±6.5	17.3±7.9	0.27	21.0±8.4	18.3±6.9	0.04
IPSS storage	9.3±3.7	8.9±5.0	0.60	8.7±4.9	6.5±2.9	0.002
QoL	4.2±1.3	3.8±2.0	0.17	3.9±2.0	3.0±1.7	0.006
Q-Max	14.3±6.8	13.7±8.1	0.64	15.6±7.0	17.5±7.2	0.12
PVRU (ml)	21.9±19.5	18.6±13.7	0.26	28.3±23.0	30.5±18.9	0.55

Reported adverse effects were very minimal in both the groups. Three out of sixty five (1.95%) reported dry mouth and constipation in mirabegron Add-on group whereas two out of sixty five (1.3%) developed stuffy nose in silodosin only group. However none of the candidate discontinued medication during the study period.

The study results showed that after eight weeks of mirabbegron Add-on therapy total IPSS, IPSS storage and QoL had improved and it was statistically significant in group B. Total IPSS score improved from 21.0±8.4 to 18.3±6.9 (*p*-0.04), IPSS storage from 8.7±4.9 to 6.5±2.9 (*p*-0.002) and QoL from 3.9±2.0 to 3.0±1.7 (*p*-0.006).

Discussion

In the present study addition of mirabegron 25 mg once daily with silodosin for 8 weeks was effective to decrease storage symptoms in comparison to silodosin monotherapy. We also noticed a significant improvement in QoL among patients in group B. Traditionally alpha blockers are the mainstay of treatment for BPH patients with LUTS. Silodosin is a highly selective alpha 1 adrenoreceptor blocker, having 162 times more affinity for alpha 1a than 1b thus exerts higher uroselectivety with minimal side effects.[**8]** It also blocks alpha 1D adrenoreceptor and believed to alleviate storage symptoms secondary to detrusor overactivity. [**9]** However, storage symptoms may persist in many men despite adequate treatment with alpha blocker and necessitate additional treatment measures. [**10]** Storage lower urinary tract symptoms are characterized by increased day time frequency, nocturia, urgency and urge incontinence. Muscarinic receptor antagonists and Beta 3 agonists (B3 AR agonists) plays a pivot role for treatment of BPH patients with predominant storage LUTS. [**11**]

There is a trend to discontinue antimuscarinic therapy in long term basis because of adverse effects and to overcome this B3 agonists are introduced. [**12**] Mirabegron is a selective B3AR agonist, introduced in the year 2012 and improves the storage capacity of the bladder without impairing the detrusor contractility. [**13]** Our study results are comparable with those of Matsukawa Y et al [**14]**, Kang TW et al [**4**] and Kwon SY et al **[7]** where QoL, IPSS storage improved after addition of mirabegron with alpha blocker.

Conclusion

The present study concludes that addition of Mirabegron 25 mg with silodosin is more effective than only silodosin therapy in benign prostatic hyperplasia patients with persistent storage symptoms. We observed that Mirabegron improves total IPSS, IPSS subscore and QoL without affecting voiding function significantly.

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