A COMPARATIVE STUDY OF THE EFFICACY AND TOLERABILITY OF SOLIFENACIN AND TOLTERODINE IN OVERACTIVE BLADDER

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ABSTRACT

AIM

To compare the efficacy and tolerability of solifenacin and tolterodine in overactive bladder.

MATERIALS & METHODS

It is an open label, comparative, randomised, parallel group and prospective study. 30 patients suffering from overactive bladder were divided into two groups. They were randomised to receive either solifenacin (5 mg once daily) or tolterodine (2 mg twice daily) for 4 weeks. At baseline, 2 weeks and 4 weeks they were assessed for average number of micturition episodes, urgency episodes, incontinence episodes, urgency episodes, incontinence episodes and volume voided per void. The number of nocturia episodes was also assessed. Global efficacy and tolerability were also assessed by patients and urologists. Adverse effect profile was also analysed.

RESULTS

Comparing the end point value of solifenacin and tolterodine groups, there was significant improvement in symptoms like frequency ($P<0.001$), urgency ($P<0.05$), incontinence ($P<0.05$), volume voided per void ($P<0.05$) and nocturia ($P<0.05$), efficacy ($P<0.05$) and tolerability were also favourable for solifenacin.

CONCLUSION

Solifenacin 5 mg once daily is effective and well tolerated than tolterodine 2 mg twice a day in the management of overactive bladder. Solifenacin is also better tolerated.

KEYWORDS

Overactive bladder, solifenacin, tolterodine, urgency, incontinence, nocturia.

HOW TO CITE THIS ARTICLE: Vijayarangan S, Rajaram G, Sharmila B. A comparative study of the efficacy and tolerability of solifenacin and tolterodine in overactive bladder. J. Evid. Based Med. Healthc. 2016; 3(33), 1599-1603.

DOI: 10.18410/jebmh/2016/359

INTRODUCTION: Overactive bladder (OAB) is becoming an internationally "hot topic." The tremendous number of patients with problem is just now becoming recognised, and the potential economic impact is staggering. Worldwide, OAB is known to affect 50-1100 million people. The condition is probably under-reported and undertreated, since patients have not become totally aware that they are suffering from OAB. Moreover, the patients do not recognise that their condition is not normal and needs treatment[1]. Overactive bladder is a syndrome characterised by collection of symptoms composed of urinary frequency, urgency, urge incontinence and nocturia. It is further characterised by reduction in volume voided per void and thus decreased bladder capacity, in the absence of pathological or metabolic factors that would explain these symptoms.[2,3] Such symptoms are known to be highly prevalent within the general population, contributing to a significant impairment in Health Related Quality of Life [HRQoL].

The antimuscarinic drugs have become the gold standard treatment for OAB. The two antimuscarinic agents used most often in clinical practice include oxybutynin and tolterodine. Oxybutynin is selective for M1 and M3 receptors subtypes, while tolterodine is a non-selective muscarinic antagonist. The nonselective antimuscarinics are associated with myriad of side effects. The most commonly reported adverse events with these agents include dry mouth, constipation, dizziness, headache, dry eyes and drowsiness. Aside from the aforementioned tolerability profile, the use of these agents is also contraindicated in patients with obstructive uropathy, glaucoma, urinary retention and a number of gastrointestinal complaints.[4,5,6] Hence introduction of a more bladder-specific muscarinic antagonists with fewer side effects and contraindications is needed. Solifenacin is a highly potent and bladder selective muscarinic (M3) receptor antagonist developed for the treatment of OAB with fewer side effects. [M3 subtype receptor is responsible for normal and involuntary bladder contraction.][7,8] Solifenacin succinate is a once-daily oral antimuscarinic agent that shows apparent functional

Financial or Other, Competing Interest: None.
Submission 05-03-2016, Peer Review 15-03-2016,
Acceptance 26-03-2016, Published 25-04-2016.
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DOI: 10.18410/jebmh/2016/359

selectivity for bladder over other organs. Solifenacin has been shown to be effective in reducing the symptoms of OAB in reducing incontinence episodes per day, decreasing the number of micturition in 24 hours and increasing mean voided volume. In addition significant reduction in urinary urgency was also reported.

This study was taken up to assess the efficacy and tolerability of solifenacin given once daily compared with the commonly used drug tolterodine given twice daily in patients with OAB.

STUDY OBJECTIVES:

- To compare the efficacy of solifenacin (5 mg once daily) and tolterodine (2 mg twice daily) in reducing the number of incontinence episodes, urgency episodes in patients with overactive bladder (OAB).
- To compare the efficacy of solifenacin and tolterodine on volume voided per void in patients with OAB.
- To evaluate the tolerability of solifenacin and tolterodine in OAB.

MATERIALS AND METHODS:

Study Centre: Department of Urology, Government General Hospital and Department of Urology, Kasturba Gandhi Government Hospital for Women & Children, Madras Medical College, Chennai.

Study Design: Open label, comparative, randomised, parallel group, prospective study.

Study Duration: 4 Weeks.

Study Sample: 30 Patients.

Inclusion Criteria:

1. Age between 18 to 75 years.
2. Sex: both males & female.
3. Urine culture should be negative for microorganisms.
4. Patients with overactive bladder must have experienced frequency of micturition on an average of >8 times per 24 hours and >3 episodes of urgency or incontinency during the 3 days, immediately prior to randomization.

Exclusion Criteria:

1. **Patients with:**
   - History of hypersensitivity to the study drugs solifenacin & tolterodine and other anticholinergic drugs.
   - History of stress incontinence, urinary outflow obstruction recurrent or symptomatic urinary tract infection, interstitial cystitis, uninvestigated haematuria or haematuria due to malignant disease.
   - Presence of neurological cause for detrusor muscle over activity.
   - Any condition in which the use of antimuscarinic therapy is contraindicated such as patients with urinary retention, gastric retention or uncontrolled narrow–angle glaucoma.
   - An indwelling catheter or use of intermittent catheterisation.
   - QT interval prolongation in ECG.
   - Significant hepatic, cardiac, renal, haematological, neurological, psychiatric or endocrinological disorder.
   - History of diabetes mellitus, hypertension and tuberculosis.
2. **Patients who have:**
   - Received previous pelvic irradiation or currently have malignant diseases of the pelvic organ.
   - Received treatment with any antimuscarinic drug or any drug for urinary incontinence or any non-pharmacological treatment for overactive bladder including electro-stimulation bladder training within two weeks before the study.
   - Taken part in other investigational study in the last one month prior to enrolment.
3. Urine culture positive growth for microorganisms.
4. Pregnant or breast-feeding women or women of childbearing potential not using a reliable method of contraception.

Study Procedure: The study was conducted after obtaining approval from the Institutional Ethical Committee (IEC). All study related procedures in a patient were initiated only after obtaining written informed consent. Patients attending Outpatient Department of Urology in Government General Hospital and Kasturba Gandhi Government Hospital for Women & Children, Chennai, with symptoms of overactive bladder were explained about the study purpose and procedures.

Screening: Written informed consent was obtained from those who were willing to participate in the study. The patients were enrolled and a screening identification number was assigned to each patient. The demographic data, contact number and address were recorded. They were screened by medical history, physical examination and laboratory investigations like, urine routine analysis, mid-stream urine for microbial culture. Blood sample for haematological and biochemical analysis was collected. X-Ray chest and ECG were also taken.

A voiding diary card was issued to each patients and they had to undergo a 3 days run in-phase during which they were instructed to record the following details in the voiding diary card for 3 consecutive days.

1. Voiding frequency [number of times patients passing urine in 24 hours].
2. Number of urgency episodes [number of times in a day where there is a strong need to go to the toilet right away].
3. Urge incontinence episodes [number of leaking/wetting episodes in a day].
4. Incidence of nocturia [number of times the patients had to wake up at night to pass urine].

5. Volume of urine passed per void [one litre plastic measuring jar was provided to each patient and they were instructed to collect and measure the volume of urine passed per void and enter it in the voiding diary card]. They were asked to report to the outpatient department after three days with the completed voiding diary card.

Baseline [0-day]: The voiding diary card and laboratory results were reviewed for the 63 patients screened, 10 patients were found to have diabetes mellitus and 23 patients' urine culture showed positive for microorganisms. The remaining 30 patients, those who fulfilled the inclusion and exclusion criteria were recruited for the study and a separate study number was assigned. The voiding diary card and the laboratory results were collected.

Baseline clinical assessment of urinary symptoms as entered in the voiding diary card and subjective assessments of problems associated with bladder symptoms were recorded. They were then randomised to receive either solifenacin or tolterodine.

Solifenacin 5 mg once daily to be taken with or without food for 4 weeks.

Tolterodine 2 mg twice daily to be taken with or without food for 4 weeks.

- Drugs were issued for 2 weeks only. They were asked to report to the outpatient department at the end of 2 weeks.
- In the four weeks' study, patients had to make two followup visits to the outpatient department once in 14 days.
- If any adverse effect was observed, the patients were instructed to contact the physician immediately over telephone or to attend the outpatient department at any point of the study.
- A new voiding diary card was issued and the patients were instructed to enter the micturition symptoms on the 12^{th}, 13^{th} and 14^{th} day for each followup visit.
- Medication compliance card was also issued to each patient to check the regularity of drug therapy and they were instructed to enter the dates of medication taken. The patients were reminded by post/telephone regarding the filling of the voiding diary card and the followup visit date.

The subjective assessment of problems associated with bladder symptoms consists of 6-point Likert scale.

0 – No problem.
1 – Very Minor Problem.
2 - Minor Problem.
3 – Moderate Problem.
4 – Severe problem.
5 – Many severe problems.

Post treatment, improvement in symptoms was assessed by the betterment in the score scale.

Global assessment of efficacy and tolerability was done by the patient and the urologist at the end of study.

Patient	Urologist
0-Very good	0-Very good
1-Good	1-Good
2-Satisfactory	2-Satisfactory
3-Poor	3-Poor
Global assessment by patient and urologist for overall efficacy	

Patient	Urologist
0-Very good	0-Very good
1-Good	1-Good
2-Satisfactory	2-Satisfactory
3-Poor	3-Poor
Global assessment by patient and urologist for overall tolerability	

At the end of the study, global assessment of efficacy and tolerability of solifenacin and tolterodine were done by the patient and urologist.

RESULTS: Sixty three patients were screened for their eligibility to participate in the study. Among them, 30 patients who fulfilled the inclusion criteria were enrolled for the study, in which there were 4 males and 26 females. All the patients completed the study. There were no dropouts in either group. The following tests were used for statistical analysis of data. Paired t test – to compare the base line data with end point data of efficacy variables and laboratory parameters of each group. Two sample t test-to compare the end point data of solifenacin and tolterodine. Chi square test–to compare the global assessment of efficacy and tolerability of solifenacin in and tolterodine.

Number of Micturition episodes	Solifenacin (n=15)	Tolterodine (n=15)	Solifenacin vs. Tolterodine (end point analysis)
Baseline	13.07±2.66	12.27±2.09	Two sample t test P <0.05
End point (28 days)	6.20±1.32	7.53±1.46	
% change over from baseline	51.89±8.26	36.88±16.03	
Statistical test and significance level	Paired t test P <0.001	Paired t test P <0.001	
Table 1: Average number of micturition episodes			

Number of urgency episodes	Solifenacin (n=15)	Tolterodine (n=15)	Solifenacin vs. Tolterodine (end point analysis)
Baseline	6.67±3.56	6.00±2.55	Two sample t test P <0.05
End point (28 days)	1.60±1.68	2.07±0.88	
% change over from baseline	78.29±16.51	63.09±14.09	
Statistical test and significance level	Paired t test P <0.001	Paired t test P <0.001	
Table 2: Mean number of urgency episodes			

Number of incontinence episodes	Solifenacin (n=15)	Tolterodine (n=15)	Solifenacin vs. Tolterodine (end point analysis)
Baseline	1.80±2.27	2.23±1.68	Two sample t test P <0.05
End point (28 days)	0.13±0.52	0.43±0.74	
% change over from baseline	96.26±8.43	84.61±18.67	
Statistical test and significance level	Paired t test P <0.001	Paired t test P <0.001	

Table 3: Mean number of incontinence episodes

Number of volume voided	Solifenacin (n=15)	Tolterodine (n=15)	Solifenacin vs. Tolterodine (end point analysis)
Baseline	168.87±50.45	157.07±39.58	Two sample t test P <0.05
End point (28 days)	268.87±83.76	217.16±32.88	
% change over from baseline	61.67±31.27	42.27±22.55	
Statistical test and significance level	Paired t test P <0.001	Paired t test P <0.001	

Table 4: Mean number of volume voided per void

Number of nocturia episodes	Solifenacin (n=15)	Tolterodine (n=15)	Solifenacin vs. Tolterodine (end point analysis)
Baseline	5.40±4.31	4.67±3.31	Two sample t test P <0.05
End point (28 days)	0.87±1.24	1.07±1.10	
% change over from baseline	89.52±11.89	80.05±13.28	
Statistical test and significance level	Paired t test P <0.001	Paired t test P <0.001	

Table 5: Mean number of nocturia episodes

Efficacy assessment		Groups				X2 test
		Solifenacin		Tolterodine		
		N	%	N	%	
Patient	Very good	2	13.3%	0	0 %	P=0.05
	Good	11	73.4%	7	46.7%	
	Satisfactory	2	13.3%	8	53.3%	
Doctor	Very good	2	13.3%	0	0%	P<0.05
	Good	13	86.7%	10	66.7%	
	Satisfactory	0	0%	5	33.3.7%	

Table 6: Global efficacy assessment

Tolerability assessment		Groups				X2 test
		Solifenacin		Tolterodine		
		N	%	N	%	
Patient	Very good	1	6.7%	0	0%	P <0.05
	Good	14	93.3%	15	100%	
	satisfactory	0	0%	0	0%	
	Poor	0	0%	0	0%	
Doctor	Very good	3	20.0%	1	6.7%	P <0.05
	Good	12	80.0%	14	93.3%	
	satisfactory	0	0%	0	0%	
	Poor	0	0%	0	0%	

Table 7: Global tolerability assessment

Adverse Events: No adverse events were experienced in the solifenacin group, whereas 5 patients (33.3%) in the tolterodine group experienced dryness of mouth which did not require discontinuation of therapy.

Assessment of Compliance: The compliance was assessed at the end of 2 weeks and 4 weeks. In this study, all the 15 patients in solifenacin group and 15 in tolterodine group had taken all the prescribed medications as per schedule. The compliance was assessed by reviewing the compliance assessment diary card and by checking the medication container.

Symptoms of OAB: In our study, frequency of micturition which is a very troublesome symptom of OAB was reduced. When comparing baseline to the end point within the groups, there was a statistically significant reduction in frequency of micturition (p< 0.001). On comparing end point value of solifenacin and tolterodine groups, there was a statistically significant reduction in solifenacin group (P<0.05). The percentage reduction in frequency of micturition with solifenacin 5 mg once a day was 51.89%, but with tolterodine 2 mg twice a day it was 36.88%. But in a study conducted in Sheffield, United Kingdom 2003, the percentage reduction was 18% with solifenacin 5 mg OD.[9] (Table 1)

In our study, urgency episodes were reduced in both the groups. On comparing the end point value of solifenacin and tolterodine groups, there was a statistically significant reduction in solifenacin group (P <0.05). The percentage reduction in urgency episodes in our study was 79.29% for solifenacin and 63.09% for tolterodine. But in a study conducted in New Jersey USA, 2003, it was observed that reduction in urgency episodes for solifenacin 4 mg was 51.9% and 37.9% for tolterodine.[10] (Table 2).

The incontinence episodes reduced in both the trial drugs during our study (P <0.001) in comparing the baseline to end point values within the groups. In comparing the end point value of solifenacin and tolterodine, solifenacin was statistically significant (P <0.05) than tolterodine conducted in Birmingham, UK 2005,[11] it was reported that the percentage of reduction in incontinence episodes from baseline to the end of the study was 50% with solifenacin 5 mg. But in our study, the reduction in incontinence episodes

was 96.26% with solifenacin 5 mg and 84.6% for tolterodine 2 mg. (Table 3).

In our study, both the drugs reduced the frequency of micturition, and the volume voided per void was increased by these drugs significantly ($p < 0.001$). In comparing end point of the two drugs, the effect of solifenacin was more significant ($p < 0.05$). In our study, percentage improvement for solifenacin 5 mg was 61.67% and for tolterodine it was 42.27%. (Table 4).

Nocturia was reduced in both groups in this study. In between end point of two drugs, solifenacin was better ($P<0.05$) (Table 5). The overall efficacy assessment by the patient and the urologist were in favour of solifenacin. (Table 6). Tolerability was also better for solifenacin than tolterodine, when assessed by patients and urologist. (Table 7).

Adverse Effects: In our study, solifenacin group experienced on adverse effect, whereas tolterodine group 5 patients reported dryness of mouth (33.3%) which did not require discontinuation of therapy.

Laboratory Parameters: There was no statistically significant change in the laboratory parameters when comparing baseline and end point values within the groups. The results of our study were well in accordance with the studies conducted abroad. Solifenacin produced better control of symptoms in overactive bladder and was well tolerated.

CONCLUSION: From our study, we conclude that solifenacin 5 mg once daily is effective and well tolerated than tolterodine 2 mg twice a day in the management of overactive bladder by reducing the number of micturitions per day (24 hours), number of incontinence episodes, urgency episodes, more effective in increasing the volume voided per void and better tolerance.

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