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A PROSPECTIVE RANDOMISED TRIAL TO COMPARE THE EFFICACY OF TOLTERODINE, SOLIFENACIN AND DARIFENACIN AS BLADDER RELAXANT

General Surgery

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ABSTRACT

Aim: The aim of this study was to compare the relative efficacies as well as side effects of the three bladder smooth muscle relaxants, Darifenacin, Solifenacin and Tolterodine.
Methods: The study was a prospective randomised trial carried out in Surgery Department at M.L.N. Medical College, Allahabad from September 2010 to August 2013.
Results: Mean age of patients suffering from OAB was 44 years. To decrease the number of micturition episodes, efficacy of Solifenacin > Tolterodine > Darifenacin. To decrease urgency, efficacy of Solifenacin = Tolterodine > Darifenacin. For mixed incontinence Solifenacin was better than both Darifenacin and Tolterodine. Regarding nocturia, efficacy of Solifenacin = Darifenacin > Tolterodine. Most common side-effects associated with these drugs were dry mouth, constipation and blurred vision but latter was significantly less with Solifenacin.
Conclusion: For treatment of overactive bladder Solifenacin can be suggested as the first line drug.

KEYWORDS:

Solifenacin, Darifenacin, Tolterodine, Overactive bladder.

INTRODUCTION

Many patients come to outdoor clinics with complaints suggestive of overactive bladder (OAB). This condition causes significant deterioration in the quality of life of such patients[4,5,30] and also a substantial economic cost[1,2]. The prevalence of OAB increases with age with a mean prevalence of 10% - 20% during middle life[6,7,8]. Despite the decreased quality of life many patients do not seek professional help[7,14,15] but those that do can attain significant relief[9] by use of pharmacological treatments such as antimuscarinic drugs which have proven to be cost effective, efficacious and tolerable in several studies[10,11,12,13,14]

OAB is symptom based and defined by the International Continence Society (ICS) standardization committee as urgency, with or without urgency incontinence, usually with frequency and nocturia, but there should be no proven infection or other obvious pathology (So other causes of similar symptoms must be excluded before diagnosing OAB)[3]. Urgency (essential parameter) with at least one other LUT symptom relating to storage is essential to diagnose OAB[3].

Though many studies have been carried out among smooth muscle bladder relaxants but any single randomised trial between these commonly used drugs is lacking, so a need was felt to carry out this study.

AIMS AND OBJECTIVES

Aim of the study was to assess the effect of the three smooth muscle relaxants viz. Darifenacin, Solifenacin and Tolterodine used for the treatment of overactive bladder.

- Comparison of these drugs with regard to their efficacy and side effects on a predetermined set of symptoms.

MATERIAL AND METHODS

This study was a prospective randomised control trial to compare the relative efficacies of Darifenacin, Solifenacin and Tolterodine and was conducted on patients enrolling in urology/general surgery OPD of SRN Hospital Allahabad from September 2010 to August 2013.

Inclusion criteria:-

- Any patient attending the above OPDs with the complaints of overactive bladder who gave consent for the study.
- Exclusion criteria:-
- Patients who did not give consent or dropped out of study midway
- Presence of any other obvious pathology such as liver disease, close angle glaucoma, stress incontinence, neurological/other obvious cause of abnormal over activity.
- Patients who had history of hypersensitivity to any drugs used in the study, urinary retention, previous lower urinary tract surgery or instrumentation were excluded from the study.

All patients were subjected to a predetermined history and examination protocol.

Treatment protocol

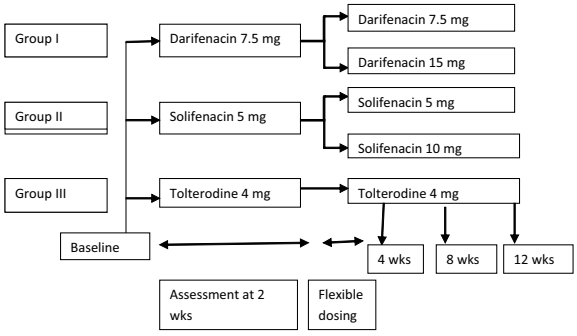
Patients were initially randomly allocated to three treatment arms

Group I : Taking Darifenacin 7.5 mg daily, later increased to a maximum of 15 mg if suboptimal response occurred.

Group II : Taking Solifenacin 5 mg daily, later increased to a maximum of 10 mg if suboptimal response occurred.

Group III : Taking Tolterodine 4 mg daily.

Study Design



Follow up protocol

Each group of patients took their respective treatment drug therapy for at least 12 wks. All patients were evaluated at 2, 4 8 and 12 wks after initiation of therapy. After 2 wks, if a patient needed increment in dosing then further increase in dose of Solifenacin and Darifenacin was permitted as shown in study design. At each follow up symptom control was evaluated as under

Name of patient					
Date of starting treatment					
Symptoms	Base line	Evaluation at			
		2 wks	4 wks	8 wks	12 wks
Micturition frequency/24hrs					
Urgency episodes/ 24 hrs					
Mixed incontinence episodes/24 hrs					
Urge incontinence episodes /24 hrs					
Nocturia episodes /24 hrs					

After completion of the study parameters were analysed using appropriate statistical test – ANOVA and Paired Student T test.

OBSERVATIONS

Table 1 : Patient Characteristics

Demographics		Group I	Group II	Group III
No. of patients		14	14	14
Mean age (yrs)		44.71 (Range 18-62yrs)	44.28 (Range17-62yrs)	44.57 (Range18-62 yrs)
Gender	Male	10 (71.43%)	8(57.14%)	8(57.14%)
	Female	4(28.57%)	6(42.86%)	6(42.86%)

Table 2 : Baseline characteristics of symptoms of patients

Symptoms	Mean +/- SD			P value (ANOVA)
	Group I	Group II	Group III	
Micturition frequency/ 24 hrs	9.71+/- 1.38	9.85 +/- 1.40	9.92 +/- 1.33	0.92
Urgency episodes/ 24 hrs	1.57+/- 0.64	1.43 +/- 0.65	1.50 +/- 0.65	0.84
Incontinence episodes/ 24 hrs	0.78 +/- 0.43	0.78 +/- 0.43	0.85 +/- 0.36	0.86
Urge incontinence/ 24 hrs	0.57 +/- 0.51	0.57 +/- 0.51	0.57 +/- 0.51	Not significant
Nocturia episodes/ 24 hrs	1.14 +/- 0.36	1.07 +/- 0.27	1.21 +/- 0.43	0.58

Table 3: Efficacy regarding decrease in micturition episodes/24 hours

Mean +/- SD of micturition episodes/ 24 hours. P value, baseline vs 12 wks, T test (paired)

Groups	Mean+/- SD					P value
	Baseline	2 weeks	4 weeks	8 weeks	12 weeks	
Group I	9.71+/- 1.38	9.00 +/- 2.52	8.43 +/- 1.62	7.86 +/- 1.34	7.86 +/- 1.34	0.0006
Group II	9.85 +/- 1.40	9.28 +/- 2.28	8.71 +/- 2.28	6.86 +/- 0.89	6.71 +/- 0.95	0.0001
Group III	9.92 +/- 1.33	9.28 +/- 2.28	8.29 +/- 1.60	7.57 +/- 0.78	7.00 +/- 0.82	0.00004.

P value (ANOVA) = 0.001

Table 4 : Efficacy regarding improvement in urgency episodes/24 hours

Mean +/- SD of urgency episodes/ 24 hours. P value, baseline vs 12 wks, T test (paired)

Groups	Mean+/- SD					P value
	Baseline	2 weeks	4 weeks	8 weeks	12 weeks	
Group I	1.57 +/- 0.64	1.43 +/- 0.38	1.21 +/- 0.49	1.21 +/- 0.49	1.00 +/- 0.39	0.001
Group II	1.43 +/- 0.65	1.21 +/- 0.49	1.00 +/- 0.38	0.79 +/- 0.43	0.79 +/- 0.43	0.002
Group III	1.50 +/- 0.65	1.14 +/- 0.89	1.00 +/- 0.81	1.00 +/- 0.81	0.86 +/- 0.36	0.002

P value (ANOVA) = 0.35

Table 5 : Efficacy regarding improvement in mixed incontinence episodes/24 hours

Mean +/- SD of incontinence episodes/ 24 hours. P value, baseline vs 12 wks, T test (paired)

Groups	Mean+/- SD					P value
	Baseline	2 weeks	4 weeks	8 weeks	12 weeks	
Group I	0.78 +/- 0.43	0.43 +/- 0.53	0.29 +/- 0.49	0.29 +/- 0.49	0.36 +/- 0.49	0.008
Group II	0.78 +/- 0.43	0.57 +/- 0.79	0.29 +/- 0.49	0.29 +/- 0.49	0.21 +/- 0.43	0.001
Group III	0.85 +/- 0.36	0.57 +/- 0.79	0.43 +/- 0.53	0.29 +/- 0.49	0.43 +/- 0.51	0.008

P value (ANOVA) = 0.49

Table 6 : Efficacy regarding improvement in urge incontinence episodes/24 hours

Mean +/- SD urge incontinence episodes/24 hours. P value, baseline vs 12 wk, T test (paired)

Groups	Mean+/- SD					P value
	Baseline	2 weeks	4 weeks	8 weeks	12 weeks	
Group I	1.14 +/- 0.36	0.71 +/- 0.76	0.71 +/- 0.76	0.71 +/- 0.76	0.71 +/- 0.49	0.008
Group II	1.07 +/- 0.27	0.86 +/- 1.07	0.51 +/- 0.52	0.51 +/- 0.52	0.51 +/- 0.52	0.001
Group III	1.21 +/- 0.43	1.00 +/- 0.28	0.93 +/- 0.27	0.93 +/- 0.27	0.93 +/- 0.27	0.04

P value (ANOVA) = 0.042

Table 8 : Comparison of side effects of the three drugs

Groups	Tolterodine	Solifenacin			Darifenacin
	4 mg	5 mg	10 mg	7.5 mg	15 mg
Dry mouth	28.56 %	14.28 %	28.56 %	28.56 %	28.56 %
Constipation	14.28 %	14.28 %	14.28 %	0 %	14.28 %
Blurred vision	14.28 %	0 %	0 %	14.28 %	28.56 %

DISCUSSION

In the SOLIDAR study[26] by But l. et al, Solifenacin showed statistically greater improvements in QOL, better overall treatment satisfaction, and a decreased incidence of dry mouth after 3 months of treatment compared to the Darifenacin group.

In a study by Zinner N et al[28], Darifenacin treatment resulted in statistically significant improvements in PPBC (Patient's Perception of Bladder Condition) scores, micturition frequency, urgency and UUI episodes from baseline at 12 weeks which were similar for patients previously treated with oxybutynin ER or Tolterodine ER.

In a study by Chapple et al published in European urology in 2007 (STAR)[30] which compared 5/10 mg Solifenacin and Tolterodine ER 4mg, it was shown that Solifenacin showed greater efficacy than Tolterodine in decreasing the urgency episodes, incontinence, urge incontinence and increasing the volume voided per micturition. In another study by the same author[22], mean number of urgency episodes per 24 h, episodes of incontinence, mean number of voids/24 h, mean volume voided were all favourably and statistically significantly affected by Solifenacin as compared to Tolterodine.

Similar results were also obtained in Cochrane Database Syst Rev. 2012 Jan 18, by Madhuvrata P et al.[20]

In the VERSUS (VESIcare Efficacy and Research Study US) study done Swift SE et al published in Clinical Drug Investigation in 2009 Solifenacin as compared to Tolterodine improved urgency, incontinence, micturition frequency, nocturia and nocturnal voids in patients. Patients also experienced improvements in Health related quality of life indices and perceived bother from OAB[17].

In an open-label, non-comparative, flexible-dosing, multicenter carried out by Zinner N et al comparing Tolterodine and Solifenacin, Solifenacin showed greater improvement in productivity, activity participation, and decreased medical care use.[18]

In another study done by Chancellor et al which compared Solifenacin and Tolterodine, daily symptoms of urgency, urge incontinence, frequency, nocturia, and nocturnal voids were better controlled by Solifenacin[19].

In a study by Cardozo L et al, Solifenacin provided the greatest clinical benefit and associated QALYs for all three outcomes of interest viz. urgency, frequency and incontinence across all therapies considered (Fesoterodine, Tolterodine extended-release (ER) and Tolterodine immediate-release (IR), Oxybutynin IR and Propiverine ER)[27].

In our study, the greatest difference perceived among the different drugs was with regard to decrease in micturition episodes/ 24 hours (ANOVA P value = 0.001) and the patient continued to have progressively better control over subsequent follow-ups during the course of the study. All the three drugs had a statistically significantly impact on the number of micturition episodes/ 24 hours (P values of paired T test 0.0006, 0.0001 and 0.00004 respectively).

The next significant difference was seen with regard to decrease in nocturia episodes (ANOVA P value = 0.042) and this improvement almost plateaued within the 1st four weeks without further improvement. Nevertheless, all the three drugs individually had a significant impact on the nocturia episodes when compared by paired T test (P = 0.008, 0.001, 0.04) .

Improvement in urgency, mixed incontinence and urge incontinence was seen greater with Solifenacin as compared to other drugs but the difference between the drugs did not reach statistical significance most probably due to less number of subjects in each of the three arms (ANOVA P value 0.35, 0.49, 0.69 respectively for the three categories). Individually, however, the three drugs caused significant improvement in mixed incontinence and nocturia episodes when compared to their respective baseline values (P value paired T test 0.001, 0.002, 0.002 for urgency and 0.008, 0.001, 0.008 for mixed incontinence). The impact on urge incontinence did not reach statistical significance for Darifenacin and Tolterodine and only Solifenacin showed significant improvement over baseline values.

In a study by Bilal Chughtai[23] et al side effect profile of Darifenacin included constipation 14.8% and 21.3% with 7.5 mg and 15 mg dose respectively. It also had a 20.2% incidence of dry mouth at 7.5 mg and 35% at the 15 mg dose.

In the Zinner analysis[25], the most common side effect of Tolterodine was dry mouth, and it occurred in similar rates between the elderly and nonelderly (24%). The rate of constipation and CNS side effects of somnolence, headache, and dizziness were similar to placebo in the ≥65 and < 65 yrs group.

In Madhuvrata systemic review[20], dry mouth (RR 0.69, 95% CI 0.51 to 0.94) was statistically significantly lower with Solifenacin when compared to Immediate Release (IR) Tolterodine. In the same review Solifenacin had less risk of dry mouth when compared with Tolterodine IR. Overall ER preparations had lower risk of dry mouth.

Similar results were also borne by Conchrane database systemic review 2005, by Hay- Smith J et al[21].

In the Chapple study[22] also, Solifenacin was well tolerated. Compared with placebo (4.9%), dry mouth (the most common side-effect), was reported in 18.6% of patients receiving Tolterodine, 14.0% receiving 5 mg and 21.3% receiving 10 mg Solifenacin.

In our study, no definite recommendations can be made with respect to the side effects except with regard to blurred vision which was significantly less with Solifenacin.

CONCLUSIONS

Following conclusions could be drawn from the study

- Efficacy of drugs with regard to decrease in number of micturition episodes / 24 hrs
- Solifenacin > Tolterodine > Darifenacin
- Efficiency with regard to decrease in nocturia episodes /24 hrs
- Solifenacin= Darifenacin>Tolterodine
- Efficacy of drugs with regard to decrease in number of urgency episodes / 24 hrs
- Solifenacin = Tolterodine > Darifenacin (but not significant statistically)
- Efficacy of drugs with regard to decrease in number of incontinence episodes / 24 hrs
- Solifenacin > Tolterodine = Darifenacin (but not significant statistically)
- Efficacy of drugs with regard to decrease in number of urge incontinence episodes / 24 hrs Solifenacin > Tolterodine = Darifenacin (but not significant statistically)
- Most common side effects associated with these drugs were dry mouth, constipation and blurred vision, but blurred vision is significantly lower in patients taking Solifenacin.
- Solifenacin 5 mg is associated with lesser side effects as compared to higher doses.
- Therefore with regard to treatment of overactive bladder Solifenacin appears to be the first choice drug. Studies with larger cohorts are needed to see if there are differences in efficacies between the drugs with regard to urgency, urge incontinence and mixed incontinence.

CONFLICT OF INTEREST None

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