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

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CERTIFICATE

This is to certify that "**A COMPARATIVE STUDY OF THE EFFICACY AND TOLERABILITY OF SOLIFENACIN AND TOLTERODINE IN OVER ACTIVE BLADDER"** has been carried out in the Institute of Pharmacology, Madras Medical College, Chennai, combined with the department of urology, Government General Hospital, Chennai by **Dr. S. VIJAYARANGAN**, under my guidance and supervision, in partial fulfillment of regulations laid down by The Tamil Nadu Dr. M.G.R. Medical University for the final M.D. Pharmacology Examination to be held in March 2007.

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CONTENTS

SL.NO.	TITLE	PAGE NO.
1.	INTRODUCTION	1
2.	REVIEW OF LITERATURE	6
3.	OBJECTIVES OF THE STUDY	33
4.	METHODOLOGY	34
5.	RESULTS	44
6.	DISCUSSION	53
7.	CONCLUSION	58
8.	BIBLIOGRAPHY	
9.	APPENDIX	

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ABBREVIATIONS

OAB- Over Active Bladder.

QOL- Quality of Life.

ICS- International Continence Society.

EUS- External Urethral Sphincter.

PMC- Pontine Micturition Centre.

PSC- Pontine Storage Centre.

PFE- Pelvic Floor Exercise.

DEO- Diethyl Oxybutynin.

HRQoL- Health related Quality of life.-

SEM- Standard error of the mean

BOO- Bladder outlet obstruction.

DI- Detrusor instability

BPO- Benign prostatic obstruction.

BPE-Benign prostatic enlargement

NE- nor epinephrine.

ICI- International Consultation on Incontinence.

SGOT- Serum gltamic oxaloacetic transaminases

SGPT- Serum glutamic pyruvate transaminases.

Ach- Acetylcholine.

5 HM- 5 Hydroxy Methyl Tolterodine.

4 RHS- 4R- Hydroxy Solifenacin.

WHO - World Health Organisation

Summary of study procedures

Day	Screening	Baseline	14-16 Day	28-32 Day
VISIT	1	2	3	4
Informed consent	√			
Demographic data/medical history	√			
Vital signs & physical examination	√	√	√	√
Clinical assessment	√	√	√	√
Subjective assessments		√	√	√
Inclusion & exclusion criteria	√	√		
Laboratory investigations	√			√
Urine for culture -ray& ECG	√			
Voiding dairy card.	√ [issue]	√ [collect & issue a new card}	√ [collect & issue a new card}	√ [collect]
Issue study medication		√	√	
Medication compliance card		√ [issue]	√ [Collect & issue a new card]	√ [collect]
Medication pack returned			√	√
Adverse events			√	√
Study termination				√

Clinical assessment about urinary symptoms

[Appropriate information entered from voiding card]

Mean number of micturition per 24 hours (Averaged over last three days)	☐☐
Number of incontinence episodes	☐☐
Number of urgency episodes	☐☐
Mean volume of urine voided per void (Averaged over last 3 days)	☐☐
Nocturia (If YES number of times)	Yes☐ No☐ ☐☐

Voiding Dairy Card

Please make appropriate entries in the last three days before the next visit

Date (Day, month, year)			
Number of times you urinate in a day (24 hrs): micturitions (Enter appropriate number)			
Number of leaking/wetting episodes in a day (24 hrs.): incontinence (Enter appropriate number)			
Number of times in a day (24 hrs), there is a strong need to go to toilet for urination right away: urgency (Enter appropriate number)			
Number of times you had to wake up to urinate at night: nocturia (Enter appropriate number)			
Volume of urine each time you urinate (ml) as collected in the measuring cylinder: volume voided per void (Enter appropriate number, Use different boxes each time)			

CASE RECORD FORM

Centre:

Patient Name: Initials ☐☐☐

Informed Consent: Yes ☐ No ☐

√ Tick appropriate

Age & Sex :

Height :

Weight :

Criteria for : Inclusion ☐ Exclusion ☐

√ Tick appropriate

SCREENING **SCREENING NO.** ☐

Medical History

Present OAB Complaints and Duration :

Past History

Previous treatment for OAB details :

Clinical Examination

Vital signs : t° P/R

B.P. RR

1. Laboratory Investigation

Haemogram : Hb%

TC

BC

Platelet

2. Blood Chemistry

Blood sugar

Blood urea

Serum creatinine

Total bilirubin

SGOT

SGPT

3. Urinalysis

Urine routine

Alb

Sugar

Deposits

4. X-ray chest PA view

5. ECG

Clinical Assessment :

Instruction to the patient:

[Regarding filling of voiding Diary cord]

BASELINE 0 DAY **Study No.** ☐

Clinical Examination :

Clinical Assessment :

[Review of voiding dairy card Lab Results]

Confirm Inclusion criteria :

Randomization with trial medication (for two weeks)

date and instruction

Instruction to patients:

[Regarding filling up of voiding dairy and

medication compliance card]

FOLLOW UP I

Clinical Examination :

Clinical Assessment :

[Voiding dairy card + medication compliance card]

Adverse events :

Trial medication date :

Instruction to patient :

[Regarding filling up of voiding dairy and

medication compliance card]

FOLLOW UP II

Adverse events :

Clinical assessments :

Clinical examination :

Laboratory investigation :

Global assessment :

Study termination :

Patient signature or thumb impression address: _____

Witness signature or thumb impression address: _____

Signature of study doctor:_____

Medication Compliance Card

[Solifenacin Group]

Please enter in the space provided below after you have consumed the study medication.

Patient Name: _____ Date: _____

Next Follow up date: _____

Base line	Day	Date	One tablet daily with a glass of water in the morning (√ in the column)	Follow up I	Day	Date	One tablet daily with a glass of water in the morning (√ in the column)
	1				1		
	2				2		
	3				3		
	4				4		
	5				5		
	6				6		
	7				7		
	8				8		
	9				9		
	10				10		
	11				11		
	12				12		
	13				13		
	14				14		

Medication Compliance Card

[Tolterodine group]

Please enter in the space provided below after you have consumed the study medication.

Patient Name: _____ Date: _____

Next Follow up date: _____

Base line	**Day**	**Date**	**One tablet daily with a glass of water in the morning (√ in the column)**		**Follow up I**	**Day**	**Date**	**One tablet daily with a glass of water in the morning (√ in the column)**	
			Mor	Eve				Mor	Eve
	1					1			
	2					2			
	3					3			
	4					4			
	5					5			
	6					6			
	7					7			
	8					8			
	9					9			
	10					10			
	11					11			
	12					12			
	13					13			
	14					14			

Informed consent form

EFFICACY AND TOLERABILITY OF SOLIFENACIN

Subject's Name/Age……

Subject's Initials:……

		initials / thumb impression of subject
(i)	I confirm that I have read and understood/have been explained the patient information sheet for the above study and have had the opportunity to ask questions	
(ii)	I understood that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my Medical care or legal rights being affected.	
(iii)	I understood that the Ethics committee and the regulatory authorities will not need my permission to look at my health records both in respect the current study and any other further research that may be conducted in relation to it, even if I withdrew from the trial. I agree to this access. However I understand that my identity will not be revealed in any information released to third parties or published	
(iv)	I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purposes	
(v)	I agree to take part in the study	

Signature or thumb impression of the **subject/Legally Acceptable**

Representative

_____

Date: | | | | | | | | |
Day Month Year

Signatory's Name: _____

Signature of Impartial Witness: _____

Date: | | | | | | | | |
Day Month Year

Name of the impartial Witness:_____

Signature of the Investigator/Sub Investigator: _____

Date: | | | | | | | | |
Day Month Year

Study investigator's Name: _____

Name of the Institution/ Location: _____

INTRODUCTION

Over active bladder [OAB] is becoming an internationally “hot topic.” The tremendous number of patients with this problem is just now becoming recognized, and the potential economic impact is staggering. World wide, OAB is known to affect 50-100 million people. The condition is probably under reported and under treated, since patients have not become totally aware that they are suffering from OAB. More over the patients do not recognize that their condition is not normal and needs treatment.[1]

In the United States alone, there are an estimated 32 or 33 million people affected by OAB. It costs an estimated $26 billion a year in the United States to manage loss of bladder control. With continued ageing of the populations in all developed countries, the problems associated with bladder control will certainly continue to increase[2].

The industry and medical fraternity there fore can make a substantial contribution to the quality of life [QoL] of these patients by spreading awareness and education of OAB, thanks to the latest advances in the disease understanding and therapy options to treat this condition.

- In US one in eleven incontinent patients suffers from OAB.
- Approximately 55% of individuals with OAB are women and 45% are men.

- The prevalence of the condition is reported to be around 16 to 22% and it increases with advancing age.

- Women with urinary problems during childhood are more likely to develop OAB as adults. The connection between childhood urinary symptoms and adult symptoms of OAB raises the possibility of early identification of a population at risk for adult OAB symptoms.

- The prevalence of OAB is 29.9% in Asian men. OAB is more common in professional workers [43%], the high-income group and urban dwellers [64%].

- With increasing age the incidence of OAB increases, i.e., the prevalence is 53% in men aged >70 years.

- Among patients who seek help, 30%, do not receive assessment and approximately 80% are not treated. [3, 4, 5]

Over active bladder is a syndrome characterized by collection of symptoms composed of urinary frequency, urgency, urge incontinence and nocturia. The current International Continence Society (ICS) definition states that OAB syndrome is characterized by

1. Urgency [a sudden desire to pass urine which is hard to delay]

2. Urge incontinence [involuntary leakage of urine accompanied or preceded by urgency], usually with

3. Increased frequency, and

4. Nocturia

It is further characterized 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. [6, 7]

Such symptoms are known to be highly prevalent with in the general population, contributing to a significant impairment in Health Related Quality of Life [HRQoL].

It is a distressing condition that can diminish people's self esteem and quality of life. Frequently, sufferers do not seek medical care because they believe that their symptoms are part of the normal aging process. While OAB is idiopathic, in most cases it is described as a pathophysiological process and not merely a part of normal aging.

The anti muscarinic drugs have become the gold standard treatment for OAB. The two antimuscarinic agents used most often in clinical practice include oxybutynin and tolterodine. Ideally with any drug it is desirable to have it work selectively on the target of interest (e.g. the M3 muscarinic receptor),

because this could, in theory, minimize adverse effects. However because of the extremely high sequence homology of the five identified muscarinic receptors. It has been difficult for medicinal chemists to develop selective compounds at these receptors. Neither oxybutynin nor tolterodine has much selective for the various subtypes of the muscarinic receptors and each has about the same affinity for the M3 subtypes. [8, 9, 10]

Oxybutynin is selective for M1 and M3 receptors subtypes, while tolterodine is a non–selective muscarinic antagonist. The non-selective anti muscarinics 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 afore mentioned tolerability profile, the use of these agents is also contraindicated in patients with obstructive uropathy, glaucoma, urinary retention and a number of gastrointestinal complaints.[11,12.13]

These drugs have limited effectiveness, as well as significant side effects, which lead the patient often to discontinue the therapy.

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.][14, 15]

Solifenacin succinate is a once-daily oral antimuscarinic agent that shows apparent functional 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.

REVIEW OF LITERATURE

Over active bladder is a new terminology defined in terms of either urodynamic findings or symptoms. It is a chronic disease that is usually caused by involuntary contractions of the detrusor muscle during bladder filling. The urodynamic definition of OAB approximates that of International Continence Society (ICS) term.

The bladder is a four – sided pyramid like structure. Its capacity is about 200 – 300 CC. When it is full it is ovoid in shape. The bladder wall is made of longitudinal and circular muscles called the detrusor[16].

The bladder performs several important functions. It must store an adequate volume of urine. The proper understanding of voiding and continence requires some working knowledge of the contractile properties of the smooth and striated muscles of the bladder. The lower urinary tract has two main functions, storage and periodic elimination of urine. These functions are regulated by unique biomechanics of bladder and urethral muscle as well as complex neural control system located in the brain and spinal cord.[17]

As a result of extensive research the complex neural circuit regulating normal function of the lower urinary tract is now better understood. A quick review of the normal neurophysiologic control of lower urinary tract function makes it easier to understand the rationale for pharmacological approach in the management OAB.

The smooth muscle lining of the bladder neck and urethra form the internal sphincter, which is surrounded by striated muscles called rhabdo sphincter. Together, the striated muscle fibers surrounding the urethra and rhabdo sphincter constitute the external urethral sphincter (EUS).

Neurophysiology of urinary bladder[18 - 20]

Para sympathetic nerves innervate the detrusor where as the smooth muscles of the bladder neck and urethra (the internal sphincter) are innervated by sympathetic nerves. The striated muscles of the EUS receive their primary innervations from somatic nerves.

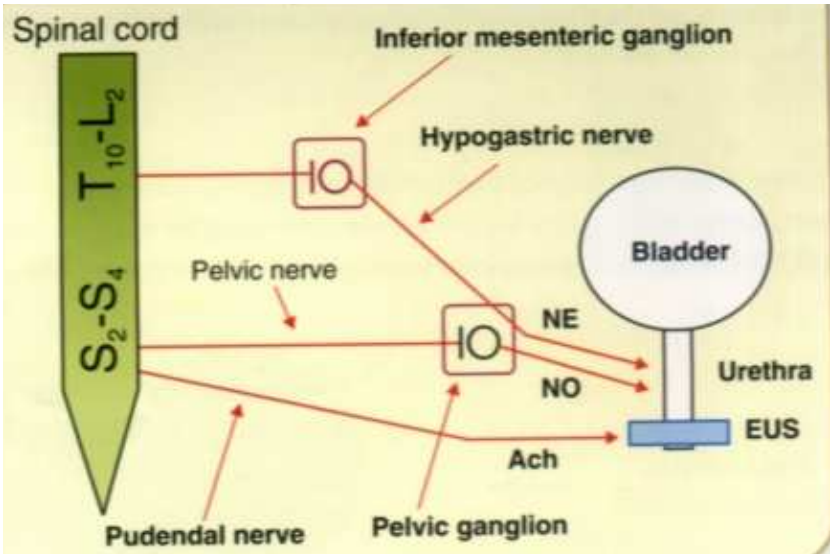


Fig.1 : Sympathetic and para sympathetic pathway

The parasympathetic pathway of the detrusor comes as the pelvic nerve from the nucleus in the intermediolateral column of segments S2 – S4 and synapse in the pelvic ganglia, as well as in small ganglia on the bladder wall, releasing acetylcholine (Ach). The postganglionic axons continue for a short distance in the pelvic nerve and terminate in the detrusor layer where they

release Ach to the smooth muscle fibers, with consequent contractions of the bladder. Effect of Ach is mediated by muscarinic receptors in detrusor cells. Although M2 is most abundant in detrusor cells, the M3 sub- type is the major receptor mediating stimulation of detrusor contractions.

In addition to this, some postsynaptic parasympathetic neurons exert a relaxation effect on urethral smooth muscles, most likely via nitric oxide (NO) Fig.1. Thus when the bladder contracts during micturition phase, the internal urethral sphincter relaxes.

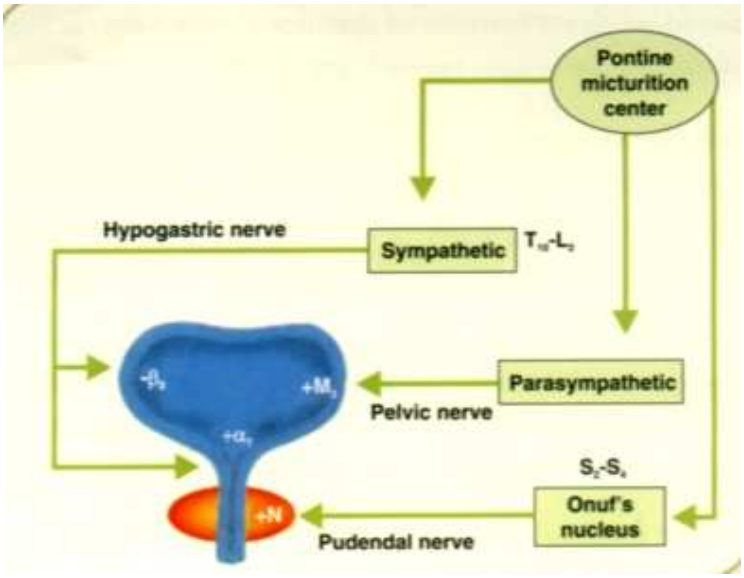


Fig.2 : Reflex Pathway

Sympathetic nerves stimulate smooth muscle contraction in the urethra and bladder neck and cause relaxation of the detrusor. Sympathetic neurons in the intermediolateral column of segments T10 – L2 synapse with postganglionic neurons in the inferior mesenteric ganglia. Postganglionic axons travel in the hypo gastric nerve and release nor epinephrine (NE) at their terminals in the urethra, the bladder neck, and the bladder body. NE stimulates contraction of urethral and bladder neck smooth muscles via α1–adrenoceptors

and causes relaxation of detrusor via β2 – adrenoceptors and β3 – adrenoceptors, the latter being most predominant.

Somatic nerves provide excitatory innervations to the striated muscles of the EUS and pelvic floor. The efferent motor neurons are located in Onuff's nucleus in spinal cord segments S2 – S4. The motor neuron axons are carried in the pudendal nerve and release Ach at their terminals. Ach acts on nicotinic receptors in the striated muscles, inducing muscle contraction to maintain closure of the EUS.

Decades of experiments and clinical studies have shown that normal coordination of storage and voiding function requires integration from supraspinal input. Besides as yet undetermined, the regions in the brainstem that act as components of the supraspinal – spinal – lower urinary tract pathway are the laterodorsal tegmental nucleus, known as the pontine micturitition center (PMC).

Ventrolateral to the PMC is a region referred to as the pontine storage center (PSC). The PMC and PSC are the final integrative centers, receiving and integrating input from afferent spinal cord nerves and more rostral brain regions and controlling the lower urinary tract. Neurons in the PSC project directly to the motor neurons in Onuff's nucleus and stimulation of PSC neurons cause EUS contractions. Neurons in the PMC project to the sacral parasympathetic nucleus, and stimulation of PMC neurons results in bladder contractions as well as relaxation of the internal urethral sphincter and EUS (Fig.2).

Multiple reflex pathways operate between the CNS and the lower urinary tract. At the simplest level, the central pathways operate as on / off switching. These circuit switches are timed precisely so that, when urethral smooth muscle is being stimulated by the hypogastric nerve to contract the bladder detrusor is not receiving stimulatory input from the pelvic nerve.

CAUSES OF OAB [21]

1. Idiopathic – Majority of cases do not have a demonstrable cause.

2. Neurological injuries – spinal cord injury or cerebro vascular accident.

3. Neurological disease – Multiple sclerosis, Dementia, Parkinson's disease, Medullary lesions.

4. Non – neurological causes – urinary tract infection, carcinoma bladder, Bladder calculi, Bladder inflammation, or Bladder out Let obstruction (BOO)

5. Drug therapy – Diuretics can lead to symptoms of urge incontinence. This is due to increased filling of the bladder, stimulating the detrusor. Drugs used in urinary retention can also lead to increased contractions of detrusor leading to OAB.

When the bladder fills, detrusor activity may be either normal or increased (over activity). The normal bladder may also be termed as "stable" in comparison to OAB which is termed as "unstable". In normal function; detrusor relaxes and stretches to allow the bladder to increase the volume without any change in pressure. This low – pressure system is important for

two principal reasons. Firstly, it allows efficient transport of urine through the ureters. Second, it is an essential factor in maintaining continence.

Detrusor Instability (DI)

It occurs during the filling phase. These are involuntary detrusor contractions that the patient cannot suppress. These contractions may be spontaneous or else may only occur on provocation. The unstable detrusor may be asymptomatic and its presence does not necessarily imply a neurological disorder. This is the commonest form of detrusor over activity.

DI can manifest in different patterns:

- Spontaneous DI – The instability has no particular trigger.
- Provoked DI – Instability is triggered by a certain factor, and is categorized by the provoking factor. The commonest are change in position, for e.g. rising from sitting or lying to standing and coughing.
- Hand – washing or putting hands into cold water.
- Latchkey incontinence where a patient wishing to pass urine reaches the front door but before they can turn the key they have extreme urgency and leak
- Telephone urgency (where telephone conversation can lead to urgency)

Normal patients with over active bladder can be divided mainly into two broad groups a) Idiopathic DI. b) DI and Bladder outlet obstruction.

a. Idiopathic DI.

Idiopathic DI, with or without urge incontinence, is a common urological problem. It is more prevalent in females and men are also not excluded from this. The incidence increases significantly with age.

b. DI and Bladder outlet obstruction

DI may or may not occur in the presence of bladder outlet obstruction. In majority of cases this is due to benign prostatic obstruction (BPO) secondary to benign prostatic enlargement (BPE). DI occurs in 50 – 75% of men with bladder outlet obstruction.

Detrusor Hyper reflexia

Detrusor hyper reflexia is defined as bladder over activity due to disturbance of the nervous control mechanisms. There are a number of neurological conditions which commonly lead to lower urinary tract dysfunction. These conditions may be congenital, for example meningomyelocele or sacral agenesis or else acquired including multiple sclerosis, cerebrovascular accidents, spinal cord trauma and parkinsons disease.

Urge Incontinence

Urinary urgency and urge incontinence are two of the common symptoms that characterize OAB syndrome[22]. Other symptoms include urinary frequency (more than 8 micturitions in 24 hours) and nocturia.

Urge incontinence is an abrupt and intense urge to urinate that cannot be suppressed, followed by an uncontrollable loss of urine. Some people experience the abrupt and intense urge to urinate but are still able to remain continent. People with urge incontinence usually have little time to get to the bath room before they have an accident.

Urge incontinence is reported in around 20% of men and 40% of women with over active bladder symptoms, and is the most bothersome & upsetting symptom of an over active bladder[23].

Urge incontinence is the most common type of persistent incontinence in older people and often has no clear cause. Urge incontinence in older people may be caused by a combination of over activity of the muscles in the bladder along with poor squeezing ability of those muscles. Chronic over activity of the bladder is common in older people and cause abrupt and intense urge to urinate as well as frequent urination during the day and night.

MANAGEMENT OF OVER ACTIVE BLADDER

Treatment of detrusor over activity can be divided into

I. Non pharmacological and

II. Pharmacological aspects

I Non pharmacological

A. Conservative

B. Electrical stimulation

C. Surgical management

II Pharmacological

- Anti – cholinergic agents
- Calcium antagonists
- Potassium channel openers
- Prostaglandin inhibitors
- Adrenergic drugs
- Tricyclic anti depressants

I. Non – Pharmacological

A. CONSERVATIVE [24]

A- 1. Behavioral therapy

Advice on fluid intake, this includes the volume, timing and the type of fluid taken. Patients should be advised

- Not to drink before going out
- Not to drink prior to bed time or during night.

- To maintain an adequate fluid in take i.e. one to two liters.

- To avoid fluids which precipitate symptoms, like caffeine and alcohol.

A – 2. Bladder training

Bladder training, behavioral therapy, behavioral modifications are the terms used interchangeably in this.

- Patient education about lower urinary tract function

- Which includes instituting intervals of timed voiding and gradually increasing these intervals

A – 3. Pelvic floor exercises (PFE)

The patients are taught to do “quick flicks” of the pelvic floor musculature, to inhibit the micturition reflex.

A – 4. Bio feed back

It is a technique that provides visual and or auditory signals to an individual with respect to his or her performance of a physiologic process, in this case pelvic floor muscle contraction, EMG or vaginal pressure measurement are generally used.

B. ELECTRICAL STIMULATION

Neuro stimulation of the pudendal nerves or sacral roots has been shown to inhibit detrusor contractions presumably by the recruitment of the inhibitory

neural pathways. To date, there are still no clinical predictors for the out come of neuro stimulation.[25]

C. SURGICAL MANAGEMENT

This is reserved for those patients who have failed conservative treatment. The various procedures described are

- Cystoplasty: At present it is the most effective procedure for the symptomatic relief of over active bladder.
- Detrusor myomectomy

It is considered to be inferior to cystoplasty, it involves removal of a segment of detrusor muscle.

II. Pharmacological

By pharmacological as well as molecular cloning techniques muscarinic receptors have been divided into five subtypes.[26]

M1 - In brain – cortex, Hippo campus, glands, sympathetic ganglia

M2 - In heart, hind brain, smooth muscles

M3 - In smooth muscles, glands, brain

M4 - In basal fore brain, striatum

M5 - Substantia nigra

The drugs for over active bladder are:

1. Anti-cholinergic

    a. Oxybutynin chloride

b. Propiverine

c. Dicyclomine hydrochloride

d. Flavoxate hydro chloride

e. Propanthaline bromide

f. Trospium chloride

g. Darifenacin

h. Tolterodine chloride

i. Solifenacin.

2. Calcium antagonists

a.Terodiline

3. Potassium channel openers

4. Prostaglandin inhibitors

5. β - Adrenergic Agonists

6. α - Adrenergic Antagonists

7. Tri cyclic anti – depressants

1.a. OXYBUTYNIN CHLORIDE

It is approved for use in OAB since 1972 and it remained the comer stone of OAB therapy for over 20 years. It is selective for M_1 and M_3 muscarinic receptors. It has a direct anti spasmodic and has some local anesthetic effect in urinary bladder.

It under goes extensive first pass metabolism to N-des ethyl oxybutynin (DEO) an active anti cholinergic metabolite that has properties six fold higher

than the parent compound. In humans, it has higher affinity for parotid gland than bladder[27]. The drug was developed originally for gastro intestinal hyper motility disorders. Its direct smooth muscle relaxant effects are 500 times weaker than its anti – muscarinic effects[28]. DEO is responsible for the majority of the adverse effects of oxybutynin. Alternate routes of administration are by intravesical, skin patches, or rectal routes. High incidence of side effects particularly related to salivary gland secretion is often significant enough to cause patients to discontinue taking the medication.

1.b. PROPIVERINE

It is a tertiary amine similar to oxybutynin. It has direct muscle relaxant properties and local anaesthetic activity. The urodynamic effect is similar to oxybutynin. The incidence of dryness of mouth is lower than oxybutynin with propiverine.

1.c. DICYCLOMINE HYDROCHLORIDE

It has a direct relaxant effect on smooth muscles in addition to anti muscarinic action. Dicyclomine is not widely used in the treatment of OAB.

1.d. FLAVOXATE HYDROCHLORIDE

It has a weak anti cholinergic effect, moderate calcium antagonist activity, local anaesthetic properties and ability to inhibit phosphodiesterase. It has no effect on detrusor hyper reflexia.

1.e. PROBANTHALINE BROMIDE

It is a non – selective muscarinic antagonist. High doses produce symptoms of ganglionic blockade. Toxic doses block the skeletal neuromuscular function.

1.f. TROSPIUM CHLORIDE

It has anti muscarinic action having higher specificity towards M_3 receptor in the bladder. Because this drug does not undergo hepatic metabolism by cytochrome P-450 system at therapeutic levels, 80% of the drug is execrated unchanged in the urine. Additionally, its safety profile for reducing CNS effects is promising due to the hydrophilic design, which minimizes passage of the drug through the blood brain barrier. [29, 30]

1.g. DARIFENACIN

It is a selective M_3 receptor antagonist with selectivity for urinary bladder over the salivary glands. It has adverse effects like dry mouth, constipation, dizziness and somnolence. 10mg dose of darifenacin showed urodynamic improvements in patients with OAB, with significant reduction in salivary flow. 2.5 mg dose not have any effect on salivation, but this dose is not effective for bladder. [31, 32]

2. CALCIUM CHANNEL BLOCKERS: - TERODILINE [33]

The role of calcium as a messenger in linking extracellular stimuli to the intracellular environment is well established including its involvement in

excitation – contraction coupling in striated, cardiac and smooth muscles. The dependence of contractile activity on changes in cytosolic calcium varies from tissues to tissue, as do the characteristics of the calcium channels involved. It has both calcium antagonist and anti cholinergic properties. At low concentration, it has mainly anti cholinergic effect, whereas at higher concentration it is totally a calcium antagonist action. Its side effects are hypotension, facial flushing, head ache, dizziness, constipation, rashes, weakness and palpitation. Because of cardiac toxicity it was withdrawn. A bladder specific calcium channel antagonist is not known to exist.

3. POTASSIUM CHANNEL OPENER

They efficiently relax various types of smooth muscles, including detrusor smooth muscle, by increasing potassium efflux, resulting in membrane hyperpolarisation. Pinacidil and cromokalim perhaps are found to be 200 times more potent as inhibitors of vascular preparations than detrusor muscle.[34]

4. PROSTAGLANDIN INHIBITORS

It has a role in the excitatory neuro transmission to bladder and in the development of bladder contractility. There is a theoretical basis for the use of COX – 2 Inhibitors in OAB, but there is no objective evidence available at this time.

5. β - ADRENERGIC AGONISTS – TERBUTALINE.

The presence of β - adrenergic receptor in human bladder has promoted attempts to increase bladder capacity. Its stimulation cause no change in lung

capacity in normal human where as it does affect patients with bronchial asthma.

It also produces palpitation, tachycardia and tremors. The ICI committee does not recommend this drug for the management of OAB.[35]

6. α - adrenergic antagonists

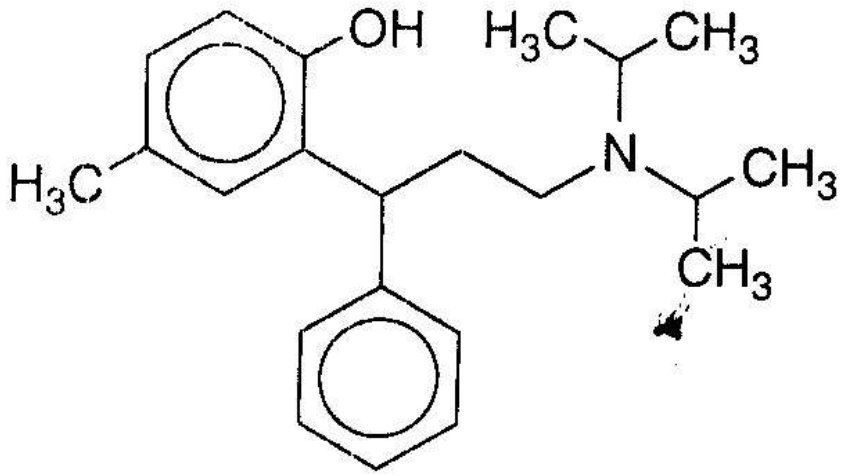
These drugs have no significant role to decrease detrusor contractility or increase bladder capacity, because α - adrenergic antagonists have minimal contractile effects on human detrusor smooth muscle from normal individuals. However, the peripheral contribution of these receptors of the bladder get changed in neurological diseases or injury and in bladder outlet obstruction. Parasympathetic decentralization has been reported to lead to a marked increase in adrenergic innervations of the bladder, with a resultant conversion of the usual beta (relaxant) response of the bladder in response to sympathetic stimulation to an alpha (contractile) effect. ICI committee judged the pharmacologic and physiologic evidence and they did not recommend it for OAB.

7. Tricyclic anti depressants

Tricyclic anti depressants such as imipramine are useful agents for facilitating urine storage. They act by decreasing bladder contractility and by increasing outlet resistance. They have central and peripheral anti – cholinergic effects. It is effective in the treatment of nocturnal enuresis in children.[36]

TOLTERODINE

It is a new competitive muscarinic receptor antagonist with good clinical efficacy. It was one of the most frequently prescribed single agent for the treatment of OAB in USA.



Structural formula of Tolterodine

It is not receptor selective but at least in some experimental models, it showed selectivity for bladder tissue over salivary tissue[37].

Pharamacokinetics [38]

Absorption: It is rapidly absorbed from gastro intestinal tract. The bioavailability of tolterodine is approximately 86% and plasma concentrations of tolterodine are proportional to the dose administered. Its passage across blood brain barrier is restricted.

Metabolism: Tolterodine is extensively metabolized in the liver. The primary pathway for metabolism is by CYP2 D6. It is converted into an active metabolite, 5 hydroxy methyl tolterodine (5 – HM) that has 100% potency of toltrodine. Following an oral dose 4mg, the peak serum concentration of 5 HM, achieved is 5mg/mL. Variation in CYP2 D6 level do not affect the duration of action of drug.

Excretion: It is excreted in the urine and feces.

No significant gender difference is present in the kinetics of tolterodine. It is contraindicated in pregnancy and lactating mothers. It should be used with caution in hepatic impairment.

Stahl and coworkers studied the effect of a single dose 6.4mg of tolterodine on bladder and salivary function. They found that the inhibitory effect on bladder function persisted upto 5 hours. But it was observed that the stimulated salivation was inhibited only around the time of peak serum levels. 5 hours after administration of tolterodine, the effect on bladder was maintained, where as no significant effect on salivation could be detected[39].

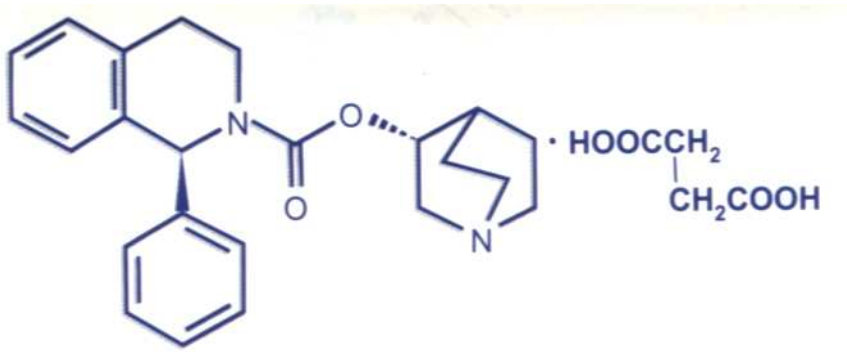
In another study, Appell analysed a total of 1120 patients in whom the effect of tolterodine 1 or 2mg given twice daily was compared with immediate release oxybutynin 5mg given three times a day. It was found that both the drugs significantly reduced the OAB symptoms and increased the volume voided per void. There was no difference in efficacy between the 2 mg dose of tolterodine and the 5mg dose of oxybutynin. But tolerance was significantly

better with tolterodine. The adverse effects such as dry mouth leading to dose reduction and patient withdrawals were more with oxybutynin.

In the year 2000, Chancellor and his colleagues reported that in a double blind study [40] where tolterodine 2mg twice daily was compared with placebo, the symptoms of OAB were significantly reduced from baseline in tolterodine group. But the incidence of severe and moderate dry mouth was 2% and 10% respectively with tolterodine as against 0% and 2% of placebo. The other adverse events such as constipation were also significantly high in the tolterodine group.

SOLIFENACIN

Solifenacin succinate is a muscarinic antagonist. Chemically, solifenacin succinate is butanedioic acid, compounded with (1S) – (3R) – 1 azabicyclol (2.2.2) oct-3 – yl3. 4-dihydro-1-phenyl-2 (1H) - isoquinolinecarboxylate (1;1) having an empirical formula of C_{23} H_{26} N_2 O_2 C_4 H_6 O_4 [41]



Structural formula of solifenacin succinate.

Solifenacin is competitive muscarinic receptor antagonist. Muscarnic receptors play an important role in several major cholinergically mediated functions, including contractions of urinary bladder, smooth muscles and stimulation of salivary secretion. As we know that contraction of bladder is carried out by the release of acetylcholine from cholinergic nerves leading to stimulation of muscarinic receptors on the detrusor smooth muscle.

Solifenacin acts as a direct antagonist at muscarinic acetylcholine receptors in cholinergically innervated organs. Its antiocholinergic-parasympatholytic action reduces the tones of smooth muscle in the bladder, effectively reducing the number of required voids, urge incontinence episodes, urge severity and improving retention, facilitating increased volume per void.

Pharamacokinetics:

Absorption: After oral administration, peak plasma levels of Solifenacin are reached within 3-8 hours and at steady state ranged from 32.3 to 62.9ng/ml for the 5 and 10mg solifenacin tablets respectively. The absolute bioavailability of solifenacin is approximately 90% and plasma concentrations of solifenacin are proportional to the dose administered.

Effect of food: There is no significant effect of food on the pharmacokinetics of Solifenacin.[42]

Distribution: Solifenacin is approximately 98% bound to human plasma proteins, principally to ∝1-acid glycoprotein. Solifenacin is highly distributed to non-CNS tissues.

Metabolism: Solifenacin is extensively metabolized in the liver. The primary pathway for elimination is by way of CYP3A4; however, alternate metabolic pathway exists. The primary metabolic routes of solifenacin are through N – oxidation of the quinuclidin ring and 4R – hydroxylation of tetrahydroisoquinoline ring. One pharmacologically active metabolite (4R – hydroxy Solifenacin), occurring at low concentrations and unlikely to contribute significantly to clinical activity, and three pharmacologically inactive metabolites (N-glucuronide and the N-oxide and 4R hydroxyl-N-oxide of Solifenacin) have been found in human plasma after oral dosing.

Excretion: It is excreted mainly in urine and feces. The major metabolites excreted in urine are N – oxide of solifenacin, 4R-hydroxy N-oxide of solifenacin, and in feces 4R-hydroxy solifenacin. The elimination half – life of solifenacin following chronic dosing is approximately 45-68 hours.

Pharmacokinetics in special populations

Age: Multiple dose studies of solifenacin in elderly volunteers (65-80 years) showed that plasma half life values were 20-25% higher as compared to the younger volunteers (18-55 years).

Pediatric population: The pharmacokinetics of solifenacin has not been established in pediatric patients.

Gender: The pharmacokinetics of Solifenacin is not significantly influenced by gender.

Race: The number of subjects of different races studied are not adequate to make any conclusion on the effect of race on the pharamacokinetics of Solifenacin.

Renal impairment: Solifenacin should be used with caution in patients with renal impairment. Doses of Solifenacin greater than 5mg are not recommended in patients with severe renal impairment. It is contraindicated in severe hepatic impairment.

Pregnancy and Lactation

There are no adequate and well-controlled studies in pregnant women, because animal reproduction studies are not always predictive of human response. The effect of solifenacin on labor and delivery in human has not been studied. After oral administration of solifenacin to lactating mice, radioactivity was detected in maternal milk. It is not known whether solifenacin is excreated in human milk. Because many drugs are excreted in human milk, solifenacin should not be administered during breast feeding.

Drug – drug interaction: At therapeutic concentrations, solifenacin does not inhibit CYP 1A1/2, 2C9, 2C19, 2D6 or 3A4 derived from human liver microsomes. Inducers or inhibitors of CYP 3A4 may alter solifenacin pharmacokinetics.

The administration of 10mg of Solifenacin, in the presence of 400mg of ketoconazole, a potent inhibitor of CYP3A4, the mean plasma concentration

maximum and AUC of solifenacin are increased by 1.5 and 2.7 – fold respectively.

Therefore it is recommended not to exceed a 5mg of daily dose of Solifenacin when administerd with therapeutic doses of ketoconazole or other CYP 3A4 inhibitors.

Oral contraceptives: There are no significant changes in the plasma concentration of combined oral contraceptives (ethynyl estradiol/levogestrel) when administered along with solifenacin.

Warfarin: Solifenacin has no significant effect on the pharmacokinetics of R-warfarin or S-warfarin.

Digoxin: Solifenacin has no significant effect on the pharmacokinetics of digoxin (0.125mg/day) in healthy subjects.

Indications

Solifenacin is indicated for the treatment of OAB with symptoms of urge urinary incontinence, urgency and urinary frequency.

Contraindications

It is contraindicated in patients with urinary retention, gastric retention, and uncontrolled narrow angle glaucoma and in patients who have demonstrated hypersensitivity to the drug.

Precautions

- Bladder out flow obstruction
- Gastrointestinal obstruction disorders and decreased GI motility
- Controlled narrow – angle glaucoma
- Reduced renal function
- Reduced hepatic function.

Geriatric use: The safety and effectiveness between older and younger patients treated with solifenacin is similar.

Adverse reactions

Expected side effects of anti muscarinic agents are dry mouth, constipation, blurred vision (accommodation abnormalities), urinary retention and dry eyes. The most common adverse events reported in patients treated with solifenacin were dry mouth and constipation and the incidence of these side effects was higher in the 10mg compared to the 5mg group.

Dosage and Administration

The recommended dose of Solifenacin is 5mg once daily.

The tolerability of Solifenacin was assessed in single dose and multiple dose studies conducted at Netherland Europe in 2003[43]. The single dose study was a dose escalating study in which the patients were asked to take only one dose of solifenacin 5, 10, 20, 30, 40, 60, 80 and100 mg. They were advised to return for post study visit 10-17 days after dosing. In the multiple doses study the patients were given Solifenacin 5, 10, 20 & 30 mg once daily for 28 consecutive days. The incidence of adverse events were analysed and was found that the adverse events were more in multiple dose studies than single dose studies and there was a dose dependant increase in the incidence of adverse events. The incidence of adverse events with 5 mg solifenacin given for 28 days was 62.5%. There were no cases of dry mouth (0%), but 37.5% the patients suffered from blurred vision and 12.5% patients had headache & somnolence.

In another study conducted Sheffield, United Kingdom 2003, a total of 225 patients aged between 21 to 83 years, with OAB were randomized to receive solifenacin or tolterodine or placebo. 85% of the subjects [192 patients] completed the study.[44] Patients received once daily doses of solifenacin 2.5, 5, 10 and 20mg or tolterodine 2mg twice daily or placebo for 28 days. The results were analyzed after 2 weeks.

It was observed that the frequency of micturition reduction occurred rapidly with 2.5, 5, 10, and 20mg/day dosages of solifenacin compared with placebo. It was significant for 5 & 10mg and highly significant for 20mg. Though tolterodine was superior to placebo, solifenacin produced better results when compared with tolteradine. The other parameter, volume voided per void

showed statistically significantly increase from baseline to study end point with solifenacin group, when compared with placebo and tolterodine.

5 mg solifanacin was found to be as effective as higher doses of solifenacin (10 & 20 mg). 5 mg solifenacin resulted in 18% reduction of number of micturition episodes in 24 hrs, 28% improvement in mean volume voided per void and 42% reduction in urgency episodes.

In an international multicentre randomized, double blind study conducted at New Jersey, USA, 2003[45] of 12 weeks duration, solifenacin was compared with tolterodine and placebo. In this study, adult patients with symptoms of OAB were treated with solifenacin 5mg or 10mg once daily, tolterodine 2mg twice daily and placebo. 1281 patients were enrolled and 1033 patients completed the study. Both solifenacin and tolterodine were observed to be significantly superior to placebo. But the reduction of mean number of micturition/24 hours, reduction of mean number of urgency episodes (5 mg solifenacin – 51.9%, 2 mg tolterodine – 37.9%) and reduction in the number of incontinence episodes were significantly in favor of solifenacin than tolterodine.

STAR trial Brimingham, UK, 2005 conducted in patients with OAB published in 2005 reported a comparative evaluation of efficacy and tolerability of solifenacin and extended release tolteradine in treating OAB. This was a prospective, double blind, double dummy, parallel group, 12 week study, conducted with 5 & 10 mg of solifenacin and tolterodine extended release tablet 4 mg. It was concluded that solifenacin was superior to tolteradine ER with respect to majority of the efficacy variables. They analised the efficacy

variables such as urgency episodes, incontinence episodes, urge incontinence and pad usage. In this study 50% reduction in incontinence episodes was observed. The majority of side effects were mild to moderate in nature and discontinuations were low and comparable in both solifenacin & tolterodine groups. [46]

Tolterodine has been tested in patients for a duration ranging from 2 to 12 weeks. But it was observed that after 2 weeks of treatment, a dose – related improvement in micturition variables was observed. The difference was significant for urgency, frequency of micturition and average volume voided per micturition.[47]

In different studies conducted with solifenacin, effect of solifenacin on micturiton variables was evaluated after 4 weeks and 12 weeks of therapy. It was observed that maximum effect was evident as early as in 4 weeks.[44]

This study is planned to evaluate the efficacy and tolerability of solifenacin 5 mg once daily in comparison with tolterodine 2 mg twice daily in 30 patients with OAB. Since the antimuscarinic effect of tolterodine and solifencain becomes evident by 2 to 4 weeks of therapy, the duration of this study was limited for 4 weeks.

STUDY OBJECTIVES

- To compare the efficacy of solifenacin (5 mg once daily) and tolterodine (2 mg twice daily) in reducing the number of micturitions per day (24hours), number of incontinence episodes, urgency episodes in patients with over active 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 center

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, randomized, parallel group, prospective study.

Study duration

4 weeks.

Study period

01-05-05 to 15-06-2006

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 24hours and >3episodes 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 anti muscarinic therapy is contraindicated. such as patients with urinary retention, gastric retention or uncontrolled narrow- angle glaucoma.
- ❖ An indwelling catheter or use of intermittent catheterization.
- ❖ QT interval prolongation in ECG
- ❖ Significant hepatic, cardiac, renal, hematological, 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 anti muscarinic drug or any drug for urinary incontinence or any non- pharmacological treatment for over active bladder including electro- stimulation or bladder training within two weeks before the study.

- ❖ Taken part in any other investigational study in the last one-month prior to enrollment.

3. Urine culture positive growth for microorganisms.

4. Pregnant or breast-feeding woman or woman of child bearing 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 out-patient department of Urology in Government General Hospital and Kasturba Gandhi Government Hospital for Women& Children, Chennai, with symptoms of over active bladder [Increased frequency of micturition more than 8 times per day and more than 3 episodes of urgency, with or without urge incontinence and nocturia in three days consecutive days] 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 haematalogical 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 liter 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 out patient 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 randomized to receive either solifenacin or tolterodine.

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

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

- Drugs were issued for 2 weeks only. They were asked to report to the out patient department at the end of 2 weeks.

- In the four weeks study, patients had to make two follow up visits to the out patient 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 out patient 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 12th, 13th and 14th day of each follow up 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 follow-up visit date.

Followup-1

After 14 days the study participants were instructed to report to the outpatient department along with the filled voiding diary card, medication compliance card and empty medication pack, which were collected. Adverse effect if any reported was recorded. A new medication compliance card, voiding diary card and medication for the subsequent 2 weeks were issued and were instructed to follow the same procedure as done before.

Followup-2

At the end of 28th day, the voiding diary card, drug compliance card and**.** **e**mpty medication packs were collected. Adverse effect if any was recorded. Routine clinical examination, clinical assessment about urinary symptoms, subjective assessments of problems associated with bladder symptoms were recorded and compliance with medication were assessed at the end of 14th day and 28th day.

Global assessment of over all efficacy and tolerability by patient and urologist was recorded. Complete Haemogram, blood biochemistry and urine routine analysis were done at the end of the study.

Clinical assessment was based on the urinary symptoms which were recorded in the voiding diary. The improvement in urinary symptoms was decided based on the following efficacy variables, the reduction in the number of micturition per 24 hours, number of incontinence episodes, urgency episodes, volume of urine voided and nocturia.

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 problem

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

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

Global assessment by patient and urologist for over all 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 over all tolerability

Patient	**Urologist**
0 - Very good	0 - Very good
1 - Good	1 - Good
2 - Satisfactory	2 - Satisfactory
3 - Poor	3 - Poor

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

LABORATORY ASSESSMENT

The following laboratory parameters were done

1. Haemogram

   Haemoglobulin [Hb%], platelet count, Total count, Differential count.

2. Blood chemistry

   Blood sugar

   Blood urea

   Serum Creatinine

   Total bilirubin

   Serum glutamic oxaloacetic transaminase [SGOT]

   Serum glutamic pyruvate transaminase [SGPT]

3. Urinalysis

   Urine routine albumin, sugar, deposits

   Urine culture for microorganism.

4. X- Ray chest

5. ECG

   1, 2, 3, were done at screening & at the end of 28 days.

   4, 5, were done at screening only

Lab parameters were concidered to be abnormal as shown below

Hb% decrease by 5% difference- significant.

TC increase/ decrease by 5% difference- significant.

Serum creatinine increase by 5% difference- significant.

Glucose increase/decrease by 20%- significant

Bilirubin increase by1.5 times- significant

SGOT/SGPT increase by1.5 times- significant.

The results were analyzed statistically.

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 solifenac in and tolteradine.

Table-1 Shows the statistical value of average number of micturition

- Values are mean ± SEM

- The reduction from the base line to end point was statistically significant for both soliteracin and tolterodine.[$p<0.001$]

- The reduction in the average number of micturition at the end of the study in both solifenacin group and tolterodine group was compared. It was statistically significant for solifenacin ($p < 0.05$).

Figure-3 Shows the graphical representation of average number of micturition between two drugs

- The average no of micturition by the drug solifenacin reduced from 13.07 at base line to 6.2 at the end of 28 days [end point].

- The average no of micturition by the drug tolterodine reduced from 12.27 at base line to 7.53 at the end of 28 days [end point].

Table-2. Shows the statistical value of urgency episodes

- Values are mean ± SEM

- The reduction from the base line to end point was statistically significant for both soliteracin and tolterodine.[$p<0.001$]

- The reduction in the average number of urgency at the end of the study in both solifenacin group and tolterodine group was compared. It was statistically significant for solifenacin ($p < 0.05$).

Figure-4 Shows the graphical representation of urgency episodes between two drugs

- The reduction of mean no of urgency episodes by the drug solifenacin from base line 6.67 to 1.6 at 28 days [end point]. was represented in the graph.

- The reduction of mean no of urgency episodes by the drug tolterodine from base line 6 to 2.07 at28 days [end point]. was marked in the graph.

Table-3 Shows the statistical value of mean number of incontinence

- Values are mean ± SEM

- The reduction from the base line to end point was statistically significant for both soliteracin and tolterodine.[$p<0.001$]

- The reduction in the average number of incontinence at the end of the study in both solifenacin group and tolterodine group was compared. It was statistically significant for solifenacin ($p < 0.05$).

Figure-5 Shows the graphical representation of mean number of Incontinence between two drugs

- The reduction of mean no of incontinence episodes by the drug solifenacin from base line to 28 days [end point] 1.8 to 0.13 is represented in the graph.

- The reduction of mean no of incontinence episodes by the drug tolterodine from base line to 28 days [end point] 2.23 to 0.43 was shown in the graph.

Table-4 Shows the statistical value of mean number of volume voided

- Values are mean ± SEM

- The increased mean volume voided from base line to 28 days [end point] was significant for both the drugs [P<0.001].

- The increase of volume voided at the end point of both drugs was compared it was statistically significant for solifenancin (P<0.05).

Figure-6 Shows the graphical representation of mean number of volume voided between two drugs

- The increase in mean volume voided by the drug solifenacin from base line to 28 days [end point] was 168ml to 268ml represented in the graph.

- The increase in volume of urine voided by the drug tolterodine from base line to 28 days [end point] was 157ml to217ml represented in the graph.

Table-5 Shows the statistical value of nocturia

- Values are mean ± SEM

- The reduction of nocturia from base line to 28days[end point] was significant for both the drugs.[$p<0.001$].

- The reduction of nocturia at the end point for solifenacin was significant when compared with the tolterodine end point value ($P<0.05$).

Figure-7 Shows the graphical representation of mean number of nocturia between two drugs

- The reduction of mean no of nocturia by the drug solifenacin from base line to 28 days [end point] was 5.4 to 0.87, which is shown in the graph.

- The reduction of mean no of nocturia by the drug tolterodine from base line to 28 days [end point] was 4.67 to 1.07, which is shown in the graph.

Table-6. Shows the statistical analysis of global efficacy assessment by patient and urologist

- The efficacy analysis of reduction in urinary symptoms from baseline to 28 days [end point]. The percentage was better in solifenacin groups.

Figure-8 Shows the graphical representation of global efficacy assessment by patient and urologist

- The efficacy analysis of urinary symptoms by patients and urologist was represented in the graph for both the drugs.

Table-7. Shows the statistical analysis of global tolerability assessment by patient and urologist

- In tolerability analysis the percentage of tolerability to drug solifenacin is more than the drug tolterodine.

Fig-9: Shows the graphical representation of tolerability of both the drugs by patients and urologist.

ADVERSE EVENTS

No adverse events were experienced in the solifenacin group. Where as 5 patients (33.3%) in the tolterodine group experienced dry ness 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.

DISCUSSION

OAB is more prevalent in older age groups and more common in women. Generally anticholinergics are useful in OAB. But atropine was rarely used to treat this condition due to its systemic side effects. The clinical utility of available antimuscarinic agents is limited because of their lack of bladder specific action.

Propantheline bromide was first used in OAB, but it has systemic antimuscarinic action which approximates atropine. Oxybutynin a M1 & M3 receptor blocker was in use for more than 20 yrs. Having high affinity for parotid gland than bladder, its use is also on decline.

Tolterodine, a non selective muscarinic blocker shows selectivity to bladder with antimuscarinic side effects. Then Darifenacin which is said to be uro selective but still in impairs salivary flow. Solifenacin is a new drug having high potency and bladder specific muscarinic (M3) blocking property with minimal side effects.

There were only few foreign studies which described the comparative efficacy of tolteroadine and solifenacin in OAB. No study was done with these two drugs in India to evaluate the efficacy and safety in OAB.

Institute of Pharmacology, Madras Medical College, Chennai in collaboration with Dept. of Urology, Government General Hospital, Chennai and Department of Urology, Kasturba Gandhi Government Hospital for

Women & Children, Madras Medical College, Chennai has undertaken the study to compare the efficacy and tolerability of solifenacin and tolerodine in OAB.

In our study 30 patients with the clinical features of OAB were included. They were treated with either solifenacin 5 mg /day or tolterodine 2 mg twice daily for 4 weeks.

The efficacy variables such as, reduction in the number of micturition per 24 hours, number of incontinence episodes, urgency episodes, volume of urine voided and nocturia were recorded during baseline and at the end of the study (after 28 days) was analysed statistically. Global assessment of efficacy and tolerability by both patient and urologist was done at the end of the study. Adverse events, it reported or observed were recorded.

Symptoms of OAB

In our study **frequency** of micturition which is a very trouble some symptom of OAB was reduced. When comparing baseline to the end point with in the groups, there was a statistically significant reduction in frequency of micturition ($p < 0.001$). On comparing end point value of solifenacin and tolerodine groups, there was a statistically significant reduction in solifenacin group ($P < 0.05$). The percentage reduction in the frequency of micturition with solifenancin 5 mg once 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 solifenancin 5 mg od.[44]

In our study **Urgency** episodes were reduced in both the groups. When comparing the base line to the end point within the groups, there was a statistically significant reduction in urgency of micturition ($P < 0.001$). On comparing the end point value of solifenacin and tolterodine groups, there was a statistically significant reduction in soliferacin group ($P < 0.05$). The percentage reduction in urgency episodes in our study was 79.29% for solifenancin and 63.09% for tolterodine. But in a study conducted in New Jursy USA, 2003[45], it was observed that reduction in urgency episodus for soliferancin 4 mg was 51.9% and 37.9% for tolterodine.

The **Incontinence** episodes reduced in both the trial drugs during our study ($P < 0.001$) in comparing the baseline to end point values with in the groups. In comparing the end point value of solifenacin and tolterodine, solifenacin was statistically significant ($P < 0.05$) than tolterodine. In Star Trial conducted in Brimingham, UK 2005[46], it was reported that the percentage of reduction in continence episodes from baseline to the end of the study was 50% with soliferacin 5 mg. But in our study the reduction in incontinence episodes was 96.26% with solifenancin 5 mg and 84.6% for tolterodine 2 mg.

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 soliferacin 5 mg was 61.67% and for talterodine it was 42.27%.

Nocturia was reduced in both groups in this study. Nocturia reduction also shows the same results ($P < 0.001$). In between end point of two drugs solifenacin was better ($P < 0.05$).

Efficacy analysis by the patient showed solifenacin to be better than tolterodine. Of the 15 patients in solifenacin group 2(13.3%) assessed the therapy to be ‘very good’, 11(73.4%) patients attributed the efficacy to be ‘good’ and two patients 13.3% were satisfied. Where as in tolterodine group none of the patients claimed the therapy to be very good, 7(46.7%) patients responded with the reply ‘good’ and the rest ‘satisfactory 53.5%. Statistical analysis also stand soliferacin to be better than tolterodine, ($p < 0.05$).

The efficacy analysis by the urologist also showed solifenacin to be a better drug in OAB. According to the assessment by urologist solifenacin produced ‘very good’ results in 2 patients (13.3%) and the rest were ‘good’ (86.7%) responder. The effect of tolterodine was good in 10 patients 66.7% and satisfactory in 5 patients. 33.3% Onanalysis statistically solifenacin was better than tolterodine ($P < 0.05$).

The over all efficacy assessment by the patient and the urologist were in favour of solifenacin.

Tolerability was also better for solifenacin than tolterodine, when assessed by patients and urologist.

Adverse effects:

In our study solifenacin group experienced no adverse effect, where as tolterodine group 5 patients reported dryness of mouth (33.3%) which did not require discontinuation of therapy.

In a study conducted at Ntherland Europe 2003[43] 5 mg soliofenacin resulted in 37.5% of blurred vision and 12.5% of head ache & somnolence. But in our study there was no adverse event with solifenacin 5 mg.[43]

Laboratory parameters

There was no statistically significant change in the laboratory parameters, when comparing baseline and end point values with in the groups.

The results of our study were well in accordance with the studies conducted abroad. Solifenacin produced better control of symptoms in over active bladder and was well tolerated.

CONCLUSION

From our study we conclude that solifenacin 5mg once daily is effective and well tolerated than tolterodine 2mg twice a day in the management of over active 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.

* Better tolerance.

Table - 1: Average number of micturition episodes

Number of micturition episodes	Solifenacin (n=15)	Tolterodine (n=15)	Solifenacin Vs Tolterodine (end point analysis)
Baseline	13.07 ± 2.99	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	

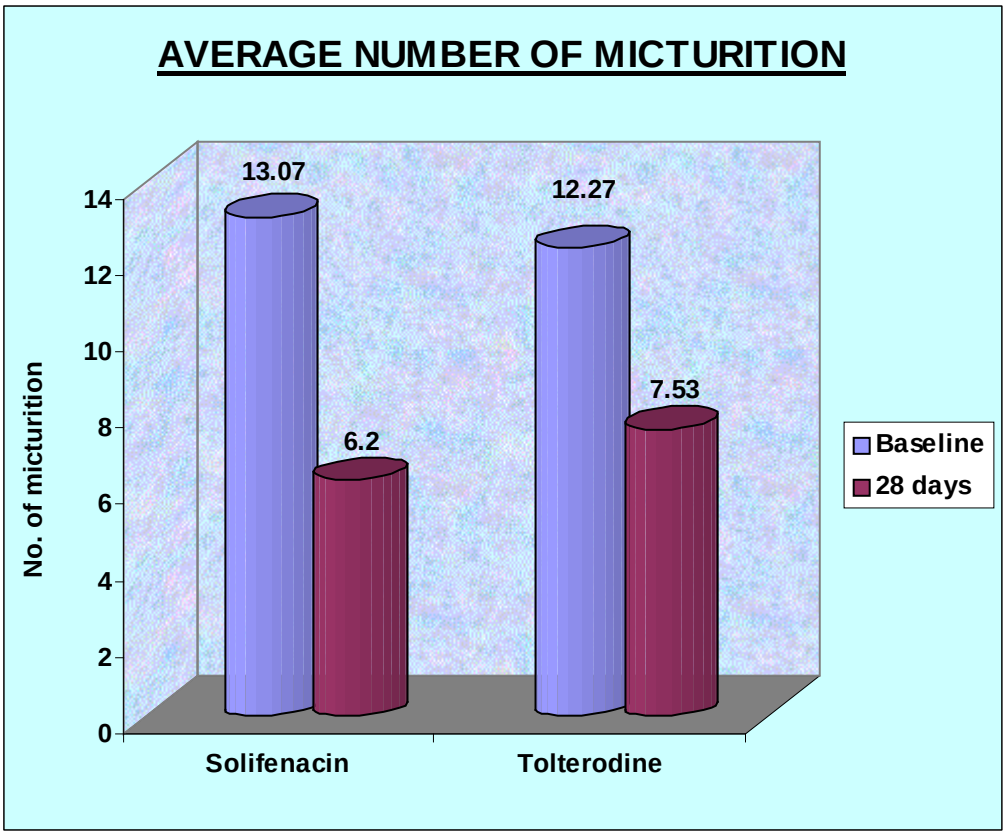


Fig-3 is graphical representation of table-1

Table-2: Mean number of urgency 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	

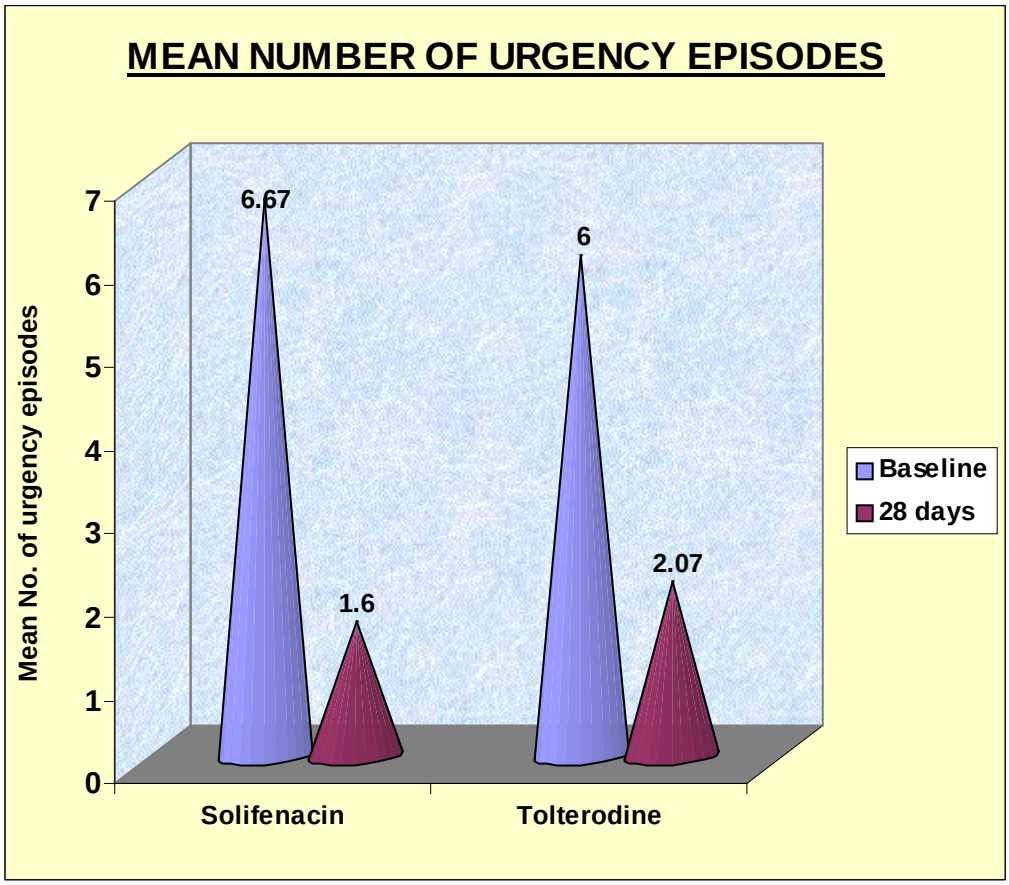


Fig-4 is the graphical representation of table-2

Table - 3: Mean number of incontinence episodes

Mean number of incontinence	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	

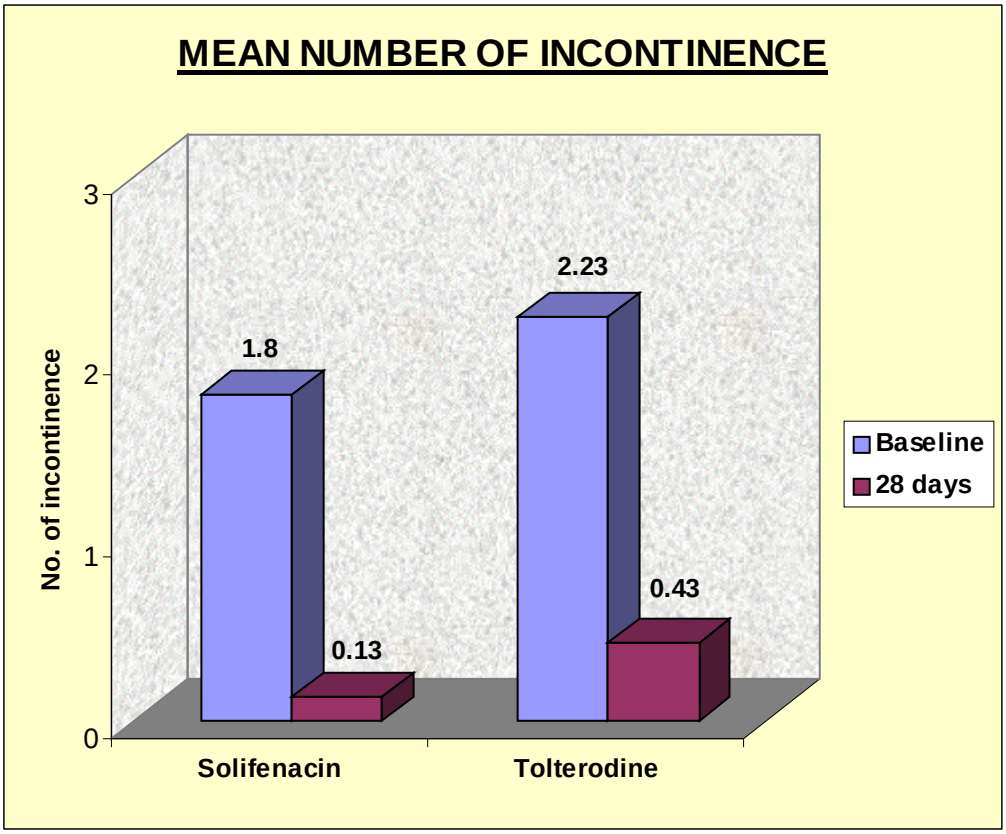


Fig-5 is graphical representation of table-3

Table - 4: Mean number of volume voided per void

Mean number of volume voided	Solifenacin [n=15]	Toltreodine [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	

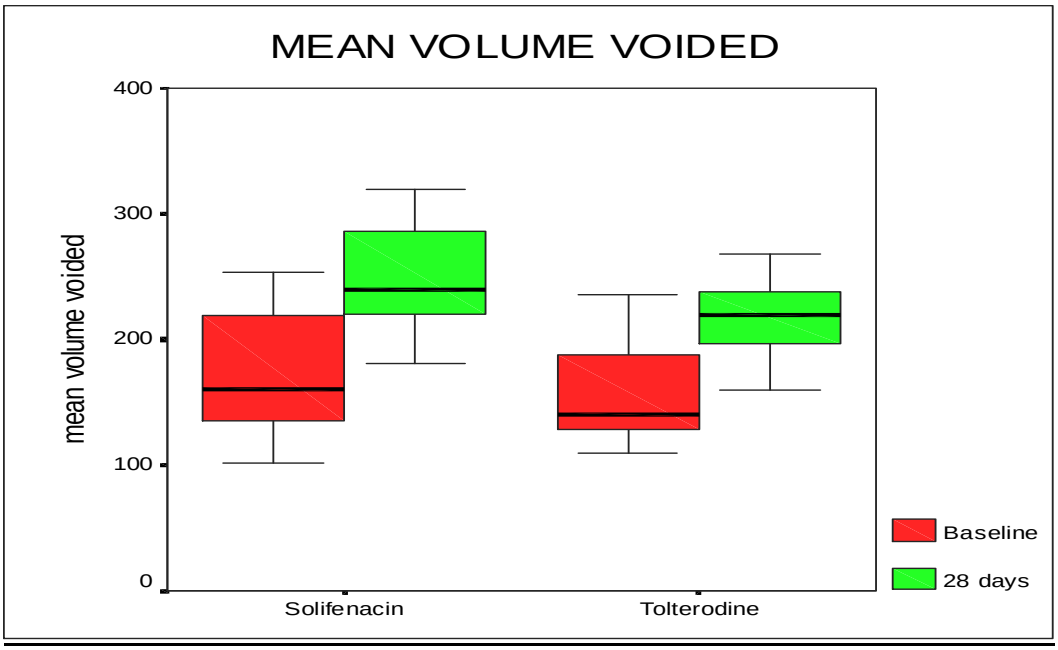


Fig-6 is graphical representation of table-4

Table-5 Mean number of nocturia episodes

Number of nocturia episodes	Solifenacin	Tolterodine	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	

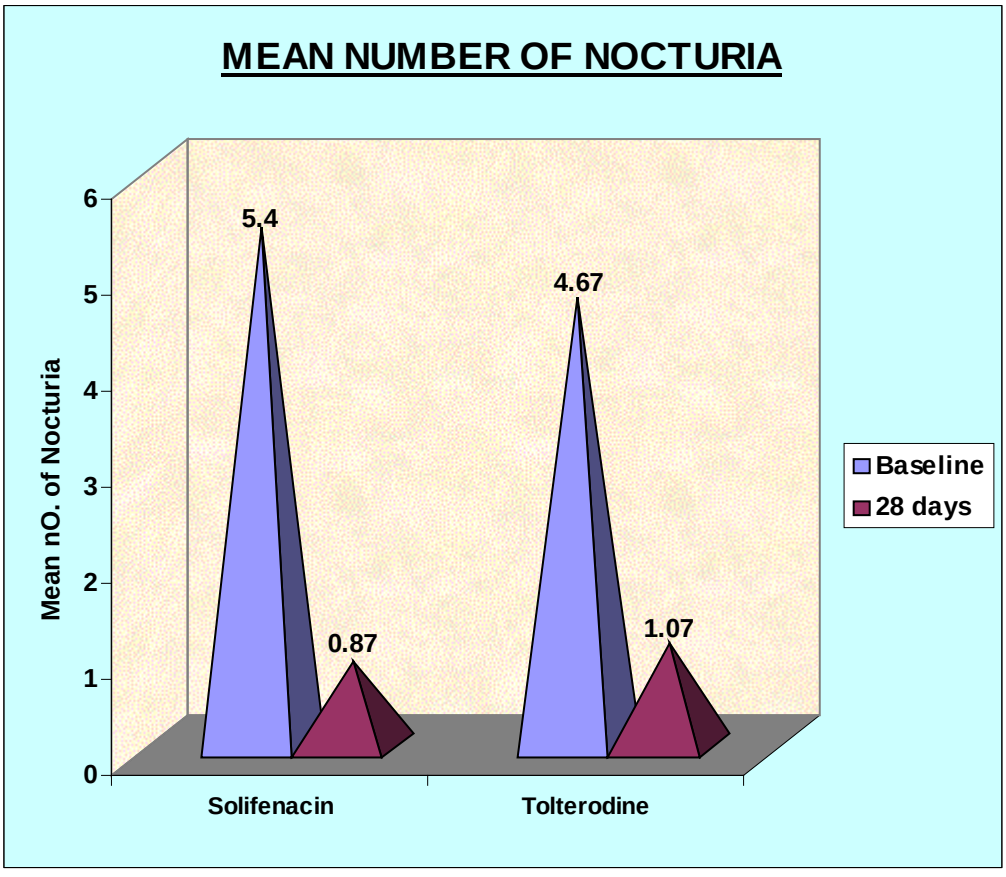


Fig-7 is graphical representation of table-5

Table -6: Global efficacy assessment

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

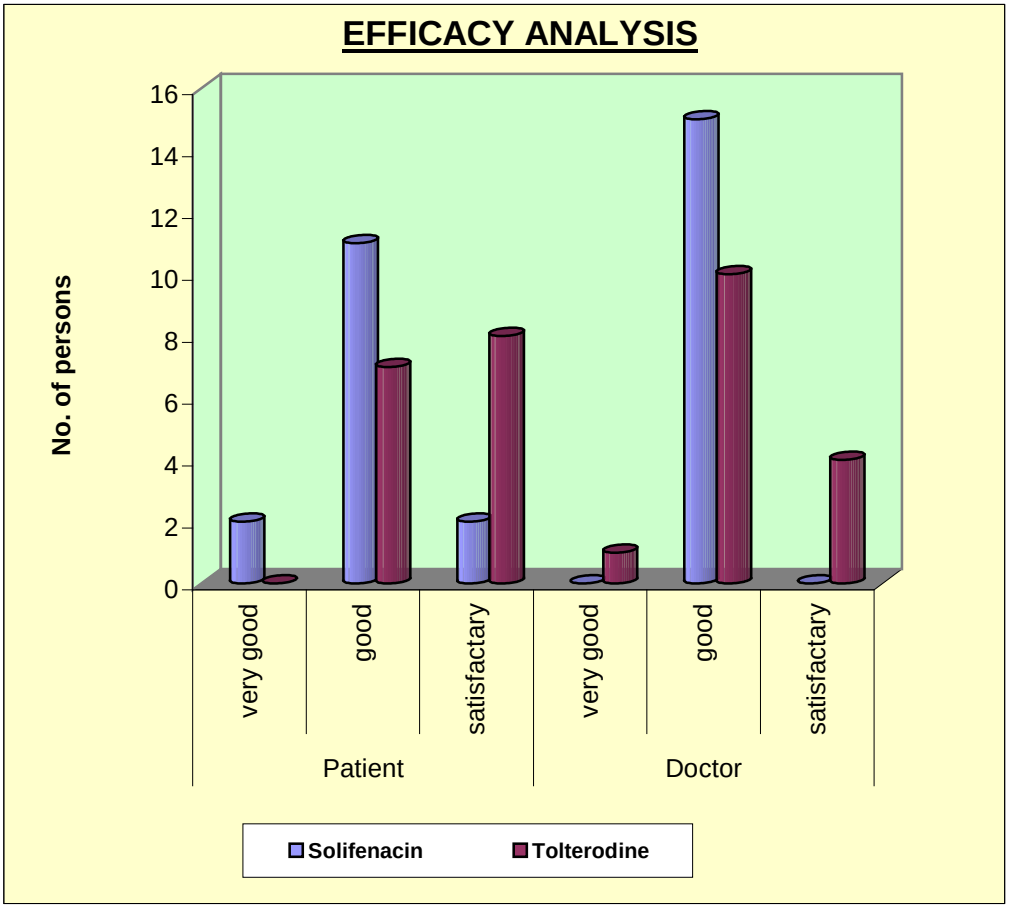


Fig-8 is graphical representation of table-6

TABLE - 7: Global tolerability assessment

Tolerability		Groups				χ^2 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%	

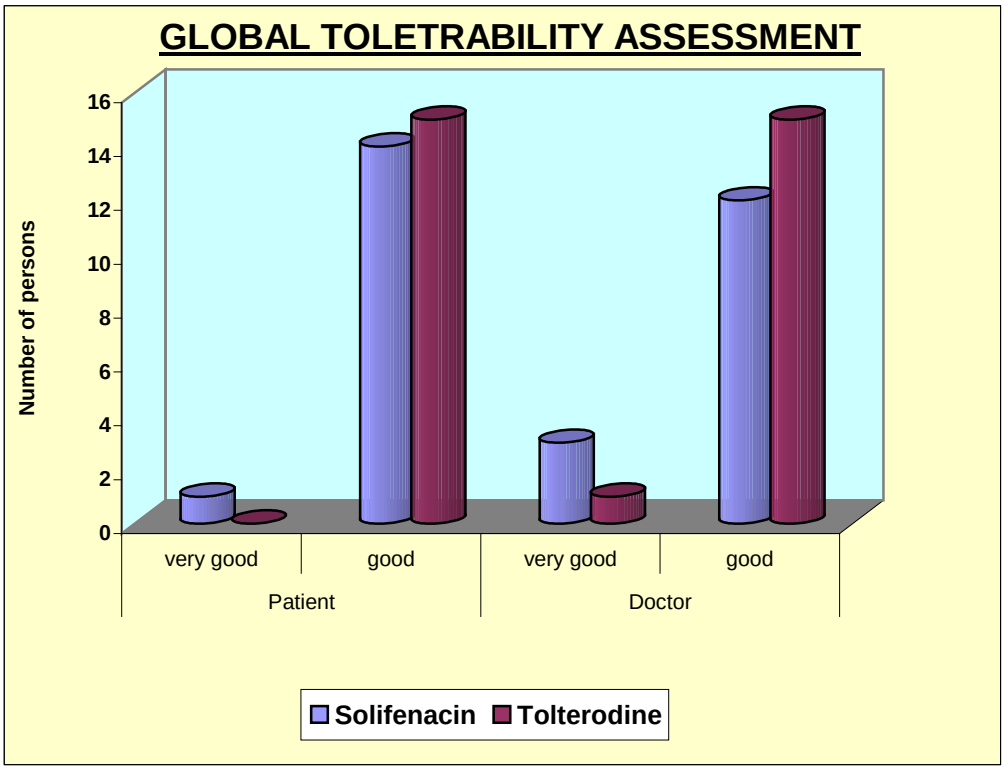


Fig-9 is graphical representation of table-7

Table - 1: Average number of micturition episodes

Number of micturition episodes	Solifenacin (n=15)	Tolerodine (n=15)	Solifenacin Vs Tolterodine (end point analysis)
Baseline	13.07 ± 2.99	12.27 ± 2.09	Two sample t test P <0.005
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	

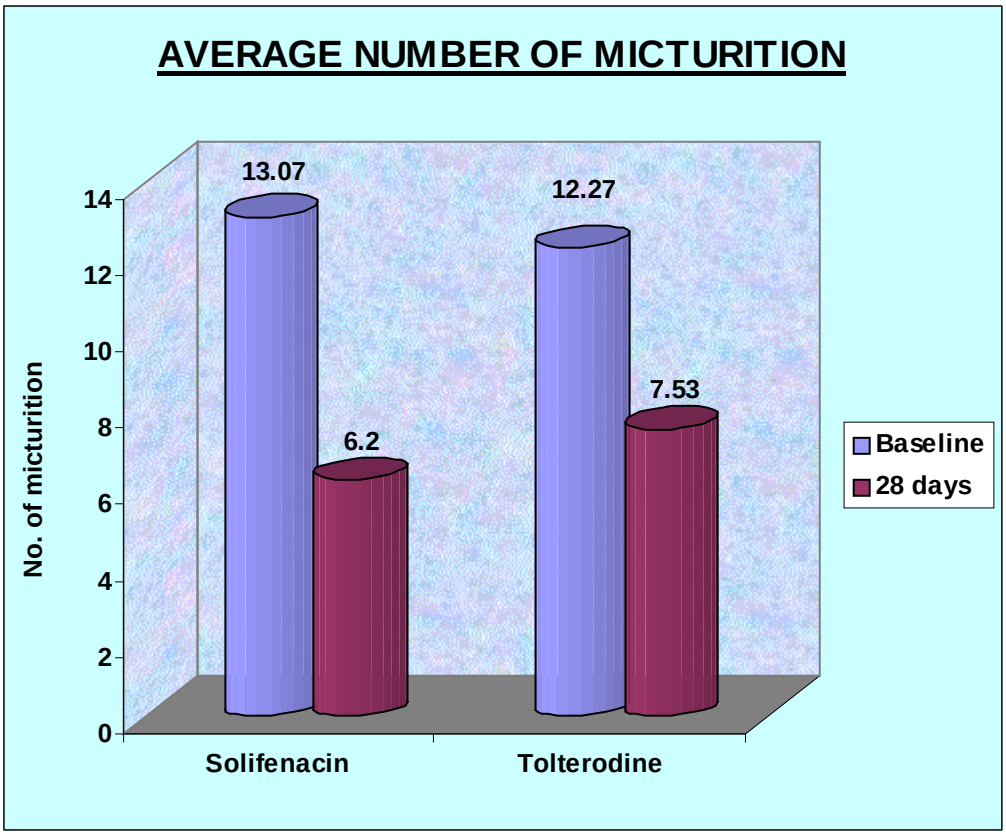


Fig-1 is graphical representation of table-1

Table-2: Mean number of urgency 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 <0.005
End point (28 days)	1.60 ± 1.68	2.07 ± 0.88	
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Statistical test and significance level	Paired t test p < 0.001	Paired t test p < 0.001	

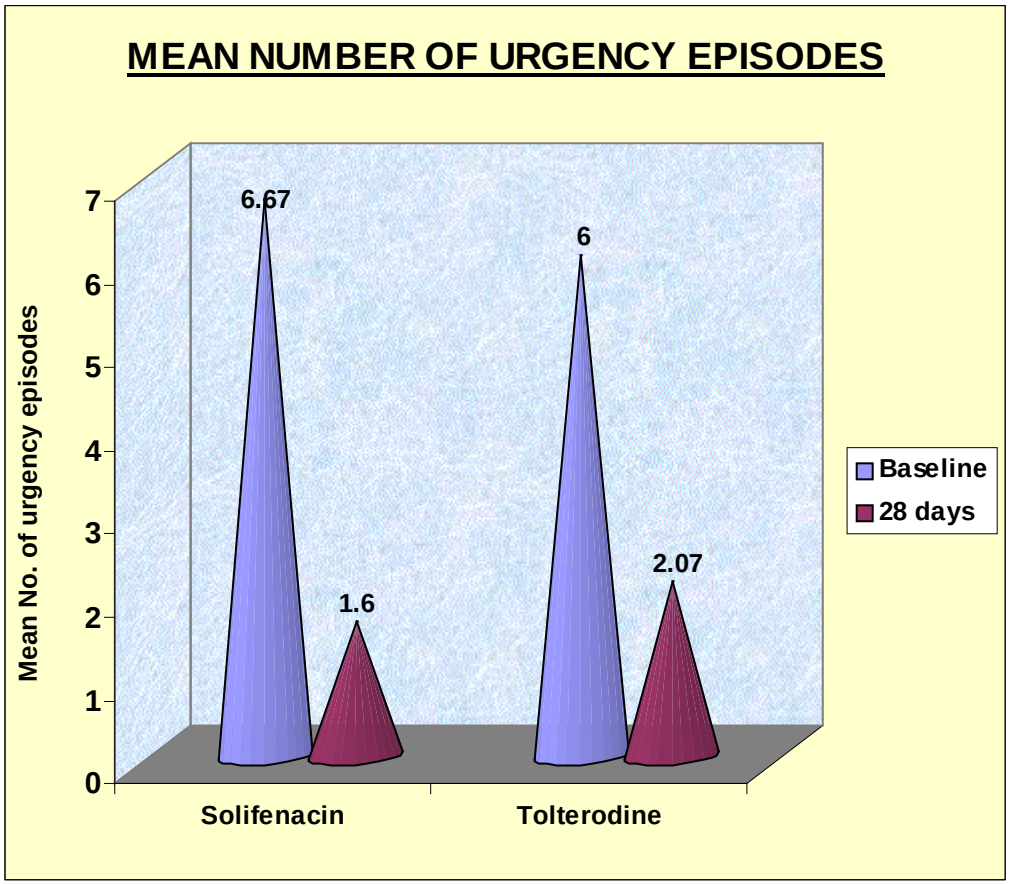

Figure-2 is the graphical representation of table-2

Table - 3: Mean number of incontinence episodes

Mean number of incontinence	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	

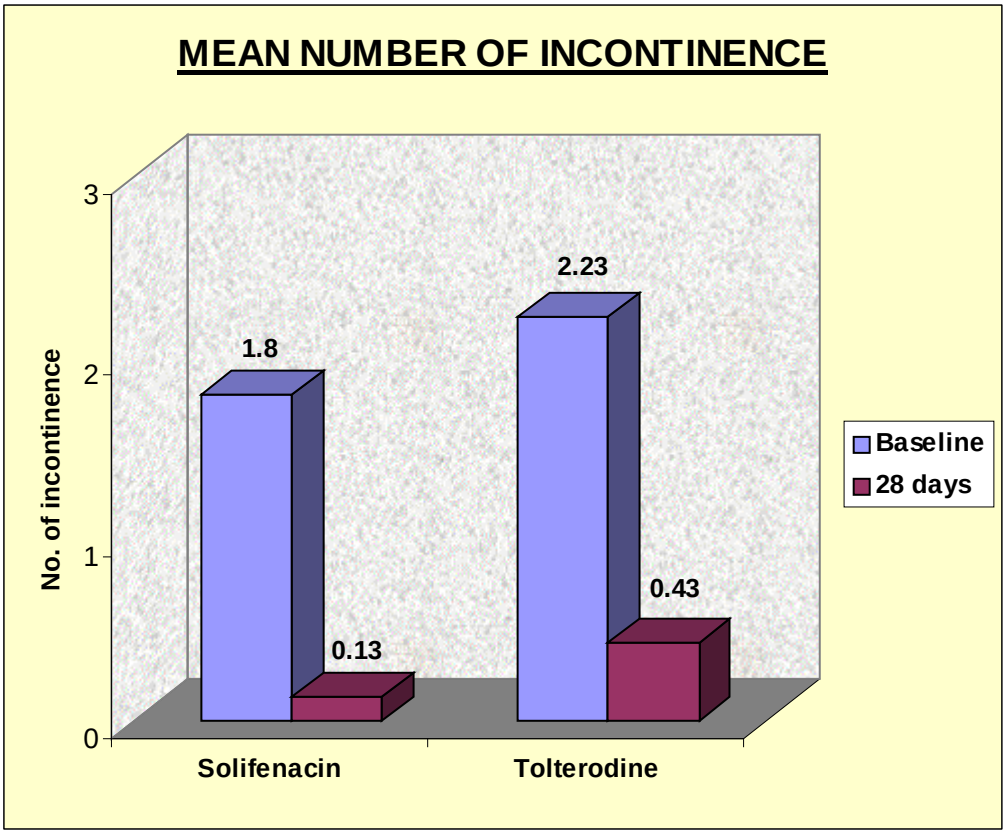

Fig-3 is graphical representation of table-3

Table - 4: Mean number of volume voided per void

Mean number of volume voided	Solifenacin [n=15]	Toltreodine [n=15]	Solifenacin Vs Tolterodine (end point analysis)
Baseline	168.87 ± 50.45	157.07 ± 39.58	Two sample t test P< 0.03
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Statistical test and significance level	Paired t test p < 0.001	Paired t test p < 0.001	

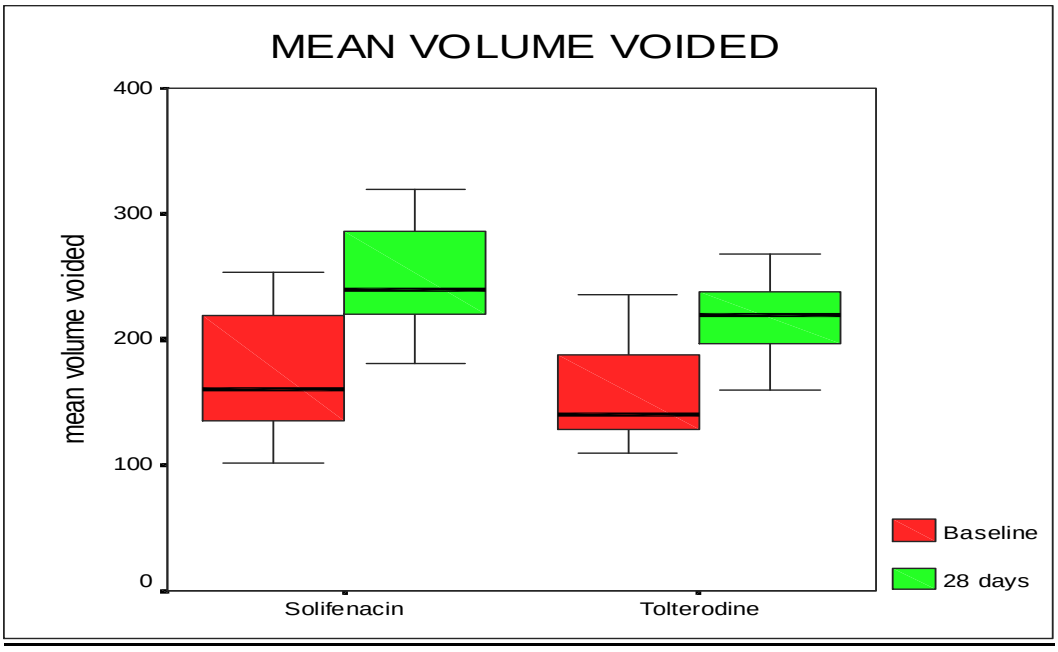

Fig-4 is graphical representation of table-4

Table-5 Mean number of nocturia episodes

Number of nocturia episodes	Solifenacin	Tolterodine	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	

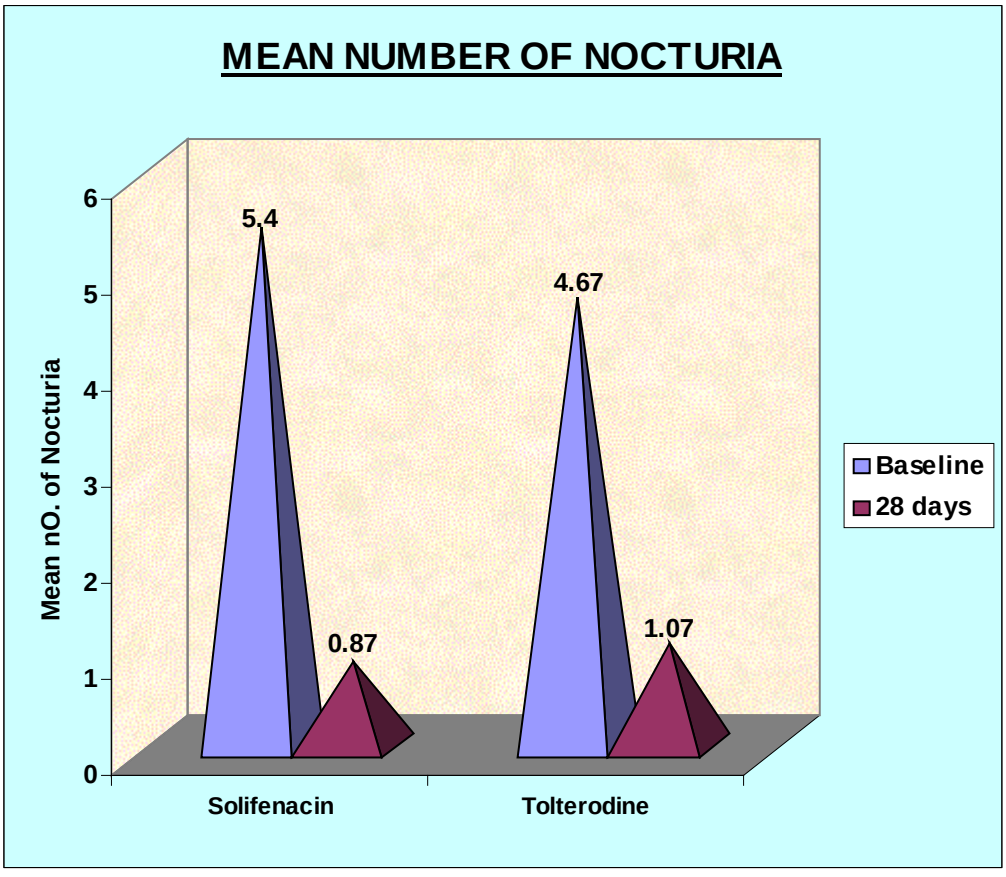

Fig-5 is graphical representation of table-5

Table -6: Global efficacy assessment

Efficacy assessment		Groups				χ^2 test
		Solifenacin		Tolterodine		
		N	%	N	%	
Patient	Very good	2	13.3%	0	0%	
	Good	11	73.4%	7	46.7%	
	Satisfactory	2	13.3%	8	53.3%	P = 0.04
Doctor	Very good	2	13.3%	0	0%	
	Good	13	86.7%	10	66.7%	P < 0.05
	Satisfactory	0	0%	5	33.3.7%	

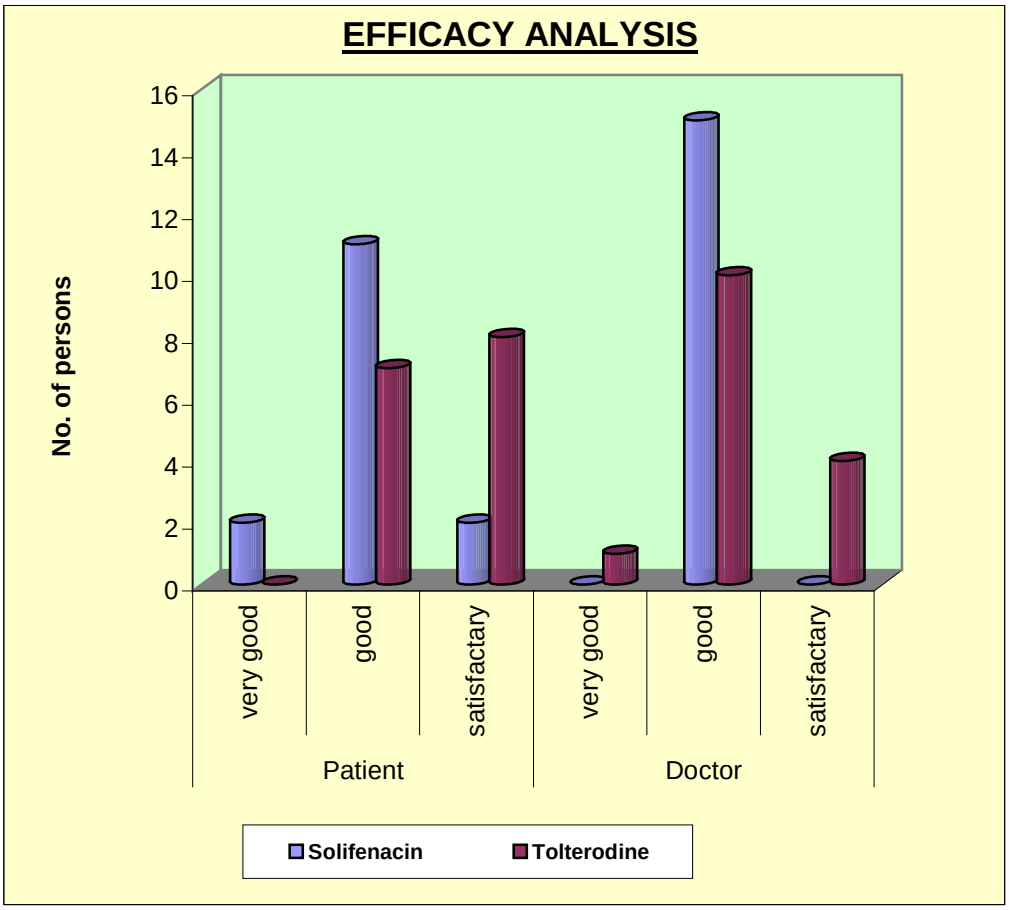

Fig-6 is graphical representation of table-6

TABLE - 7: Global tolerability assessment

Tolerability		Groups				χ^2 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%	

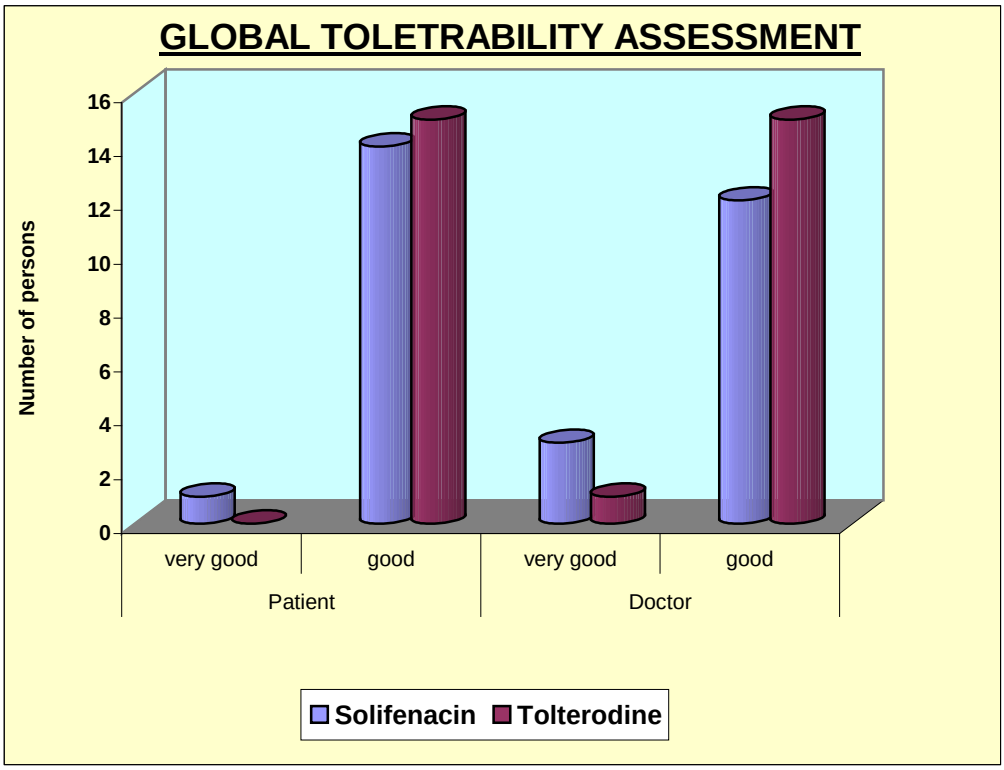

Fig-7 is graphical representation of table-7