

# Safety and Efficacy of Intermittent Versus Continuous Anticholinergic Medication in Management of Overactive Bladder in Adult

Magdy Fath Alla, Mahmoud Ahmed Mahmoud, Abd El-Rahman Sayed Youssef

Department of Urology, Faculty of Medicine, Ain Shams University

## ABSTRACT

**Background:** overactive bladder (OAB) also referred to as the urgency-frequency syndrome, with or without urge urinary incontinence can considerably impair the patient's quality of life. It is widely accepted that diet and life style modifications, behavioral therapy and medication belong to the standard conservative therapeutic options and considered as the first-line measures. The International Consultation on Incontinence (ICI) guidelines reported that when the first line approach is not fully satisfactory or fails after 8-12 weeks, alternative therapies should be sought out. It is worthwhile and justified to proceed to second-line therapy if patients are refractory to antimuscarinic therapy or if the treatment is contraindicated. Second-line of therapies include less-invasive measures such as percutaneous posterior tibial nerve stimulation, sacral neuromodulation, detrusor injections with botulinum toxin (BTX) and whereas more-invasive measures constitute surgical techniques e.g. bladder augmentation or substitution. Pelvic neuromodulation has been proven effective and is today an established treatment option for patients refractory to or intolerant of conservative treatments.

**Objective:** this study aimed to compare between the efficacy of continuous anticholinergic therapy and intermitted anticholinergic therapy for treatment of the overactive bladder.

**Patients and Methods:** our study included 60 patients categorized into two groups: continuous anticholinergic therapy group and intermitted anticholinergic therapy. By using 12 weekly intermitted anticholinergic therapies, remarkable clinical results were obtained. Percent of the patients who complained OAB in the intermitted anticholinergic group reported a statistically significant subjective success. These patients chose to continue treatment to maintain the response.

**Results:** patients in the intermitted anticholinergic therapy group showed significant improvement of frequency (31%) urgency (50%) urge incontinence (50%) and nocturia (53%) compared to propiverine group frequency (50%) urgency (60%) urge incontinence (67%) and nocturia (67%). No serious side effects were reported, in group A 8 patients had harm of dry mouth in 5 cases (16.7%), constipation in 2 cases (67%) 8 blurred vision in one case (33%). In group B, there were 5 patients (16.7%) in the harm of dry mouth in 3 cases (10% constipation in one case (3.3) and blurred vision in one case (3.3%).

**Conclusion:** our study concluded that intermittent anticholinergic therapy induced improvement of bladder over activity symptoms and less side effects than continuous anticholinergic group.

**Keywords:** bladder outlet obstruction , lower urinary tract symptoms , overactive bladder ,urinary urge incontinence , neurogenic detrusor overactivity , detrosor overactivity

## INTRODUCTION

Overactive bladder (OAB) refers to a complex of urinary symptoms defined by the International Continence Society (ICS) as urgency, with, or without urgency incontinence, usually accompanied by frequency and nocturia and without proven infection or other obvious pathology. The symptom complex is suggestive of detrusor overactivity, which can be further defined as being of unknown cause (idiopathic detrusor overactivity or due to a neurological condition (neurogenic detrusor overactivity) <sup>(1)</sup>.

The mainstay of treatment currently is the use of anticholinergic drugs. Although there has been considerable development in these drugs over the last decade, with more bladder specific preparations available, many patients even if they find them effective can struggle with side-effects. These commonly included dry mouth, constipation

and heartburn. Of particular concern in the elderly, is possible cognitive side-effects seen with some drugs such as confusion or memory loss which may limit their use. New approaches such as using a transdermal route of administration may be helpful in reducing the side-effects although skin irritation can be a problem <sup>(2)</sup>.

Newer second line treatment options included the use of intravesical botulinum toxin, sacral nerve stimulation and percutaneous posterior tibial nerve stimulation <sup>(3)</sup>. So we conducted a systematic review of the intermittent versus continuous anticholinergic medication in the treatment of overactive bladder trying to minimize the side effects of the medication and also measure its safety and efficacy in both groups.

At birth, the bladder stores and

discharges urine in a rhythmic manner independent of cortical control. This pattern gradually comes under voluntary control sometime during the first 5 years of life. The development of voluntary control probably requires a number of maturational developments<sup>(9)</sup>.

It originates in the thoraco-lumbar cord. The preganglionic neuron supplying the bladder and urethra arises from T12 to L2 spinal cord. They exit the spinal cord in the ventral roots and can either course through or synapse on postganglionic neurons in the sympathetic chain. The sympathetic efferent divided into two branches at this point and run in the left and right hypogastric nerves; they are joined by parasympathetic pelvic nerves bilaterally in the inferior hypogastric plexuses from which they spread out to innervate the pelvic organs, including the lower urinary tract<sup>(5)</sup>. Muscarinic receptors are functionally coupled to G proteins, but the signal transduction systems vary. M1, M3 and M5 receptors are excitatory, whereas M2 and M4 receptors are inhibitory<sup>(6)</sup>. Detrusor smooth muscle of humans as well as animals contains mainly M2 and M3 receptors. In the human detrusor, 70% of the total muscarinic receptor population was of the M2 subtype, 20% of the M3 subtype and 10% of the M1 subtype. The ratio between muscarinic M2 and M3 receptors in binding studies has been estimated as 9:1<sup>(7)</sup>.

Absolute contraindications to use anticholinergic medications included narrow-angle glaucoma, intestinal obstruction, cardiac arrhythmia, and myasthenia gravis. Ultimately, establishing realistic and individualized treatment options is essential for all patients. When optimized patients can expect a 43% to 70% reduction in their OAB and urge incontinence symptoms<sup>(8)</sup>.

### AIM OF THE WORK

This study aimed to illustrate the safety and efficacy of intermittent versus continuous anticholinergic medication in management of overactive bladder in adult patient.

### PATIENTS and METHODS

Our study comprised a prospective randomized double armed study without cross

over. It included sixty patients who were complaining from frequency, urgency, nocturia and urge incontinence, enrolled from Ain Shams University Hospital and the Fayoum General hospital.

#### Inclusion criteria

Patients attending the outpatient clinics in the previous hospitals complaining from overactive bladder symptoms (Frequency, urgency, nocturia, urge incontinence). Detrusor over activity diagnosed by urodynamic study. No pharmacological treatment for one week before beginning the study. Age between 20 and 45 years. The condition persisted for more than 6 months.

#### Exclusion criteria

Urinary tract infection. (Evidence of urinary tract infection manifested by WBCs in urine). Stable bladder diagnosed by urodynamic study. Neurological problems as cerebrovascular stroke, parkinsons disease, (evidence of neurogenic voiding dysfunction) Presence of stress or mixed urinary incontinence. History of surgery for urinary incontinence.

#### All patients were subjected to:

**1- History taking:** all patients included in this study had complete medical history including urological symptoms as frequency, urgency, nocturia or urge incontinence. Medical history included drugs as anti-cholinergics, anti-diabetic drugs should be considered. Previous operations especially the pelvic surgeries.

**2-Examination:** all patients underwent physical examination which included neurological assessment of perianal sensation, anal sphincter tone and a brief screening for any neurological factors as Parkinson's disease or cerebrovascular stroke.

**3-Voiding diaries:** all patients underwent 3 days voiding diary at base line and at week 13 with evaluation of frequency, urgency, urge incontinence and nocturia symptoms.

**4-investigations:** complete urine analysis, pelvi-abdominal ultrasound, urodynamic evaluation before treatment to confirm the diagnosis of detrusor overactivity and at 13 week to assess response to therapy.

The study was approved by the Ethics Board of Ain Shams University.

## RESULTS

Table 1: comparison of sex distribution between both groups.

Sex	Groups					
	Group A		Group B		Total	
	N	%	N	%	N	%
Female	21	70.0	19	63.3	40	66.7
Male	9	30.0	11	36.7	20	33.3
Total	30	100.0	30	100.0	60	100.0
Chi-square	X2		0.300			
	P-value		0.584			

Table 2: mean age in both groups

Groups	Age (years)		T-test	
	Range	Mean $\pm$ SD	t	P-value
Group A	20 - 35	26.55 $\pm$ 5.51	0.963	0.339
Group B	21 - 37	28.15 $\pm$ 7.24		

Table 3: comparison of frequency, urgency, urge incontinence and nocturia improvement in both groups after 12 weeks

Symptoms		Group A	Group B	T-test	
No. Frequency /24h	Pretreatment	Mean $\pm$ SD 14 $\pm$ 2.3	Mean $\pm$ SD 13 $\pm$ 3.4	t	P-value
		At 13 week	7 $\pm$ 1.5	9 $\pm$ 1.9	0.062
P-value		0.190	0.522		
No. Urgency /24h	Pretreatment	5 $\pm$ 0.84	6 $\pm$ 0.57	3.000	1.000
	At 13 week	2 $\pm$ 0.31	3 $\pm$ 0.16	0.000	1.000
P-value		0.449	0.505		
No. Urge incontinence 124 h	Pretreatment	3 $\pm$ 0.19	4 $\pm$ 0.12	0.000	1.000
	At 13 week	1 $\pm$ 0.02	2 $\pm$ 0.04	0.000	1.000
P-value		0.617	0.683		
Nocturia	Pretreatment	3 $\pm$ 0.1	3 $\pm$ 0.3	0.000	1.000
	At 13 week	1 $\pm$ 0.04	2 $\pm$ 0.06	0.000	1.000
P-value		0.617	1.000		

Table 4: evaluation of detrusor over activity pretreatment and at 13 week in both groups

Detrusor Over activity	Groups								Chi-square	
	Group A (N=30)				Group B (N=30)				X <sup>2</sup>	P-value
	Pretreatment		At 13 week%		Pretreatment		At 13 week			
	N	%	N	%	N	%	N	%		
Present	30	100.0	25	83.3	30	100.0	28	93.3	1.456	0.228
Delay in occurrence	-	-	7	23.3	-	-	4	13.3	1.002	0.317
Decrease in duration	-	-	4	13.3	-	-	3	10.0	0.162	0.688
Decrease in amplitude	-	-	4	13.3	-	-	3	10.0	0.162	0.688
Overall improvement	-	-	20	66.7	-	-	12	40.0	4.286	0.038*

**Table 5: comparison between the side effects in both groups**

Symptoms	Groups				Chi-square	
	Group A (N=30)		Group B (N=30)		X2	P-value
	N	%	N	%		
Dry mouth	5	16.7	3	10	11.000	0.027*
Constipation	2	6.7	1	3.3		
Blurred vision	1	3.3	1	3.3		
Overall side effects	8	26.7	5	16.7		

## DISCUSSION

Overactive bladder (OAB) refers to a complex of urinary symptoms defined by the International Continence Society (ICS) as urgency, with or without urgency incontinence, is usually accompanied by frequency and nocturia and without proven infection or other obvious pathology. The symptom complex is suggestive of detrusor overactivity, which can be further defined as being of unknown cause (idiopathic detrusor overactivity) or due to a neurological condition (neurogenic detrusor overactivity)<sup>(4)</sup>. In 2002, the International Continence Society (ICS) comprehensively reviewed the terminology of lower urinary tract functions and dysfunctions; consequently, they introduced a new term, "overactive bladder", for symptom-based diagnosis and recommended the term "detrusor over activity" for urodynamic findings characterized by involuntary detrusor contractions 'during the filling phase'<sup>(9)</sup>.

The objective of our study was to investigate the efficacy and safety of intermittent anticholinergic therapy versus continuous therapy for OAB in sixty patients and confirm efficacy of continuous anticholinergic therapy over intermittent therapy, the number of micturitions/ 24h was reduced at 13 weeks in both intermittent anticholinergic therapy & continuous therapy. The difference between the groups in change was insignificant. The number of urgency episodes, micturitions and urgency incontinence episodes and urine volume/micturition over 12 weeks after treatment improved in both groups. Improvements were greater in the continuous group than in the intermittent group throughout the evaluation period with

fewer side effects in the intermittent anticholinergic group.

In our study, group A included 30 patients and showed evaluated pretreatment at 13 weeks, mean number of voids /24 hours at baseline was 14 and at 13 weeks it was 7(improved by 50%). Mean number of urgency episodes-24 hours at baseline was 5 and at 13 weeks they were 2(improved by 60%). Mean number of urge incontinence episodes / 24 hours at baseline was 3 and at 13 weeks it was 1(improved by 67%). Number of nocturia at baseline was 3 and at 13 week was (improved by 67%).

In group B which included 30 patients, evaluated pretreatment and at 13 weeks, mean number of voids-24 hours at baseline was 13 and at 13 week was 9(improved by 31%). Mean number of urgency episodes-24 hours at baseline was 6 and at 13 weeks was 3(improved by 50%). Mean number of urge incontinence episodes-24 hours at baseline was 4 and at 13 week was 2, improved by 50%. Number of nocturia at baseline was 3 and at 13 weeks they were 2(improved by 33%).

Improvement of symptoms is better in group A than in group B at 13 week of treatment, frequency improved by 50% versus 31%, urgency improved by 60% versus 50%, urge incontinence improved by 67% versus 50% and nocturia improved by 67% versus 33%.

Urodynamic evaluation pretreatment and at 13 weeks showed that overall improvement in detrusor overactivity in group A in 20 cases (67%) versus in group B in 12 cases (40%), so in group A improvement in urodynamic study was better than improvement in group B. In group A 8 patients showed dry mouth in 5 cases (16.7%), constipation in 2 cases (6.7%)

8 blurred vision in one case (33%). In group B, 5 patients (16.7%) showed dry mouth in 3 cases (10%) constipation in one case (3.3) and blurred vision in one case (3.3%). The incidence of adverse effects was higher with continuous anticholinergic group intermittent group, but their severity was mild. The cost of one case subjected daily solifenacin 10 mg once daily for 12 weeks was about 840 Egyptian pounds, while the cost of one case subjected every other day solifenacin 10 mg oral tablet was 540 pounds.

## CONCLUSION

Overactive bladder syndrome significantly impacts the lives of those affected with OAB symptoms and this may decrease quality of life and increase social isolation. Following behavioral and pelvic floor therapies, anti-muscarinic agents are the mainstay of treatment such as solifenacin with results may be similar to other antimuscarinic agents with less side effects. However, the costs appeared to limit the adherence to this therapy and ultimately limit benefit for many patients. Surgical treatment such as augmentation cytoplasty is invasive and is increasingly limited to rare cases. Neuromodulation of the sacral nerves requires a permanent surgical implant with up to a 40% complication rate in 5 years. Pudendal nerve stimulation has recently been more closely studied but also requires surgical implantation Intermittent anticholinergic therapy (solifenacin 10mg) is an effective option for the treatment of patients complaining of overactive bladder with less side effects and much more affordable to OAB patients.

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