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Role of gabapentin and anticholinergics in management of neurogenic bladder after repair of spina bifida – a randomized controlled study☆,☆☆

Vedarth Dash, Monika Bawa *, J.K. Mahajan, Ravi P. Kanojia, Ram Samujh, K.L.N. Rao

Department of Pediatric Surgery, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

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ABSTRACT

Background: Anticholinergics are well established in the management of neurogenic bladders. However, some patients do have sub-optimal response or severe side effects. This study is designed to assess and compare efficacy of gabapentin with oxybutynin in neurogenic bladders after surgery for spina bifida.
Methods: Patients were randomized into three groups after urodynamic studies and started on oxybutynin, gabapentin, and combination of both, respectively. Thorough clinical and urodynamic reassessment was done at 6 months and one year after starting treatment.
Results: Forty-four patients (3–19 years) were studied. Improvement was noted in symptoms as well as urodynamic parameters in all groups. Maximal improvement of symptom score was with combination of drugs at 1 year. In urodynamic studies, compliance, pressures, and capacity showed improvement, which was significant between the groups at both six months and 1 year for bladder pressures and volume. Improvement in compliance though marked was not statistically significant. Best response was seen in group receiving both drugs. Gabapentin was better tolerated than oxybutynin.
Conclusion: Gabapentin is a good alternative to oxybutynin for management of neurogenic bladder, both as monotherapy and as an add-on therapy. It has potential application in patients with inadequate response to anticholinergics.
Level of evidence: prospective competitive treatment study – level II.

In the recent decades, increasing number of children and adolescents are living with sequelae to neural tube defects (NTDs), most distressing of which is incontinence because of neurogenic bladder sphincter disorder (NBSD). Wider application of urodynamic assessment and renal scintigraphy has led to recognition of long term renal damage because of elevated bladder pressures even in yet asymptomatic children [1]. This has shifted the focus of management, from incontinence to long-term preservation of renal function [1].

The main stay of management of neurogenic bladder continues to be clean intermittent catheterization (CIC) with or without anticholinergics [2]. Surgical augmentation of bladder and continent urinary diversion form the last option for patients who have failed medical management. Anticholinergics are associated with various side effects like heat intolerance, fever, dryness of the mucosae, constipation, blurred vision, reduced alertness and itching [1]. Many children therefore tend to be either intolerant or non-compliant to the standard anticholinergics. Another subset of patients continue to have elevated bladder pressures and incontinence [2]. This prompted us to study gabapentin as an alternative drug since it is already being used in adults with satisfactory results.

It is an anti-epileptic drug approved for pediatric use by FDA in 2000. It appears to have inhibitory action on the type C afferents from the bladder that are postulated to mediate pathological detrusor hyper activity [3,4]. This study was proposed to study the effect of gabapentin both as stand-alone and as combination with conventional anticholinergic drugs in the management of NBSD associated with spina bifida.

1. Material and methods

This prospective randomized controlled study was conducted between July 2013 and December 2015 on patients of lumbosacral myelomeningocele (LSMMC) who had undergone repair and were at least 3 years old at the time of enrolment. Patients who were not on any anticholinergics and had detrusor instability in the baseline urodynamics were included in the study after obtaining proper consent from the parents or guardians. Children who had vesicoureteric reflux on micturating cystourethrogram (MCU) or baseline bladder areflexia were excluded from the study. Also excluded were the patients who were already on medication or who had undergone any kind of surgical procedure for neurogenic bladder.

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* Corresponding author at: Department of Pediatric Surgery, Advanced Pediatric Center, Post Graduate Institute of Medical Education and Research (PGIMER), Sector 12, Chandigarh. Pin 160012. Tel.: +91 172 2755352, +91 9815677997.
E-mail address: monikabawa@hotmail.com (M. Bawa).

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Table 1
Grading of incontinence to urine.

GRADE	
1	Just a few drops
2	Wet underpants
3	Soaking wet

A complete clinical and urological work up was done for all the patients including a baseline ultrasound, renal function tests, micturating cystourethrogram and nuclear scan for evaluation of the upper tracts. The patients were asked to maintain a 3 day bladder diary. The number of wet episodes as well as the maximal incontinence grade (Table 1) was recorded. Symptomatology was compared using the dysfunctional voiding symptom score (DVSS). Cystometry was performed via a 6 Fr double luminal catheter introduced into the bladder via the urethra. The bladder was filled initially at a slow rate of 2 ml/min gradually increased up to 5 ml/min (10% of the expected bladder capacity for age). Expected bladder capacity was calculated with the formula {[age (yrs) + 2] × 30}. The bladder filling pressures, compliance, leak point pressures and the maximal bladder capacity were recorded.

If the patients showed detrusor over activity on cystometry they were randomly grouped using an online random number generator (Fig. 1). Group A was started on oxybutynin (5 mg twice a day), group B on gabapentin (20 mg kg^{-1} day^{-1}) and group C on a combination of both. All patients who had incontinence were counseled and started on CIC. The patients were followed up clinically and urodynamic studies were repeated at six months and one year after starting the medication. All the drugs were stopped for 3 weeks before doing the urodynamic studies. The results were compared and analyzed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 15.0 for Windows). Two patients did not tolerate the drug and were excluded. Institutional ethics committee approval was taken before the study was started.

2. Results

A total of seventy six patients were initially enrolled and underwent urodynamic studies as per the protocol. However, only 44 of them who had detrusor instability on cystometry were included in the study and were randomized into three groups (Fig. 2). Male to female ratio was 1.9:1 and the age ranged from 3 to 19 years (mean 6.1 years).

The most common presentation was incontinence to urine. Eight (18.2%) patients had no obvious neurological deficit but had detrusor instability on urodynamic assessment. The differences of the age distribution, sex ratio, neurological deficit and MCU findings between the groups were insignificant.

The DVSS was calculated for all the patients at presentation and then after six months and one year of starting the medication. Threshold score was taken to be 9 in males and 6 in females. All the patients showed improvement in the scores at six months and one year. The improvement in the scores was maximum at one year in patients in group C (mean 4.615 +/− 1.894) followed by group B and group A (Table 2).

The number of wet episodes per day for children reduced across the study population with all patients gaining some degree of dryness (Table 3). The maximal incontinence grade also reduced over the study period (Table 2).

Detrusor compliance increased in all the patients. Group C patients had the maximal improvement 5.1 ml/cm of H_2O at six months and 8.485 ml/cm of H_2O at the end of the study (Table 2).

The difference in the detrusor pressures was not significant at presentation among the three groups but showed significant differences both at six months and at one year with the *p*-values being 0.020 and 0.004, respectively. Patients who were on gabapentin monotherapy had comparably higher bladder pressures of 54.533 (±16.813) cm of H_2O at six months and 44.733 (±17.404) cm of H_2O at one year (Table 2).

The bladder capacity was calculated as percentage of expected bladder capacity for age. The mean improvement in the bladder capacity at

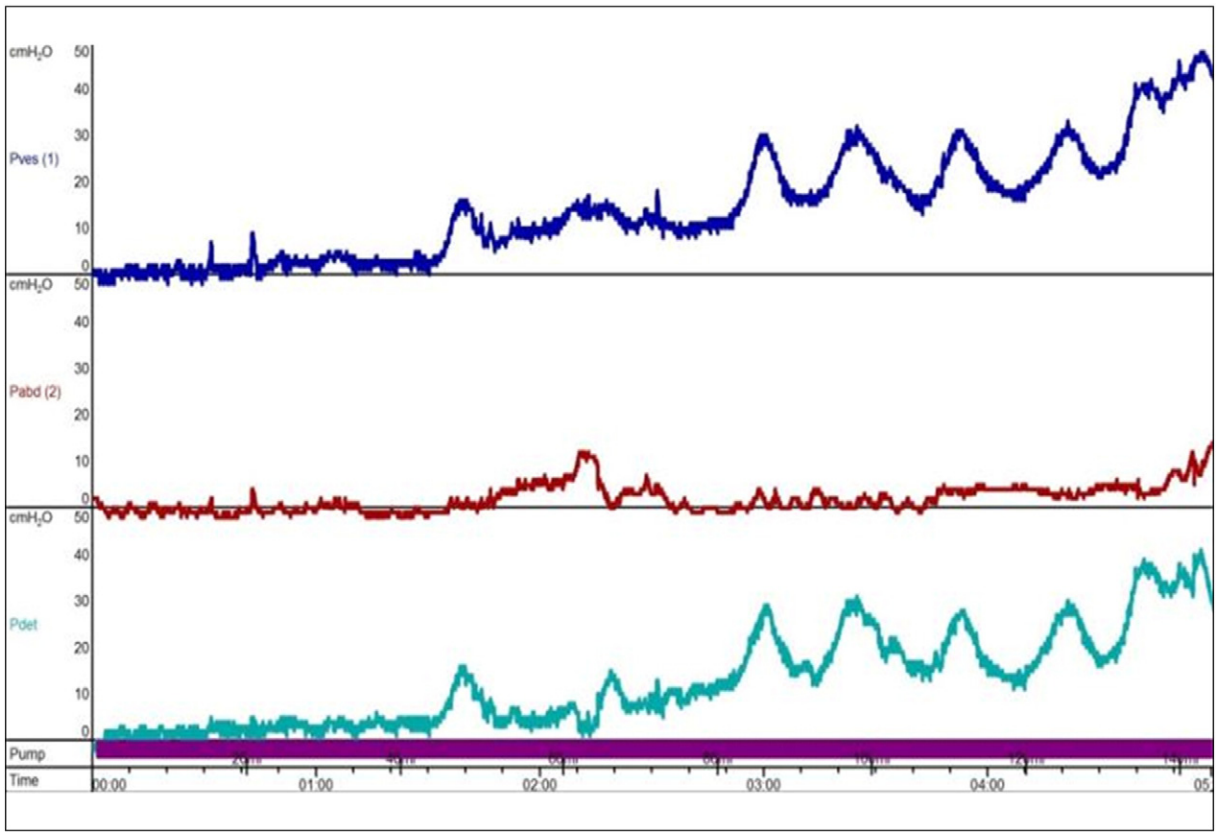

Fig. 1. Cystometric curve showing detrusor instability.