Conservative management in neurogenic bladder dysfunction

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Purpose of review

A few decades ago, urinary diversion, usually with an ileal conduit, was the ultimate outcome for most children with spina bifida. The revolutionary institution of clean intermittent catheterization has changed the algorithm totally. Furthermore many new drugs have been developed during the past decade and have decreased the need for surgery dramatically. In this article, we will focus on the most recent data on new modalities of therapy to help avoid urinary diversion or bladder augmentation.

Recent findings

In addition to clean intermittent catheterization and oxybutynin treatment, a new generation of anticholinergic medications, such as tolterodine, has been developed. For patients who drop out because of the side-effects of oral administration, new methods of administration are now available, including extended release and intravesical instillation. For those unresponsive, botulinum-A toxin and resiniferatoxin are two relatively new drugs in the field, administered as intravesical injection and instillation, respectively. Intravesical or transdermal electrical stimulation, sacral nerve stimulation and biofeedback therapy are under development, but as currently administered, are not yet completely successful.

Summary

Although life-saving in many respects, bladder augmentation introduces life-long risks of its own. Our goal in describing 'conservative' management is to prevent this step. Many alternatives to surgery are available now and more effective strategies are under development.

Keywords

Children, conservative, myelomeningocele, treatment

Curr Curr Opin Urol 12:473–477. © 2002 Lippincott Williams & Wilkins.

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Current Opinion in Urology 2002, 12:473–477

Abbreviations

BTX	botulinum-A toxin
CIC	clean intermittent catheterization

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0963-0643

Introduction

The neurological conditions that cause urinary tract damage in children may be congenital, idiopathic, or less frequently are secondary to a trauma. The details of the etiological factors are beyond the scope of this paper, but it is important to realize that the vast majority of neurogenic bladder dysfunction in the pediatric population is secondary to neural tube defects, in particular myelomeningocele.

The outcome of the upper urinary tract is related to the combination of the detrusor and sphincteric function. A hyperreflexic detrusor has a detrimental effect on the upper urinary tract only when the sphincter fails to relax simultaneously, a situation called detrusor–sphincter dyssynergia. When the sphincter is weak or areflexic, the kidneys are protected, but in this situation incontinence becomes a problem. Based on these basic concepts, the objectives of therapy for neurogenic bladder dysfunction are well defined: protecting the kidneys from progressive damage by reducing the intravesical pressure during both filling and emptying, and improving the quality of life by providing urinary continence. Therapy is individualized, e.g. to reduce high intravesical pressure in a patient with detrusor hyperreflexia, or clean intermittent catheterization (CIC) in a child who cannot empty his/her bladder adequately.

When to start therapy?

It is well known in spinal cord injuries that there is a spinal shock period that lasts typically 6–12 weeks (but may be as long as 1 year), characterized by an areflexic bladder and urinary retention. After this, the detrusor may be hyperreflexic or areflexic, and coordination or dyssynergia with the urethral sphincter occurs depending on the level of spinal cord injury. It is likely that closure of the neural tube defect (or the placement of a ventriculoperitoneal shunt) causes spinal shock, as in children with myelomeningocele. Baskin *et al.* [1] found five patients (out of 35) in whom an areflexic bladder matured to a hyperreflexic bladder over the first few months of life. In a more recent study, Stoneking *et al.* [2•] confirmed this finding. In a retrospective analysis of 54 children who underwent myelomeningocele repair, nearly all patients required CIC for urinary retention after surgery. In 74% this lasted less than 2 weeks, but in 26% the effect was seen for up to 6 weeks after surgery [2•]. Baskin *et al.* [1] obtained excellent results in preventing upper urinary tract changes with an aggressive program of anticholinergic agents combined with CIC. In contrast, after the period of spinal shock, Stoneking *et al.* [2•]

observed their patients and ultimately 38% of children needed CIC or vesicostomy before toilet training. This suggests that preventive institution of therapy would be beneficial. In a retrospective analysis of 46 children treated before or after 1 year of age, Wu *et al.* [3] reported confirmatory results. There was a significantly lower rate of bladder augmentation in the group treated early. In addition, the early institution of CIC also seems to have psychological benefits, with an apparent improvement in family compliance and the ability to assist the child in coping with their disease and with CIC. In a similar comparison of prophylactic treatment to observation in a high-risk group of 45 patients with myelodysplasia, the group treated early again had a decreased rate of augmentation cystoplasty (17 versus 41%) and improved bladder function [4].

These data suggest a beneficial effect of early evaluation and therapy, especially in high-risk groups. Initial evaluation should include renal/bladder ultrasound and fluoro-urodynamic study. The urodynamic study is crucial because the intravesical pressure and the coordination of the detrusor with the external sphincter are good predictors of future renal and bladder function [5]. If sophisticated urodynamic studies are not possible, a relatively simple leak point pressure has been shown to be predictive of upper tract outcome [6]. A leak point pressure higher than 40 cm of water will result in a high rate of upper tract changes. Both anticholinergic therapy and CIC should be instituted in this group in order to avoid damage secondary to high intravesical pressures.

Clean intermittent catheterization

Thirty years of worldwide experience has made CIC the primary choice for bladder emptying in the treatment of children with neurogenic bladder dysfunction. Although there are some concerns about the risk of infection and patient/family compliance, CIC remains the best method to empty areflexic bladders with maximum efficacy and minimal side-effects. In a recent study of the risks of infection [7••], two techniques of intermittent catheterization were compared in patients with myelomeningocele. Ten patients compared using a sterile catheter four times a day for 4 months with a reusable clean catheter for another 4 months. The results showed that bacteriuria was present in almost 75% of patients, but there was no difference in its frequency with either regimen. Only two symptomatic urinary tract infections were seen in each group in a total of 158 urine samples. These data show that the use of sterile catheters is an unnecessary expense, and confirm that CIC with a reusable catheter is an excellent method of bladder emptying in this patient group.

Although traditional, reusable catheters have been shown to be effective, some newer technologies are available that enable the production of very low friction catheters. These have been shown to have less hematuria than traditional catheters, as well as a high rate of patient/family satisfaction [8]. However, they are not disposable and are significantly more expensive than the traditional technique. We consider them very valuable in high-risk patients with urethral/stomal false passages or very tense sphincters, but unnecessary in routine cases.

Children with voiding dysfunction without neurological and anatomical pathology also benefit from the use of CIC. In a review of 23 patients with non-neurogenic neurogenic bladder, detrusor hyperreflexia was detected in 13 and all had a high post-void residual urine [9•]. Of the 23 children, 16 accepted the use of CIC. This group was completely dry during the follow-up while on CIC, either with or without anticholinergic therapy (eight in each group).

Anticholinergic therapy

Patients with an areflexic detrusor and high post-void residual urine are the best candidates for CIC therapy. Patients with hyperreflexic detrusor require conversion to a lower pressure detrusor. Although this can be performed surgically, the preference is to do this by non-operative means.

Oxybutynin chloride is a well-known anticholinergic and antispasmodic agent. Its efficacy on clinical and urodynamic parameters has been documented in infants and neonates [1,10]. In a study of 41 children with myelomeningocele and detrusor hyperreflexia [11], who were evaluated urodynamically before and within 3 months after the initiation of combined therapy, oxybutynin significantly increased the maximal bladder capacity, and decreased the detrusor pressure at maximal capacity. Continence was improved also in 70% of patients over 6 years of age who were incontinent before therapy.

The major problem with oxybutynin is the high rate of side-effects. Dry mouth, constipation and heat intolerance may be seen in almost a third of patients and are the main reason for dropout. Because of the pharmacokinetics of the drug, oxybutynin should be administered three times a day, which results in reduced patient compliance. To overcome this problem, a slow-release form of the drug has been developed. Studies in adults have demonstrated the same success rate with better tolerability with the slow-release formulation [12], and we studied retrospectively the efficacy and safety of the extended-release oxybutynin in children with bladder dysfunction (neurogenic or urge incontinence without neurological abnormalities) [13••]. We confirmed that treatment with extended-release oxybutynin was effec-

tive and well tolerated. This formulation is suggested for any children who require anticholinergic medication and can swallow a pill.

Another promising drug is tolterodine tartrate. Like oxybutynin, it is a muscarinic receptor antagonist, and its efficacy in treating the overactive bladder has been demonstrated in adults [14]. Compared with oxybutynin, its selectivity for the bladder is similar, but it is eight times less potent at the antimuscarinic receptor in the parotid gland [15], suggesting that it will cause less dry mouth. In a study of 22 children (0.1 mg/kg) with detrusor hyperreflexia (21 myelomeningocele and one spinal cord trauma), Goessl *et al.* [16] used tolterodine as either a replacement therapy for oxybutynin or as an initial therapy. Tolterodine was found to be equal to oxybutynin in efficacy and had fewer adverse effects in the group that had previously been treated with oxybutynin. Although not directly applicable to patients with neurogenic dysfunction, in a study of 33 children with overactive bladder (urgency, frequency and urge incontinence), different dosages of oral tolterodine demonstrated linear pharmacokinetics and excellent efficacy in decreasing voiding frequencies and incontinence episodes [17••]. Only two patients discontinued the treatment because of adverse effects. A new form of extended-release tolterodine has been introduced recently. It should have equal efficacy and fewer side-effects. In summary, extended-release formulations of either oxybutynin or tolterodine are excellent new options for the treatment of children with detrusor hyperreflexia.

Intravesical agents

Another alternative to reduce side-effects is the intravesical administration of oxybutynin. Many different preparations have been described, and there are therefore many discrepancies in results and particularly patient compliance [18]. One popular method consists of the dissolution of a 5 mg tablet of oxybutynin chloride in 30 ml sterile saline and the instillation of this suspension into the bladder via a catheter. The daily dosage and frequency of intravesical instillation remain controversial, but most authors recommend using the medication three times a day. It has been demonstrated that intravesical oxybutynin chloride is absorbed rapidly, and greater serum levels are obtained than after oral administration [19]. In a study that compared the side-effects, Ferrara *et al.* [20] demonstrated that intravesical administration was safer and better tolerated than oral oxybutynin chloride. However, out of 34 children, six still had side-effects such as drowsiness, hallucinations and cognitive changes. In contrast, though, out of 67 children who underwent treatment with oral oxybutynin, 11 discontinued the therapy because of side-effects.

Di Stasi *et al.* [21•] looked at the plasma levels of oxybutynin and its metabolite *N*-desetyl oxybutynin after oral administration, intravesical instillation (passive diffusion), and intravesical instillation combined with electric current (electromotive administration). The authors found that electromotive administration increased the intravesical uptake of the oxybutynin, resulting in an improvement in urodynamic parameters compared with oral administration or passive diffusion. They concluded that some part of the intravesical oxybutynin (3 of 15 mg in their study) must be sequestered in the urothelium during intravesical instillation, and electric current might be useful for refractory cases.

Another new medication that has been shown to be effective in the treatment of patients with 'overactive bladder' is resiniferatoxin. It acts via desensitization of unmyelinated C fibers (afferent nerves of the bladder). Whether this mechanism of action will be effective in patients with spina bifida is questionable. There is a single case report in the literature on the use of resiniferatoxin in a child with myelomeningocele [22•]. A 9-year-old boy with low bladder compliance and grade II bilateral vesicoureteral reflux failed both oral and intravesical oxybutynin. Resiniferatoxin was tried intravesically. Three months after one instillation, the boy was without evidence of reflux and had improved bladder compliance. Because the results in adults with 'overactive bladder' are promising, this medication has significant potential for use in children with spina bifida, but many more studies are needed to determine the efficacy and safety of the drug in this population.

Intravesical injection therapy

Since the 1980s, botulinum-A toxin (BTX) has been used for the treatment of various conditions such as strabismus, dystonia, spasticity and other disorders that cause inappropriate striated muscle contraction. It is a selective blocker of acetylcholine release at the neuromuscular junction [23]. In urology, it was first studied in adult patients with spinal cord lesions that resulted in either detrusor/sphincter dyssynergia [24] or detrusor hyperreflexia [25]. Promising results in temporarily paralyzing the sphincter in the adult population have led the investigators to study the efficacy of BTX in the bladders of children with high intravesical pressure. In a prospective study of a highly selected group [26••], BTX was injected under anesthesia at 30–40 sites into the bladder wall of 17 children. All had intravesical pressures greater than 40 cm of water despite a high dosage of anticholinergic medication. A repeat urodynamic study 2–4 weeks after the injection showed a significant increase in maximal bladder capacity and detrusor compliance. Although there was a decrease in incontinence episodes, this difference was not statistically

significant. No side-effect was noted, except one child who had increased post-void residual urine. To date, long-term results on the efficacy and safety of BTX use in children are not available. Moreover, in other settings the effects last only for a few months, making repeat treatments necessary. Although promising, much more research is needed on this therapy before it can be considered an alternative to augmentation cystoplasty.

Intravesical electrical stimulation of the bladder

After an experience of almost 45 years in Europe and 20 years in North America, the benefits from the use of electrical stimulation of the bladder in children with myelomeningocele are still controversial. The technique is not complicated and consists of filling the bladder with saline and giving the electrical stimulation transurethrally via an electrocatheter. The technique is however very labor intensive. A series of 20–90-min sessions is performed before evaluating the response. Unfortunately, a multi-institutional study of 335 patients [27] demonstrated that only 16% of patients responded and those had only a 53% increase in bladder capacity and a 25% decrease in detrusor pressure. A smaller study [28] demonstrated an increase in bladder capacity in 33% and a decrease in pressure in 28% after 4 years' follow-up of 25 patients. Although these data are not convincing scientifically, controversy continues regarding the benefits of this therapy [29,30]. A fair summary would be that transurethral electrical stimulation of the bladder is very labor intensive, and has failed to enable volitional voiding in these patients. Nor are there data to suggest that this technique reduces the rate of surgical interventions. Therefore it is not used commonly at this time.

Sacral nerve stimulation

There has been an increase in popularity of this therapy for patients with voiding dysfunction in the past few years. Unfortunately there are few studies of its use in children with myelomeningocele. In an original work [31], this modality had significant effects in children with intact sacral nerves. Unfortunately, volitional voiding was not possible. Moreover, the optimal use of the technique is to increase outlet resistance in those children with inadequate sphincteric function; however, this is the group that has maldeveloped sacral nerves and therefore is least amenable to the technique. Further modern studies with this interesting modality are warranted.

Transcutaneous neuromodulation

Low-frequency electrical current has been used commonly in adults and less frequently in neurologically normal children to inhibit detrusor activity and treat urge incontinence [32]. The stimulator can be applied over the anterior tibial nerve, but most commonly the stimulation is performed via an anal electrode. A recent study [33•] investigated how effective neuromodulation would be when applied at home, via a self-applied surface electrode in the sacral area instead of a traditional anal electrode. After at least one month of application lasting 1 h twice a day, a 73% improvement in continence was observed. However, only seven out of 15 children were completely dry. To date, the long-term results of transcutaneous neuromodulation are not available. More prospective studies of this modality are needed.

Biofeedback

Biofeedback therapy is an alternative treatment to CIC and anticholinergic agents for children who have voiding dysfunction and are unable to relax their pelvic floor during voiding [34,35]. The basic technique involves learning to contract and relax the pelvic floor muscles using visual and auditory monitors of electromyographic activity. Like many of the techniques described above, this technique is very labor intensive, and motivation and patient cooperation are very important for successful treatment. A recent study [36••] suggested combining a non-invasive urodynamic method with various psychological techniques (such as externalizing the problem, empowerment and homework), to overcome the difficulties with conventional treatment. A total of 77 children with detrusor/sphincter dyssynergia were treated, and after a relatively short follow-up period (mean of 8.6 months), 61% had improvement in both urinary symptoms and urodynamic parameters. Experience in myelomeningocele patients is very limited. Only one out of six girls with spina bifida had improvement after biofeedback, probably because there were so few healthy nerves remaining. It appears that biofeedback has great potential in children with non-neurological voiding dysfunction, but limited efficacy in children with myelomeningocele.

Conclusion

CIC and oral pharmacological agents are the first-line treatment in most patients with bladder dysfunction and incontinence regardless of the etiology. The early institution of therapy seems very beneficial. Highly selected patients may also benefit from new forms of anticholinergic agents, as well as electrical stimulation and biofeedback. Surgical therapy should be reserved for cases that are totally unresponsive to conservative therapies.

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