

Committee 10 E

**Conservative Management in
Neuropathic Urinary Incontinence**

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A. INTRODUCTION

This chapter deals with the conservative treatment of urinary incontinence due to neurological pathology, which can be caused by (a) suprapontine, (b) spinal cord and (c) subsacral (cauda equina and peripheral nerves) lesions (Figure1).

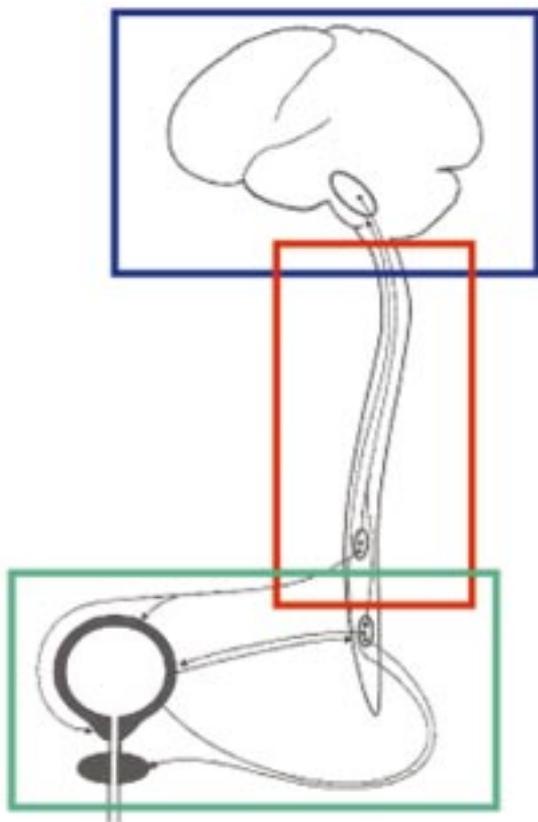


Figure 1 : Nervous control of continence and micturition is organised on a cerebral, spinal and peripheral level. All three are cross-linked, the circuiting is complex and contentious.

I. SUPRAPONTINE LESIONS

In suprapontine lesions urinary incontinence results from uninhibited detrusor contractions [Brocklehurst et al 1985]. This detrusor hyperreflexia is caused by damage to the cerebral inhibitory centers. Patients with lesions above the level of the pons characteristically demonstrate synergetic activity of the detrusor and the external sphincter [Tsuchida et al 1983]. Patients with suprapontine lesions may, however, purposely increase sphincteric activity during an uninhibited detrusor contraction to avoid urge incontinence. This guarding reflex or pseudo-dyssynergia may be confused with true dyssynergia by those less familiar with the interpretation of urodynamic studies [Siroky et al 1982].

In the absence of other urinary disease, such as outflow obstruction, as long as external sphincter activity remains coordinated with detrusor contraction, intravesical pressure should remain physiologic and therefore preserve the function of the urinary tracts. Residual urine may either be due to a coexisting morphologic infravesical obstruction, rigidity and spasticity of the pelvic floor (e.g. Parkinsons Disease) or due to a voluntary contraction of the external sphincter to control unhibitable detrusor contractions, a phenomenon, which has already become a reflex pattern in some patients.

A frequent reason for supraspinal detrusor hyperreflexia, causing reflex incontinence, are cerebrovascular accidents. A significant number of new stroke patients develop urinary retention for several weeks before detrusor hyperreflexia occurs. This phase of detrusor areflexia may be named "cerebral shock" much alike the classic "spinal shock" phase immediately after a spinal cord injury. Parkinsons Disease is one of the most common neurological entities causing voiding dysfunction, classically resulting in detrusor hyperreflexia, detrusor bradykinesia and an impairment of relaxation of the striated sphincter. According to Holli-

ger et al (2001, in press), detrusor overactivity increases with progress and severeness of the disease and can then be found in up to 90 % of patients [Berger et al 1987]. Another reason for supraspinal reflex incontinence is dementia. The defect in cognitive function is responsible for the lack of social continence in these patients. In brain neoplasms alterations in lower urinary tract function tend to relate directly to the area of the brain affected.

Shy and Drager described a neurological syndrome characterized by autonomic dysfunction consisting of orthostatic hypotension, anhidrosis, impotence, extrapyramidal symptoms and poor urinary and fecal control [Wulfsohn et al 1981], however, the term multiple system atrophy nowadays involves various syndroms, resulting in degeneration of neurons and associated fibers of motor and extrapyramidal systems including the cerebellum and brain stem. The urinary symptoms of incontinence are primarily caused by detrusor hyperreflexia although some element of external sphincter weakness may be present, with an open bladder neck during cystography indicating peripheral sympathetic dysfunction. The combination of detrusor dysfunction and sphincter denervation contraindicates the surgical management of symptoms [Beck et al 1994].

II. SPINAL CORD LESIONS

The degree of dysfunction is related to the disease process itself, the area of the spinal cord affected by the disease, and the severity of neurological impairment. Neurological injury, which can involve parasympathetic, sympathetic, and somatic nerve fibers, can result in a complex combination of signs and symptoms. The urodynamic investigation of those with neurological impairment can provide objective information regarding the nature and extent of the effect on lower urinary tract function. For this reason, urodynamic testing should be an integral part in the evaluation of all patients with complete and incomplete spinal cord dysfunction. In spinal cord injury (SCI) nearly 55% of patients develop tetraplegia, while 45% become paraplegic, neurologically incomplete injuries are slightly more common (53.8%) than complete injuries (46.2%) [Watanabe et al 1996].

Neurogenic lower urinary tract dysfunction resulting from SCI is an excellent model for the understanding of neuro-urological dysfunction (see below).

In multiple sclerosis voiding dysfunction is mainly due to spinal lesions, although cerebral lesions may contribute. Impairment of neurological function results from demyelinating plaques of the white matter of the brain and spinal cord, especially the posterior and lateral columns of the cervical cord, which serve as pathways

for neurologic control over vesical and urethral function [Nathan & Smith 1982]. Symptoms of voiding dysfunction are appreciated by 90% of patients having the disease more than 10 years. These include not only frequency, urgency, and urge incontinence, but also urinary hesitancy, intermittency, and poor urinary stream.

Urodynamically, the most common pattern seen is detrusor hyperreflexia (in about 70%), 50% accompanied by detrusor-external sphincter dyssynergia [Goldstein et al 1982; Weinstein et al 1988; Sirls et al 1994]. Detrusor areflexia, associated with lower cord and cauda equina plaques, is seen in 20% to 30% of cases, and these patients usually strained to void [Gonor et al 1985]. The latter symptoms are caused by plaque formation in the sacral cord, impairing motor outflow to the detrusor.

Beside these most important reasons many other neurological lesions, affecting the spinal cord, may cause storage and emptying problems, e.g. transverse myelitis or the tethered cord syndrome, caused by a short filum terminale, intraspinal lipoma or fibres adhesions resulting from the surgical repair of spinal dysraphism [Al-Mefty et al 1979]. Detrusor areflexia has been reported to occur in 60% of the patients.

III. SUBSACRAL (CAUDA EQUINA AND PERIPHERAL NERVES) LESIONS

These lesions may affect the cauda equina including the sacral roots and the peripheral nerves. According to neurological classifications lesions of the conus, causing dysfunction of the peripheral neuron, are classified as peripheral lesions. For practical reasons these lesions, named for decades as lower motor neuron lesions of the spinal cord, are subsummarized under spinal lesions.

Pelvic plexus injury, common with abdominal perineal resection and hysterectomy, contains both parasympathetic and sympathetic fibers in a branching array, parasagittally adjacent to the rectum. Disruption of the pelvic plexus function may occur with traumatic pelvic fracture. Injury to the hypogastric, pelvic and sometimes also pudendal nerves results in damage to sympathetic, parasympathetic and somatic nerve fibers and, consequently, lower urinary tract dysfunction. Decreased parasympathetic innervation generally results in decreased detrusor contractility and potentially areflexia, while impaired sympathetic transmission results in incomplete bladder neck closure, internal sphincter dysfunction, and stress incontinence. Up to 80% of patients with voiding disturbances after significant pelvic procedures will resume normal voiding within 6 months [Blaivas, Chancellor 1995], if the urological management inbetween is adequate.

Another common medical condition, which causes neurogenic lower urinary tract dysfunction, is diabetes mellitus.

Deficits in bladder sensation occur initially, with insidious onset, usually associated with other sensory impairment. Classically, patients experience decreased urinary frequency, urinary hesitancy, and slowing of the urinary stream, symptoms which may progress even to urinary dribbling from overflow incontinence [Appel, Whiteside 1991]. Urodynamic studies commonly reveal impaired bladder sensation, increased cystometric bladder capacity, decreased detrusor contractility, an impaired uroflow, and an elevated post-void residual urine volume [Blaivas 1988]. One urodynamically controlled study showed detrusor hyperreflexia in 55%, while only 33% had either impaired contractility or areflexia [Kaplan et al 1995]. Diabetics with voiding symptoms are generally elderly people and subject to infection, outlet obstruction, and uninhibited detrusor contraction like others in this age group, which may contribute to these results.

Moreover, herpes zoster affecting the dorsal ganglion, Lyme disease with symptoms caused by encephalopathy, polyneuropathy and leukoencephalitis as well as Guillain-Barré syndrome, which represents an inflammatory demyelinating polyneuropathy affecting mainly the peripheral nervous system with a predilection to the nerve roots, may cause neurogenic voiding dysfunction with recovery depending on the course of the neurological disease.

Pattern of Lower Urinary Tract Dysfunction and Therapeutic Principles

Neurogenic urinary incontinence may be due to

1. **dysfunction of the detrusor,**
2. **dysfunction of the sphincter** and
3. **a combination of both.**

1. **Detrusor hyperreflexia leads to reflex-incontinence, detrusor areflexia to incontinence associated with poor bladder emptying** (previously and in the following named overflow-incontinence),

2. **an areflexic (incompetent) sphincter causes neurogenic stress-incontinence, a hyperreflexic (spastic) sphincter overflow-incontinence** and

3. quite often **detrusor and sphincter are affected simultaneously mostly from the same type** by the neurogenic lesions but also a dissociation may be possible, moreover, a normal functioning counterpart may be present with basically eight combinations, as shown in figure 2.

In most patients the storage problem, leading to incontinence, is associated with an emptying problem; therefore both aspects have to be considered at the same time.

Therapy of neurogenic incontinence is primarily a conservative one. Timed bladder emptying, by whatever means, controlled fluid-intake and avoidance of urinary tract infections are the prerequisites for successful treatment.

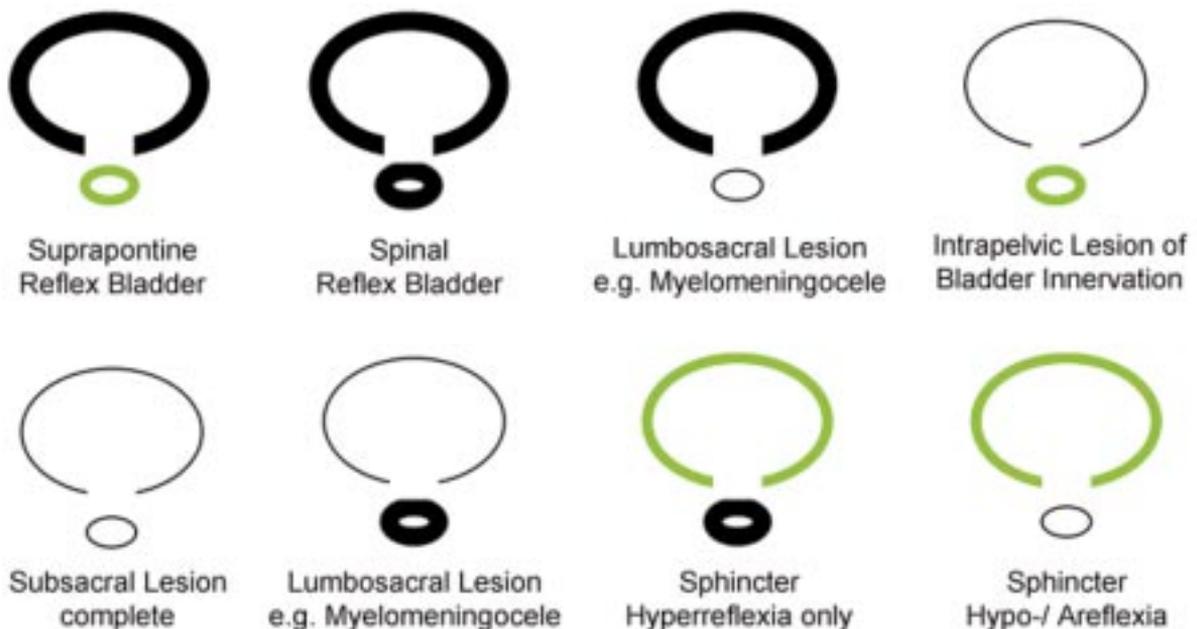


Figure 2 : Patterns of neurogenic detrusor-sphincter dysfunction Heavy lines symbolize hyperreflexia, thin lines hypo- or areflexia and green lines a normal innervation of the relevant structure, for further explanation see text.

In **I. Supraspinal lesions** detrusor hyperreflexia is mostly combined with normal sphincter function, reflex incontinence is the main symptom and anticholinergic therapy together with behavioural treatment, especially in patients with cognitive impairment, is the method of choice.

II. Spinal lesions mostly cause simultaneous dysfunction of the detrusor and the sphincter.

In **suprasacral lesions** the combination of a hyperreflexic detrusor with a hyperreflexic sphincter is characteristic for the spinal reflex bladder. Basically spontaneous reflex voiding is possible, however, it is uncontrolled, causing reflex-incontinence and is mostly unbalanced and basically unphysiologic. Detrusor contractions are mostly inadequate, and detrusor striated sphincter dyssynergia is present, both leading to unbalanced voiding with the possibility of a dangerous high pressure situation (Figure 3).

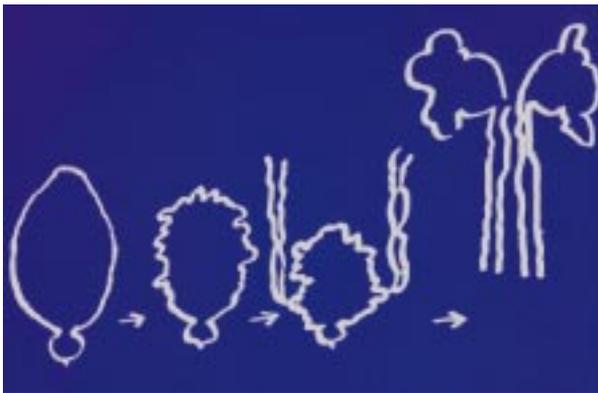


Figure 3 : Consequences of detrusor-sphincter dyssynergia: it creates a functional infravesical obstruction with the possible consequence of an intravesical high pressure situation, causing reflux, hydronephrosis and kidney-deterioration

Triggered reflex voiding is recommended only if it is urodynamically safe and reflex incontinence is manageable. The method of choice nowadays to empty an unbalanced reflex bladder and to manage reflex-incontinence is *intermittent (self-) catheterization*. However, to achieve the aims of therapy, - a low pressure situation and continence between catheterizations - additional *pharmacotherapy* may be necessary.

If bladder relaxing agents fail or are not tolerable, *electrotherapy* is an alternative in incomplete lesions: anogenital electrostimulation (penile, clitoral, vaginal and anal) can inhibit detrusor hyperreflexia by stimulating pudendal nerve afferents.

If none of the above mentioned treatment modalities is effective to control reflex incontinence and if operative procedures are not indicated/possible, appliances are the next choice, condom-catheters in males and pads in females.

The indwelling catheter – a suprapubic catheter is preferable to transurethral – remains the last resort for conservative therapy.

For complete **conus lesions**, also named lower motor neuron lesions, **areflexia of the detrusor with areflexia of the sphincter** is characteristic. Sphincter incompetence causes neurogenic urinary stress incontinence and may be combined with overflow-incontinence if adequate emptying is not achieved.

Basically, regular bladder emptying achieved by bladder expression, according to the individual bladder capacity, in combination with controlled fluid intake may decrease neurogenic urinary stress incontinence. However, continence is hard to achieve. *Bladder expression* is potentially dangerous. Pharmacotherapy is not helpful in this situation, appliances and condom catheters are therefore often necessary, continence can often be achieved only by operative therapy.

Areflexia of the detrusor combined with hyperreflexia of the sphincter may occur in lesions, comprising the conus and nearby areas above, however, this pattern may be also due to a decompensation of a hyperreflexic bladder after chronic urinary retention.

With this combination overflow incontinence can be controlled by intermittent catheterization mostly without additional pharmacotherapy. If intermittent catheterisation is not possible an indwelling catheter, preferable suprapubically, may be needed.

If **hyperreflexia of the detrusor is combined with areflexia of the sphincter**, a pattern sometimes found in epiconal lesions, especially in myelomeningoceles, reflex incontinence is combined with neurogenic stress incontinence. Bladder relaxant agents may abolish or diminish detrusor hyperreflexia. In incomplete lesions electrical stimulation of the pelvic floor musculature may improve sphincter function. Thus the combination of pharmacotherapy to treat reflex incontinence with electrotherapy of the pelvic floor muscle improves continence. However, with this type of neurogenic lower urinary tract dysfunction conservative treatment alone is generally unable to restore continence; therefore either appliances or operative treatment must be considered.

III. Subsacral (cauda equina and peripheral nerves) lesion are often incomplete lesions, hyporeflexia or areflexia of the detrusor may be combined with a normally functioning external striated sphincter, a combination which can be seen after intrapelvic surgery, when the pudendal nerve remains intact. On the other side if the pudendal nerve is lesioned and the pelvic plexus remains more or less intact, a combination of a normally functioning detrusor with a hypo- or areflexic external sphincter may be present. For a hyperreflexic

detrusor, again, pharmacotherapy is the first choice. In the hyporeflexic detrusor cholinergics may increase the tone. If the lesions were incomplete, intravesical electrotherapy was reported to increase detrusor contractility. The chances for pharmacotherapy to improve external sphincter weakness as well as to decrease external sphincter spasticity are poor and operative therapy remains the therapy of choice.

B. BEHAVIOURAL THERAPY

I. TRIGGERED REFLEX VOIDING

1. BACKGROUND

Following severe cord or cauda equina injury, the paralysed bladder behaves like an inert elastic bag and is unable to adapt itself to its contents or expel them. This areflexic phase is followed gradually by recovery of detrusor activity. The true automatic or reflex bladder occurs following recovery from spinal shock in spinal cord lesions not involving the conus or cauda equina. If the latter or the efferent branches of the pelvic nerve are involved, the reflex emptying is much less complete and considerable voluntary straining is required to empty the bladder to a satisfactory degree. It was just before World War II that Denny-Brown and Robertson (1933) did recognise this evolution of disturbance of micturition [Dick et al 1952].

With time concepts have been evolving and referring to Bors & Comarr (1971), stimulation of the sacral and lumbar dermatomes should be used to elicit reflex contractions of the detrusor in cases with upper motor neuron bladders and during treatment with intermittent or continuous catheterization, to evaluate if reflex voiding would be possible and an alternative.

The aims of regular triggered reflex voiding are to achieve balanced voiding [Corcos, Schick 1996], to decrease incontinence and/or to achieve continence [Wein et al 1984]. The prerequisites for this type of bladder emptying are: (1) the possibility of collecting the urine in a socially acceptable way and (2) the time needed for bladder emptying is adequate.

2. OBJECTIVES

To find evidence to answer the following questions:

1. How and when to do it?
2. Is it effective?
3. Is it safe?
4. Is it cost-effective?
5. Complications and how to treat them

3. CRITERIA FOR CONSIDERING STUDIES

The search was made from 1966 to 2000. Considering the historical aspect of this voiding management of bladder dysfunction, passed references are taken from books reporting on neurogenic bladder before 1970's [Bors, Comarr 1971].

Through Pubmed the following keywords were searched: Bladder, Neurogenic/etiology; Bladder, neurogenic/physiopathology. Case report. Child. Female. Human. Infant. Male. Urination disorders/congenital. Urination disorders/complications.

Quality of included studies. We did not find any prospective cohort study of patients using triggered voiding or any controlled or randomised study (Level evidence 4).

There are a few new references published within the last 3 years (1998- 2000) to be added to the previous report (1st ICI 1998).

4. RESULTS

a) How and when to do it?

Referring to the ICS committee on standardisation of terminology [Andersen et al, 1992] bladder reflex triggering comprises various manoeuvres performed by patients in order to elicit reflex detrusor contractions by exteroceptive stimuli (Figure 4). The most commonly used manoeuvres are: suprapubic tapping, thigh scratching and anal/rectal manipulation. Frequency of use, intervals and duration have to be specified for each patient. Integrity of sacral reflex are requested for such voiding manoeuvres.



Figure 4 : Triggered reflex voiding comprises various techniques, the patient must find the best individual trigger zone and points (the technique on the left side is probably more effective than that on the right side ...)

Stimuli consist of [Bors, Comarr 1971; Wein et al 1984]:

- squeezing of glans penis or scrotal skin
- pulling on the pubic hair
- tapping the suprapubic areas
- stroking the skin of the thigh or the sole of the foot
- rectal digital stimulation

The latter has been described as the most effective sti-

mulu for “triggered voiding” [Rossier, Bors 1964]. However the most popular and probably the most efficient and easy to do is inducing contractions with rhythmic suprapubic manual pressure. These manoeuvres are assumed to produce a summation effect on the tension receptors in the bladder wall, resulting in an afferent neural discharge, which activates the bladder reflex arc [Wein, Barret, 1988].

Today, learning of triggered voiding should not be done without taking care of:

1. Bladder outlet obstruction management;
2. Continence;
3. Appliances;
4. Gender; and
5. Level and type (complete or incomplete lesions). Literature cannot be seriously interpreted due to retrospective studies with none or poor specification of bladder outlet obstruction management associated with triggering reflex voiding.

There are two different steps in the management of reflex voiding in the neuropathic. Guidelines could be proposed as follows:

1. Period of recovery of bladder activity and type of drainage waiting for it: Use intermittent catheterization as soon as possible with voiding diary and do urodynamic study when signs of bladder wake-up are arriving (leakage, autonomic dysreflexia related to filling of the bladder, bladder sensation)
2. Period of full bladder activity: regular watching of bladder pressures, dyssynergia and upper tract deterioration (every six months).

Special attention must be taken to the problems of balance between continence and protection of upper tract, sex differences, level of the lesion and neurological handicap (para- vs tetraplegic patients).

There are few data comparing different types of voiding management. One is Bennett et al (1995) in female (Level of evidence 4). It shows that a definite trend as the management method of choice in contrast to reflex voiding and padding (or also indwelling catheter) is intermittent catheterization with anticholinergic therapy (statistically significant difference in long-term groups from 11 to 23 years). Some authors, Yokoyama et al, 1996 (Level of evidence 4) argue against triggered voiding because of high risk of upper tract deterioration during long periods with a full bladder.

The best choice of treatment for long-term use can be done with help of the analysis of 8 factors described by Maynard & Diokno (1982) (Level of evidence 4):

- Type of neurogenic bladder
- Prognosis of recovery
- Incontinence
- History of urethral trauma
- Decreased host resistance
- Dependence in catheterization
- Compliance (of patient)
- Patient preference (with informed choices)

One additional indication could be a tetraplegic patient who is unable to perform self-catheterization but able to do tapping or triggered voiding. They choose this option because it gives possible independence.

b) Is it effective?

The question of effectiveness of triggered voiding is separated as follows:

Is it an effective way of protecting upper urinary tract?

Is it an effective way of emptying the bladder?

Is it an effective way of ensuring a good quality of life for patients?

Is it an effective way of controlling incontinence?

So far no studies in the literature are able to give good answers to all these questions.

c) Is it safe?

This technique could be safe if patients are able to have adequate follow-up and monitored (see recommendations). As it is reported that complications occur more often in the first 15 years [Lamid 1988; van Kerrebroeck 1993; Gupta, Chawla 1994; Weld 2000] (Level of evidence 4), it is not recommended for patients who may fail to return for regular urological follow-up. Canupp et al (1997) reported reasons for poor compliance with regular follow-up: belief that follow-up was not necessary, cost of investigations, good local doctors, distance and transportation. These indicate a need to improve patient education.

According to Frankel et al (1998) reporting on a fifty year investigation in a spinal cord injury cohort, the risk of death related to a urological dysfunction is decreasing 50% each ten years. This was due to improvement of evaluation, indications, follow-up and urodynamics study. In addition the rate of patients using CISC was increasing and could be part of this success. Therefore it is not possible to give conclusion on the safety of triggered voiding (Level of evidence 4).

d) Is it cost-effective?

No studies on cost-effectiveness are available.

e) Complications

Complications such as clinically significant infections, upper urinary tract alteration/deterioration, autonomic dysreflexia have been reported in the past reports, levels of evidence 4 or lower. New publications did not report specifically on this topic [Weld 2000; Canupp et al 1997; Sekar 1997; McKinley 1999; MacDiarmid 2000; Yavuzer et al, 2000].

CONCLUSIONS

Reflex voiding is based on an unphysiological sacral reflex. It is potentially dangerous and has a limited role in managing the reflex bladder at present.

The long-term complication rate is not as high as with indwelling catheter, but enough to suggest a trend to avoid this triggered reflex voiding in detrusor hyperreflexia.

Costs of appliances and of adjuvant therapies (pharmacotherapy, surgery, urethral prosthesis etc) have to be evaluated.

Treatment of infralesional spasticity and co-morbidity should be taken into consideration.

5. IMPLICATIONS FOR PRACTICE

Before considering triggered reflex emptying, check if the bladder situation is urodynamically safe and if regular follow-up is guaranteed. The frequency of check-up is not validated, depends on risk factors, but should be between 6 months and 2 years.

Each patient has to find his best way of triggered reflex voiding. Adequate management of reflex incontinence is essential. Social continence may be achieved only by controlling fluid intake and regular bladder emptying according to each personal schedule.

Be sure that type of bladder emptying is socially (and sexually) acceptable to permit an adequate quality of life.

To improve emptying and control autonomic dysreflexia related to bladder filling and contraction, alpha-blockers should be tried before sphincterotomy and/or bladder neck incision is performed.

In a well-developed country, triggered voiding should not be recommended as the first line management of bladder hyperreflexia and micturition. Intermittent catheterization has become the gold standard to achieve continence, upper urinary tract protection and improvement of quality of life (see recommendations in the chapter of intermittent catheterization).

RECOMMENDATIONS

Triggered voiding could be recommended for patients whose situation has proven to be urodynamically safe and stable, and who can manage reflex incontinence. Moreover it is recommended for patients after sphincterotomy and/or bladder neck incision and/or alpha-blockers, in order to improve spontaneous reflex voiding.

Reflex voiding can only be recommended if an adequate follow-up is guaranteed. (Grande of recommendation C)

6. IMPLICATIONS FOR RESEARCH

Due to lack of controlled studies and less patients using such bladder management nowadays, clinical research is recommended on the following issues:

- Alpha-blockers effect (see related chapter)
- Urodynamics pre- and post-sphincterotomy and/or bladder neck incision
- Long-term retrospective cohorts comparing triggered voiding with other types of management (e.g. CISC)
- Quality of life assessment

For future developments this topic should be analysed in accordance to sphincter status (sphincterotomy or not, alpha-blockers or not, bladder neck incision or not) and not as an isolated voiding management.

7. ACKNOWLEDGEMENT

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8. POTENTIAL CONFLICT OF INTEREST:

None

II. BLADDER EXPRESSION (CREDE´ AND VALSALVA)

1. BACKGROUND

Bladder expression has been recommended since a long time for patients with so-called lower motor neuron lesions, resulting in a combination of an underactive detrusor with an underactive sphincter or with an incompetent urethral closure mechanism of other origin (e.g. after sphincterotomy).



Figure 5 : *Bladder expression comprises various manoeuvres, aimed at increasing intravesical pressure to enable / to facilitate bladder emptying.... (for details see text).*

Difficulties in emptying the bladder by expression may be due to (1) an inability to open the bladder neck. However, especially in men, these techniques induce (2) a functional obstruction at the level of the striated external sphincter despite complete paralysis of the musculature of the pelvic floor. The pathophysiological mechanism of the bladder expression via Valsalva and Credé was evaluated by Madersbacher (1977) : voiding-cystourethrograms during these techniques show a typical bending, deformation and narrowing of the membranous urethra at the level of the pelvic floor. The interpretation of this phenomenon is, that during Valsalva and Credé, the bladder and its outlet are forced downwards and backwards, while the penile urethra is fixed via the Lig. suspensorium penis to the pubic symphysis. Thus the urethra becomes compressed by the musculature of the pelvic floor. Any further increase of the intraabdominal pressure increases the deformation of the membranous urethra and makes bladder emptying worse. This functional narrowing cannot be recognized by a retrograde urethrogram, nor felt by catheterization, nor it is visible endoscopically. However, through experience, some patients have learned that voiding can be improved by a manual counter pressing against the perineum.

Moreover, Clarke & Thomas (1981) studied static urethral pressure profiles in paraplegics with an acontractile bladder: (3) the urethral pressure in all flaccid male paraplegics investigated was much higher at the external sphincter than at the bladder neck. It was largely abolished by alpha-blockers. They conclude in flaccid male paraplegics the major component of urethral resis-

tance is a constant, adrenergically innervated muscular resistance in the external sphincter region; however, this is still under discussion.

2. OBJECTIVES

To find evidence to answer the following questions:

1. How to do it?
2. Is it effective?
3. Is it safe?
4. Is it cost-effective?
5. How to treat complications?
6. Comparing between techniques
7. Long-term results and quality of life

3. CRITERIA FOR CONSIDERING STUDIES AND SEARCHING STRATEGY

All types of studies, adults and children only if necessary for understanding, dealing with Credé- and the Valsalva manoeuvre for emptying bladder in neurogenic lower urinary tract dysfunction were included.

Search from Medline through Pubmed 1966-2001/April and the list of publications used in the First International Consultation on Incontinence 1998.

Keywords: Credé, Credé voiding, Valsalva, Valsalva voiding in neurogenic bladder, in spina bifida, in spinal cord injury, in cauda equina syndromes, intervertebral disc protrusion, in lower urinary tract disorders, combined with anal stretch

All studies were considered in regards to efficacy, safety and cost-effectiveness (languages English, German). Eleven studies (1 in Japanese languages, but with an abstract in English) were considered.

Quality of included studies. There were 7 case-series (level of evidence 4); 2 were case-reports, 1 of them with 1 patient and the other with 2 patients (level of evidence 5); 2 comprise basic research of bladder expression, one with operative therapy based also on a case-series.

4. RESULTS

a) *How to do it?*

Bladder expression comprises various techniques aimed at increasing intravesical pressure in order to enable/to facilitate bladder emptying. The most commonly used are the Valsalva (abdominal straining) and the Credé (manual compression of the lower abdomen).

b) *Is it effective?*

There is no randomised controlled study on bladder expression, however, Barbaliás et al (1983) prospecti-

vely evaluated the efficacy of Credé to promote voiding in 207 patients with a variety of lower urinary tract disorders using urodynamics, including urethral pressure measurement. They found an increase in urethral pressure during Credé manoeuvre while the vesical neck remained closed. Only 2% in this series the bladder neck opened and the external urethral sphincter relaxed. They concluded that Credé manoeuvre is an inefficient method of bladder emptying, in the majority of patients associated with a significant urethral obstruction.

Clinical experience shows that by straining and increasing abdominal pressure patients are able to empty their bladders, albeit mostly incompletely.

c) Is it safe?

With the development of urodynamics/videourodynamics, it could be demonstrated that despite high intravesical pressures created by these techniques, the urinary flow may be very poor and residual urine may also be present. This echoes Watkins' statement, 1936, that micturition by the Valsalva or Credé can be impeded despite flaccid paresis of the pelvic floor (see Background).

Reinberg et al (1984) reported a case of renal rupture with development of a large perinephrec urinoma and deterioration of renal function after the Credé technique in a girl with neurogenic bladder and detrusor sphincter dyssynergia (without vesico-ureteral reflux). Therefore bladder expression is not safe unless urodynamics have proved the contrast.

d) Is it cost-effective?

There are no data that evaluate the cost-effectiveness of bladder expression.

e) How to treat complications?

Complications with this method are caused by high intravesical pressure to overcome outflow resistance. Therefore complications with bladder expression can be treated either by lowering outflow resistance (see below) or by replacing bladder expression by CISC.

f) Comparing between techniques

Only Momose et al (1997) compared the clinical significance between Credé voiding (n=56, mean follow-up period 14.6 years) and Valsalva voiding (n=22, mean follow-up 13.7 years) in the urological management of spina bifida patients. **Although their findings suggest a possible superiority of Valsalva voiding over Credé voiding in the preservation of the urinary tract, the differences between the two groups were not statistically significant and they suggest further studies in neurogenic bladder patients.**

In other papers [Leroi et al 1994; Fanciullacci et al 1989; Sperling 1978] Credé and Valsalva are mentioned as part of the treatment without further judgement. Only Redman (1976) report on two cases with upper urinary tract improvement with Credé. Madersbacher (1977) as well as Clarke & Thomas (1981) documented a functional urethral obstruction at the level of the pelvic floor during bladder expression (as above-mentioned).

g) Long-term results and quality of life

Madersbacher (1977) demonstrated that with increasing time of using Valsalva and Credé techniques, more than 50% of patients showed demonstrable influx into the prostate and the seminal vesicles and other complications, e.g. epididymo-orchitis. Moreover, the high pressures cause reflux into the upper urinary tract with all known complications. The stress to the pelvic floor with these techniques several times a day also has a negative influence on existing minimal storage function of these structures and therefore makes incontinence worth, causing additional genital-rectal prolapse and haemorrhoids.

Adjunctive therapy to decrease outflow assistance includes alpha-blockers, if they are effective they usually cause or increase neurogenic urinary stress incontinence. Juraschek et al (1974) and Wyndaele (1998) advocated cystoprostatopexy to the abdominal wall to prevent kink of the urethra, however, no long-term results are available.

CONCLUSIONS

Bladder expression by Valsalva or Credé is potentially hazardous for the urinary tract due to functional obstruction at the level of the pelvic floor.

It is contraindicated if it creates a high intravesical pressure, or/and if prostatic reflux or/and a vesico-uretero-renal reflux are present. In addition, hernias, recto-genital prolapse and hemorrhoids as well as urethral pathology (stricture formation) and recurrent symptomatic UTIs are further contraindications.

It may have a negative influence on an existing minimal storage function of the flaccid pelvic floor and therefore incontinence may become worse.

Alpha-blockers may reduce the outflow resistance, and may also induce or increase urinary stress incontinence.

5. IMPLICATIONS FOR PRACTICE

Bladder expression is often recommended especially for patients with an underactive detrusor with an underactive / incompetent sphincter mechanism.

Expression of the bladder for voiding by Credé and Valsalva is effective. To empty the bladder, the pressures measured may be high and potentially dangerous for the upper urinary tract. **Bladder expression is not safe.**

According to the above-mentioned, it is clear that sphincter-hyperreflexia and detrusor-sphincter dyssynergia are contra-indications for bladder expression. However, there is one exception i.e., when used in the reflex bladder with the anal sphincter stretch described by Low & Donovan (1981). This method, by inserting one or two gloved fingers into the anal canal and then stretching the anal sphincter, does relax the external urethral sphincter; and voiding is then achieved by abdominal straining. Therefore, it can be used in those who have a reflex bladder with unbalanced voiding due to detrusor weakness and/or detrusor-sphincter dyssynergia. There is no evidence that Credé or Valsalva are superior or less dangerous as the other.

If complications, caused by high pressure during bladder emptying, occur, CIC is the alternative. Long-term results are good only if no contraindication exists or occurs over the years, urodynamic controls are mandatory. If the situation remains safe and stable the method is cost-effective and guarantees an adequate quality of life. However if complications occur, patients have to be persuaded to change to CIC.

RECOMMENDATIONS

Before recommending bladder expression by Valsalva or Credé, it must be proved that the situation in the lower urinary tract is urodynamically safe. Basically the method is rather dangerous.

Exclude contraindications, such as a vesico-ureterorenal reflux, prostatic reflux, genito-rectal prolapse, hernias, urethra pathology and symptomatic UTIs before recommending this type of bladder emptying.

In general, bladder expression should be replaced by CIC in most patients with neuropathic bladder-sphincter dysfunction.

Alpha-blockers are not recommended as they may induce or increase urinary stress incontinence.

Valsalva and Credé only guarantee a good quality of life and are cost-effective in long term when the indication is proper and when the situation remains stable throughout the years. (Grande of recommendation C)

6. IMPLICATIONS FOR RESEARCH

A urodynamically controlled prospective study should be conducted to prove that Crede and/or Valsalva are really safe in patients with normal range intravesical pressure created by these techniques.

7. ACKNOWLEDGEMENT:

None

8. POTENTIAL CONFLICT OF INTEREST:

None

III. TOILETTING ASSISTANCE: TIMED VOIDING, HABIT RETRAINING, PROMPTED VOIDING

Bladder retraining and toileting assistance aim to restore control over the urinary bladder. The different techniques have been reviewed especially in older persons with urinary incontinence, however, there are only few references directly related to neuropathic incontinence. Therefore in behalf of the bladder retraining and toileting assistance see chapter on Incontinence in the Elderly. Randomised controlled studies are needed to get evidence also in patients with neuropathic incontinence.

C. CATHETERS

I. INTERMITTENT CATHETERIZATION [IC]

1. BACKGROUND

The use of catheters for bladder emptying dates back to many thousands of years [Brosman 1965].

Intermittent catheterization (IC) and self-catheterization (ISC) have become properly introduced during the last 40 years [Guttman, Frankel 1966; Lapidés et al 1972].

The main aims of IC and ISC are to empty the bladder and to prevent bladder overdistension in order to avoid complications and to improve urological conditions. Many studies showed good results in continence with less complications leading to a better prognosis and a better quality of life in many with neurologic bladder [Maynard, Diokno 1982; Diokno et al 1983; Sutton et al 1991].

IC and ISC are nowadays considered as the methods of choice for the management of neurologic bladder dysfunction.

2. OBJECTIVES

To find evidence to answer the following questions:

1. What is the best technique and what are the best materials for IC?

2. *Is IC effective for treating neurogenic urinary incontinence and voiding dysfunction?*
3. *Is IC safe?*
4. *How to prevent complications?*
5. *How to treat complications?*
6. *Is IC preferable to other forms of bladder emptying/catheter drainage in the neuropathic patients?*
7. *What are the long-term results including the impact on quality of life?*
8. *What does IC cost?*

3. CRITERIA FOR CONSIDERING STUDIES AND SEARCH STRATEGY

All types of studies in adults dealing with IC and ISC in neurogenic bladder have been included in this search.

Medline through Pubmed from 1966-2000, and the list of publications used in First International Consultation Report if not included in the former list.

a) Keywords

Catheterization, catheterization, neurogenic, neurogenic bladder, bladder, urinary, intermittent catheterization, intermittent selfcatheterization

b) Method of review

All studies were considered in regards to outcome, efficacy, safety and cost effectiveness, in all languages. When written in Japanese the information in the English translation of the abstract was used.

c) Description of the review

477 studies were reviewed and 119 were in first instance selected because dealing with conservative treatment in adults with neurogenic bladder. Further analysis excluded 25 articles dealing with suprapubic or indwelling catheter. Fifty one articles were added to this list from a previous survey, bringing the total number to 145.

d) Methodological quality of the included studies

The articles withheld for evaluation are 9 randomized controlled trials, 23 prospective cohort studies, 12 retrospective case control studies, 87 case series, and 14 expert opinions.

4. RESULTS

a) What is the best technique and what are the best materials for IC?

There exists not one best technique nor one best material as both depend greatly on patients' individual anatomic, social and economic possibilities.

Material and catheter type: Many types of catheters are used for IC and ISC, e.g. Nelaton, O'Neil, Tiemann and Foley. They are made of rubber, latex, plastic (PVC), silicon. They may be siliconized or of teflon coated rubber, glass or stainless steel. Some are packed in a sheet/bag [Wu et al 1981], others are reusable. A urethral introducer has been described which permits to bypass the colonized 1.5 cm of the distal urethra and which resulted in a significant lower infection rate in hospitalized men with spinal cord injury [Bennett et al 1997]. Most catheters need the use of some kind of lubricants, especially in men, e.g. jellies or aqueous solution but no studies were found comparing these. Lubricants are applied on the catheter or are instilled into the urethra [Burgdörfer et al 1997]. In developing countries, where resources are limited, patients sometimes use oil [Kovindha 1998] or just water [Orikasa et al 1976] as lubricant. For those with preserved urethral sensation, a local anesthetic jelly may be needed. Jellies would seem most effective when instilled into the urethra. This has been studied in endoscopy [Vogler 1980, Scholtmeijer, Dzoljic-Danilovic 1990] but can be accepted for catheterization too. The advantage is multiple: Lubricants injected into the urethra permit the catheter to glide in a film of jelly into the bladder; the disinfectant effect of jellies containing antiseptic substances is optimal; the local anesthetic effect, if one waits 5-10 min. after instillation, is fully developed. Many female patients do not use catheter lubrication. Some catheters have special properties such as a hydrophilic and self lubricated surface which can be activated with tap or sterile water. Regarding the size of the catheters, for adults 10–14 Fr for adult males and 14-16 Fr for adult females are mostly used but bigger size/lumen may be necessary for those with bladder augmentation. No studies on IC compared sizes in a randomized way.

Studies comparing materials in a randomized controlled way are scarce. Some recent studies evaluate the hydrophilic catheters. In an animal study in the rabbit, Lundgren et al (2000) found that osmolality of hydrophilic catheters is important in regards to removal friction and urethral trauma. To minimize the risk of urethral trauma high osmolality catheters are recommended especially when the catheterization times are a few minutes or more. Waller et al (1997) compared two different hydrophilic catheters in a crossover study of 14 male spinal cord injury patients, as to the maximum friction force during the removal of the catheters after bladder emptying. The catheter with the highest osmolality (approximately 900mOsm/kg) had much less sticking to the urethral epithelium and had a significantly lower friction force. Biering-Sorensen et al (1999) compared two types of hydrophilic catheters and found no difference regarding the number of urethral epithe-

lial cells on the surface of the catheters after catheterization. Wyndaele et al (2000) evaluated the use of a hydrophilic catheter in 39 male patients with neurogenic bladder using conventional catheters for a long time. The hydrophilic catheter proved as easy to use but was better tolerated. Satisfaction was better especially in patients who experienced problems with conventional catheters. Some patients were unsatisfied for reasons of practical use or for economical reasons. Very recently Hedlund et al (2001) pleaded for a prospective, randomized longterm multicentre study in order to reach reliable conclusions. Studies comparing the use of hydrophilic catheters with the use of ordinary catheters and lubricant must take into account how this jelly is used: applied on the catheter or injected into the urethra.

Technique: Two main techniques have been adopted, a sterile IC (SIC) and a clean IC (CIC) (Figures 6, 7). The sterile non-touch technique advocated by Guttman and Frankel implicates the use of sterile materials handled with sterile gloves and forceps. In an intensive care unit, some advocate wearing a mask and a sterile gown as well. In some centres, during a bladder training programme, SIC has been done only by a catheter team,



Figure 6 : Sterile non-touch technique of intermittent catheterization (Guttman & Frankel, 1966)



which has proven to obtain a very low infection rate [Lindan, Bellomy 1971]. The sterile technique is used only during a restricted period of time and in a hospital setting. In the majority of cases a clean technique is used. Catheterization is done in many different positions: supine, sitting or standing. Female patients may use a mirror or a specially designed catheter to visualize the meatus [Bruijnen and Boer 1981]. After a while most women do not need these aids anymore. The catheter is introduced in a non-infecting and atraumatic way. The requirements for this have been described many times: non infecting means cleaning hands, using a non infected catheter and lubricant, cleaning the meatal region before catheter introduction. Here again different ways of application are used: the use of sterile components with the catheter introduced out of the sheath into the urethra as well as the use of resterilized catheters introduced by hand which have been washed before.

Individual variation can be found in every patient group. Atraumatic requires a proper catheter size, sufficient lubrication, gentle introduction through the urethra, sphincter area and bladder neck [Wyndaele 1983, Corcos 1996]. The catheter has to be introduced until urine flows out. Urine can be drained directly in the toilet, in a urinal, a plastic bag or other reservoir. The catheter should be kept in place until urine flow stops. Then it should be pulled out slowly while gentle Valsalva or bladder expression is done in order to completely empty residual urine. When properly done the residual urine should be maximum 6 ml as demonstrated by Stribran and Fabian with fenolftalëine washing (1961). But routine can be different as shown by Jensen et al (1995). They measured residual urine repeatedly with ultrasonography and found rest urine in 70% of the catheterizations in their group of 12 patients with spinal cord lesion. The residual could exceed 50 ml and even 100 ml. Finally the end of the catheter should be blocked to prevent backflow of the urine or air into the bladder. Hydrophilic catheters can be left in place for a short time only to prevent suction by the urethral mucosa which may make removal difficult.



Figure 7 : Clean (self-) intermittent catheterization technique with catheterization out of the sheath.

During the rehabilitation phase clean ISC (CISC) can be taught to patients with good hand function fairly soon. Wyndaele and De Taeye compared the results of 25 paraplegic patients (23 men and 2 women) starting on CISC at a mean of 35 days (7 to 85+ days) post trauma with those of 48 paraplegic patients catheterized by nurses with a non touch technique. They found comparable results in final outcome of the bladder training and infection rate. Early self-catheterization permitted the patients to go home for weekends earlier and was considered positive by the majority of those participating. Champion (1976) found no bacteriological difference in urine specimens one year after 7 patients changed from sterile IC to CISC.

When resources are limited, catheters are reused many times, up to weeks and months. Some re-sterilise or clean them by soaking in an antiseptic solution or boiling water. Microwave to re-sterilise rubber catheters has been described by Silbar et al 1980. A silicone Japanese type self catheter has been reused for a long time [Igawa 1998, Kovindha 1998]. Van Hala et al (1997) used a questionnaire in 97 patients with pediatric onset neurogenic bladders to evaluate differences between IC with a sterile new catheter and IC with reused material. 98% used a clean technique. Their data suggest that reused supplies are not related to an increased likelihood of urinary tract infection. As only 2% used a sterile technique comparison between sterile and non sterile technique is not possible.

Frequency of catheterization: This depends on many factors as bladder volume, fluid intake, postvoid residual, urodynamic parameters (compliance, detrusor pressure). Usually it is recommended to catheterize 4 – 6 times a day during the acute stage after spinal cord lesion. Some will need to keep this frequency if IC is the only way of bladder emptying. Others will catheterize 1 – 3 times a day to check and evacuate residual urine after voiding or on a weekly basis during bladder retraining [Opitz 1976]. Clinical utility of a portable ultrasound device in IC has been evaluated in a randomized controlled trial by Anton et al (1998). The results show that the device reduces the number of required catheterizations and is associated with a high degree of patient satisfaction. De Ridder et al (1997) had used a similar device in multiple sclerosis patients and found some decrease in incontinence over 24 hours and one catheterization less needed a day in a small number of patients.

Adjunctive therapy: To overcome high detrusor pressure anticholinergic drugs or bladder relaxants can be indicated. As shown in the table 2 this is often needed in most series published. For those who develop a low compliance bladder, upper tract deterioration or severe incontinence, injection of Botuline toxin into bladder wall [Schurch et al 2000] or surgery as bladder augmentation may be necessary. Where a too high diuresis

is noted during the night due to diurnal variation of antidiuretic hormone [Kilinc et al 1999], DDAVP can safely and effectively be used [Chancellor et al 1994]. In cases of catheterization difficulty at the striated sphincter, botulinum toxin injection in the sphincter can help [Wheeler et al 1998]. In individuals with tetraplegia reconstructive handsurgery is indicated [Kiyono et al 2000]. For those with poor handfunction or difficulty in reaching the meatus assistive devices might be needed [Bakke et al 1993].

Education: This is very important. Patients and caregivers must understand what is wrong with the bladder/sphincter, what the cause is and why IC is proposed for treatment. They have to learn how to catheterize properly. Teaching programmes have been successful in non-literate persons in developing countries [Parmar et al 1993] and in quadriplegic patients [Sutton et al 1991].

CONCLUSION

There is a wide variety of materials used and techniques applied for IC which does not seem to change the practical outcome much if the basic principles are applied: good education and training, clean and atraumatic technique, good patient compliance in the longterm.

b) Is IC effective for treating neurogenic urinary incontinence and voiding dysfunction?

In general, the purpose of catheterization is to empty the bladder and of IC is to resume normal bladder storage and regularly complete urine evacuation. With IC and ISC there is no need to leave the catheter in the lower urinary tract all the time, thus avoiding complications of indwelling catheterization (ID). Data on the results of continence in different neurological pathologies are given in table 1. It is striking that before the 1970's the articles on IC in neurogenic did not comment on continence specifically. Later the continence outcome was better reported. Some studies used bladder relaxants or surgery to obtain continence. (Table 1)

It is clear that IC can improve incontinence or make patients with neurogenic bladder continent if bladder capacity is sufficient, bladder pressure kept low, urethral resistance high enough, and if care is taken to balance between fluid intake, residual urine and frequency of catheterization.

c) Is IC safe? Several complications have been described

1. URINARY TRACT INFECTION (UTI)

Prevalences of UTI vary widely in the literature. This is due to the various evaluation methods used, different techniques of IC, different frequencies of urine analy-

Table 1 : Outcome of continence

Authors	Number of patients	Follow-up	Adjunctive treatment	Result of continence
Lapides et al 1976	168	3 m – 5y	Anticholinergic + alfa-adrenergic	Majority dry
Madersbacher - Weissteiner 1977	12 women	2 – 4y		50% dry, other 50% some grade of incontinence
Wyndaele et al 1980	30 (18m,12f)	3m-30m	6 anticholinergic, 1 colocystoplasty	73% continent + 13% improvement
Iwatsubo et al 1984	60 spinal cord lesion (sci)		Overdistension during shockphase	100% continent
McGuire – Savastano 1986	22 f	2 – 11 y	Surgery 27%	Continent 73%
Kornhuber – Schultz 1990	197 multiple sclerosis			Continence improved with elimination of residual urine
Wyndaele –Maes 1990	75 (6 neurogenic)	1.5-12y	38 anticholinergics	47 dry, 22 seldom wet, 6 wet at least once a day
Kuhn et al 1991	22 sci	5 y	No	Continence did not change
Lindehall et al 1994	26 meningo-myelocoele	7.5 – 12 y		24/26 better
Waller et al 1995	30 sci	5 – 9 y	6 anticholinergics	22 dry, 8 incontinent
Vaidyanathan et al 1998	7 sci	14 – 30 m	Bladder relaxants intravesically	84 % dry, 3 dampness at awaking

sis, different criteria for infection, the administration or not of prophylaxis, the group of patients studied, et al. Some publications give the percentage of sterile urine: between 12% and 88% [Guttmann-Frankel 1966, Pearman 1971, Lapides et al 1974, Donovan et al 1978, Maynard et al 1984, Murray et al 1984, Wyndaele et al 1990]; others of asymptomatic: 11% [Sutton et al 1991] and others of symptomatic bacteriuria: 53% [Whitelaw et al 1987]. Bakke (1993) found in 407 patients, 206 men and 201 women, 252 with neurogenic bladder, during an observation period of one year, 24.5% with asymptomatic UTI, 58.6% with minor symptoms, 14.3% with more comprehensive or frequent symptoms while 2.6% claimed major symptoms. Also in other studies the prevalence of all types of UTI are given [Kass et al 1979, Webb et al 1990, Thirumavalavan et al 1992, Perrouin-Verbe et al 1995, Yadav et al 1993] with very different results. Biering-Sorensen et al (1999) studied 77 SCI patients on CIC after 5 years and found that 81% had been treated for at least one UTI, 22% had 2 – 3 UTI/year and 12% had 4 or more/year. Still it remains difficult from literature to get a proper estimate of the risk of infection when IC is done in a short- and in a longterm: the data differ so much that many factors must play a role in the prevalence of this complication.

In the acute stage of SCI with proper management urine can be kept sterile for 15-20 days without antibiotic

prophylaxis and for 16-55 days if prophylaxis is given [Ott-Rossier 1971, Rhame -Perkash 1979, Anderson 1980]. Prieto-Fingerhut et al (1997) determined in a randomized controlled trial the effect of sterile and non sterile IC on the incidence of urinary tract infection in 29 patients after SCI. With urine analysis on a weekly basis they found in the group on sterile IC a 28.6% UTI incidence while in the nonsterile catheterization group 42.4% incidence was found. The cost of antibiotics for the sterile IC group was only 43 % of the cost for those on nonsterile IC. However the cost of the sterile IC kits was 371% of the cost of the kits used by the nonsterile IC group bringing the total cost of the sterile program on 277% of the other program. Rhame and Perkash (1979) published the results of UTI prevalence in 70 SCI patients in the initial rehabilitation hospitalization treated with sterile IC and a neomycin-polymixin irrigant. 54% developed an infection at an over-all rate of 10.3 infections per 1000 patient-days on IC. Bakke and Volset (1993) studied factors that may predict the occurrence of bacteriuria and clinical UTI in 302 patients using CIC. Predictive factors of clinical infection were low age and high mean catheterization volume in women; low age, neurogenic bladder dysfunction and nonself-catheterization in men, in addition to urine leakage in patients with neurogenic dysfunction. Bacteriuria was a risk factor of future clinical infection. Risk

factors for bacteriuria were present in men: low frequency of catheterization, high age and nonself-catheterization. If antibacterial prophylaxis was used fewer episodes of bacteriuria were noticed but significantly more clinical UTI. Shekelle et al (1999) made a systematic review of risk factors for UTI in adults with spinal cord dysfunction. In this review article they evaluated 22 studies from which many however had important methodological deficiencies. They found two studies that provide evidence supporting increased bladder residual volume as a risk factor. Patients on IC had fewer infections than those with ID. They found conflicting evidence over the value of sterile or "non touch" catheter techniques compared with CIC. They found insufficient evidence to assess risk due to psychological, behavioral and hygiene factors, sex, level of function and time since injury.

Schlager et al (1999) examined how frequently periurethral bacterial species produced bacteriuria in children followed longitudinally. Bacteriuria frequently occurs after inoculation of periurethral *E.coli* into the urine during CIC. Hull et al (1998) investigated virulence factors of *E. Coli* isolated from patients with symptomatic and asymptomatic bacteriuria and neuropathic bladders due to spinal cord and brain injuries. The results suggest that *E. Coli* isolated from patients who develop symptomatic UTI may be distinguished from bacteria recovered from patients who remain asymptomatic and possibly from normal fecal *E. Coli*. In order to diagnose UTI, Barnes et al (1992) found arguments that it should be recommended to obtain the urine by catheterization. The frequency of examining urine samples differs greatly between studies. Some advocate daily use of a dipslide technique during the acute phase after SCI, once a week during the subacute phase and monthly or a few times a year in longterm care [King et al 1992, Darouiche et al 1993, National Institute on disability and rehabilitation research consensus statement 1992]. If a urine culture reveals more than 10,000 cfu/ml, it indicates significant bacteriuria. Pyuria alone is not considered reliable in patients with neurogenic bladder [Gribble et al 1989, Menon -Tan 1992]. The bacteria found are *E. Coli*, *Proteus*, *Citrobacter*, *Pseudomonas*, *Klebsiella*, *Staphylococcus aureus* and *faecalis* in most short-term cases while the same bacteria plus *Acinetobacter* and *Streptococcus faecalis* are found in the longterm IC patients [Noll et al 1988, Yadav et al 1993]. *E Coli* is considered the dominant species in several studies [Bakke 1993]. The detection of *E. Coli* on the periurethra corresponded in much higher percentage (93%) with bacteriuria than if other bacteria were present on the periurethra (80% or less) [Schlager et al, 1999]. Urinary sepsis is fortunately rare [McGuire et al 1977, Sperling 1978, Barkin et al 1983]. Previous treatment with an ID represented a special risk

to develop sepsis in the series of Barkin et al (1983). In his thesis Wyndaele (1983) found sepsis in 21 of 115 patients with SCI during the in hospital rehabilitation. The prevalence of sepsis was highest in those treated beforehand with an ID. Factors of risk were the period of 24 hours to 3 days after changing from ID to IC drainage when UTI was present. The study of Wyndaele and Maes on 69 patients with neurogenic bladder and a literature survey till 1989 on CIC, found justification of several conclusions concerning the relationship between CIC and UTI: If catheterization is begun by patients with recurrent or chronic UTI and urinary retention, the incidence of infection decreases and patients may become totally free of infection. If symptomatic infections occur, improper CIC or misuse often can be found. Chronic infection persists if the cause of the chronicity remains.

2. GENITOURINARY COMPLICATIONS: Urethritis and epididymo-orchitis have been reported in several case series (table 2). Again the prevalence figures vary widely. This is probably due to the many differences in technique, material used, primarily treatment and investigation method. Genital infections can lower fertility in SCI patients. In 1991 Allas reported on 14 paraplegics performing CIC. In each patient he performed two spermograms, one before and one after an episode of epididymitis (unilateral in 13). Azospermia increased from 7% to 50% when epididymitis occurred. However if IC was used to empty the neurogenic bladder, slightly better sperm quality was seen. In a study by Ohl et al (1992) on 29 SCI men on electroejaculation, much better pregnancy rates than those patients using an alternative bladder management was the outcome. Also Rutkowski et al (1995) found in patients on IC a higher percentage of mobile sperms compared to those using ID.

Prostatitis, either acute or chronic is difficult to diagnose in patients with neurogenic bladder. Special tests have been developed [Kuhlemeier et al 1982; Wyndaele 1985]. The overall incidence was thought to be probably around 5% to 18% [Cukier et al 1976] but this may be underestimated. Perrouin-Verbe et al (1995) used the Meares-Steamy test and found a rate of 33%.

3. OTHER COMPLICATIONS: Urethral bleeding is frequently seen in new patients and occurs regularly in one third on a long-term basis [Webb et al 1990]. Trauma of the urethra especially in men can cause false passage, meatal stenosis but the incidence is rare (table 2). The incidence of urethral strictures increases with a longer follow-up. Wyndaele and Maes followed 75 patients on CIC for a mean period of 7 years with a maximum of 12 years, the majority using CIC for neurogenic bladder. They found 11 urethral complications in 15 patients, mostly male, some of which were recurrent. Most events occurred after 5 years of CIC. Also Per-

Table 2 : Genitourinary complications (m=men)

Authors	Total no. of patients	Urethritis	Meatal stricture	Epididymitis	Urethral stricture
Lapides et al 1974	100(34m)	2 m	-	-	-
Lapides et al 1976	218 (90m)	2 m	-	2	
Orikasa et al 1976	26 (13m)			1	
Wyndaele et al 1980	30 (18m)	2 m		2	
Maynard,Diokno 1982	28 (m?)			4 (1 with infected penile prosthesis)	
Labat et al 1985	68 (48m)	9 m		3	
Maynard –Glass 1987	34 (m?)			3	2
Wyndaele-Maes 1990	75 (33m)		3	6	7
Webb et al 1990				2%	
Hellstrom et al 1991	41 (26m)			3	
Kuhn et al 1991	22 (11m)		1		1
Thirumavalan –Ransley 1992				12%	
Bakke 1993	407 (206m)	1%		1%	
Perkash –Giroux 1993	50 m			5	
Perrouin-Verbe et al 1995	159 (113m)			10% short-term, 28% long-term	5.3%
Waller et al 1995	30 SCI (26 m)			2	4

rouin-Verbe et al (1995) found that the risk of urethral stricture seems to increase with the number of years on CIC. These authors also showed that patients who developed strictures had a slightly higher catheterization rate than those who did not. Günther et al presented in 2000 their results in 230 men on IC and found urethral changes in 26.9% (3.7% strictures) when also in their history an ID had been used. In men with IC and no history of ID the prevalence was 16.9% urethral changes and no strictures. These results were compared with those in 311 men not on IC. In this last group with history of ID 25.4% urethral changes (2.5% strictures) and in those without history of ID 17.9% urethral changes (1.5%) strictures were found.

Urethral changes were also documented by Kovindha et al (2000) in 27 spinal cord injured men on CIC for an average of 5 years (between 1 to 14 years) and using one single re-usable silicone catheter for an average of 3 years (from 1 to 7 years). Urethrograms showed 70% normal, 11% minor abnormalities, 15% narrowed urethra and 4% with stricture (1 case) that needed operation.

The surface of the catheter is claimed to be an important factor with less stricture development when hydrophilic catheters are used. Vaidyanathan et al (1994) stu-

died the degree of urethral inflammation by urethral cytology in two groups on CIC, one using ordinary catheters in PVC with lubricant, the other using hydrophilic catheters. The group using hydrophilic catheters had significantly less urethral inflammation. Waller et al (1995) found no extra stricture occurring in their patients using hydrophilic catheters after a mean follow-up of 7 years. Such data are suggestive for an advantage of using hydrophilic catheters to prevent stricture formation in the long-term but comparative studies have not been published.

Other complications such as hydronephrosis, vesico-ureteral reflux, bladder cancer seem to relate to infection, bladder trabeculation, detrusor pressure or neuropathy but not to CIC [Damanski 1965]. Bladder calculi caused by the introduction of pubic hair [Solomon et al 1980, Amendola et al 1983], loss of the catheter in the bladder [Morgan et al 1990], bladder perforation and bladder necrosis [Reisman, Preminger 1989] have been case reports on rare complications of CIC.

d) How to prevent complications?

To prevent UTI a non-infecting technique is needed. Barber et al (1999) evaluated the importance of nursing education and found this educational intervention by a

clinic nurse to be a simple, cost-effective mean to decrease the risk of UTI's in SCI individuals on CIC who are at risk. Some other factors have been found to probably play a role in infection prevention: the frequency of IC is important as shown in several studies. Anderson (1980) found a fivefold incidence when IC is done 3 times a day compared to 6 times a day. In addition prevention of bladder overdistention is important [Lapides et al 1976, Shekelle et al 1999]. Cross infection is less if IC during hospitalization is done by a catheter team [Lindan, Bellomy 1971] or by the patients themselves [Wyndaele, De Taeye 1990]. As residual urine plays a role in infection, attention must be made to completely empty the bladder [Shekelle et al 1999].

Several studies have evaluated the infection rate during antibacterial prophylaxis. Randomized controlled trials are scarce. Pearman (1979) compared 2 groups of patients with acute SCI treated with non-touch IC: 22 had kanamycin colistin solution instilled into the bladder at the end of each catheterization and 25 patients were not given such instillations. Those with the instillation had only half the incidence of significant bacteriuria. The same effect could not be found in a comparison study by Haldorson et al (1978) with instillations of neomycin. Ascorbic acid has been used by several authors. It is considered only useful as adjuvant therapy together with other antibacterial drugs [Murphy et al 1965, Stover and Fleming 1980]. Johnson et al 1994 did a 3 months study of nitrofurantoin prophylaxis in 56 children with CIC. They found a reduction from 39% on placebo to 19% on single daily dose prophylaxis. Anderson (1980) in a randomized prospective study compared infection rate between control patients, patients treated with intravesical neomycin/polymyxin-B, with low dose of nitrofurantoin and with a combination of the intravesical and oral prophylaxis. There was a significant reduction in infection rates when oral and intravesical antibacterials were used.

Kevorkian et al (1984) evaluated the effect of methenamine mandelate with acidification in a randomized controlled trial with 17 and 22 patients. They found a statistically significant difference in infection rate between the group with methenamine and the group with placebo. Mohler et al (1987) on the other hand found no difference in infection rate in a controlled clinical trial in 46 patients comparing trimethoprim-sulfamethoxazole and placebo. Bakke (1993) found in 407 patients on CIC significant bacteriuria in 57.5% of those who used no prophylaxis while the corresponding figures in patients using methenamine hippurate and antibiotics were 42.5% and 37.5%. Cranberry juice has been evaluated recently. Schlager et al (1999) did a study in children on IC and found no effect on bacteriuria. Hofstetter (1987) showed a positive effect in vitro of chlo-

rexidine in the lubricant but no clinical data have evaluated this finding. But more studies are needed to permit a proper conclusion. Several studies have asked attention for the risk to develop dangerous resistance against antibiotics when either orally or by instillation prophylaxis is given [Dollfus, Molé 1969; Pearman 1971; Vivian, Bors 1974; Pearman et al 1991]. Gallo-way et al (1986) state that the threat of emergence of resistant organisms, the risk to patients for side effects of the antibiotics, the expense and the risk to other patients from cross infection with resistant organisms are strong arguments against prophylactic antibacterials.

To prevent urethral strictures gentle introduction of the catheter, lubrication of the catheter and perhaps the use of hydrophilic catheters can play a role. Forceful manipulation during catheter insertion and significant bleeding proved important contributory factors for the development of urethral strictures in patients on CIC studied by Mandal and Vaidyanathan (1993).

e) How to treat complications?

Treatment of UTI is necessary if the infection is symptomatic. Waites et al (1999) treated 25 men with SCI on IC to determine efficacy of ciprofloxacin 1 g per day for 10 days in to eradicate susceptible organisms from urine, urethra and perineum. Susceptible bacteria disappeared from urine in all and were significantly reduced in perineum and urethra. However they were replaced shortly after by resistant Gram-positive cocci. It is important to reserve the drug for symptomatic patients only and look closely into the antibiogram. This follows the conclusions of a study by Lewis et al (1984) on the significance of asymptomatic bacteriuria in neurogenic bladder disease: their results in 52 patients indicate the value of non-treatment for chronic non symptomatic bacteriuria throughout hospitalization.

In neurogenic patients on CIC, urethral trauma with false passages have been treated by Michielsen and Wyndaele (1999) with 6 weeks indwelling catheter and 5 days antibiotics. The false passages disappeared on cystoscopy and CIC could be restarted. Mandal and Vaidyanathan (1993) successfully treated urethral strictures in 6 patients, with urethral dilatation in 4 and with optical internal urethrotomy in 2, followed by urethral stenting for 2 weeks.

f) Is IC preferable to other forms of bladder emptying/catheter drainage in the neuropathic patients including longterm results?

Almost all publications clearly state that IC is the preferable method for bladder drainage. It has less complications and give a better outcome. Most endorse this opinion by comparing the outcome with previous treat-

ment methods. Wyndaele et al (1985) compared in a series of 115 SCI patients four different methods of bladder drainage used during spinal shock: suprapubic fine bore cystostomy, indwelling Foley catheter, IC and both ID and IC consecutively. The methods of bladder drainage used did not influence the number of patients becoming catheter-free but determined significantly the length of period before they acquired catheter-freedom. Patients on IC had the shortest time from injury to established micturition. Patients on IC and on cystostomy had few complications but the complication rate in the group treated with ID was high. McGuire and Savastano (1986) compared urological outcome in 35 women from 2 – 12 years after SCI and found that the 13 with ID had frequent and serious complications compared to those on IC. Bennett et al (1995) compared the outcome in 70 female SCI patients retrospectively after a mean follow-up of more than 15 years. The group on IC had significantly better outcome than those on reflex voiding and incontinence pads or the group on ID. Giannantoni et al (1998) compared the renal outcome in a small group of patients on IC with those on tapping, abdominal straining and Credé. The incidence of both urinary tract dilatation and vesicoureteral reflux was significantly lower in the IC group. The finding of upper tract complications also in patients on IC showing high intravesical pressures stresses the need of adding anticholinergic drugs. Weld et al (2000) compared the evolution in bladder compliance with time in association with the type of bladder management in 316 SCI patients. Logistic regression analysis revealed that IC and spontaneous voiding were associated more with normal compliance than Foley catheterization. This also explains why there are less upper tract complications in their IC group.

g) Reasons to stop IC.

Not all patients starting with IC continue this treatment. Reasons for this are given in several studies summarized in table 3.

Table 3 : Reasons for stopping IC

Authors	Catheter-free	Incontinence	Inconvenient	Infection	Physical status	Choice of patient
Diokno et al 1983	17%	2%	2%		7%	
Maynard-Glass 1987	12%					6%
Whitelaw et al 1987	5%		5%		5%	5%
Webb et al 1990	9%		3%		2%	2%
Timoney-Shaw 1990		36%				
Sutton et al 1991		6%	6%	3%	3%	3%
Bakke et al 1993	10%		5%	4%	3%	
Hunt et al 1996	10 %					

Perrouin-Verbe et al 1995 found in their global population of 159 SCI patients that only 8 having practised CIC for at least 2 years stopped the technique. This indicates that in most SCI cases the definitive choice of voiding is made after 2 years post injury. A main reason to stop was continuing incontinence. The first factor of acceptance of the technique was continence. The second factor related to the patients' autonomy for practising IC. In a population of 50 patients Perlash and Giroux (1993) had also found that 4 out of 7 tetraplegics stopped IC because they needed to be catheterized by others. In addition 66% stopped IC mainly after surgery on sphincter and prostate or initiation of voiding.

Bakke and Malt (1993) found that among those who practiced IC independently 25.8% were sometimes and 6% always averse to IC. Young patients and females were more averse to CIC. In 30% aversion seemed to be related to a subjective evaluation of their situation, to an emotional status and above all to non-acceptance of their chronic disability. In a recent study [Yavuzer et al 2000] a retrospective analysis was made on the compliance with bladder management in SCI patients. Of 38 patients on CIC at discharge 52% discontinued the method and reverted to ID during follow-up. Dependence on caregivers, spasticity interfering with catheterization, incontinence despite anticholinergic agents and lack of availability of external collective devices for female patients were the main reasons for stopping CIC.

h) Is IC cost-effective?

There are no data about the cost and cost/efficacy available. In a study mentioned above Prieto-Fingerhut et al (1997) compared the cost of sterile and non-sterile IC and found that clean IC was less costly taking into account the price of sterile sets used for IC. Grundy et al (1983) compared the price of IC and suprapubic fine-bore catheterization after SCI and found the latter cheaper for material, average antibiotic cost and labour.

Duffy et al (1995) evaluated cost-effectiveness in a population of male residents of VA nursing homes comparing CIC and SIC. In this randomized clinical trial they found similar outcome but less expenses if a clean technique was used.

5. IMPLICATION FOR PRACTICE

RECOMMENDATIONS

It should be recommended to use CIC as the first choice of treatment for those with inability to empty the bladder adequately and safely. It is a valuable tool for achieving continence in the neuropathic voiding dysfunction

Proper education and teaching are necessary to permit a good outcome

To prevent and reduce complications, a non-traumatizing technique with adequate frequency of catheterization and complete emptying should be strictly performed

Minimal requirements for regular follow-up are history taking, physical examination, imaging, laboratory results and urodynamic tests, in order to early detect risk factors and complications

There is still need for research in different parts of the world to determine the best catheter, the optimal technique and the best means to prevent and treat complications

Longterm results, cost and quality of life need to be further documented

CONCLUSIONS

CIC is effective and safe to treat the neuropathic bladder in the shortterm and in the longterm.

Complications such as UTI are regularly seen and seem to be related to both the catheterization itself and the existing lower urinary tract condition.

Urethral complication seem to be increase in the longterm.

In order to reduce and prevent complications, appropriate materials and correct techniques should be taught and performed

Adequate frequency of CIC, a non-traumatizing technique and suitable materials are the key factors for a successful outcome

So far, no study exists that proves that one catheter, one lubricant, or one special technique is significantly superior to another

5. CONFLICT OF INTEREST

None

6. ACKNOWLEDGEMENT:

None

II. INDWELLING URETHRAL CATHETERS –TRANSURETHRALLY/ SUPRAPUBICALLY

1. BACKGROUND

In early 19th century, a urinary catheter with a balloon bag (Foley catheter) was developed. After the World War I, majority of spinal cord injured (SCI) as well as other neuropathic patients were treated with *indwelling urethral catheterization (ID)* or *suprapubic catheterization (SC)* due to difficulty in voiding or urinary incontinence. Nowadays, *intermittent catheterization (IC)* is recommended for neuropathic patients. Nevertheless many chose ID as a mean of treating urinary incontinence due to difficulty in performing IC or persistent leakage between catheterizations. In developing countries ID is still the method of choice for those with urinary retention or incontinence.

Studies have shown that ID caused and were associated with various complications such as urethral trauma and bleeding, urethritis, fistula due to pressure effect caused by improper size of the urethral catheters and improper technique of securing the catheters, bladder and renal stones, cystitis, acute and chronic urinary tract infection (UTI), bladder neck incompetence and urethral sphincter erosion, and bladder carcinoma. Many of these complications were related to long-term usage. Therefore instead of ID many experts advocate removal of the urethral catheter as soon as possible, use other methods such as IC or SC to decrease urethral complications. However nowadays these complications are much less due to better materials, using smaller size catheters and proper technique of securing the catheter.

2. CRITERIA FOR CONSIDERING STUDIES AND SEARCH STRATEGY

Types of studies: all types of studies.

Types of participants: mainly adults with spinal cord injuries/lesions (myelodysplasia), stroke, MS; animals and laboratories

Types of outcome measures: efficiency, safety, and quality of life

Search: Medline from 1966 to 2001

Keywords: neurogenic bladder, urethral catheter, indwelling catheteris(z)ation

Description of studies: randomised control trials (RCT); clinical trials, cohort studies, retrospective case-controlled studies, case series / case studies and reviews

Over all: there were 50 paper sorted and reviewed.

3. RESULTS

a) Technique and Care of ID

Quality of included studies:

5 RCTs: Bull et al 1991; Liedberg, Lundeborg 1990; Liedberg et al 1990; Talja et al 1990; Prierer et al 1982. (Level of evidence 1)

5 clinical trials: Sugarman 1982; Cox et al 1989; Kunin et al 1987; Morris, Stickler 1998; Morris et al 1997. (Level of evidence 2/3)

1 case-controlled study: Burr et al 1993. (Level of evidence 3)

3 case series/case report: Warren et al 1982; Feneley 1983; Cuttino, Clark 1987. (Level of evidence 4)

3 experts' opinions: Kunin 1997; Wong 1983; Burgdoerfer et al 1997 (Level of evidence 5)

Transurethral ID needs a lot of meticulous skill and care. Materials used should be sterile and handled properly by a well-trained person such as a physician, a nurse, a patient or a carer. In some centers, a well-trained catheter team has proved to lessen complications related to catheterizations.

The following are procedures of urethral catheterization and catheter care recommended by Kunin (1997). First, cleanse the urethral meatus/perineum with antiseptic solution before catheterization. Followed by lubricating the catheter, using (non-touch) aseptic technique (either with sterile gloves or forceps). Then, gently insert the catheter into the meatus. Make sure to insert the catheter 1 inch beyond the balloon to provide enough room for inflation. In males fix the catheter and the penis to the abdomen (Figure 8), in females fix the catheter to the thigh. Wong (1983) also suggests maintaining aseptic closed drainage system according to the guidelines for catheter care developed by the Center of Disease Control. Besides, proper catheters and frequency of changing the catheter are also important in preventing complications related to the transurethral ID (Table 4).

• Materials

Nowadays there are various materials used for catheters e.g. rubber, latex, silicone, siliconised latex, taflon coated latex, silver coated latex, hydrogel coating catheter etc. Sugarman (1982) investigated different catheter materials to determine the extent of and differences among them in regards to bacterial adherence. He found that the adherence was significant less to siliconised rubber than to pure latex or teflon coated rubber. Generally, taflon coated rubber values exhibited intermediate and latex rubber the highest adherence.

Cox et al (1989) studied infection of catheterised patients by electron microscopy. Fifty catheters, of all-silicone or silicone elastomer-coated latex construction, studied were from long-stay geriatric patients. The duration of each catheter used was not mentioned. They found that bacteria had colonised the surfaces of nearly

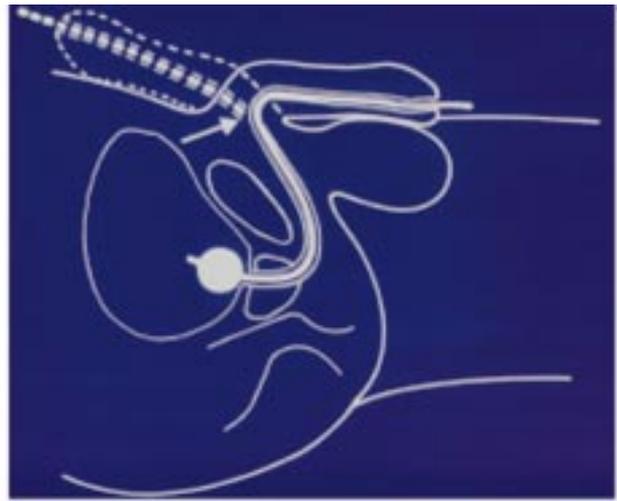


Figure 8 : In males the catheter should be fixed to the abdomen, especially in spinal cord injured patients in order to avoid a pressure sore of the urethra with the possibility to develop abscess, fistula and diverticulum; when the penis is fixed to the lower abdomen this punctual pressure to the urethra can be avoided.

Table 4 : Shows studies of different materials used for transurethral indwelling catheterisation

Authors	Study	Results
Sugarman B (1982)	Bacteria adherence to catheters	Significant less adherence to siliconised rubber than to others; taflon coated rubber values exhibited intermediate and latex rubber the highest adherence
Cox AJ et al (1989)	Biofilm on catheter's surface by electron microscope	Bacteria had colonised the surfaces of nearly all the catheters examined (all-silicone or silicone elastomer-coated latex catheters)
Liedberg H. Lundeberg T. (1990)	RCT: Catheter-associated bacteruria after 6 days of catheterisation	Much less in the silver-coated catheters than in the taflon-coated latex catheters
Liedberg H, Lundeberg T, Ekman P. (1990)	RCT: Rate of bacteriuria after 5 days of catheterisation	Significant difference between a silver alloy and hydrogel-coated Foley catheter (SHC) and a non-coated (NC) catheter. No significant difference between the SHC catheter and a hydrogel-coated (HC) catheter, between the HC catheter and the NC catheter.
Talja M et al (1990)	RCT: Encrustation and degree of urethral inflammation	Hydrogel-coating catheter effectively prevented encrustation, siliconised latex catheters were the least resistant to encrustation. Full silicone catheters induced the mildest degree of inflammation.
Morris NS et al (1997)	Encrustation	None of the 18 types of catheter tested, including those coated with hydrogel or silver, were capable of resisting encrustation by <i>P.mirabilis</i> biofilm

all the catheters examined. This thick layer of bacteria (biofilm) appears not only to precede mineral deposition but also to bind the crystals together as encrustation proceeds.

In 1990 Liedberg & Lundeberg did an RCT to study catheter-associated bacteruria in hospitalised patients. Sixty patients had a Foley catheter coated with silver alloy and 60 others used a taflonised latex catheter. After 6 days' catheterization, there was a statistically significant difference in the incidence of catheter-associated bacteriuria in the 2 groups, much less in the silver-coated catheters group and in 1989 they showed that *Pseudomonas auruginosa* cells did not grow on silver-coated. In addition, Liedberg et al (1990) did another RCT study. They found the significant difference in the rate of bacteriuria after 5 days of catheterization between a silver alloy and hydrogel-coated Foley catheter (SHC) and a non-coated (NC) catheter (p less than 0.002). However there was no significant difference between the SHC catheter and a hydrogel-coated (HC) catheter, nor was there a significant difference between the HC catheter and the NC catheter.

Besides, Talja et al (1990) did an RCT study and found that the full silicone catheters induced the mildest degree of inflammation in the urethra. Moreover, the hydrogel-coating catheter effectively prevented encrustation, while siliconised latex catheters were the least resistant to encrustation.

Morris et al (1997) studied different ID catheters and found that none of the 18 types of catheter tested, including those coated with hydrogel or silver, were capable of resisting encrustation by *P. mirabilis* biofilm.

• Frequency of catheter change

An optimal interval between catheter changes remains controversial. Some changes the catheters only when obstruction occurs, others propose routine weekly to monthly changes. Warren et al (1982) showed a high incidence (98%) of bacteriuria in SCI patients with a long-term ID (i.e. > 28 days).

According to a randomised study done in elderly patients by Priefer et al (1982), it showed that the practice of monthly catheter change had fewer symptomatic urinary tract infection (UTI) than those who changed the catheters when obstruction or infection had already occurred. However the number of patients in this study were small and done in elderly male patients, not in neuropathic patients; and types of catheters used were not mentioned.

Regarding elderly persons, Kunin et al (1987) reported the results of a clinical trial in which encrustation of siliconised rubber catheters was significantly less than that of teflon-coated latex or latex catheters. Bull et al (1991) addressed the relative performance of hydrogel-coated(HC)latex and silicone rubber coated (SC) latex

catheters in a RCT involving 69 long-term catheter users (elderly patients), about half of whom evaluated each catheter. The HC latex catheters had to be changed less frequently than those of SC rubber catheters (mean times between changes of 89.6 and 56.7 days, respectively; $p < 0.0014$). Over the 16 weeks of the study, the HC and the SC rubber catheters required 17 and 39 changes, respectively, and the main causes were bypassing (6% and 41% of changes) and encrustation (77% and 13% of changes).

The time it takes for encrustation to block a catheter will be affected by the lumen size as well as the rate of deposition of encrusting material. Morris & Stickler (1998) have shown in experiments using a simulated laboratory bladder containing real urine that the time to blockage is proportional to lumen diameter for catheters made from a range of different materials. This suggests that, for example, the tendency of silicone rubber catheters to block less quickly than those made from latex has more to do with the larger lumen in silicone rubber catheters than to differences in material properties.

• Size of the catheters and the balloons

According to size of the Foley catheters for neuropathic patients, Burgdoerfer et al (1997) recommended smaller size such as 12-14F for men and 14-16F for women to reduce the pressure effect to the urethral surface and to minimise obstruction of the urethral glands in males. It should be noticed that full-silicone catheters size of 12-14F have bigger lumens than taflon-coated or siliconised catheters especially (Burr et al 1993).

Feneley (1983) studied 24 female with neuropathic bladder with incontinence. Six patients had a patulous and shortened urethra due to the use of large diameter urethral catheters and the instillation of increasing volumes of fluid into the self-retaining balloon. In addition, Cuttino & Clark (1987) reported a case that a 30 ml Foley balloon obstructed the ureteral orifices in a neuropathic patient with a contracted bladder and caused obstructive nephropathy. After partial deflation of the balloon by withdrawing 20 ml of fluid, the patient's creatinine fell from 1.8 on admission to 0.7 two days later.

CONCLUSIONS

Whenever transurethral catheter is applied, full silicone or hydrogel-coated catheters are preferable.

Catheters size 12-16F with as large a lumen as possible and smaller (5-10 ml) self-retaining balloons are recommended for adults to minimise the pressure effect on the bladder neck and to maximise time to blockage by encrustation.

Use sterile materials and aseptic technique followed by the routine catheter care to maintain aseptic closed drainage system.

Catheters should be changed regularly, if possible, before obstruction or infection occurs. Frequency of change depends on materials and size of catheter lumen e.g., every 1-2 weeks for siliconised latex catheters, every 2-4 weeks or longer for silicone or hydrogel-coated catheters.

In developing countries, siliconised catheters widely available and costing less may be used with more frequent change.

b) Effectiveness in controlling urinary incontinence

Quality of included studies as mentioned in 5.1 and

2 case series/case report: Stickler et al 1993; McGuire & Savastano 1986 (Level of evidence 4/5)

According to the above mentioned, ID with the Foley catheter does control urinary incontinence as long as there is no outflow obstruction or bladder neck or urethral erosion due to the self-retaining balloon or the strong bladder uninhibited contractions.

McGuire & Savastano (1986) studied SCI women, 13 with ID and 22 with IC. Incontinence occurred in 92% of those with ID, and 54% suffered urethral erosion or a totally incompetent or patulous urethra 2-4 years after ID. These were caused by pressure necrosis of the self-retaining balloon or by spontaneous extrusion that occur during bladder spasm.

Stickler et al (1993) reported an old woman whose indwelling urethral catheter became blocked regularly due to 'worm-like' structures found either in the catheter, completely occluding the lumen, or in the drainage tube thereby blocking the valve of the drainage bag. These structures were composed of bacteria e.g., *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterococcus faecalis* and *Proteus mirabilis*.

CONCLUSIONS

To control urinary incontinence, ID is effective if there is no blockade or urethral/bladder neck erosion.

c) Safety for a short-term user

Quality of included studies

2 case-controlled studies: Jacobs & Kaufman 1978; Lloyd et al 1986 (Level of evidence 3)

According to the study of Jacobs & Kaufman (1978) the group of SCI patients who had a short-term ID during the acute phase had the least complication rate (0.11) compared to other groups with intermediate (0.26) and long-term (0.25) ID. They were those of bladder, genital and renal but not urethral complications. No bladder cancers were found in the short-term ID group.

Lloyd et al (1986) studied initial bladder management in 204 SCI patients during acute and rehabilitation phases. Data showed no significant differences in regard to fever and chill, urinary tract infection, upper tract changes, and pyelocaliectasis between those with ID and those with IC or SC. Moreover, after one-year follow-up, they found that the duration of the initial period of ID was not the major determinant accounting for the high infection rate.

CONCLUSIONS

A short-term ID during the acute phase is still a safe method for neuropathic patients.

d) Long-term Results and Complications

Quality of included studies

1 Cohort studies: Chen et al 2000 (Level of evidence 2)

4 case-controlled studies: Jacobs, Kaufman 1987; Chao et al 1993; Jackson, DeVivo 1992; Burr 1993.(Level of evidence 3)

9 case series/case reports: West et al 1999; Chancellor et al 1994; Shenot et al 1994; Trop, Bennett 1992; Hall et al 1989; Andrews et al 1988; Lamid S 1988; Lindan et al 1987; Feneley 1983. (Level of evidence 4)

• Urethral trauma

Andrews et al (1988) reported 16 SCI men with iatrogenic hypospadias caused by the downward pressure of an indwelling urethral catheter. The majority of such patients find the penile appearance unacceptable.

• Urine leakage

In neuropathic women with long-term ID, one major complication seen is leakage around the Foley catheters. Frequently this is due to urethra and sphincter erosion following ID with large urethral catheters and large balloons. In addition, Lindan et al (1987) and Feneley (1983) showed that the balloons provokes detrusor contractions and sometimes the contractions are strong enough to expel the catheter balloon and rupture the urethra.

In addition catheter blockage leads to urinary leakage. Burr et al (1993) studies factors related to the blockage of ID. They found that patients with frequent catheter blockage had significantly elevated urinary pH and ammonium and calcium concentration, and could be avoided by adequate fluid intake and proper diet.

Chancellor et al (1994) reported a series of 14 female with neurological disease and a patulous and non-functioning urethra. The duration of ID ranged from 2 to 17 years. Half of them had bladder capacity less than 100 ml. Trop & Bennett (1992) reviewed 48 neurologically compromised women treated primarily with ID. They found that patulous urethra expelling catheter and urinary incontinence were seen more over years.

• Renal function

In 1978 Jacobs & Kaufman reviewed the effect of permanent bladder catheter drainage on the course of 59 long-term SCI patients. Those with long-term use (> 10 years, average 20 years), had the lowest creatinine clearance (CCr) and also had a significantly higher complication rate (0.25 per year) than those short-term ID (0.11 per year). This means that a SCI patient with a long-term ID should expect 1 major urinary tract complication every 4 years, compared to 9 years for patients who are free of ID. Among major complications, bladder cancer was found more in the long-term ID group.

Jackson & DeVivo (1992), did a prospective long-term follow-up of renal function in SCI women with ID and compared to SCI men with condom catheter (CC). They found that renal function appears to be equally reduced for both women and men with SCI. Regardless of methods of bladder management, SCI women seem to have a slightly lower risk for post-injury urological complications than men do. This is supported by the retrospective study of Chao et al (1993) done in 81 SCI persons with more than 20 years post-injury. There were no significant difference in either renal function or upper tract images/complications except of a higher prevalence of scarring and caliectasis in the ID/SC group compared to the spontaneous group (with balanced bladder or IC). In the latter group a mean total bladder capacity was 350 ml with a mean maximum voiding pressure of 55 cm H₂O and a mean residual urine of 85 ml. However there were no urodynamic data of the ID and SC group and they did not mention whether an adjunctive therapy such as bladder relaxants were used in such group to prevent bladder contracture and involuntary detrusor contractions.

• Reflux

According to the study of 32 SCI patients by Lamid (1988), free drainage such as a Foley catheter did not prevent reflux formation. It was not effective in reflux

treatment because in the long run it did not prevent progression of vesico-ureteral reflux (VUR) and did not protect the refluxing kidney from damage. Moreover, incidence of VUR was higher in those with an upper motor neuron lesion.

• Bladder cancer

Chao et al (1993) 6 patients developed bladder cancer: 3 were in the ID/SC group, 2 in the spontaneous voiding (SV) group and 1 had ileal conduit. The average time from injury to bladder cancer development was 25.7 years (range 9 to 34 years). West et al (1999) reported a large retrospective study on SCI patients with chronic ID. They found that 0.39% (130 out of 33,565 patients) had bladder cancer. An average age at diagnosis was 57.3 years. The histologic finding was transitional cell carcinoma in 23 (55%), squamous cell carcinoma in 14 (33%), and adenocarcinoma in 4 (10%). Bladder management of these patients was an transurethral ID in 18 (43%), SC in 8(19%), CIC in 8 (19%) and CC in 6. Squamous cell carcinoma was common in those with ID/SC than those without chronic catheterization.

• Stones

In the study of Trop & Bennett (1992), 22 out of 48 patients (46%) of long-term ID had bladder stones, and only 6 (12%) had renal stones. Hall et al (1989) reported higher incidence of 53% of bladder stones and 36% of renal stones.

Chen et al (2000) did a multi-center longitudinal study estimating the current trend in the incidence of first kidney stone among persons with SCI and delineating the potential contributing factors. They showed that bladder management played a stronger role during year 2 and later. Those with catheter-free at discharge less than 2% were estimated to get stones within 5 years, while 7% in those with ID, 5% in CC, 5% in IC and 3% in SC group.

• Allergy

Besides, urethral catheters induced latex allergy leading to a life-threatening reaction. Shenot et al (1994) reported a SCI woman with chronic ID who underwent bladder augmentation surgery. Intraoperatively, she developed cardiovascular collapse. Subsequent skin testing to a purified latex antigen revealed latex hypersensitivity.

CONCLUSIONS

Transurethral ID is not a safe method for a long-term use in neuropathic patients.

Bladder screening for bladder cancer is mandatory especially those with ID/SC more than 5-10 years. (Level of evidence 4)

4. PREVENTION AND MANAGEMENT OF COMPLICATIONS

Quality of included studies

3 RCTs: Garibaldi et al 1980, Muncie et al 1989; Classen et al 1991; (Level of evidence 1)

6 case series/case study: Stickler et al 1985; Kunin et al 1985, Elliot et al 1989; Trop & Bennett 1992; McGuire, Savastano 1986; Feneley 1983.(Level of evidence 4)

2 reviews: Galloway 1997, Wong, Hooton 1981. (Level of evidence 4/5)

A proper catheter protocol is essential in order to control and prevent complications. Wong & Hooton (1981) gave strong recommendations for prevention of catheter-associated UTI as follows: educate personnel in correct techniques of catheter insertion and care, catheterize only when necessary, use antiseptic technique and sterile equipment, secure catheter properly, maintain closed sterile drainage.

Galloway (1997) did an extensive review of prevention and management of urinary tract infection in SCI patients. He proposed 4 essential strategies: choice of drainage system, i.e. ID should be used for as short a time as possible in the early stage; treatment of complicating factors e.g., outflow obstruction and stones; infection control by hygiene catheter care, staff and patient education; and urological follow-up.

• Meatal care

Regarding catheter care, some suggest routine cleansing of external meatus, proper fixation of the catheter, bladder irrigation etc. Garibaldi et al (1980) showed evidence that the mucous sheath between the catheter and urethra is the major pathway for entry of bacteria into the bladder when closed drainage is used and that colonisation of the urethral meatus with potentially pathogenic bacteria is a major risk factor for subsequent bacteriuria. However in RCT done in 17 adult patients, a routine meatal care with providone-iodine twice a day or with soap and water did not prove to be better than non-treated group.

• Bladder irrigation

According to the study on infected Foley catheters of Stickler et al (1985) and other study of Kunin et al (1985) external agents such as antibiotics have difficulty penetrating the encrustation and effecting bacteria present on the catheter surface. In addition, bladder irrigation increased risk of infection from frequently breaking the closed drainage system, bacterial resistance and chemical cystitis. Elliot et al (1989) showed that bladder irrigation causes mechanical damage to the

bladder and may lead to bacterial invasion into deeper mucosal layers.

Muncie et al (1989) performed a randomized crossover trial comparing ten weeks of once-daily normal saline irrigation with ten weeks of no irrigation in 32 long-term catheterized women. They concluded that it is a time-consuming and costly procedure that is unlikely to have an impact on the morbidity associated with such catheters.

• Combined measures

Classen et al (1991) conducted an RCT to assess the prevention of bacteriuria, using a three-way system including a hydrophilic polymer-coated and pre-connected sealed catheter system, daily catheter care, and disinfection of the outflow tube of the drainage bag with povidone-iodine. They concluded that the use of several simultaneous measures to prevent catheter-associated urinary infections is no more effective than the use of pre-connected catheters with junction seals alone and is clearly more expensive.

CONCLUSIONS

Use less irritating catheters and closed drainage system to minimise complications.

Bladder irrigation and antibiotic prophylaxis are not recommended as a routine infection-control measure.

Patient education on daily cleanliness and hygiene care and a thoroughly urological check-up are mandatory.

5. SUPRAPUBIC CATHETERIZATION – SPECIAL ASPECTS

An alternative to indwelling urethral catheterization is an indwelling catheter placed in the lower abdomen into the dome of the bladder. This is most commonly called the suprapubic catheter (SC).

Overall the benefit and risks of the SC is very similar to the indwelling urethral catheter including the risk for urinary tract infection, stone formation, bladder cancer, and maintenance cost of catheter and bag. However, there are several benefits for the SC and one key disadvantage. Its advantages include: (1) minimized risk of urethra trauma in men and women, (2) minimized the risk of the urethral destruction that can sometime be seen in neurologically impaired women with even relatively short-term indwelling urethral catheters, and (3) minimized urethral pain. The key disadvantage is that it requires a minor surgical procedure to insert the supra SC with potential to injury adjacent structures to the bladder especially the large intestine. There are a large number of techniques described for the insertion of the

SC. The preferred technique appears to be quite variable by region and country. There is no evidence that there is one best way to insert the SC.

Long-term management of the neurogenic bladder with the SC is a controversial topic in neurourology. The issue of controversy is that some rehabilitation centers across the world highly favor the suprapubic catheter as a safe and effective long-term management of the neuropathic bladder. On the other hand, a large number of experts have personal experience with suprapubic tube complications during its long-term use.

a) Description of studies and their results

The literature on suprapubic catheterization is small and most of them are 20 years or older. There are no prospective studies and no RCT on suprapubic catheterization. The bias of favorable single center case series is that the follow-up is short with a worrisome large number of patients who are lost to follow-up. It is concerned that patients lost to follow-up may have developed complications and have died or were treated with alternative bladder management at a different hospital.

There are 11 reports that discuss the management of the neurogenic bladder with the suprapubic catheter. There are no prospective randomized studies. All the studies are also limited by short follow-up time frame. It is well established that the risk of urological complications, especially urethral destruction and bladder cancer occurs most commonly beyond after 5-10 years. Therefore a favorable report of SC after two years is relatively meaningless [Grundy et al 1983; Barnes et al 1993] (Level of evidence 3-4). There are evidence that the complications associated with SC is similar to ID and both higher than IC in the long-term management of SCI patients [Weld & Dmochowski 2000] (Level of evidence 3-4).

Complications of the SC have been reported in seven case reports (Level of evidence 4). The unique complication associated with the suprapubic tube that non-urologists who takes care of neurologically impaired patients may not be aware of is bowel perforation during the insertion of the suprapubic catheter [Farina & Palou 1992]. Bowel injection would present with acute peritonitis and warrants emergency care [Browning 1977].

There are eight reports of short-term use of suprapubic catheter as adjunct management of abdominal or pelvic operations (Level of evidence 3). The consensus is that in the short-term in none neurogenic bladder patients the suprapubic tube appears to be better than indwelling urethral catheter. However, the risk of urinary tract infection appears to be the same [Horgan et al 1992].

CONCLUSIONS

Suprapubic catheter is a reasonable alternative to indwelling urethral catheter but both are clearly inferior to intermittent catheterization.

It is a safe and effective short-term management of urinary retention.

It is not recommended for the routine use for the long-term management of the neurogenic bladder.

6. COMPARISON BETWEEN ID AND SC

Quality of included studies

6 case series/case study: MacDiarmid et al 1995; Barnes et al 1993; Lloyd et al 1986; McGuire & Savastano 1986; Feneley 1983; Hackler 1982. (Level of evidence 4)

Regarding female incontinence after long-term ID, Feneley (1983) managed by SC with urethral closure and 19 out of 24 patients had satisfactory results. McGuire & Savastano (1986) suggests that SC may have advantage over ID with less urethral complications.

According to a comparison study between long-term SC and ID or external drainage, Hackler (1982) evaluated 31 SCI patients maintaining on SC for a least 5 years (average 8 years) by intravenous urography (IVU) and cystourethrography (CUG). Results showed that only 39% of 62 renal units were normal, 33% had evidence of chronic pyelonephritis, 18% with stones and 10% with hydronephrosis and hydroureters. He then compared this study with his previous studies on SCI patients with long-term (20 years) external appliance or ID. The renal units remained normal in 66% (128/195) of those with external appliance drainage, in 51% (77/152) of those with ID but in only 39% of those with SC. The incidence of VUR was significantly higher in the SC patients but the incidence of hydronephrosis was higher in the ID patients. He concluded that five years with SC might cause as much renal damage as 20 years with ID. However, only 6 were on anticholinergic therapy.

Lloyd et al (1986) did a study on initial bladder management in 204 SCI patients. Twenty-one patients were initially treated with fine bore SC but there was only 1 with such drainage one year after discharge. When compared those with SC to those with ID or IC, there were no difference in rate of UTI, bladder calculi and upper tract changes during acute and rehabilitation phases.

In addition, Barnes et al (1993) studied 40 neuropathic patients managed by SC. All received anticholinergics

and daily clamped the catheter. Catheter-related problem reduced and 84% of the patients accepted it and it did not accelerated renal deterioration during the 2-year follow-up.

MacDiarmid et al (1995) reported a case series of 44 SCI patients with SC for a mean duration of 58 months. They used latex Foley catheters and weekly irrigation with 500 ml to 1,000 ml of normal saline or 1:5,000 chlorhexidine solution; and changed the catheter every 2 weeks. In addition, after discharge the patients had routine urological check-up with cystometry and renal ultrasound every 6 months or annually. None of their patients had renal deterioration, vesicoureteral reflux (VUR) or bladder carcinoma. Uncomplicated infection (43%), bladder calculi (41%), catheter blockage (36%) and incontinence (11%) were reported.

CONCLUSIONS

Due to less urethral complications, SC is an alternative for a short-term management for neuropathic patients.

Adjuvant anticholinergic therapy, to minimise leakage and the development of bladder and renal abnormalities, is necessary especially in those with detrusor hyperreflexia.

7. LONG-TERM QUALITY OF LIFE

Quality of included studies

2 Case-control studies: Dewire et al 1992; Watanabe et al 1996

Dewire et al (1992) did a retrospective study of 57 tetraplegic SCI patients who were followed for a minimum of 10 years and compared urological complications between those with ID and without ID. They found no difference between these 2 groups. They suggest that the decision to manage tetraplegics with or without an ID should not be based on relative risk of complications or renal deterioration. The decision to avoid ID in these patients should reflect patient comfort, convenience and quality of life.

Watanabe et al (1996) investigated the changes in sexuality and quality of life in 18 neurologically impaired women treated with ID who underwent bladder reconstruction. All patients were followed 6 to 40 months (mean 18) after reconstructive surgery using a 9-part questionnaire to score numerically the effect of surgical reconstruction on sexuality and quality of life issues. In 4 of the 15 women who were sexually active preoperatively the frequency of sexual intercourse doubled from a mean of 3 to 6 times per month, respectively.

vely, and all 4 women reported improved sexual satisfaction.

RECOMMENDATIONS

Transurethral ID and suprapubic catheter are not recommended as a safe method for long term use in the neuropathic patients. (*Grade of recommendation C*)

Nowadays with less irritating catheter materials, improved closed drainage systems and regular urological check-up long term complications can be decreased, nevertheless ID/SC is still the last resource also in neuropathic women when other methods fail or are not applicable or are not accepted by the patient. (*Grade of recommendation C*)

One should consider patient comfort, convenience, sexuality and quality of life before prescribe ID as a long-term management for neuropathic patients. (*Grade of recommendation C*)

IMPLICATIONS FOR PRACTICE (Grade of recommendation B-C)

A silicone catheter with a smaller balloon of 5-10 ml is preferable.

For developing countries, use a siliconised catheter, change every 1-2 weeks or earlier, if possible, before obstruction or infection occurs.

Long-term ID may be safe only if a careful check-up of urodynamic, renal function, and upper and lower tract imaging are performed regularly at least yearly.

Annual cystoscopy and biopsy may be necessary for those after 10 years of ID and those with an episode of gross hematuria, chronic symptomatic UTI refractory to therapy.

IMPLICATIONS FOR RESEARCH

More research to improve material used in the catheter's construction.

RCT on a proper duration of use of each type of catheters.

More research on impacts of ID on quality of life.

III. CONDOM CATHETER AND EXTERNAL APPLIANCES

1. BACKGROUND

Patients with neurogenic bladder and urinary inconti-

nence usually need some kinds of urinary drainage system. In male, a condom catheter (CC) has been one of the choices (Figure 9). All CCs are connected to a urine or leg bag to collect the urine. Till now, there have been many variety of CCs available such as a simple thin latex or plastic or silicone CC or condom sheath, a rubber condom urinal which is a non-collapsible condom with funnel weld at the end, a CC with a double row of convolutions near the catheter tip to prevent kink with a unique inner flap to prevent backflow of the urine to the shaft of the penic and inner wall coated with a self-adhesive [deHoll JD et al, 1992], a special condom with a passage for catheterization without removal of the condom [personal communication].

2. OBJECTIVES

To find evidence to answer the following questions:

1. How to apply the condom catheter?
2. Is it effective?
3. Is it safe?
4. Is it cost-effective?
5. How to prevent complications?
6. Comparison between different types of CCs
7. Long term results and quality of life



Figure 9 : Condom Urinal

3. CRITERIA FOR CONSIDERING STUDIES

SEARCH STRATEGY

Type of studies: all types of studies including experts' opinions

Type of participants: adult men

Type of outcome measure: efficiency, tolerability, safety and cost-effectiveness

Search from Medline (Pubmed) from 1966-2000:

With the keywords of 'condom catheter' and 'urinary continence' there were 37 papers sorted and only 15 papers were selected.

With the keywords of 'condom catheter' and 'neurogenic bladder' there were 18 papers sorted and only 10 were selected.

With the keywords of 'condom drainage' and 'neurogenic bladder' there were 12 papers sorted and only 6 papers were selected.

With the keywords of 'condom sheath' and 'urinary incontinence' only 1 paper was searched.

Overall 26 papers were reviewed.

4. RESULTS

a) How to apply the condom catheter?

Quality of included studies:

1 Clinical trial: Peifer, Hanover 1997.

4 Case series and case reports: Brooks 1981; Pearman, Shah 1973; Smith et al 1980; Namiki 1984.

In the past, most of the CCs need devices to secure or fasten them to the penis to prevent slipping or detachment. They are as follows: an elastic tape/a fastener [Brooks 1981]; a non-elastic tape, an adhesive band or a strip; a supporting apparatus i.e., a proximal part of a conventional rubber urinal (Stoke Mandeville type) with straps and buckles [Pearman & Shah 1973]; skin adhesives etc.

Nowadays many commercial CCs with self-adhesives allowing easier application are available in developed countries. Peifer & Hanover (1997) did a clinical study comparing between a new 'easy-flow catheter' and other CCs. All except one of the 20 subjects found the new CC easier to apply and also easiest to remove. Moreover, it increased daytime and nighttime dryness in half of the studied group.

However they are some who have difficulty in applying CCs. They are those with overweight and/or some degree of penile atrophy. Smith et al (1980) successfully implanted penile prostheses to 10 patients who had neurogenic bladder and wore CCs. All indicated that the penile prosthesis helped keep the CC in place.

Namiki (1984) reported a technique of teflon paste injection in the subdermal area directly below the glans penis to make a stopper to help maintain a secure position of the CC on the penis of a SCI patient.

In addition, to prevent the pubic hair to become trapped under the CC and to allow easy removal of the CC, the pubic hair should be removed.

b) Is it effective in preventing leakage?

Quality of included studies

1 Clinical trial: Peifer, Hanover 1997.

1 Case series: Saint et al 1999.

Saint et al (1999) did a questionnaire study in male patients and nursing staff. A major drawback of the CC is leaking and a more secure CC is needed to improve the management of male incontinence. Peifer & Hanover (1997) evaluated a new CC, the Easy-Flow External Condom Catheter in 20 subjects who were experienced user of CC. They found that the new CC reduced frequency of changing the CC, and increased daytime and nighttime dryness. Without an anatomical abnormality of the penis or overweight, cooperative neuropathic patients successfully apply CC and have no urine leakage.

c) Is it safe?

Quality of included studies

2 Case-controlled studies: Hirsch et al 1979; Kovindha & Wachirarat 1998.

7 Case series and case reports: Newman & Price 1985; de Holl et al 1992; Nanninga & Rosen 1975; Bang 1994; Pidde & Little 1994; Shenot et al 1994; Harmon et al 1995.

Hirsch et al (1979) studied urinary tract infection (UTI) among neuropathic patients with incontinence and using CCs. They found that 53.3% of those who were not cooperative had UTI while cooperative ones did not have UTI during the study. Newman & Price (1985) reported hazards and complications in 60 SCI men using CCs. Over 50% of patients in this study had positive urine cultures and 56% of patients with positive cultures had evidence of tissue invasion by bacteria. Many of these patients had numerous deficiencies in voiding habits causing incomplete bladder emptying, high residual urine and bladder overdistension. Stasis of urine within the CCs due to twisting of the CCs or kink of the drainage system was found especially when using a simple condom sheath. To overcome the twisting, those in developing countries a simple device e.g., a fixator, easily made by patients themselves may

be added to the CC drainage system [Kovindha et al 1988] or those in developed countries non-collapsible CCs may be used [de Holl et al 1992].

Nanninga & Rosen (1975) reported penetrating or non-penetration lesions due to compressive effects of the condom fasteners or the proximal hard roller ring of the condom causing. Bang (1994) reported a neurogenic patient who continuously used the CC. He developed localised chronic edema on the dorsum of the penis and urethral fistula on the ventral surface. Pidde & Little (1994) reported a SCI patient with bilateral hydronephrosis due to CC retention strap. The hydronephrosis resolved when the strap was eliminated.

Other complications such as irritative or allergic reactions to latex CCs, to skin adhesives and to urine were also reported. Shenot et al (1994) reported 2 patients of allergic reaction to the latex CCs. The first one was paraplegic with 14 years managing with CC until the development of chronic penile dermatitis. Because of the morbidity associated with the latex CCs, he underwent cystectomy and ileal conduit diversion. Immediately after entering the peritoneal cavity, he became acutely hypotensive with evidence of bronchospasm. Last he was diagnosed with latex allergy using RAST and latex antigen skin testing. The other was also a paraplegic with 4 years managing with CCs. He presented with severe dermatitis and breakdown of the phallic skin. Subsequent skin testing to the latex antigen confirmed latex hypersensitivity. He then used a silicone CC resulting in the prompt resolution of the pathologic skin changes. Harmon et al (1995) also reported a patient after 25 years of wearing CCs, recurrent blister and sloughing of the penile shaft developed. He was found to have hypersensitivities to several allergenic components of the CCs. The condition improved after switching to a silicone CC and topical application of steroids.

d) Is it cost-effectiveness?

There have been no studies of cost-effectiveness of CCs.

e) How to prevent complications?

Quality of included studies

1 Clinical trial: Edlich et al 2000.

4 Case series and case reports: Zoller et al 1988; Hirsch et al 1979; Sotolongo & Koleitat 1990; Waites et al 1993.

If a condom catheter is the choice of treatment, proper size, type, material and application should be stressed to the patients to prevent the above-mentioned complications.

Edlich et al (2000) did a pilot clinical study of latex external condom catheters (ECCs) and silicone ECCs. It demonstrated the superior performance of the silicone ECC over that of the latex ECC. Moreover, the silicone ECC has a self-adhesive that binds more securely to human skin than the self-adhesive of the latex ECC. The moisture vapour transmission through silicone is significantly greater than through latex. Therefore silicone CCs which are now available should be used for those having allergic reaction to latex or those who need long-term CC usage to minimize a chance to develop such allergic reaction.

Zoller et al (1988) evaluated the prevalence of sensitization to natural latex in 50 children with congenital neurogenic bladder. They found that elevated latex-specific IGE values were statistically correlated with the number of past operations and a history of atopic or allergic reactions. They suggested serological examinations of latex-specific IGE in addition to patient history to better identify patient at risk.

Continuous use of the CC should be avoided. If used, silicone CC with self-adhesive is preferable to lesser both compressive and irritative effects.

Although bacteriuria is commonly found in those on CCs, it might not cause serious damage to the urinary tract. Hirsch et al (1979) found that no UTI developed in 79 episodes of CC use in patients who were cooperative or not be able to manipulate the CC drainage system. Sotolongo & Koleitat (1990) did a prospective study of 56 male SCI patients on CCs within 5 months of the injuries for 5 years. All had low bladder pressures (filling maximum 35 cm water and voiding maximum of 70 cm water) ascertained by video-urodynamics. And all patients had colonized urine (asymptomatic) during the entire study period. However no patient sustained deterioration of the urinary tract on imagine or by serum creatinine. Therefore with low bladder pressure, asymptomatic bacteriuria is of no consequence to the integrity of the upper urinary tract.

Waites et al (1993) did a prospective study of 64 catheter-free SCI patients. They found that bladder management technique (IC programme, ICP or CC) was not associated with increased risk of UTI. The only factors correlated with increased risk were black ethnicity, less than excellent personal hygiene, and less than daily change of CCs.

f) How to treat complications?

Quality of included studies

2 Case series and case reports: Nanninga & Rosen 1975; Harmon et al 1995.

If there is a skin lesion, a CC should be removed and the patient may have to resume IC or wear an ID until the skin is dry or healed sufficiently to reapply the CC. An additional surgical debridement may be necessary if the lesion is ulcerated or necrotic [Nanninga & Rosen 1975]. Those with allergic dermatitis, the latex CC should be removed and topical steroid should be applied [Harmon et al 1995].

g) Comparing between different types of CCs

Quality of included studies

2 Clinical trials: Edlich et al 2000; Peifer & Hanover 1997.

Edlich et al (2000) conducted a study comparing between a silicone CC with self adhesive and a latex CC. The silicone CC is much better than the latex CC in many ways. Peifer & Hanover (1997) found the new CC easier to apply and also easiest to remove when compared to previous CCs used. It also increased day-time and nighttime dryness in half of the studied group. (As mentioned above)

h) Long-term results related to quality of life

Quality of included studies

1 Case-controlled study: Sekar et al 1997.

Sekar et al (1997) did a comparison study of long-term renal function after SCI using different urinary management methods. They used effective renal plasma flow (ERPF) to evaluate renal function and found that renal function was adequately preserved in the great majority of persons and did not appear to be influenced to any great extent by method of bladder management. Although at discharge 33% of 913 patients used IC, they found that the percentage of men using CCs increased with advancing time post-injury while the percentage using IC decreased. The majority of men used CC in each time period while the majority of women used ID.

CONCLUSIONS (Level of evidence 4)

CC still has a role in control urinary incontinence in neuropathic male patients.

Long-term use may cause bacteriuria but it does not increase the risk of UTI when compared to other methods of bladder management.

Complications may be less if apply it properly with good hygiene care, frequently change the CC and maintain low bladder pressures.

**RECOMMENDATIONS
(Level of recommendation B-C)**

To have better control of leakage, a more secure CC should be used and patients should be educated and cooperative.

To prevent latex allergy, a silicone CC should be used and serological examinations of latex-specific IGE is recommended in addition to patient history to better identify patient at risk.

To prevent compressive effects, choose proper size CC with self- adhesive.

To prevent infection, a CC should be changed at least daily.

To prevent bladder and upper tract damage, regular bladder emptying with low bladder pressures and low PVR should be persued.

D. PHARMACOTHERAPY

I. BACKGROUND

Pharmacological treatment of urinary incontinence is overviewed in the Chapter on the Pharmacological Treatment. Therefore, this section focuses on special aspects in regards to its indication and efficacy in patients with neuropathic bladder/urethral dysfunction. The principal causes of urinary incontinence in this subpopulation are detrusor hyperreflexia (DH) and/or incompetence of urethral closing function. Thus, to improve urinary incontinence the treatment should aim at decreasing detrusor activity, increasing bladder capacity and/or increasing bladder outlet resistance. Pharmacologic therapy has been particularly helpful in patients with relatively mild degrees of neurogenic bladder dysfunction. Patients with more profound neurogenic bladder disturbances may require pharmacologic treatment to augment other forms of management such as intermittent catheterization (IC).

Although the two most commonly used classes of agents are anticholinergics and alpha-adrenergic blockers, the drugs used for treating neuropathic bladder/urethral dysfunction should be classified as follows:

a) Drugs for incontinence due to detrusor hyperreflexia and/or low compliant detrusor

1. BLADDER RELAXANT DRUGS

a) Oxybutynin

- b) *Propiverine*
- c) *Trospium*
- d) *Tolterodine*
- e) *Propantheline*
- f) *Oxyphencyclimine*
- g) *Flavoxate*
- h) *Tricyclic Antidepressants*

2. DRUGS FOR BLOCKING NERVES INNERVATING THE BLADDER

- a) *Vanilloids*
 - 1) *Capsaicin*
 - 2) *Resiniferatoxin*

b) Botulinum toxin

b) *Drugs for incontinence due to neurogenic sphincter deficiency*

- 1. ALPHA-ADRENERGIC AGONISTS
- 2. ESTROGENS
- 3. BETA-ADRENERGIC AGONISTS
- 4. TRICYCLIC ANTIDEPRESSANTS

c) *Drugs for facilitating bladder emptying*

- 1. ALPHA ADRENERGIC BLOCKERS
- 2. CHOLINERGICS

II. OBJECTIVES

1. Is each of the drugs listed above effective for treating neurogenic urinary incontinence ?
2. Is the drug safe?
3. How to prevent complications?
4. Is the treatment cost-effective?
5. What are the long-term results including the impact on quality of life?

III. CRITERIA FOR CONSIDERING STUDIES AND SEARCHING STRATEGY

All types of publications dealing with pharmacotherapy in adult patients with neurogenic bladder/urethral dysfunction have been included in this search.

1. Medline through Pubmed from 1966-2000, and the list of publications used in first International Consultation Report if not included in the former list.
2. Keywords: Pharmacotherapy, urinary incontinence,

neurogenic bladder, and the drug names listed above.

3. Method of review: all publications in adults (≥ 19 years old), humans were considered in regards to outcome, efficacy, safety and cost-effectiveness, in all languages.
4. Description of the review: There are 688 articles found by searching with the keywords-combination of “pharmacotherapy” & “urinary incontinence”, and 319 articles with “pharmacotherapy” & “neurogenic bladder”. The number of the reviewed studies dealing with each of the drugs listed above is described separately in each section on the corresponding subtopics. Methodological quality of the included studies is indicated separately based on the subtopics dealing with each of the drugs listed above in each section on the corresponding subtopics.

IV. RESULTS/CONCLUSIONS

1. DRUGS FOR INCONTINENCE DUE TO DH AND/OR LOW COMPLIANT DETRUSOR

a) *Bladder relaxant drugs*

Anticholinergic agents are by far the most useful pharmacologic agents in the management of neurogenic bladder. Anticholinergic agents are employed to suppress DH. Although there is an abundance of drugs available for the treatment of DH, for many of them, efficacy is estimated based on preliminary open studies rather than on controlled clinical trials [Andersson 1988]. However, drug effect in individual patients may be practically important. In developing countries, most of the bladder relaxant drugs listed below are not available mainly due to economical reasons, which makes the pharmacological treatment of DH in these countries difficult.

General indications of pharmacological treatment in DH are (1) to improve or eliminate reflex incontinence, (2) to eliminate/to prevent a high intravesical pressure situation and (3) to enhance the efficacy of intermittent catheterization (IC), triggered voiding and indwelling catheters (ID). Spinal DH is mostly associated with a functional outflow obstruction due to detrusor-sphincter-dyssynergia (DSD). For the most part, pharmacotherapy is used to suppress reflex detrusor activity completely and facilitate IC. On the other hand bladder relaxant drugs decrease detrusor-contractility also during voiding. With this situation residual urine increases and must then be assisted or accomplished by IC (Figure 10).

1. **OXYBUTYNIN** (total 178 articles reviewed, including 36 articles searched in combination with the keyword

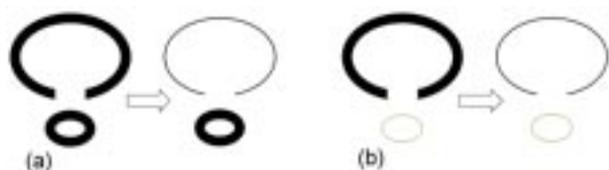


Figure 10 : *The effect of bladder relaxant drugs on the hyperreflexic detrusor (schematic drawing). Aims of treatment are to change a hyperreflexic into a hyporeflexic detrusor. In the spinal reflex bladder (a) voiding may become unbalanced, as the spastic striated sphincter muscle remains unaffected; this problem does not occur in the suprapontine reflex bladder (b), as the sphincter mostly remains normally functioning*

of neurogenic bladder, 16 clinical trials (CTs) and 2 randomized controlled trials (RCTs), and 89 articles with the keyword of urinary incontinence, 35 CTs and 20 CRTs).

Oxybutynin hydrochloride is a moderately potent antimuscarinic agent with a pronounced muscle relaxant activity and local anesthetic activity as well [Andersson 1988; Anderson & Fredericks 1972; Yarker et al 1995; Wein 1997].

- Oral Administration

Several double-blind controlled studies have shown its efficacy for DH (Level of evidence 1) [Thompson & Lauvetz 1976; Hehir & Fitzpatrick 1985; Gajewski & Awad 1986; Koyanagi et al 1986; Zeegers et al 1987; Thüroff et al 1991]. The overall rates of good results (more than 50% symptomatic improvement) are 47 % with 3 mg t.i.d. and 61-86% with 5 mg t.i.d. Side effects were noted in all studies and severity increased with dosage. The overall incidence of possible side effects is 24.5% for 3 mg t.i.d. and 12.5% to 68% for 5 mg t.i.d. Most of them are related to antimuscarinic action with dry mouth as the most common complaint (incidence of 12.2% with 9 mg/day and between 12.5% to 47.6% with 15 mg/day).

A once-a-day controlled-release formulation of oxybutynin, oxybutynin XL (Ditropan XL®) was recently developed. Parallel-group, randomized, controlled clinical trials comparing the efficacy and safety of controlled-release oxybutynin, oxybutynin XL with conventional, immediate-release oxybutynin in patients with overactive bladder demonstrate that the urge urinary incontinence episodes declined log-linearly, and no significant difference was observed between the two formulations (Level of evidence 1) [Anderson et al 1999; Birns et al 2000; Versi et al 2000]. However, there was a trend toward higher efficacy with oxybutynin XL than with immediate-release oxybutynin at the same dose in one study. Dose-dry mouth analysis sho-

wed that the probability of dry mouth with an increasing dose was significantly lower with oxybutynin XL than with immediate-release oxybutynin [Gupta et al 1999]. However, no studies have been published on the efficacy and safety of oxybutynin XL dealing especially with neuropathic subgroup of patients.

Despite its adverse effects, oxybutynin (2.5-5 mg taken twice or three-times daily), especially Oxybutynin XL, a once-a-day controlled-release formulation of oxybutynin, is recommended for the treatment of overactive bladder (Grade of recommendation A). Further studies, however, are necessary to determine whether its controlled-release formulation has better tolerability also in neuropathic subpopulation. Clinical practice should aim at individual titration of drug dosage for a maximum therapeutic effect with minimal side effects [Yarker et al 1995; Wein 1997, Thüroff et al 1991].

- Intravesical application

Intravesical instillation of oxybutynin has been demonstrated its efficacy in patients with DH in whom oral oxybutynin failed or was not tolerated (Level of evidence 4) [Brendler et al 1989; Madersbacher & Jilg 1991; Greenfield & Fera 1991; Weese et al 1993; Prasad & Vaidyanathan 1993; Kasabian et al 1994; Mizunaga et al 1994; Connor et al 1994; Buyse et al 1995; Kaplinsky et al 1996; Painter et al 1996; Palmer et al 1997; Saito et al 2000; Pannek et al 2000], although no randomized controlled study has been reported. The rate of symptomatic improvement ranged from 55% to 90%. No antimuscarinic systemic side effects have been reported in early short-term follow-up studies. In recent relatively long-term studies [Madersbacher & Jilg 1991; Kasabian et al 1994; Buyse et al 1995], however, the incidence of side effects was 25-55%, and treatment was discontinued in 25-65 % mainly due to inconvenience and also due to side effects.

Intravesical instillation of oxybutynin is recommended for selected patients, who are already on IC but still incontinent between, due to persistent DH, if oral medication is not successful or not tolerated [Yarker et al 1995; Madersbacher & Jilg 1991] (Grade of recommendation C). The usual dose is a 5 mg pill dissolved in 10-30 ml saline or water. The solution is instilled intravesically twice daily and retained for at least 30 minutes. There has been no commercial preparation of this medication for direct instillation into the bladder.

2. PROPIVERINE (total 22 articles reviewed, including 14 CTs and 4 RCTs , 4 CTs and 2 RCTs searched in combination with the keyword of neurogenic bladder).

Propiverine hydrochloride is a benzylic acid derivative with muscolotropic (calcium antagonistic) activity and moderate antimuscarinic effects [Tokuno et al 1993]. Several randomized double-blind, controlled clinical

studies of this drug in patients with DH have been reported [Stöhrer et al 1999; Takayasu et al 1990; Madersbacher et al 1999]. In a placebo-controlled, double-blind, randomized, prospective, multicentric trial, Stöhrer et al (1999) evaluated the efficacy and tolerability of propiverine (15 mg t.i.d. for 14 days) as compared to placebo in 113 patients suffering from DH caused by spinal cord injury. The majority of patients practised intermittent catheterization for bladder emptying. The maximum cystometric bladder capacity increased significantly in the propiverine group, on average by 104 ml. Sixty-three % of the patients expressed a subjective improvement of their symptoms under propiverine in comparison to only 23% of the placebo group. Takayasu et al (1990) conducted a double-blind, placebo-controlled multicentric study in 70 neurogenic patients. During a treatment period of 14 days, 20 mg propiverine once daily or placebo were administered. An increase of maximum bladder capacity, a decrease of maximum detrusor pressure and an increase of residual urine were also obtained in this Japanese study, all statistically significant compared to placebo. Madersbacher et al (1999) in a placebo-controlled, multicentre study demonstrated that propiverine is a safe and effective drug in the treatment of DH; it is as effective as oxybutynin, but the incidence of dry mouth and its severity is less with propiverine (15 mg, three times daily) than with oxybutynin (5 mg twice daily).

Propiverine has a documented beneficial effect in the treatment of DH, and seems to have an acceptable adverse effect profile (Level of evidence 1). The drug is recommended in the treatment of DH (Grade of recommendation A). The standard oral adult dose is 10-15 mg two or three times daily.

3. TROSPIUM (total 6 articles refer to the topic reviewed, including 6 CTs and 5 RCTs, and 3 RCTs searched in combination with the keyword of neurogenic bladder).

Trospium is a quaternary ammonium derivative with mainly antimuscarinic actions. In a placebo controlled, double-blind study in 61 patients with spinal DH, significant improvements in maximum cystometric capacity and maximal detrusor pressure were demonstrated with 20 mg b.i.d for 3 weeks compared with placebo [Stöhrer et al 1991]. Few side-effects were noted, comparable with placebo. Madersbacher et al (1995) compared the clinical efficacy and tolerance of trospium (20 mg b.i.d.) and oxybutynin (5 mg t.i.d.) in a randomized, double-blind, urodynamically controlled, multicentre trial in 95 patients with spinal cord injuries and DH. They found that the two drugs are equal in their effects on DH (increase of the cystometric bladder capacity by 30% and decrease of the maximum detrusor pressure by

30%), but trospium has fewer severe side effects (incidence of severe dry mouth 5% with trospium vs. 25 % with oxybutynin) [Madersbacher et al 1995].

Trospium has a documented effect on DH (Level of evidence 1). The drug is recommended to use for DH (Grade of recommendation A).

4. TOLTERODINE (total 28 articles refer to the topic reviewed, including 15 CTs and 8 RCTs, and 4 CTs and 2 RCTs searched in combination with the keyword of neurogenic bladder)

Tolterodine is a new competitive muscarinic receptor antagonist [Nilvebrant et al 1997a; 1997b]. Recently, several randomized, double-blind controlled studies in patients with overactive bladder have demonstrated its beneficial effect [Jonas et al 1997; Appel et al 1997; Rentzhog et al 1998; Abrams et al 1998; Van Kerrebroeck et al 1998; Goessl et al 2000; Malone-Lee et al 2001; Van Kerrebroeck et al 2001; Appel et al 2001] (Level of evidence 1). Jonas et al (1997) reported on a randomized, double-blind, placebo-controlled study of tolterodine including urodynamic analysis in a total of 242 patients. Two mg b.i.d. was significantly more effective than placebo in increasing maximum cystometric bladder capacity and volume at first contraction after 4 weeks treatment. However, there are no published reports on the specific effect on DH. The better tolerability profile of tolterodine compared to oxybutynin has been confirmed in another randomized studies on detrusor overactivity [Abrams et al 1998]. Tolterodine (2 mg b.i.d.) appears to be as effective as oxybutynin (5 mg t.i.d.), but is much better tolerated, especially in regards to dry mouth. In a meta-analysis of 4 multicenter prospective trial of 1,120 patients, moderate to severe dry mouth was reported in 6% of the placebo, 4% of the 1 mg bid tolterodine, 17% of the 2 mg b.i.d. tolterodine and 60% of those patients receiving conventional 5 mg t.i.d. oxybutynin [Appel et al 1997]. An another randomized controlled trial by Malone-Lee et al (2001) demonstrated superior tolerability than and comparable efficacy to oxybutynin in individuals 50 year old or older with overactive bladder.

Van Kerrebroeck et al (2001) reported a comparative study of the efficacy and safety of tolterodine extended release (ER; 4 mg once daily), tolterodine immediate release (IR; 2 mg twice daily), as well as placebo in 1,529 adult patients with overactive bladder. The primary efficacy variable was the change in mean number of incontinence episodes per week, which decreased 53% from baseline in the tolterodine ER group, 45% with tolterodine IR, and 28% in the placebo group. Tolterodine ER and IR provided a similar significant reduction in incontinence episodes versus placebo. Post hoc analysis of the data using median values, based on rational of skewed data distribution, demons-

trated improved efficacy of tolterodine ER versus IR. Dry mouth was significantly lower with tolterodine ER than tolterodine IR (23% tolterodine ER 31% tolterodine IR, and 8% placebo). The incidence of other side effects was similar to placebo in the tolterodine ER and tolterodine IR groups.

A comparative study between controlled release oxybutynin (oxybutynin XL) and immediate release tolterodine (tolterodine IR), was recently published [Appel et al 2001]. Three hundred seventy-eight patients were randomized to receive either oxybutynin XL 10 mg. (n=185) or tolterodine IR 4 mg. (2 mg. b.i.d.) (n=193). The populations were evenly matched with respect to demographics. Oxybutynin XL reduced the number of weekly episodes of urge incontinence from 25.6 to 6.1 instances. Tolterodine IR decreased the number of weekly episodes from 24.1 to 7.8 instances. Oxybutynin XL demonstrated better efficacy (P=0.03) compared to tolterodine IR. Dry mouth and central nervous system side effects were similar between oxybutynin XL and tolterodine IR.

Although tolterodine has a documented effect on overactive bladder (Level of evidence 1), further studies on the effect of the drug on DH in the neuropathic population are necessary. Comparative studies of tolterodine ER with propiverine, trospium or oxybutynin XL, especially in regards to tolerability, could be useful to evaluate its position amongst other bladder relaxant drugs beside conventional oxybutynin or tolterodine IR.

5. PROPANTHELINE (total 8 articles searched in combination with the keyword of neurogenic bladder) including 2 CTs. No RCT was found.)

Proprantheline bromide was the classically described oral antimuscarinic drug. Despite its success in uncontrolled case series [Andersson 1988; Blaivas et al 1980; Level of evidence 5], no adequate controlled study of this drug for DH is available. The usual adult oral dosage is 7.5 to 30 mg three to four times daily, although higher doses are often necessary [Wein 1997].

6. OXYPHENCYCLIMINE (total 1 CT refer to the topic reviewed)

Oxyphencyclimine is a cheap antimuscarinic that is usually used for treatment of peptic ulcer.

Kitisomprayoonkul and Kovindha (2000) reported their experience in 10 complete SCI patients who had urinary incontinence, treated with oxyphencyclimine HCl (15-20 mg/day) for 1-2 weeks.

All patients had clinical improvement even though some reported dry mouth and constipation that were tolerable. Significant improvement was observed regarding the mean frequency of incontinence per day, mean catheterization volume, mean maximum detrusor pressure, mean volume at the initial detrusor contraction

and the cystometric capacity at the first leaking point (Level of evidence 4).

Due to its availability and very low cost, oxyphencyclimine may be an alternative bladder relaxant for SCI patients in developing countries where other potent bladder relaxant drugs are not available or too expensive (Grade of recommendation D).

7. FLAVOXATE (total 18 articles refer to the topic reviewed, including 11 CTs and 4 RCTs)

Flavoxate hydrochloride has a direct inhibitory action on detrusor smooth muscle *in vitro*. Early clinical trials with flavoxate have shown favorable effects in patients with DH [Kohler & Morales 1968; Pedersen et al 1972]. Several randomized controlled studies have shown that the drug has essentially no effects on detrusor overactivity (Level of evidence 1) [Zeegers et al 1987; Robinson & Brocklehurst 1972; Chapple et al 1990].

8. TRICYCLIC ANTIDEPRESSANTS (total 20 articles refer to the topic reviewed with the keyword of imipramine, including 3 CTs and 0 RCTs, and no CTs searched in combination with the keyword of neurogenic bladder)

Many clinicians have found tricyclic antidepressants, particularly imipramine hydrochloride, to be useful agents for facilitating urine storage, both by decreasing bladder contractility and by increasing outlet resistance [Wein 1997; Barrett & Wein 1991]. However, no sufficiently controlled trials of tricyclic antidepressants in terms of DH in neuropathics have been reported. Nevertheless in some developing countries tricyclic antidepressants are the only bladder relaxant substances which people can afford. The down side with tricyclic antidepressants is the narrow safety profile and side effects. The potential hazard of serious cardiovascular toxic effect should be taken into consideration [Andersson 1988]. Combination therapy using antimuscarinics and imipramine may have synergistic benefits (Level of evidence 5).

b) Drugs for blocking nerves innervating the bladder

1. VANILLOIDS

The vanilloids, capsaicin and resiniferatoxin, activate nociceptive sensory nerve fibers through an ion channel, recently discovered by Caterina et al (1997), known as vanilloid receptor subtype 1 (VR1). This receptor is a nonselective cation channel, and is activated by increases in temperature to within the noxious range and by protons, suggesting that it functions as a transducer of painful thermal stimuli and acidity *in vivo*. When activated the channel opens, allowing an influx of calcium and sodium ions that depolarizes the nociceptive afferent terminals, initiating a nerve impul-

se that travels through the dorsal root ganglion into the central nervous system. Noxious temperature uses the same elements, which explains why the mouth feels hot when eating chili peppers [Clapham 1997]. Previously called the capsaicin receptor, VR1 has been localized in the spinal cord, dorsal root ganglia and visceral organs, including the bladder, urethra and colon. Activation of VR1 results in spike-like currents [Liu & Simon 1996], and selectively excites and subsequently desensitizes C-fibers. Capsaicin-desensitization is defined as long lasting, reversible suppression of sensory neuron activity [Craft et al 1995]. How fast and for how long the desensitization develops is related to the dose and time of exposure to capsaicin, and the interval between consecutive dosing [Szolcsányi et al 1975; Maggi et al 1988]. The transient increase in intracellular concentration of calcium ions also leads to activation of intracellular enzymes, peptide transmitter release and neuronal degeneration [Szallasi & Blumberg 1990a; Kawatani et al 1989].

1) Capsaicin (total 24 articles refer to the topic reviewed, including 3 RCTs and 8 CTs)

Recently, capsaicin, the "gold standard" in the vanilloid class of drugs, has been tried as an intravesical drug with limited success. If overactive bladder is due to sensitization and/or recruitment of C-fibers resulting in an overall increase in the C-fiber contribution to mechanoreception, then functional desensitization of C-fiber afferent neurons may decrease detrusor overactivity (Figure 11). However, capsaicin causes initial stimulation of the unmyelinated C-fibers, resulting in

severe discomfort or pain, along with release of the neurotransmitters substance P and/or neurokinin A in the bladder. The use of capsaicin is still largely experimental, and includes patients with DH, however some trials are ongoing with the use of capsaicin for detrusor instability, especially when the patient has failed other forms of treatment. In a capsaicin study of DH, 44% of patients had satisfactory continence, 36% were improved and only 20% failed treatment [De Ridder et al 1997].

- Clinical results of intravesical capsaicin

Detailed descriptions of the key clinical report of intravesical capsaicin for treatment of detrusor hyperreflexia can be seen in a recently published article by Chancellor and de Groat (1999) (Level of evidence 4). Most of the clinical studies report that intravesical capsaicin achieved over 60% urodynamic improvement 1-2 months after capsaicin instillation. The maximum cystometric capacity increased from 27% to 220%. The effect of capsaicin on clinical and urodynamic parameters was long lasting, exceeding one year in some patients. A meta-analysis of the six series on a total of 131 patients, mean pretreatment bladder capacity was 144 ml (range 72-195 ml). The mean post-capsaicin cystometric capacity, although at different time points, was 267 ml (range 185-321 ml). Mean symptomatic improvement was 72% (range 40-100%).

Wiart et al (1998) reported on 12 paraplegic patients treated either with 1 mM capsaicin in 30% alcohol or placebo (30% alcohol alone). One hundred ml of either

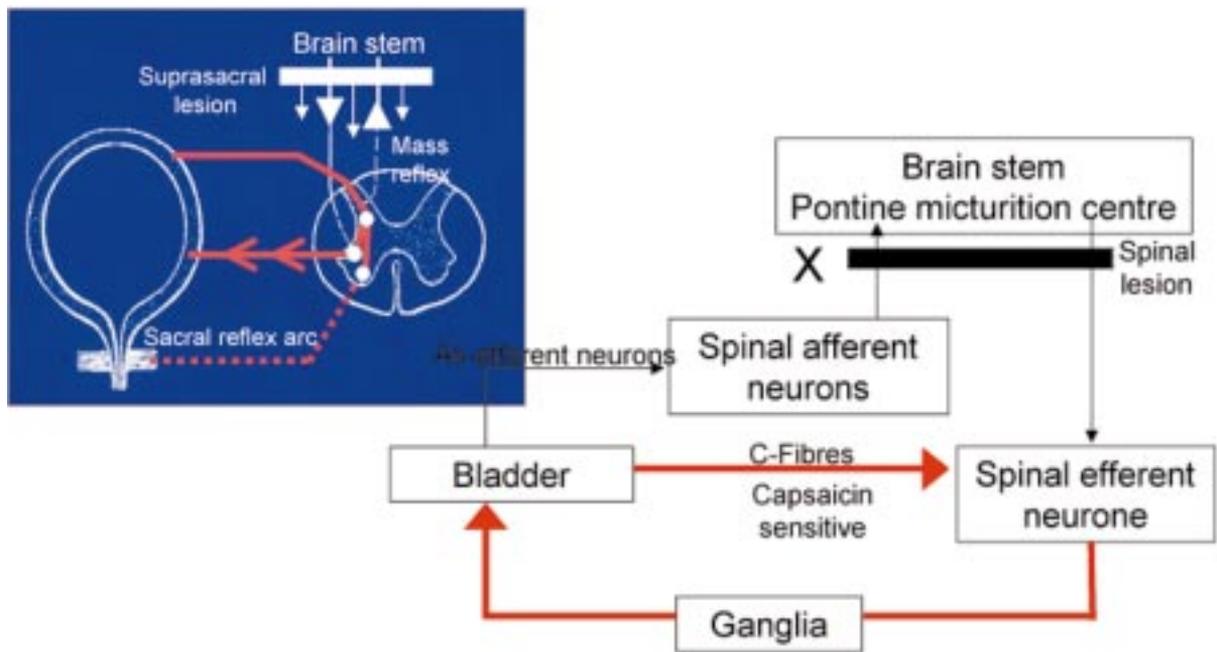


Figure 11 : With spinal cord injury, at least in the animal experiment, afferent stimuli are conducted in unmyelinated C-fibres (and not as normal, in myelinated $\alpha\delta$ -fibres); vanilloids block the C-fibre reflexes in chronic spinal cat.

capsaicin or alcohol placebo was instilled for 30 minutes using outpatient procedures without anesthesia. Urodynamic studies and bladder diaries were compared before therapy and 30 days later. All of the capsaicin patients reported clinical improvement with significant regression of urine leakage episodes ($p=0.002$), and sensory urgency ($p=0.01$). Only one placebo subject had subjective improvement. This double-blind, placebo-controlled trial confirmed the efficacy of intravesical capsaicin for detrusor hyperreflexia (Level of evidence 2).

2) *Resiniferatoxin (total 4 articles refer to the topic reviewed, including 1 CTs and 3 case series)*

Resiniferatoxin (RTX) is a much more potent sensory antagonist than capsaicin. It is approximately 1,000 times more potent than capsaicin, based on the Scoville Heat Scale [Lewis 1998]. Like capsaicin, it possesses vanilloid receptor agonist activity, resulting in desensitization. However, RTX acts without the potent neuronal excitatory effect of capsaicin, and therefore elicits less discomfort. The use of this vanilloid promises an alternative to capsaicin that would be potentially therapeutic for overactive bladder and DH. However, formal controlled trials still have to be performed to determine the precise use and dosage for this agent. The key advantage of RTX is that it is at least as effective as capsaicin, without much of the local side effects, such as pain and inflammatory neuropeptide release.

RTX is the principal active ingredient in the classic drug Euphorbium, the air-dried latex (resin) of the cactus-like plant *Euphorbia resinifera* Berg [Hergenhahn et al 1975]. In 1990, RTX was recognized as an ultrapotent analogue of capsaicin [Szallasi & Blumberg 1990a]. At the same time, however, it was also realized that although RTX mimics most capsaicin actions, it also has unique pharmacological effects [Szallasi & Blumberg 1990b], such as the desensitization without prior excitation of the pulmonary chemoreflex pathway [Szolcsányi 1990]. The mechanisms underlying the differences between RTX and capsaicin actions are just beginning to be understood. RTX induces slowly activating, persistent currents in dorsal root ganglion neurons as measured under patch-clamp conditions [Liu & Simon 1994; 1996; Oh et al 1996]. These sustained currents prefer desensitization to excitation (the change in membrane potential is not sufficient to cause action potential formation, although the rising intracellular calcium levels can activate biochemical pathways leading to desensitization), which is in accord with the general pharmacological profile of RTX.

Cruz et al [Cruz et al 1997a; 1997b] instilled 50-100 nM RTX, dissolved in 100 ml solution of 10% alcohol, for 30 minutes in seven neurologically impaired patients with detrusor hyperreflexia. Itching or mild discomfort were the only symptoms evoked in four patients during

the first minutes of the treatment. In five of the seven patients, urinary frequency decreased by 33-58%, and this effect was detected as soon as the first day after treatment. Three patients, who prior to treatment were incontinent, became dry most days following treatment. Improvement was sustained for up to 3 months. Four patients had urodynamic improvement with a rise in maximum cystometric capacity increasing from 50-900% of pretreatment measures. Lazzeri et al (1997) reported using intravesical RTX (10 microM) in eight normal patients, and seven patients with overactive bladder. RTX did not decrease the volume required to elicit the first desire to void and did not produce warm or burning sensations at the suprapubic or urethral level during instillation in normal subjects. However, in patients with overactive bladder, mean capacity increased from 175 ± 36 to 281 ± 93 ml ($p<0.01$) immediately after instillation, but was not significantly increased after four weeks (217 ± 87 ml).

RTX has also been reported to be helpful in patients who did not improve after capsaicin. Lazzeri et al (1998) presented data on 7 SCI patients with DH treated with RTX. These patients were reported to have failed intravesical capsaicin therapy. All nine patients received 30 ml of 10 microM RTX for 30 minutes. Fifteen days after RTX, mean cystometric capacity significantly increased from 188 ± 21 ml to 399 ± 120 ml ($p<0.01$) and remained increased four weeks later (402 ± 71 ml, $p<0.01$).

A recently completed North American multicenter RTX clinical trial was designed as a prospective, dose escalating, single-blind, placebo-controlled study comparing the effects of seven concentrations of RTX (0.005, 0.025, 0.05, 0.1, 0.2, 0.5, 1.0 microM of RTX 10% ethanol in saline) and placebo (10% ethanol) for treatment of neurogenic bladder [Rivas et al 1999]. Each patient received a single dose. Safety, tolerance and bladder function assessments were made at screen, immediately following dosing and at weeks 1, 3, 6, and 12 and quarterly thereafter, until a return to baseline bladder function was obtained. The final analysis of the results of this study is being compiled a few trends can be seen. First, there were no significant differences between control and RTX at the lowest doses of 0.005-0.01 microM. Second, in patients with decreased bladder capacity, the mean change in cystometric capacity was markedly greater than for the placebo dose group. Third, the mean number of incontinence episodes from pretreatment of patients treated with 0.05 microM, 0.5 microM and 1.0 mM decreased by 1 to 2 fewer episodes compared to placebo. Adverse events, considered to be related to RTX, were generally mild to moderate and transient. One patient discontinued from study due to autonomic dysreflexia. In a patient population involving many SCI patients, the occurrence of autonomic dysreflexia is an expected event especially during uro-

logic studies. Cystoscopic evaluation revealed no adverse treatment effect due to RTX. No signs of areflexia or urinary retention were noted. Clinically significant changes in laboratory abnormalities did not occur.

RTX seems to have a beneficial effect on spinal DH (Level of evidence 4). Randomized controlled studies need to determine its place in the treatment of DH.

2. BOTULINUM TOXIN A (total 13 articles refer to the topic reviewed, including 7 CTs)

Botulinum toxin A first isolated by van Ermengem in 1897, is the most potent biological toxin known to man [Van Ermengem 1897]. Through basic research, clinicians have been able to transform this lethal toxin into a health benefit. Clinicians have safely and successfully used this agent for the treatment of focal dystonias, muscle spasm and spasticity [Grazko et al, 1995; Jankovic et al 1990]. The toxin acts by inhibiting acetylcholine release at the presynaptic cholinergic junction (Figure 12). Inhibited acetylcholine release results in regionally decreased muscle contractility and muscle atrophy at the site of injection [Duchen 1970]. The chemical denervation that results in a reversible process as axons resprout in approximately 3-6 months [Borodic et al 1990].

Clinically, the urologic community has utilized botulinum toxin A to treat spinal cord injured patients who suffer from detrusor external sphincter dyssynergia (DESD) [Dykstra et al 1988; 1990; Schurch et al 1996; Petit et al 1998; Phelan et al 2001].

The toxin acts at the neuromuscular junction of the external sphincter to block vesicle transport of acetyl-

choline; in essence, producing a chemical denervation, a reversible chemical “sphincterotomy”, which avoids a major surgical procedure (external sphincterotomy) with its attendant risks (bleeding, stricture, fistula). The clinical effects begin within 3-5 days and are reversible as terminal nerve sprouting occurs within 3-6 months [Phelan et al 2001]. Phelan et al (2001) have expanded the role of urethral injections to include patients with urinary retention secondary to pelvic floor spasticity and have even treated a female patient with MS and an acontractile bladder who wished to void by Valsalva.

More recently, Schurch et al (2001) reported successful treatment of spinal cord injured patients with DH using intravesical injections of botulinum toxin A. Under cystoscopic control a total of 200 to 300 units of botulinum toxin A (Botox®) were injected into the detrusor muscle at 20 to 30 sites (10 units per ml. per site), sparing the trigone. The authors demonstrated a significant increase in mean maximum bladder capacity (296ml to 480ml, $p<0.016$) and a significant decrease in mean maximum detrusor voiding pressure (65 to 35cm H₂O, $p<0.016$) in patients injected with the toxin when evaluated at 6 weeks after the injections. At the 6-week follow-up complete continence was restored in 17 of the 19 patients examined after the treatment. Ongoing improvement in urodynamic parameters and incontinence was already present in all 11 patients reevaluated at 36 weeks after treatment.

Intravesical injection of botulinum toxin A into the detrusor muscle is promising therapy for spinal DH (Level of evidence 4) and this treatment may be recommended when standard pharmacotherapy using bladder relaxant drugs fails (Grade of recommendation C). Fur-

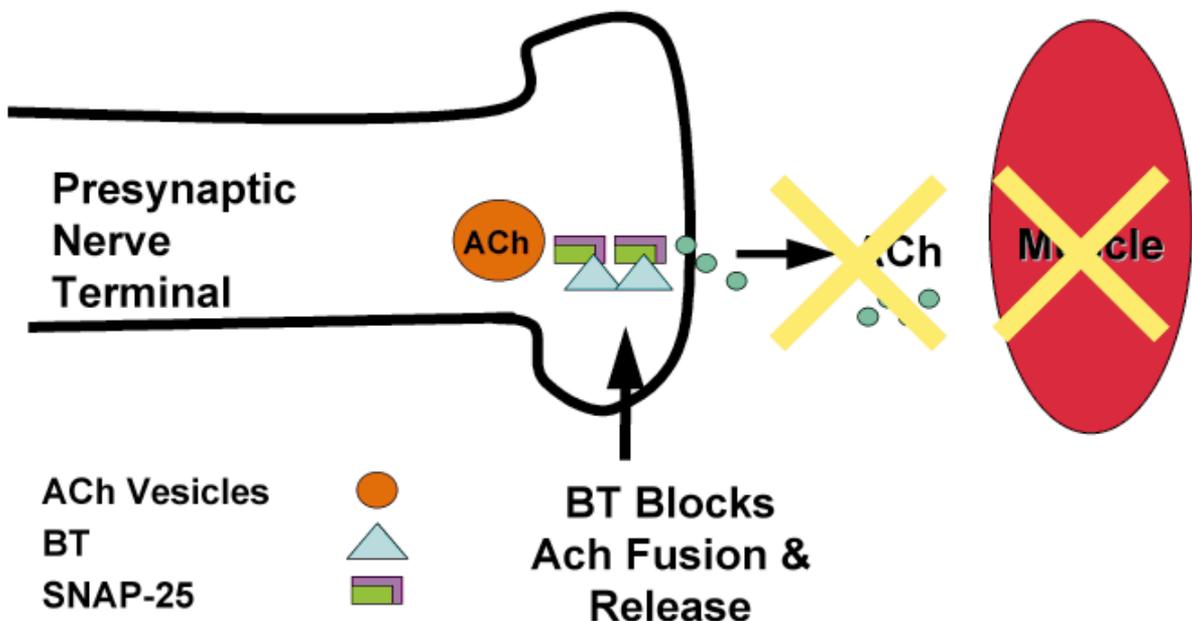


Figure 12 : Botulinum Toxine acts by inhibiting acetylcholine release at the presynaptic cholinergic junction

ther studies, however, are necessary to confirm the efficacy of this treatment and to determine the duration of the therapeutic effect.

2. DRUGS FOR INCONTINENCE DUE TO NEUROGENIC SPHINCTER DEFICIENCY

Several drugs, including alpha-adrenergic agonists [Diokno & Taub 1975; Raezer et al 1977; Awad et al 1978; Ek et al 1978, Stewart et al 1976; Bauer 1994], estrogens [Beisland et al 1981], beta-adrenergic agonists [Gleason et al 1974] and tricyclic antidepressants [Gilja et al 1984], have been used to increase outlet resistance (Level of evidence 4). No adequately designed controlled studies of any of these drugs for treating neuropathic sphincter deficiency have been published. In certain selected cases of mild to moderate stress incontinence a beneficial effect may be obtained [Andersson 1988; Grade of recommendation D].

3. DRUGS FOR FACILITATING BLADDER EMPTYING

a) Alpha adrenergic blockers (total 61 articles refer to the topic searched in combination with the keyword of neurogenic bladder, including 13 CTs and 3 RCTs)

Alpha-adrenoceptors have been reported to be predominantly present in the bladder base, posterior urethra and prostate. Alpha-blockers have been reported to be useful in neurogenic bladder by decreasing urethral resistance during voiding. Recently, a multicenter placebo-controlled, double-blind trials of urapidil, an alpha-blocker on neurogenic bladder dysfunction [Yasuda et al 1996; Yamanishi et al 1999] by means of pressure/flow study demonstrated significant improvement of straining and of the sum of urinary symptom scores, which was associated with significant improvement of urodynamic parameters (decreases in the pressure at maximum flow rate and the minimum urethral resistance) over the placebo (Level of evidence 1).

Alpha adrenergic blockade also helps to prevent excess sweating secondary to spinal cord autonomic dysreflexia. Sweat glands, primarily responsible for thermoregulatory factors, are innervated by postganglionic cholinergic neurons of the sympathetic system. alpha receptor blockade inhibits this postsynaptic neuronal uptake of norepinephrine and reduces neurologic sweating [Chancellor et al 1994].

b) Cholinergics (total 1 CT refer to the topic searched in combination with the keyword of neurogenic bladder).

In general, bethanechol chloride seems to be of limited benefit for detrusor areflexia and for elevated residual urine volume. Elevated residual volume is often due to

sphincter dyssynergia. It would be inappropriate to potentially increase detrusor pressure when concurrent DSD [Chancellor et al 1993].

CONCLUSIONS

Bladder relaxant drugs, including oxybutynin, propiverine, trospium and tolterodine have a documented suppressive effect on incontinence by controlling overactive bladder, thereby improving storage function (Level of evidence 1).

However, all of these drugs presently available have considerably high incidence of side effects (dry mouth, constipation, urinary retention, etc.), which limits their usage. Tolterodine, propiverine, trospium and controlled-release oxybutynin have significantly less side effects compared to immediate-release oxybutynin (Level of evidence 1).

Although the oral application is the usual way, intravesical instillation (oxybutynin) may be an alternative (Level of evidence 4).

Intravesical instillation of capsaicin/resiniferatoxin has been reported to improve spinal reflex incontinence for several months after instillation (presumably blocking sensory input) (Level of evidence 4).

Botulinum toxin injections into the detrusor muscle was reported to improve incontinence and increase functional bladder capacity in spinal cord injured patients with DH (Level of evidence 4).

There is no adequately designed controlled study of any of drugs for neuropathic sphincter deficiency.

RECOMMENDATIONS FOR PRACTICE

Bladder relaxant agents should be recommended for the treatment of reflex incontinence, in patients, in whom IC alone is unable to control it (Grade of recommendation A).

Titration of the dosage of these drugs individually should be done to achieve maximum therapeutic effect and minimal side effect. If one drug is not tolerated, try another drug as it may have less side effects (Grade of recommendation D).

In most of the developing countries bladder relaxant drugs are not available or only at costs people are unable to afford. Therefore the pharmaceutical industry must be encouraged to provide cheaper drugs (Grade of recommendation D).

Intravesical RTX and botulinum toxin injections may be an alternative for DH if conventional therapy fails (Grade of recommendation C).

Further attempts for the treatment of DH should be undertaken to develop the ideal drug in terms of good efficacy, tolerability and safety (Grade of recommendation D).

For neurogenic sphincter deficiency no effective drugs are available up to now; further research is needed (Grade of recommendation D).

4. IMPLICATIONS FOR RESEARCH

During the past few years research in neurourology has stimulated the development of new therapeutic approaches for incontinence, including the intravesical administration of afferent neurotoxins, such as capsaicin and resiniferatoxin. What are the research priorities for the future? It will be important to focus on the development of neuropharmacologic agents that can suppress the unique components of abnormal bladder reflex mechanisms and thereby act selectively diminish symptoms without altering normal voiding function. To end this part we would like to speculate on a few areas of research that we feel may payoff within the next 5 years with new and better treatment of neuropathic urinary incontinence:

1. Bladder specific K channel openers. Can truly bladder smooth muscle or afferent neuron specific potassium channel openers be developed? This treatment may alleviate the overactive and sensitive bladder without any dry mouth.
2. Intravesical vanilloid treatment. Can the clinical utility of intravesical resiniferatoxin be perfected so that the preferred therapy for neurogenic bladder is a simple outpatient 30 minutes instillation of 30 ml resiniferatoxin that will last 3 months without system side effects?
3. Can pharmaceutical companies develop a truly bladder specific and effective anticholinergic drug with no dry mouth?
4. Tachykinin antagonists are appealing in that it may be effective without increasing residual urine volumes. Can clinically useful and safe NK antagonists be developed?
5. Urethral smooth and/or skeletal muscle specific alpha agonist or 5-HT reuptake inhibitor that may treat stress urinary incontinence. We need an effective drug for stress incontinence.

Beyond the horizon of near term advancement, we predict a brave new paradigm in neurourology. What has already started are the evolution of unstoppable forces of change in medicine that include pharmacogenomics, tissue engineering and gene therapy. These will change how we practice urology and gynecology:

1. Pharmacogenomics: Medicine will be tailored to the genetic make up of each individual. Through

microarray gene chip technology we will know how a patient metabolizes medication, her receptors profile and allergy risk. These factors can be screen against a list of medications prior to therapy. A physician will then be able to always prescribe the best drug for each patient without the risk of allergic reaction.

2. Tissue Engineering: Rapid advances are being made in tissue and organ reconstruction using autologous tissue and stem cells feasible. We envision a day, in the not too distant future, where stress incontinence is cured not with a cadaver ligament and metal screws into the bones but rather minimally invasive injection of stem cells that will not only bulk up the deficient sphincter but actually improve the sphincter's contractility and function.
3. Gene Therapy: Diabetic neurogenic bladder and visceral pain maybe cured with one or more injection of a gene vector that the physician will inject into the bladder or urethra. Injection of nerve growth factor via a herpes virus vector into the bladder of a diabetic bladder may restore bladder sensation and innervation. Can the introduction of a virus that express the production of endorphin for site and nerve specific help alleviate pelvic visceral pain, regardless of the cause?

5. ACKNOWLEDGEMENT:

None

6. POTENTIAL CONFLICT OF INTEREST:

None

E. ELECTROSTIMULATION

I. ELECTRICAL NEUROMODULATION

1. BACKGROUND

In the last decade sacral nerve neuromodulation [Schmidt RA 1988] has been confirmed as a valuable treatment option to treat patients with symptoms of the overactive bladder. The success with sacral neuromodulation has increased the interest in other neuromodulation techniques.

To find evidence to answer the following questions:

2. OBJECTIVES

a) *How to do it?*

The current techniques of neuromodulation for treating the overactive bladder – which includes per definition

also detrusor hyperreflexia as detrusor overactivity of neurogenic origin - are (a) anogenital electrical stimulation, (b) transcutaneous electrical nerve stimulation (TENS), (c) sacral nerve neuromodulation, (d) percutaneous posterior tibial nerve stimulation (Stoller afferent nerve stimulation, SANS) and (e) magnetic stimulation.

b) How does it work, is it effective?

It is not really known how neuromodulation works, however, there is strong evidence that neuromodulation works at a spinal and at a supraspinal level [Bemelmans et al 1999].

The most important spinal inhibitory mechanisms of the micturition reflex [Fall & Lindström 1991] are (1) the guarding reflex: increased activity of the striated urethral sphincter in response to bladder filling, reflexively reducing detrusor contraction; (2) Edvardsen's reflex: increased activity of the sympathetic nervous system in response to bladder filling; (3) anal dilation (afferent pathway: anorectal branches of the pelvic nerve, prevents voiding during defecation), (4) gentle mechanical stimulation of the genital region (afferent pathway: dorsal clitoral or penile branches of the pudendal nerve; prevents voiding during intercourse) and (5) physical activity (afferent pathway, muscle afferents from the limbs prevents voiding during fighting or fleeing).

At least two potential mechanisms are possible (1) activation of efferent fibres to the striated urethral sphincter reflexively cause detrusor relaxation and (2) activation of afferent fibres cause inhibition at a spinal and a supraspinal level.

Interesting studies supporting the second theory are those in which the dorsal or dorsal penile nerve, purely afferent branches of the pudendal nerve, were electrically stimulated: this induced a strong inhibition of the micturition reflex and of detrusor hyperreflexia [Vodusek et al 1986; Craggs et al 1998; Shah et al 1998].

Fowler et al [2000] measured the latency of the anal sphincter contraction during a peripheral nerve evaluation (PNE) and concluded that this response was mediated by a polysynaptic reflex. Experimental work in spinalized rats showed that neuromodulation reduced the degree of hyperreflexia as well as the expression of the c-fos after bladder instillation with acetic acid [Wang & Hassouna 2000]. This result shows that inhibition of afferent C fibre activity may be one of the underlying mechanism of neuromodulation. However, it does not explain the beneficial effects of neuromodulation in patients with idiopathic detrusor instability or urgency. However, stimulation of afferent pathways seems to play the crucial role.

As this chapter deals with conservative therapy sacral

nerve stimulation (S3), which has been proved to be effective in refractory neurogenic urge incontinence, will not be discussed in this chapter.

c) Is it safe?

Neuromodulation has almost no complications, the methods must be regarded as safe.

d) Is neuromodulation cost-effective?

Comparing with the costs for anticholinergic therapy after one year of treatment the costs for pharmacotherapy and for neuromodulation including stimulator are equally, after one year electrical neuromodulation becomes cheaper.

e) How to prevent / to treat complications?

There are almost no complications with this type of therapy. According to the underlying working concept, which implies that the threshold for effectiveness is below the pain threshold even pains should not occur, therefore pains and skin irritation at the site of electrode placement are not found with a correct technique.

f) Comparing between techniques

There are no randomised controlled studies comparing one technique with the other.

g) Long term results and quality of life

Although there is a certain carry over effect with these methods about 75% of the patients in the neurogenic group need to continue the treatment on an individual schedule; if the patient accepts the manipulation involved with these techniques the quality of life is good because there are almost no side effects, which is in contrast to pharmacotherapy.

3. CRITERIA FOR CONSIDERING STUDIES AND SEARCH STRATEGIES include all types of studies with adults treated with one of the techniques of electrical neuromodulation mentioned above.

From Medline through Pub.Med. 1966-2001/IV

Key words: Neurogenic bladder (4625) and urinary incontinence (13392) combined with electrical neuromodulation

Three studies were found which report on the effect of non-invasive electrical neuromodulation for detrusor hyperreflexia (Level of evidence 4)

4. RESULTS

Only three papers report on results of non-invasive electromodulation techniques for detrusor hyperreflexia. Anogenital electrical stimulation (vaginal/anal) was used by Primus et al (1996), he found that the symptomatic and urodynamic results were the same in a group of patients with detrusor instability and a group

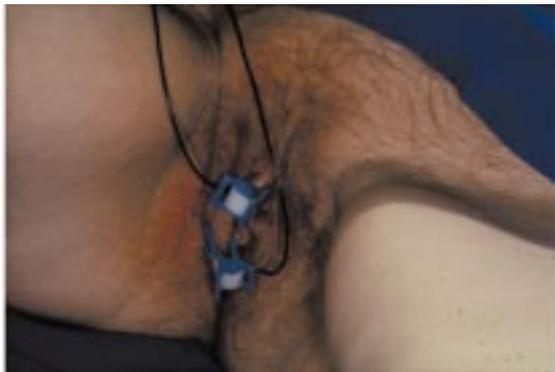


Figure 13 : For electrostimulation of the dorsal clitoral nerve clip-electrodes and of the dorsal penile nerve strip electrodes are used. Advantages: pure sensory nerves are stimulated with electrodes close to them.

of patients with multiple sclerosis. Madersbacher, Kiss & Mair (1995), by using dorsal clitoral and dorsal penile nerve stimulation (Figure 13) found even better results in the neurogenic group (detrusor hyperreflexia) than in the non-neurogenic group (detrusor instability) in regards to the increase of maximum cystometric bladder capacity and decrease of detrusor contractility. To maintain the results, however, 75% of the patients in the neurogenic group needed to continue the treatment on an individual schedule (however only 50% of the patients in the non-neurogenic group).

In contrast to these favourable results Prévinaire et al (1998) found no benefit in 6 patients with detrusor hyperreflexia due to suprasacral spinal cord injury by using continuous electrical stimulation of the penis or of the clitoris via bipolar surface electrodes and daily stimulation periods of 20 min. One possible reason for this discrepancy is the fact that in the two studies in which a beneficial effect was found, patients suffered from incomplete neurogenic lesions, however, the patients without success had complete suprasacral cord lesions. This may further support that effects of neuromodulation are mediated not only on a spinal, but, maybe even more important on a supraspinal level. In regards to percutaneous posterior tibial nerve stimulation and magnetic stimulation no reports refer to patients with neurogenic bladder dysfunction.

CONCLUSIONS

Electrical neuromodulation mostly is not the first line treatment for detrusor hyperreflexia, however it is indicated and beneficial in whom pharmacotherapy does not work or is not tolerated.

Non-invasive electrical neuromodulation should always be applied and tested before invasive electrical neuromodulation (sacral nerve stimulation of S3) is considered.

5. IMPLICATIONS FOR PRACTICE

Electrical neuromodulation is a valuable treatment option for patients with an overactive bladder, the non-surgical techniques can be applied as an alternative to standard conservative therapy or may be tried if such treatment fails. Experimental studies documented the effect of electrical stimulation of pudendal nerve afferents to inhibit detrusor hyperreflexia, however, only 3 published studies, using non-invasive techniques report on the effects on detrusor hyperreflexia: patients with detrusor hyperreflexia due to complete supraspinal cord lesions did not respond, patients with incomplete lesions did. Beneficial effects of invasive sacral neuromodulation (S3) are reported in the chapter of the surgical treatment of neuropathic urinary incontinence.

RECOMMENDATIONS

If pharmacotherapy fails to relax the hyperreflexic detrusor electrical neuromodulation is an alternative in patients with incomplete lesions and non-invasive electrical neuromodulation may be the first choice. (Grade of recommendation C/D)

Non-invasive electrical neuromodulation should always be applied before invasive electrical neuromodulation (sacral nerve stimulation of S3) is considered. (Grade of recommendation C)

6. IMPLICATIONS FOR RESEARCH

There are no sham-controlled studies with electrical neuromodulation in patients with detrusor hyperreflexia (although some studies exist for detrusor instability), therefore randomised sham-controlled studies should be undertaken in order to prove the efficacy of this method.

7. ACKNOWLEDGEMENT:

None

8. POTENTIAL CONFLICT OF INTEREST:

None

II. ELECTRICAL STIMULATION OF THE PELVIC FLOOR MUSCULATURE

1. BACKGROUND

The aim of electrical stimulation in patients with neurogenic urinary stress incontinence is to improve the function, that is strength and/or timing of the pelvic floor muscle contraction.

2. OBJECTIVES

To find evidence to answer the following questions:

a) How to do it?

Electrical stimulation is provided nowadays mostly by portable battery powered stimulation. It offers a seemingly infinite combination of wave forms, frequencies, intensities, electrode placements etc.

b) Is it effective?

The nomenclature used to describe electrical stimulation has been inconsistent. Strength training theories suggest that near maximal contractions are the most significant factor in increasing strength and ideally, contraction need to be sustained for 6-8 seconds to recruit an increasing number of motor units and fast twitch fibres [Astrand & Rodahl 1986]. There is a fixed recruitment pattern during voluntary contraction: slow twitch (ST) fibres are recruited first, but with increasing resistance more and more fast twitch (FT) fibres are recruited. All types of muscle fibres will have hypertrophy in response to strength and training, but FT fibres have a greater potential for hypertrophy than ST fibres. According to Bazeed et al (1982) it was shown that in the animal experiment over months electrical stimulation is able to transform FT fibres into ST fibres, which basically should improve incontinence. As the strongest stimulation for strength increase is the intensity of the contraction (as close to maximum as possible), the main objective would be to recruit as many motor units as possible, regardless whether they are ST or FT fibres. To improve the potential for strength gains, also electrical stimulation should be conducted over sufficient time that both, neural adaptation and hypertrophy can occur. Thus, training periods of at least 20 weeks have

been recommended [American College of Sports Medicine 1990].

c) Is it safe?

There are no complications reported with this type of therapy, if the technique is appropriate.

d) Is it cost-effective?

More studies are needed to evaluate this aspect. (see below)

e) How to prevent/treat complications?

There are no complications described

f) Comparing between techniques

There is a marked lack of consistency in the electrical stimulation protocols used in clinical practice. Even in the group of women with urinary stress incontinence of obviously non-neurogenic origin due to the variation of stimulation protocols it is difficult to interpret the findings of trials comparing electrical stimulation with placebo stimulation.

g) Long term results and quality of life

There are no adequate data available.

3. CRITERIA FOR CONSIDERING STUDIES

SEARCH STRATEGY

All studies dealing with adults suffering from neurogenic urinary stress incontinence

From Medline through Pub.Med 1966-2001/IV

Keywords: Neurogenic urinary stress incontinence, neurogenic sphincter weakness in combination of electrical neurostimulation, electrostimulation

All studies would have been considered in regards to efficacy, safety and cost-effectiveness (languages English, German).

No study was found dealing with electrical neurostimulation for neurogenic pelvic floor / striated sphincter weakness.

4. RESULTS

Although from the theoretical point of view and based on limited own clinical experience (*Level of evidence 5*) electrical stimulation via anal or vaginal plugs should be able to improve the strength of pelvic floor musculature including that of the striated sphincter muscle, there is no study published which deals with this matter. From our experience in selected patients with neurogenic urinary incontinence – patients being able to contract voluntarily pelvic floor musculature – electrical stimulation via anal or vaginal approach is able objectively, as assessed by perionometry, to improve the incontinence situation. In one of our patients the

change after electrical stimulation over 4 months was as such that continence could be achieved even with sudden intraabdominal pressure rises.

5. IMPLICATIONS FOR PRACTICE

In patients with incomplete denervation of the pelvic floor muscle and the striated sphincter electrostimulation via anal or vaginal plugs performed over months, may improve pelvic floor function, thus improve incontinence. The incompleteness of the lesion should be as such that the patient is able to contract voluntary the pelvic floor, even if this is weak. (*Grade of recommendation D*)

6. IMPLICATIONS FOR RESEARCH

It would be worthwhile to assess in a prospective controlled study whether patient is likely to benefit or not, whether electrical stimulation can improve the situation. The amount of nerves damage to the pelvic floor muscle may also be crucial.

7. ACKNOWLEDGEMENT:

None

8. POTENTIAL CONFLICT OF INTEREST:

None

III. INTRAVESICAL ELECTRICAL STIMULATION (IVES)

1. BACKGROUND

Already in 1887 the Danish surgeon Saxtorph described intravesical electrical stimulation for the “atonic bladder” by inserting a transurethral catheter with a metal stylet in it and with a neutral electrode on the lower abdomen. In 1899 two Viennese surgeons, Frankl-Hochwart and Zuckerkandl, stated that intravesical electrotherapy was more effective to induce detrusor contractions than external faradisation. In 1975 Katona introduced this method for the treatment of neurogenic bladder dysfunction. Ebner et al (1992) demonstrated in cat-experiments that intravesical electrostimulation activates the mechanoreceptors within the bladder wall.

Further basic research was undertaken by Jiang & Lindström (1991), who demonstrated that IVES at low frequencies (≥ 20 Hz) had a better modulatory effect than higher frequencies. Jiang (1998) proved in the animal experiment, that IVES induced modulation of the micturition reflex due an enhanced excitatory synaptic transmission in the central micturition reflex pathway. The observed modulation may account for the clinical benefit of IVES treatment.

The afferent stimuli induced by IVES travel along afferent pathways from the lower urinary tract to the corresponding cerebral structures. This “vegetative afferentation” [Katona 1975] results in the occurrence of sensation for bladder filling/urge to void, with subsequent enhancement of active contractions and possibly also in voluntary control over the detrusor (Figure 14).

A feedback training is mediated by enabling the patient to observe the change of the detrusor pressure on a water manometer, thus the patient is able to realise, when a detrusor contraction takes place. This also facilitates voluntary control (Figure 15).

2. OBJECTIVES

To find evidence to answer the following questions:

a) *How to do IVES?*

The technique involves a catheter with a stimulation electrode in it, introduced into the bladder and connected to the stimulator. Saline (0,9 %) is used as the current leading medium within the bladder. The neutral electrode is attached to the skin in an area with preserved sensation, usually in the lower upper abdomen. According to Ebner et al (1992) the following stimulation parameters have proved to be most effective in the animal experiment: pulse width 2 ms, frequency 20 Hz and current 1 to 10 mA. Each therapy session takes 90 minutes on a daily basis until the maximum response is achieved. For patients, who have never experienced the urge to void, e.g. children with myelomeningocele, or who have lost this ability, IVES is combined with a bio-feedback training: on a water manometer attached to the system the patient is able to observe the change of the detrusor pressure. This way he is able to realize that the experienced sensation is caused by bladder contraction. This external feedback also facilitates achievement of voluntary control (see fig.4).

3. CRITERIA FOR CONSIDERING STUDIES AND SEARCH STRATEGIES

All, clinical and experimental

from Medline 1966-2001

Intravesical electrostimulation, bladder stimulation, intravesical bladder stimulation, transurethral electrostimulation of the bladder; intravesical, transurethral bladder stimulation

30 studies were selected: 6 basic research papers (animal experiments and clinical research), only one randomised controlled trial (*Level of evidence 1*), 2 reviews within an editorial, one pro and contra IVES (*Level of evidence 2*), the rest were case series (*Level of evidence 4*).

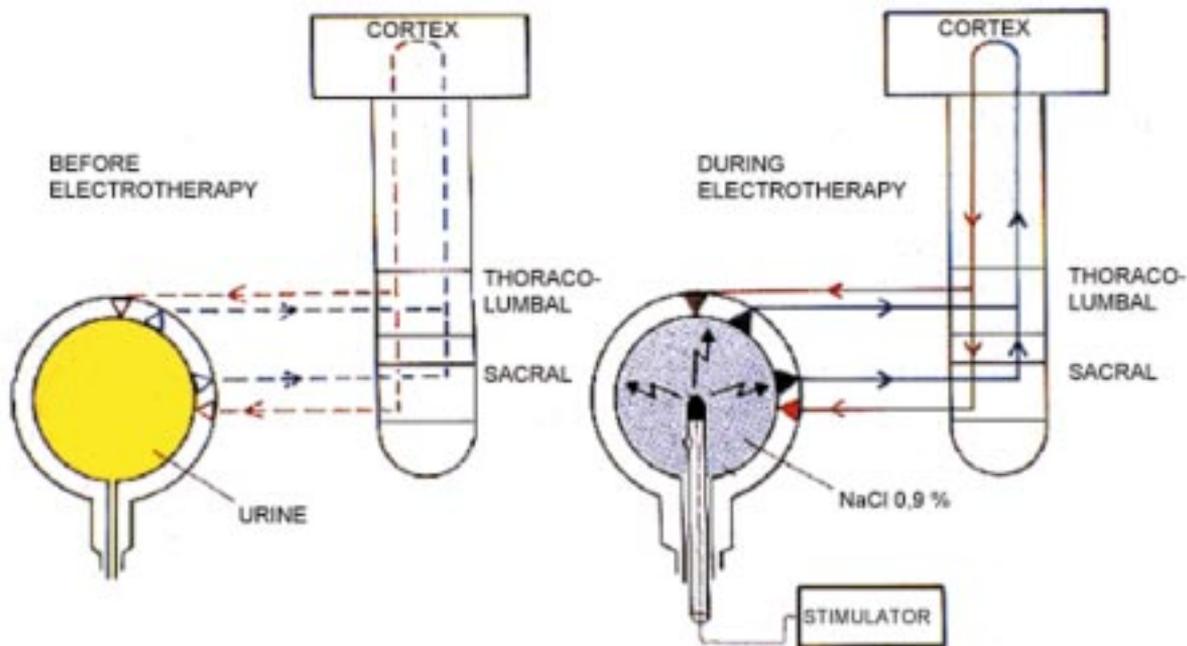


Figure 14 : Intravesical electrostimulation activates the mechanoreceptors within the bladder wall, thus increases the afferent and consequently the afferent input from and consequently also the efferent output to the bladder (Ebner et al., 1992)

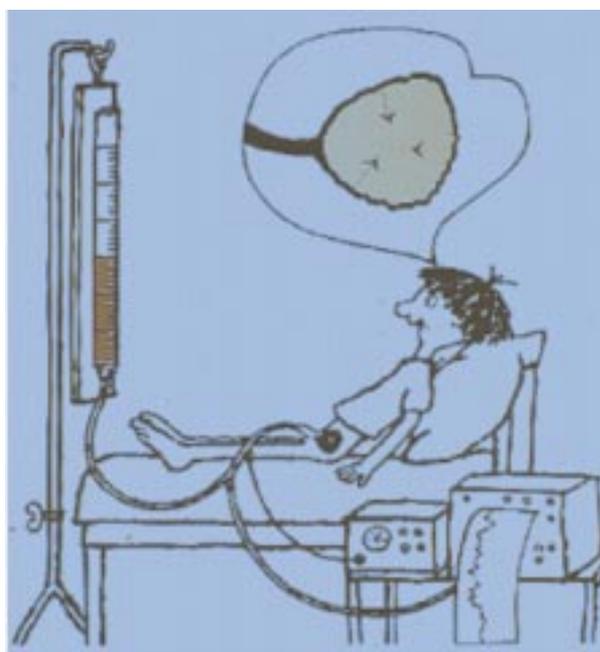


Figure 15 : With intravesical electrostimulation a feedback training is mediated by enabling the patient to observe the change of the detrusor pressure on a water manometer: the patient is able to realize when a detrusor contraction takes place.

4. RESULTS

Intravesical electrical stimulation of the bladder (IVES) is still a controversial therapy for patients with neurogenic detrusor dysfunction, although basic research

during the last decade has evidenced the mechanism of action and its efficacy [Ebner et al 1992; Jiang 1998]. At least in animal experiments optimal parameters have been determined [Ebner et al 1992; Buyle et al 1998]

Colombo et al (2000) demonstrated that intravesical electrostimulation also induces electrical changes on higher micturition centres, measured by EEG. The evaluation of viscerosensory cortical evoked potentials after transurethral electrical stimulation of the bladder neck area has been proved to be useful in determine whether a patient is suitable for IVES or not [Kiss et al 1998].

This controversy about the value of IVES for detrusor (re-)habilitation is also reflected in an editorial recently published, in which Kaplan (2000) reported favourable results in 288 children, who received at least one series (20 outpatient sessions 90 minutes long):

87% have control and void or catheterize with sensation or have improved bladder compliance 18% have gained full control, they void synergistically and are continent, when before they were either voiding poorly and incontinent or used clean intermittent catheterization and were more or less dry. Forty-four % void with sensation and are in biofeedback to try and gain control. Finally in 13 % the treatment failed, but the patients maintained their condition. Moreover, the results seen in an “early” group were followed up 10 years. As long as no intervening neurosurgical insult occurred, less than 3 % of cases needed to return for a tune up to maintain their “healthy bladder”. The average number of daily session to achieve this results was 47.

In contrast the results reported by Decter (2000) were less favourable. In 25 patients during a 5 year period with all-together 938 sessions of stimulation, bladder capacity increased greater than 20% in regards to the age-adjusted and end-filling bladder pressure showed clinically significant decreases in 28% of patients. In response to a questionnaire, 56% of parents commented a subjective improvement in their childrens bladder function. However, the urodynamic improvements achieved after IVES did not significantly alter the daily voiding routine in these children [Decter et al 1994].

The only randomised controlled prospective clinical trial [Boone et al 1992] could not find differences between active and sham treatment, however, only 15 sessions were performed at first and another 15 sessions of IVES were applied after a 3-months hiatus. Moreover, the inclusion criteria were not defined.

Other studies are either individual case-controlled studies (Level of evidence 3) or case series (Level of evidence 4). They cannot be compared due to different or non-defined inclusion criteria, different technique details (different time of electrostimulation, varying follow-ups) and some with only a small number of patients included, [Eckstein & Katona 1974 - pro; Nicholas & Eckstein 1975 - contra ; Denes 1975 - pro; Janneck 1976 - pro; Seiferth et al 1978 - pro; Seiferth et al 1978 - pro; Schwock & Tischer 1981 - pro; Madersbacher et al 1982 - pro; Kaplan & Richards 1988 - pro; Madersbacher H 1990 - pro; Lyne & Bellinger 1993 - pro; Kölle et al 1995 - pro; Cheng et al 1996 - pro; in one 7 patients, in a second study 568 patients; Primus & Trummer 1993 - pro; Kroll et al 1998 - pro; Pugach et al 2000 - contra].

None really focused particularly on the inclusion criteria. According to basic research, only those with some intact afferent fibres from the bladder to the cortex and those with spinal cord lesions with the presence of pain sensation in the sacral dermatoms S3 and S4 can benefit from IVES. (according to Nathan the pathways of the bladder proprioception and for pain are lying close together). The value of viscerosensoric cortical evoked potentials from the bladder neck was demonstrated by Kiss et al (1999). A precise indication seems to be one prerequisite for a good result. Regarding children with myelomeningocele, one must also take into account that myelomeningocele bladders at birth may have a threefold increase in connective tissue and significant decrease of cholinergic receptors compared to normal controls [Shapiro et al 1991]. According to clinical experience this tempers the enthusiasm for intravesical electrical stimulation in this particular group of patients.

CONCLUSIONS

Basic research during the last decade has proved the underlying working concept

The results reported in the literature are controversial, mainly because of different inclusion and exclusion criteria.

In the only sham-controlled study the treatment period is too short and the inclusion and exclusion criteria are not really defined.

The alternative may be either life long intermittent catheterization or bladder augmentation. In this regards IVES is **cost-effective**

It is worthwhile to apply intravesical electrostimulation, bearing in mind inclusion and exclusion criteria, especially trying to varify functioning afferent fibres between the bladder and the cortex.

5. IMPLICATIONS FOR PRACTICE

Basically intravesical electrotherapy is able to improve neurogenic bladder dysfunction, primarily by stimulating a-delta mechanoafferents inducing bladder sensation and the urge to void and consequently increasing the efferent output with improvement of micturition and conscious control. Therefore IVES is the only available option to induce/improve bladder sensation and to enhance the micturition reflex in incomplete central or peripheral nerve damage. However, proper indication is crucial and this type of therapy should only be applied in those with at least some intact afferent fibres between the bladder and the cortex if possible, proved by the evaluation of viscerosensoric cortical evoked potentials. If these premisses are respected, IVES is **effective**.

Intravesical electrical stimulation is **safe**, no side-effects have been reported, beyond an occasional urinary infection. The question of cost-effectiveness was raised by Kaplan, stating that the most commonly used alternative for these patients is bladder augmentation, which is “miles apart in terms of cost, discomfort and short- and long-term complications”.

One benefit of IVES was noted by most of the authors: improved sensation documents satisfactory long term results. The patients with successful IVES get great satisfaction from knowing when their bladder is full and when it is time to catheterise or to void. Moreover, even without direct bowel stimulation patients noted significant improvement in the warning of bowel fullness and gained greater control for their bowel movements.

IVES can only be effective with certain prerequisites, the most important one are at least some afferent fibres

between the bladder and the CNS being intact and the detrusor able to contract. The method is safe, there are no real complications reported.

RECOMMENDATIONS

Intravesical electrotherapy is able to improve neurogenic bladder dysfunction, primarily by stimulating a-delta mechano-receptor afferents inducing bladder sensation and the urge to void and consequently increases the efferent output with improvement of micturition and conscious control.

IVES is the only available option to induce/improve bladder sensation and to enhance the micturition reflex in patients with incomplete central or peripheral nerve damage.

Indication is crucial and IVES should only be applied if afferent fibres between the bladder and the cortex are still intact and if the detrusor muscle is still able to contract.

If these premises are respected, IVES is effective.

The ideal indication is the neuropathic hyposensitive and hypocontractile detrusor (Grade of recommendation C)

6. IMPLICATIONS FOR RESEARCH

There is definitely a need for placebo-(sham-)controlled prospective studies with clear inclusion- and exclusion-criteria and clear definitions of the aims. Recently De Wachter & Wyndaele (J.Urology, accepted for publication) demonstrated in the animal experiment and models that the position of the stimulating electrode, as well as the amount of saline within the bladder may be crucial for the effect. Additional research is needed to clarify these aspects of IVES.

7. ACKNOWLEDGEMENT:

None

8. POTENTIAL CONFLICT OF INTEREST:

None

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II. INDWELLING CATHETERIZATION

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