Lower Urinary Tract

The role of neuromodulation in the management of urinary urge incontinence

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Neuromodulation is increasingly becoming an important part of the treatment strategy for bladder dysfunction. In this issue a group of urologists have analysed outcome measures from all patients in pivotal clinical trials who have had this treatment, and have suggested that sacral nerve stimulation has an vital role in the management of refractory overactive bladder and retention problems.

In a carefully performed study, authors from Mansoura and Scottsdale have evaluated high-energy TUMT and found that although symptomatic improvement occurred in 82.5% of patients, and that the peak flow rate improved from a median of 9.2 to 15 mL/s, pressure–flow improvement occurred in just 50% of the group. However, they found that younger patient age and higher grade of obstruction, are good predictors of urodynamic and symptomatic success respectively. In another study, Marshall's group from Adelaide emphasize the value of urodynamics and other factors in patients having TURP. The value of trans-abdominal ultrasound is described by Foo and his colleagues from Singapore, who state that intravesical protrusion of the prostate is an important indicator of bladder outlet obstruction.

OBJECTIVE

To examine the benefit-risk profile of neuromodulation in treating refractory urinary urge incontinence and other voiding disorders.

PATIENTS AND METHODS

The outcome measures from all patients in pivotal clinical trials who had undergone sacral nerve stimulation were analysed retrospectively.

RESULTS

Neuromodulation was effective in several clinical studies; the response is durable and the benefit-risk profile good.

CONCLUSION

Sacral nerve stimulation is becoming the standard of care for refractory overactive bladder and retention problems. The potential benefit of neuromodulation should be included in female urology and gynaecology training programmes.

KEYWORDS

urinary urge incontinence, neuromodulation, neurourology, outcome

INTRODUCTION

Urinary incontinence is a common condition affecting millions of women and men worldwide, with a significant effect on quality of life (QoL) [1]. It has been calculated that as many as 38% of community-dwelling women and 19% of men experience urinary incontinence [2]. Furthermore, it is both a major source of dependency and a key factor in nursing-home entry [3]. The direct and indirect cost of treatment is considerable for patients, families and third-party payers, estimated in 1995 for patients aged >65 years as $26.3 billion in the USA [4].

Although behavioural and surgical interventions can be used to treat urinary incontinence caused by detrusor overactivity, antimuscarinic therapy, particularly oxybutynin and tolterodine, has been the mainstay of treatment for almost three decades [5]. The efficacy can be satisfactory but with the original formulations there tend

to be high rates of discontinuation caused by compliance-limiting side-effects, particularly dry mouth [5,6]. Although attempts have been made to improve the clinical profile, with extended release formulations of oxybutynin [7] and tolterodine [8], and the promised development of more 'bladder selective' antagonists, e.g. darifenacin [9], patient compliance is still considered to be an issue [5].

Overall, therefore, many patients are considered to be antimuscarinic 'failures', either through poor compliance or modest efficacy. This article examines the potential of one technique, sacral nerve stimulation, in managing this numerically large cohort of incontinent patients who are inadequately controlled with antimuscarinic agents. The review is based on the deliberations of an interdisciplinary group that met in Heidelberg in August 2002.

Variable or criterion	Value
N (%)	
women	125 (80.6)
men	30 (19.4)
Mean (SD, range)	
age, years	46 (13, 20.2–78.9)
duration of urinary symptoms before enrolment	9 (7, 0.6–35.4)
Previous medical treatment for urinary problems, n (%)*	153 (98.7)
Pharmacological	144 (92.5)
Non-surgical	55 (35.5)
Surgical	88 (56.8)
Criteria	
Inclusion	
Age >16 years	
Refractory to standard medical therapy	
Minimum 100 mL bladder capacity with normal upper urinary tract	
Good surgical candidate	
Able to complete study documentation and return for follow-up evaluation	
Exclusion	
Neurological condition including multiple sclerosis, diabetes with peripheral nerve involvement, spinal cord injury and stroke	
Stress urinary incontinence	
Primary pelvic pain	

TABLE 1
A demographic summary of patients with urge incontinence in clinical trials, and the inclusion and exclusion criteria

**Medical categories can overlap.*

BACKGROUND TO SACRAL NERVE STIMULATION

Sacral nerve stimulation, often referred to as neuromodulation, is approved by the USA Food and Drug Administration for three indications; urinary urge incontinence, urgency-frequency syndrome and voiding difficulties (incomplete and complete retention).

The use of neuromodulation is based on the knowledge that urge incontinence usually results from an imbalance of facilitatory and excitatory control systems, often causing a 'hyper-excitable' detrusor, leading to incontinence during the filling phase [10]. Neuromodulation redresses this imbalance [10] potentially via direct or indirect actions on the sacral nerve [11]. The underlying principle is based on the induction of somatic afferent inhibition of sensory processing within the spinal cord. In addition, activation of pudendal afferent input can also trigger voiding reflexes by suppressing the guarding-reflex pathways. This understanding of the basic neurophysiology of detrusor behaviour and the role of the sacral nerves culminated in the development of the technology to modulate lower urinary tract dysfunction through sacral nerve stimulation [11]. Since the pioneering work of Tanagho, the technique has been used in >8000 implants. Laboratory experiments showed the profound inhibitory effect of stimulating pudendal afferents on the parasympathetic outflow to the detrusor [11], and the inhibitory effect of pudendal afferent stimulation on detrusor activity in humans has been determined [12]. Thus it is not unreasonable to assume that sacral nerve stimulation works, at least in urge incontinence and urgency/frequency, through the same inhibitory effect as for pudendal afferent stimulation in both experimental animals and man. However, it is more difficult to comprehend how sacral nerve stimulation can restore voiding in urinary retention.

CLINICAL EXPERIENCE

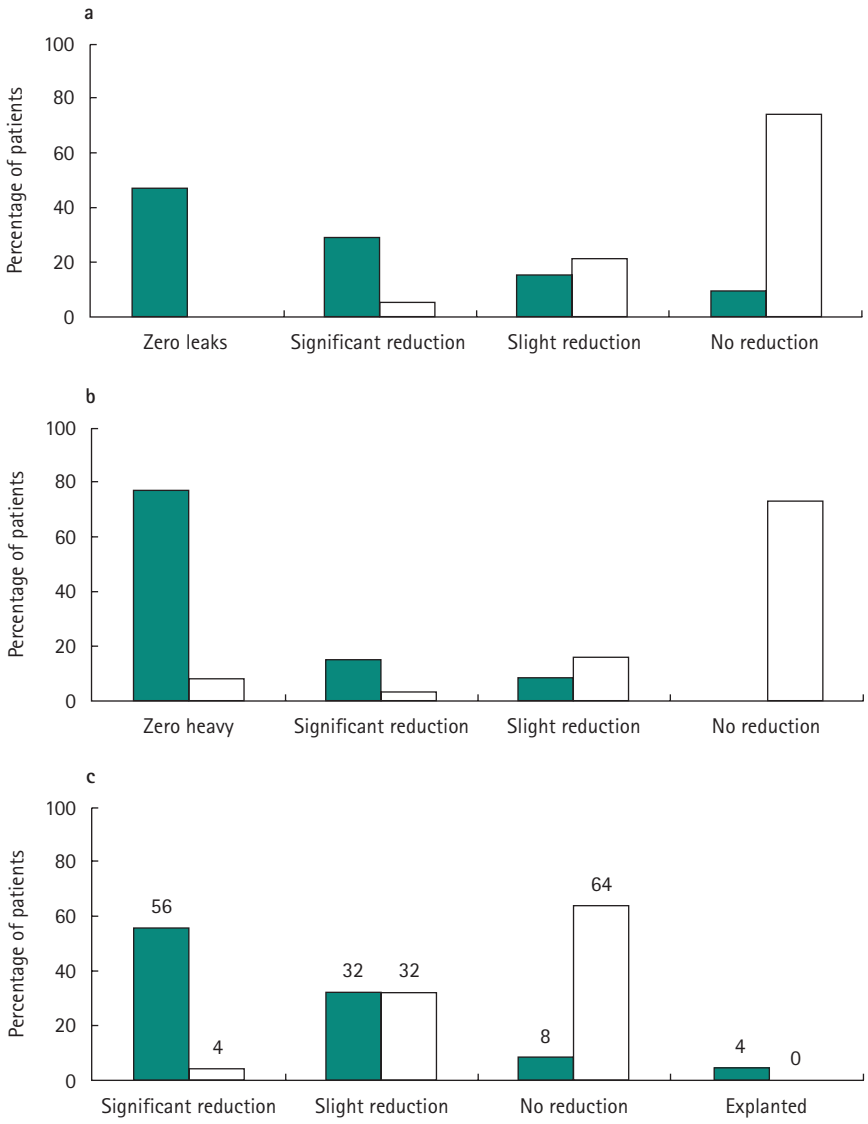
EFFICACY

The pivotal data in refractory urge incontinence originates from a large, randomized trial initiated in 1992 across 22 centres, described in detail elsewhere [13–15]. The demographics, inclusion and exclusion criteria for these studies in patients with refractory urge incontinence, urinary retention and refractory urgency-frequency symptoms are summarized in Table 1. A variety of validated urodynamic and questionnaire, and/or diary-based endpoints was used to measure frequency, voiding pattern, leakage, dryness and bothersomeness. The overall profile is represented in Fig. 1.

Importantly, at 6 months almost half (47%) of the group were completely dry, compared with none of the control group. Using a definition of clinical benefit as either no incontinence or a reduction by at least half in leakage episodes, over three-quarters of the patients (76%) achieved this level of improvement. Using similar criteria but based on pad usage, 87% of the treated group responded but only 7% of the control group improved.

There was some evidence using the Short Form-36 (a general validated QoL questionnaire) that the patients perceived these changes as having a positive effect on

*FIG. 1. The responses to treatment by sacral nerve stimulation (green bars) or delayed treatment (open bars): **a,** Incontinence episodes per day in patients with urge incontinence; 'zero leaks' was defined as no incontinence, a 'significant reduction' as ≥50%, 'slight reduction' as <50% and 'no reduction' as no change or a slight increase. **b,** The severity of episodes of heavy incontinence in patients with urge incontinence; 'zero heavy' was defined as heavy incontinence at baseline and none at 6 months, 'significant reduction' as ≥50%, 'slight reduction' as <50% and 'no reduction' as no reduction in heavy incontinence. All patients were evaluated 6 months after implantation; the neuromodulation group comprised 34 patients and the delayed-stimulation group 42. **c,** The mean number of voids daily in patients with urgency-frequency syndrome. The reduction in the number of voids daily is defined as 'significant' (> 50% at 6 months and/or normal range of 4–7 voids daily), 'slight' (< 50%), or 'no' (no change or slight increase). 'Explanted' describes a case in which the device was removed before 6 months. There were 25 patients in both groups and all were evaluated at 6 months.*



their QoL. The neuromodulation-induced improvement in QoL was consistent with that observed in other studies [16,17], but this must be confirmed using more precise disease-specific QoL instruments [18].

Importantly, urodynamic evaluations using, e.g. uroflowmetry and pressure/uroflow studies, showed that there was no deleterious effect on voiding detrusor function and no de novo urinary retention in the neuromodulation group. The response was durable, with consistent benefit for up to 18 months (Table 2). Overall, it can be concluded that in most patients the technique can provide considerable benefit that has an effect on overall QoL.

BENEFIT-RISK RATIO

When placing any procedure within a potential algorithm for patient treatment the overall benefit-risk ratio must be considered. The following discussion represents an overview of the adverse events from the pivotal randomized multicentre clinical trial described in detail elsewhere [13–15]. This analysis is likely to be more representative of actual experience than some of the earlier largely single-centre studies [16,19,20]; both efficacy and safety improved as a result of physicians' experience and improvements in the technology. The development of new percutaneous technology and the minimally invasive placement of leads has had a particular effect on patient and physician acceptability. In this context, most of the improvements in technique and equipment occurred after the pivotal study. Certainly, practitioners feel that both efficacy and safety have improved beyond that predicted from the early study.

Data on the safety of sacral neuromodulation for various types of urinary tract dysfunction (including urge incontinence, retention and urgency-frequency) have been assembled from 633 patients undergoing 914 test stimulation procedures, and 250 patients implanted with a neuromodulation system. At the end of the study period (up to 1 year) no patient had had permanent injury resulting from sacral nerve stimulation.

In 6506 months of experience with the device for the 250 patients with an implant there were no reported unanticipated adverse effects associated with neuromodulation. In all, 368 events associated with the device or use of sacral nerve stimulation were documented in 157 of the 250 patients. Overall, 89.4% (329) of the 368 events were resolved by the time the database was closed.

THE ROLE OF NEUROMODULATION IN MANAGING URINARY INCONTINENCE

When sacral nerve stimulation appeared as a treatment for incontinence ≈10 years ago

many practitioners were sceptical and it was felt that, at best, the procedure would be limited to a select group of neurourologists and only used on patients with the most serious problems. Over the last 10 years many publications have documented the efficacy and safety of sacral nerve stimulation as a treatment for overactive bladder symptoms (urge incontinence and urgency frequency) and patients with so-called 'idiopathic urinary retention' who are refractory to behavioural and pharmaceutical therapies. Both efficacy and safety (as measured by adverse events) have improved significantly since the initial studies, as a result of the increase in experience of the physicians involved, changes to the procedure (buttock placement of the stimulator and/or the new percutaneous procedure, staged implant, minimally invasive lead placement) and the equipment used in sacral nerve stimulation [21,22].

There is an impression that sacral nerve stimulation is too expensive for conditions such as an overactive bladder or retention. Several publications documented the significant expense to the health system of these disease states [1,4]. Many of these costs, both direct and indirect, are a result of concomitant health problems, the cause of which can be traced to the underlying urological condition. Apart from the cost to the health system there is also the burden to the patient and his/her family [3]. The initial expense of the therapy, especially measured over the 7–10-year life of any neurostimulator, should be considered in relation to the potential savings to the healthcare system and the effect on the patients' QoL.

Variable	% with clinical benefit at (months) 6	12	18
Any episode of leakage	47	45	52
Dry	47	45	52
≥ 50% reduction	28	34	24
Total clinical success	75	79	76
Heavy episodes of leakage	77	70	84
Eliminated	77	70	84
≥ 50% reduction	13	10	0
Total clinical success	90	80	84
Pads replaced daily	57	55	57
Eliminated	57	55	57
≥50% reduction	26	21	19
Total clinical success	83	76	76

TABLE 2
Durability of the clinical response to neuromodulation

Data were analysable for 58 patients at 6 months, 38 at 12 months and 21 at 18 months (at the time of data analysis).

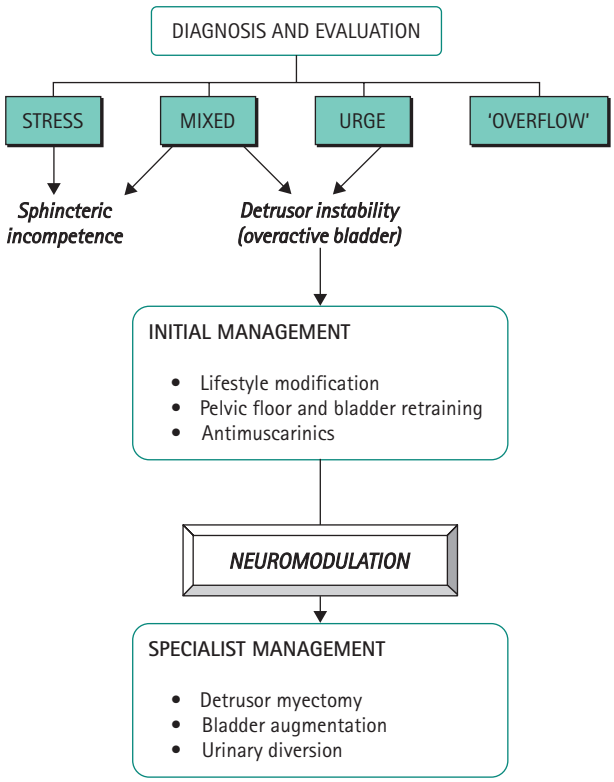


FIG. 2.
An algorithm for managing urinary incontinence.

CONCLUSION

Currently, >600 urologists and urogynaecologists worldwide have adopted sacral nerve stimulation as a treatment, and >8000 implants have taken place to date. Sacral nerve stimulation should always be discussed and considered before contemplating surgical procedures such as ileocystoplasty or detrusor myectomy for intractable urge incontinence. It is also recommended that sacral nerve stimulation be considered before committing patients to a lifetime of absorbent products (with the associated problems of odour management, skin problems and patient costs). In an increasing number of centres worldwide sacral nerve stimulation is becoming the standard of care for patients with a refractory overactive bladder or retention. The positioning of neuromodulation within the treatment algorithm for patients with voiding dysfunction is shown in Fig. 2.

Given the potential of this therapy, it is recommended that all urology training programmes that focus on female urology and incontinence should include sacral nerve stimulation as part of the curriculum.

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