Neuro-urology

Six-Year Follow-Up of Botulinum Toxin A Intradetrusorial Injections in Patients with Refractory Neurogenic Detrusor Overactivity: Clinical and Urodynamic Results

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Abstract

Background: Most reports in the literature on botulinum toxin A (BoNTA) therapy for neurogenic detrusor overactivity (NDO) are based on the results of a single injection. Because most patients may require retreatment, the efficacy and safety of multiple injections must be addressed clearly.

Objective: To investigate the effectiveness and safety of BoNTA intradetrusorial injections in a group of spinal cord–injured (SCI) patients with refractory detrusor overactivity (DO).

Design, setting, and participants: Seventeen SCI patients were prospectively included in the study and followed up to 6 yr.

Intervention: All patients received repeat intradetrusorial injections of BoNTA 300 units (Botox, Allergan, Irvine, CA) under cystoscopic control on an inpatient basis.

Measurements: The preliminary assessment included voiding diary, urodynamics, kidney and bladder ultrasound, and cystourethrography. Patients also completed a standardised quality-of-life (QoL) questionnaire. Clinical evaluation, urodynamics, urinary tract imaging, and QoL assessment were repeated every year throughout the follow-up.

Results and limitations: Before treatment, all patients complained of urinary incontinence and had DO. Bilateral and monolateral renal pelvis dilatation were detected in six and five patients, respectively, and a monolateral and third-grade vesicoureteral reflux was observed in three. At 6-yr follow-up, a significant decrease in the frequency of daily incontinence episodes (p < 0.01), a significant increase in first uninhibited detrusor contraction and in maximum bladder capacity (p < 0.001 for both), and a significant decrease in maximum pressure of these contractions (p < 0.01) were observed. Fifteen patients (88.2%) were completely continent. Renal pelvis dilatation and vesicoureteral reflux resolved in all cases, and the QoL index significantly increased. Limitations of the study are related to the small number of included patients.

Conclusions: In SCI patients with refractory NDO who do not want or are unfit for invasive reconstructive surgery, BoNTA intravesical treatment represents a valid alternative to control DO and urinary incontinence and to preserve upper urinary tract function over a long-term follow-up.

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1. Introduction

In patients with neurologic disorders, a major health problem is represented by bladder dysfunction associated with detrusor overactivity (DO), which constantly impairs quality of life (QoL) and often poses a threat for the upper urinary tract (UUT) [1]. Oral anticholinergics have widely been used as first-line treatment for patients with neurogenic DO (NDO) or neurogenic overactive bladder. However, they are ineffective in a large proportion of patients and can cause undesirable systemic side effects, which induce the brief interruption of treatment [2]. The intravesical route of administration may provide alternatives to achieve profound inhibition of NDO and avoid high systemic drug levels [3]. Botulinum toxin A (BoNTA) intradetrusor injections were introduced in 2000 as a minimally invasive treatment for NDO [4]. In 2005, the effectiveness and safety of a single BoNTA treatment were established in a randomised, placebo-controlled, 6-mo study [5]. To date, BoNTA intradetrusor injections may be considered the treatment of choice for NDO, before turning to major surgery, in patients who do not respond to or cannot tolerate conventional oral treatment and are under investigation in the treatment of other voiding dysfunction [6]. Previous studies demonstrated that BoNTA injected intradetrusorally is safe and effective in reducing DO, providing long-term efficacy. More recently, the effects of treatment on QoL were demonstrated in both neurogenic and nonneurogenic DO [7], and a cost–consequence analysis confirmed the cost effectiveness of this treatment [8]. The efficacy of a single toxin injection decreases with time, and reinjection is usually necessary 6–9 mo later to sustain the clinical effect [9−11]. Most reports in the literature on botulinum toxin therapy for NDO are based on the results of a single injection [11]. Because most patients may require retreatment, the efficacy and safety of multiple injections must be addressed clearly.

We investigated the effectiveness and safety of BoNTA injections into the detrusor muscle in a group of spinal cord–injured (SCI) patients with DO unresponsive to conventional anticholinergics who were followed up to 6 yr.

2. Methods

In October 2000, our institution began to use intravesical BoNTA to treat >100 patients with refractory neurogenic and nonneurogenic DO, hypersensitive bladder disorders, and benign prostatic hyperplasia (BPH) disease. Eighty-four patients with NDO have been treated with repeat intradetrusorial BoNTA, with a mean follow-up of 36.8 ± 34 mo. Among them, a group of SCI patients were followed up for >6 yr.

2.1. Inclusion and exclusion criteria

We enrolled patients affected by urinary incontinence and DO refractory to anticholinergics and those who reported intolerable anticholinergic side effects; all had normal renal function. Patients with myasthenia gravis and other diseases affecting cholinergic action, pregnancy, and concomitant use of aminoglycosides were excluded from the study. The study was approved by the ethics committee (clinical study 848/00), and all patients provided written consent.

2.2. Preliminary assessment

Preliminary assessment included patient history, physical examination, serum chemistries, urinalyses and culture, and urinary tract imaging by ultrasound and cystourethrography. Clinical symptoms (ie, daily frequency of urinary incontinence and of catheterisations) were assessed with a voiding diary maintained by patients for 30 d before commencing the study. Urodynamics followed the International Continence Society standards [12] and were performed in all patients 1 mo before commencing the study to allow the detection and treatment of any urinary tract infection (UTI) and to perform UUT imaging. Maximum pressure of uninhibited detrusor contractions (UDC), the lowest volume at which contractions occurred, and maximum bladder capacity were recorded. All patients had intermittent catheterisation and were taking oral anticholinergics. All patients were asked to complete the Incontinence Quality of Life Questionnaire (I-QOL) [13]. The questionnaire is a 22-item, domain-specific, validated, self-report test that has proven to be sensitive for detecting modification in self-perceived incontinence severity (Fig. 1). The QoL index is expressed as a score ranging from 0 (poor self-perceived QoL due to incontinence) to 100 (incontinence does not negatively affect QoL).

2.3. Study plan and treatment

At the beginning of the study, all patients adhered to the proposed treatment protocol and follow-up times. During the first 2 yr, clinical evaluation, urinalyses and cultures, urodynamics, and UUT imaging (kidney and bladder ultrasound) were repeated every 4 mo. When patients had a worsening of clinical symptoms (ie, recurrence of urinary incontinence episodes or increase in daily frequency of catheterisation), they underwent urodynamics and a further treatment with BoNTA intradetrusorial injections was performed. The following criteria were used for a patient’s reinjection: recurrence of urinary incontinence episodes, high pressures of DO, reduced bladder capacity, and urinary leakages on urodynamics. Voiding cystourethrography was performed every year throughout the follow-up. The voiding diary was maintained 2 d/wk throughout the follow-up. The QoL questionnaire was completed at 4 mo and every year during follow-up. Local and/or systemic side effects were
recorded during and after treatment, and patient dropout and satisfaction were also investigated during follow-up. According to the technique first described by Stöhrer et al [4], all patients received 300 U of BoNTA (Botox, Allergan, Irvine, CA, USA) at each injection treatment diluted in 30 ml 0.9% NaCl into the detrusor muscle (30 sites), sparing the trigone, under cystoscopic control. In eight patients (six with lesions above T5 and prone to autonomic dysreflexia and two with increased spasticity and leg spasms), the procedure was performed under spinal anaesthesia. In the remaining patients, who had severe spasticity, the procedures were performed in sedation only with the use of intravenous Fentanyl performed by an anaesthetist.

2.4. Data analysis

Statistical analysis was performed using the Friedman, Wilcoxon, and Mann-Whitney tests for nonparametric data. The Bonferroni correction was applied to post hoc multiple comparisons. Regression analysis was performed to correlate the QoL index with clinical results. Statistical significance was set at \( p < 0.05 \).

3. Results

There were 11 males and 6 females; the mean age ± SD was 39.7 ± 8.4 yr, and mean disease duration was 62.3 ± 12.4 mo. Neurological clinical evaluation followed American Spinal Injury Association classification [14]; type A impairment was observed in 11 patients and type B in 6. Levels of injury were as follows: T1–2 in one patient, T4–5 in three patients, T9–10 in two patients, and T11–12 in seven patients; the remaining patients had a cervical injury.

3.1. Baseline evaluation

Initially, 15 patients complained of incontinence episodes, as documented in their voiding diaries, and used pads or external collecting devices. Frequency of catheterisation and daily incontinence episodes are shown in Table 1. Urodynamics revealed high-level DO, with detrusor–sphincter dyssynergia in 15 patients and decreased bladder capacity and urinary incontinence in all patients. Two patients who did not complain of urinary incontinence had high pressure of uninhibited detrusor contractions and urinary leakages during urodynamics. Eight patients were taking oral anticholinergics (oxybutynin 5 mg two or three times per day; solifenacin 5 mg twice a day) without any substantial control of DO and urinary incontinence. The remaining patients stopped taking anticholinergics because of intolerable side effects. On kidney and bladder ultrasound, we detected bilateral and monolateral renal pelvis dilatation in six and five patients, respectively. Cystourethrography revealed monolateral, third-grade vesicoureteral reflux in three patients with high pressures of uninhibited detrusor contractions and small bladder capacities. Two of these patients did not complain of urinary incontinence. Despite the lack of data regarding the effects of BoNTA on vesicoureteral reflux, given the hypothesis of possible correction of the disease by the neurotoxin, these patients were included in the study protocol and underwent treatment.

3.2. Follow-up

Clinical and urodynamic controls were performed 3 mo after each injection treatment. The clinical and urodynamic data related to follow-ups at 4 mo and at 1, 3, and 6 yr are reported. A total of 119 injections were performed, the mean number of injections was 7.2 ± 1.3 for each patient, and the mean interval between two consecutive injections was 11.0 ± 2.4 mo. Clinical results are shown in Table 1.

3.3. Four-month follow-up

Four months after treatment, daily incontinence episodes and mean catheterisation significantly decreased compared to baseline (\( p < 0.001 \) and \( p < 0.001 \), respectively). Ten patients (58.8%) achieved
clinical and urodynamic urinary continence, which was maintained during follow-up. Urodynamic evaluation (see Table 1) revealed a significant increase in the first volume of uninhibited detrusor contractions ($p < 0.001$) and in maximum bladder capacity and a significant decrease in maximum pressure of uninhibited detrusor contractions as compared to pretreatment evaluation. We did not record any UTIs or any local or systemic side effects. Kidney and bladder were normal on ultrasound investigation, and cystourethrogram showed that vesicoureteral reflux disappeared in two cases. One patient with persisting vesicoureteral reflux again showed DO on urodynamics.

3.4. One year after treatment

Daily incontinence episodes and mean catheterisation were significantly decreased 1 yr after treatment as compared to baseline, and four other patients achieved complete clinical and urodynamic urinary continence (82.3%). Fourteen patients stopped taking anticholinergics. Three more patients, due to persistent uninhibited detrusor contractions with urinary leakages, continued to take oxybutynin per os, 5 mg/d. On urodynamics, both maximum pressure of uninhibited detrusor contractions and the first volume at which the contractions occurred remained significantly lower than baseline. Vesicoureteral reflux disappeared in all patients, and kidney and bladder were normal on ultrasound investigation. Four patients complained of UTIs, reporting three episodes in the course of the current year. During UTI episodes, they showed a recurrence of urinary incontinence.

3.5. Three- and six-year follow-up

At the 3-yr follow-up, 14 patients (82.3%) presented with complete clinical and urodynamic urinary continence in the absence of urinary tract infections. Urodynamic parameters were substantially similar to those investigated at the previous follow-up. Also, mean catheterisation was maintained stable; no patients showed any impairment of renal function nor any UUT dilatation or new vesicoureteral reflux. Three more patients continued to take anticholinergics per os (oxybutynin 5 mg twice a day). Six yr after the first treatment, 15 patients (88.2%) were continent and used pads or external collecting devices limited to UTI episodes. Two female patients (ASIA B classification, thoracic and lumbar spinal cord lesion, respectively) achieved a reduction of their urinary incontinence and continued to take anticholinergics per os. They reported some UTIs that could have induced and maintained DO and urinary leakages. After each single-injection treatment, none of these patients reported any local (infection, haemorrhage) or systemic (dysphagia, general asthenia, eyelid ptosis, diplopia) side effects which would suggest a systemic diffusion of the neurotoxin.

3.6. Assessment of quality of life

After treatment, the mean QoL index increased from $22.4 \pm 18.6$ to $77.7 \pm 20.9$ at 4 mo, $85.7 \pm 16.8$ ($p < 0.001$) at 12 mo, $83.5 \pm 22.1$ ($p < 0.001$) at 24 mo, $80.6 \pm 15.4$ ($p < 0.001$) at 36 mo, and $83.9 \pm 17$ at 72 mo (Fig. 2). At each follow-up, data analysis detected a strong relationship between daily frequency of incontinence episodes and catheterisations vis-à-vis the QoL index (Spearman’s $\rho = 0.761$ and $\rho = 0.742$, $p < 0.001$, Fig. 1).

### Table 1 – Clinical and urodynamic results of botulinum toxin A intradetrusorial injections in spinal cord-injured patients: 6-yr follow-up

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 mo</th>
<th>1 yr</th>
<th>3 yr</th>
<th>6 yr</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of catheterisations per day</td>
<td>7.4 ± 2.9</td>
<td>4.8 ± 1.3</td>
<td>4.2 ± 1.2</td>
<td>4.5 ± 2.1</td>
<td>4.1 ± 0.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Number of incontinence episodes per day</td>
<td>4.8 ± 2.7</td>
<td>2.4 ± 1.0</td>
<td>2.1 ± 2.1</td>
<td>1.8 ± 0.9</td>
<td>1.8 ± 0.1</td>
<td>0.01</td>
</tr>
<tr>
<td>UDC first volume</td>
<td>213 ± 40.8</td>
<td>344 ± 32.6</td>
<td>365.4 ± 49.7</td>
<td>410.8 ± 60.2</td>
<td>413.7 ± 58.9</td>
<td>0.001</td>
</tr>
<tr>
<td>UDC maximum pressure</td>
<td>97.6 ± 32.4</td>
<td>30.2 ± 17.6</td>
<td>26.8 ± 17.3</td>
<td>24.2 ± 13.8</td>
<td>23.8 ± 10.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Maximum cystometric capacity</td>
<td>243 ± 64.7</td>
<td>390 ± 51.8</td>
<td>389.4 ± 45.9</td>
<td>439.4 ± 41.6</td>
<td>420.8 ± 55.7</td>
<td>0.001</td>
</tr>
<tr>
<td>UTIs per year</td>
<td>6.7 ± 2.1</td>
<td>1.6 ± 1.3</td>
<td>3.3 ± 2.1</td>
<td>1.7 ± 2.0</td>
<td>1.8 ± 0.5</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviations: UDC, uninhibited detrusor contractions; UTI, urinary tract infection.

* Between baseline and 6-yr follow-up.
4. Discussion

In recent years, botulinum neurotoxins have increasingly been used to manage conditions characterised by DO. To date, numerous studies have been published on the results of BoNTA intravesical injections to treat NDO. Although many of the studies included a small number of patients, overwhelming evidence supports the efficacy, safety, and tolerability of the botulinum toxins, specifically serotype A, for the management of this condition. Nevertheless, few data have been reported about the long-term efficacy and tolerability of the neurotoxin after repeated injections in patients affected by NDO [9]. Reitz et al reported the urodynamic results after five injections of BoNTA in 20 consecutive patients with NDO [10]. They found a sustained, significant improvement in urinary incontinence and urodynamic parameters throughout the entire follow-up; however, the study was lacking in terms of data on the patients’ clinical improvements and validated questionnaires. Karsenty et al observed a significant and constant improvement in both clinical and urodynamic parameters in patients with NDO after a mean of 5.4 injections [9]. These parameters were analysed at baseline (before the first injection), after the first injection, and after the last repeated injection. In particular, the authors observed that repeated injections of the neurotoxin did not decrease bladder compliance. Grosse et al reported on 66 patients who received repeat BoNTA (Botox or Dysport) injections [15]. They observed a significant improvement in bladder function from baseline up to the third intravesical injection. Furthermore, they did not record any drug tolerance. A previous study determined the long-term effect of the English BoNTA for refractory NDO, looking for evidence of a possible reduction of BoNTA efficacy after repeated injections [16]. This study concluded that after repeat injections, the effect of BoNTA remained constant. In the paediatric field, Akbar et al described the use of BoNTA in myelodysplastic children and found it to be safe and effective [17]. In this study, any evidence for tachyphylaxis, antibody formation, or bladder fibrosis was excluded. The results reported by Schulte-Baukloh et al in children with neurogenic bladder were similar to those described by Akbar et al [18]. This study was designed to investigate the long-term efficacy and safety of BoNTA on clinical, urodynamic, and morphofunctional aspects of the lower and upper urinary tracts in patients with DO of neurogenic origin. In addition, we investigated any modification in QoL by using a standardised questionnaire. At the beginning of the study, both patients and physicians were aware of the lack of consistent data on the efficacy and safety of this treatment. Indeed, all the enrolled patients chose to continue the proposed treatment because the majority of them achieved a dramatic increase in urinary continence immediately after the first injection. The significant reduction in daily frequency of catheterisations was also an interesting result, as many patients with NDO try to prevent urinary leakages by increasing daily frequency of catheterisations. These ameliorations were sustained by a simultaneous improvement in all urodynamic parameters accounting for the severity of DO; that is, maximum pressure and first volume of uninhibited detrusor contractions as well as maximum bladder capacity, which significantly increased and remained unchanged during follow-up. One major concern was the disappearance of the morphofunctional alterations in the upper urinary tract, as vesicoureteral reflux was detected in 3 patients and kidney pelvis dilatation was discovered in 11 patients before treatment. These data are not surprising because the neurotoxin causes a profound and prolonged decrease in regional muscular contractility by chemical denervation [6]. Moreover, recent experimental and clinical observations seem to indicate a possible modulating activity of BoNTA at the level of the bladder afferent C fibres by inhibiting the release of several neurotransmitters involved in the neurogenic inflammation [19,20]. Thus, the summation of the two levels of activity of BoNTA would appear to account for its profound and long-lasting effect. Indeed, in the present study, the mean interval between two consecutive injections was quite long, about 11 mo, which is somewhat different from the intervals published in the studies by Karsenty et al (mean: 260 d), and Reitz et al (mean: 200 d) [9,10]. It is possible to argue that repeat BoNTA injections over a longer follow-up may have produced a long-lasting efficacy due to the summation of previous effects. Furthermore, the significant reduction in the frequency of UTIs in these patients may have prolonged their continence status. The results of this study also confirm that the neurotoxin injected over several years does not lead to decreased bladder compliance. In the short term, histopathological studies have not shown any enhanced pathological innervation, muscle cell damage, or excessive connective tissue deposition in the neuropathic bladder due to BoNTA injections [21]. In a recent prospective study, BoNTA injections did not produce significant inflammatory changes, fibrosis, or dysplastic changes in the human bladder urothelium or suburothelium after a single injection and in a limited number of repeat treatment biopsies [22].
These data seem to be confirmed by the present study, with its longer follow-up, and by other studies with repeat injections over time, which do not report anatomical modifications of the bladder wall nor a reduction in clinical and functional response of the patients over time. One major concern was the significant decrease in the incidence of UTIs observed at 1 yr and maintained during follow-up. This effect was recently described by Gamè et al, who attributed it to the improvement in urodynamic parameters due to the neurotoxin [23]. Also, in the present study, those patients who obtained urinary continence and detrusor areflexia presented with a lower incidence of UTIs over time. In addiction, recent observations would suggest a direct anti-inflammatory effect of BoNTA, which needs to be fully investigated [24]. The QoL questionnaire used in our study is domain-specific for urinary incontinence, and the results indicate a dramatic improvement in QoL just 4 mo after the first intradetrusoral injection. This significant improvement was maintained throughout all follow-up evaluations. In addition, the increased QoL index was correlated with a decrease in the frequency of leakage episodes and of catheterisations. This indicates a strong association between the clinical success of treatment and improved QoL. Similar results, limited to 24-wk follow-up, have been reported by Schurch et al in a randomised, double-blind, multicentre, placebo-controlled study [7]. The same authors had previously confirmed the validity and responsiveness of the I-QOL questionnaire in patients with neurogenic diseases [25].

We are conscious that the abovementioned results have been obtained in a small number of patients. Nevertheless, to our knowledge, a complete evaluation of patients as in the present study, that is, clinical, urodynamic, and morphofunctional investigations, together with the assessment of QoL over time has never been reported before. One final point which needs to be mentioned is the total cost involved in the treatment per patient, which accounted for about 2500 euros. We would argue that the obtained results, particularly the remarkable improvement in QoL, can justify these costs.

5. Conclusions

Repeat intradetrusoral injections of BoNTA can effectively treat drug-resistant NDO secondary to traumatic SCI over a long-term follow-up without inducing any systemic side effects and allows patients to avoid anticholinergic drug use. Thus, in patients who are unresponsive to conventional treatment and do not want invasive reconstructive surgery, or who are unfit for major surgery, BoNTA intravesical treatment represents a valuable alternative to control NDO and urinary incontinence and to preserve the function of the UUT.

Author contributions: Antonella Giannantoni had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Giannantoni.
Acquisition of data: Giannantoni.
Analysis and interpretation of data: Del Zingaro.
Drafting of the manuscript: Mearini.
Critical revision of the manuscript for important intellectual content: Porena.
Statistical analysis: Del Zingaro.
Obtaining funding: None.
Administrative, technical, or material support: University of Perugia.
Supervision: Porena.
Other (specify): None.

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References


**Editorial Comment on: Six-Year Follow-up of Botulinum Toxin A Intradetrusor Injections in Patients with Refractory Neurogenic Detrusor Overactivity: Clinical and Urodymanic Results**

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To date, nearly 10 years after the first publication on intradetrusor injection of botulinum toxin [1], it can be said that this technique revolutionized the treatment of overactive bladder in both neurogenic and non-neurogenic patients. A single injection is effective for 6, 9, or even 12 mo, and numerous studies proved this impressively; however, only a very few papers addressed the results of repeat treatment cycles of intradetrusor botulinum toxin injections to cure urinary incontinence due to detrusor overactivity (DO) [2,3].

Indeed, good data provided on repeated injections are rare because treatment cycles of up to 12 mo require continuous and persistent work of the study team over several years. There are some multicentre randomized controlled studies running that aim to prospectively evaluate the effects
of at least two repeated injections in neurogenic DO (NDO; phase 3 study) and in DO (phase 2 study). Most of the studies published so far report on urodynamic findings or on objective clinical data like incontinence episodes.

As we treat patients and not urodynamic conditions, the patient’s quality of life also needs to be considered and studied [4]; however, data on changes in quality of life after repeated intradetrusor injections of botulinum toxin are still missing in the literature. This study from Gian­nantoni et al [5] is very welcome, as it expands the knowledge of the repeat use of botulinum toxin in neurogenic bladder from the patient’s perspective.

References


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Editorial Comment on: Six-Year Follow-up of Botulinum Toxin A Intradertrusorial Injections in Patients with Refractory Neurogenic Detrusor Overactivity: Clinical and Urodynamic Results

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This is the first systematic report of the effect of repeated injections of detrusor botulinum toxin in an albeit small but single group of patients with only spinal cord injury, followed over a period of 6 yr [1]. The paper reports a sustained symptomatic improvement over that period and even amelioration of upper-tract function.

After the initial euphoria of the discovery of improved bladder function following botulinum toxin injection, pessimists doubted that, when repeated, it would be as effective as after the first time. In my opinion, however, the experience of the neurologists who have been using repeated injections (at much shorter intervals) over the last 20 yr was always grounds for optimism. This paper confirms there does not appear to be tachyphylaxis or diminution in the effectiveness of the treatment and that subsequent injections are as effective as the first.

Surgical proponents of clam cystoplasty have perhaps been some of the most vociferous (in the United Kingdom, at least) in arguing the continuing need for that surgery and for young people following a spinal cord injury to undergo a single, definitive operation; however, the patient group reported in this paper included those “unwilling or unfit for invasive surgery.” One wonders how many spinal cord–injured patients of the future, when given the option of an annually repeated, highly effective day case intervention with minimal morbidity, will opt for the much more invasive surgical procedure.

Reference


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