Surgical management of functional bladder outlet obstruction in adults with neurogenic bladder dysfunction

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ABSTRACT

Background

The most common type of functional bladder outlet obstruction in patients with neurogenic bladder is detrusor-sphincter dyssynergia (DSD). The lack of co-ordination between the bladder and the external urethral sphincter muscle (EUS) in DSD can result in poor bladder emptying and high bladder pressures, which may eventually lead to progressive renal damage.

Objectives

To assess the effectiveness of different surgical therapies for the treatment of functional bladder outlet obstruction (i.e. DSD) in adults with neurogenic bladder dysfunction.

Search methods

We searched the Cochrane Incontinence Group Specialised Register, which contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE In-Process, and hand searching of journals and conference proceedings (searched 20 February 2014), and the reference lists of relevant articles.

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs comparing a surgical treatment of DSD in adults suffering from neurogenic bladder dysfunction, with no treatment, placebo, non-surgical treatment, or other surgical treatment, alone or in combination.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data.

Main results

We included five trials (total of 199 participants, average age of 40 years). The neurological diseases causing DSD were traumatic spinal cord injury (SCI), multiple sclerosis (MS), or congenital malformations.

One trial compared placement of sphincteric stent prosthesis with sphincterotomy. For urodynamic measurements, results for postvoid residual urine volume (PVR) and cystometric bladder capacity were inconclusive and consistent with benefit of either sphincteric stent prosthesis or sphincterotomy at three, six, 12, and 24 months. Results for maximum detrusor pressure ($P_{det.max}$) were also inconclusive at three, six, and 12 months; however, after two years, the $P_{det.max}$ after sphincterotomy was lower than after stent placement (mean difference (MD) -30 cmH$_2$O, 95% confidence interval (CI) 8.99 to 51.01).

Four trials considered botulinum A toxin (BTX-A) injection in the EUS, either alone or in combination with other treatments. The comparators included oral baclofen, oral alpha blocker, lidocaine, and placebo. The BTX-A trials all differed in protocols, and therefore we did not undertake meta-analysis. A single 100 units transperineal BTX-A injection (Botox®) in patients with MS resulted in higher voided urine volumes (MD 69 mL, 95% CI 11.87 to 126.13), lower pre-micturition detrusor pressure (MD -10 cmH$_2$O, 95% CI -17.62 to -2.38), and lower $P_{det.max}$ (MD -14 cmH$_2$O, 95% CI -25.32 to -2.68) after 30 days, compared to placebo injection. Results for PVR using catheterisation, basal detrusor pressure, maximal bladder capacity, maximum urinary flow, bladder compliance at functional bladder capacity, maximal urethral pressure, and closure urethral pressure at 30 days were inconclusive and consistent with benefit of either BTX-A injection or placebo injections. In participants with SCI, treatment with 200 units of Chinese manufactured BTX-A injected at eight different sites resulted in better bladder compliance (MD 7.5 mL/cmH$_2$O, 95% CI -10.74 to -4.26) than participants who received the same injections with the addition of oral baclofen. Results for maximum uroflow rate, maximal cystometric capacity, and volume per voiding were inconclusive and consistent with benefit of either BTX-A injection or BTX-A injection with the addition of oral baclofen. However, the poor quality of reporting in this trial caused us to question the relevance of bladder compliance as an adequate outcome measure.

In participants with DSD due to traumatic SCI, MS, or congenital malformation, the results for PVRs after one day were inconclusive and consistent with benefit of either a single 100 units transperineal BTX-A (Botox®) injection or lidocaine injection. However, after seven and 30 days of BTX-A injection, PVRs were lower (MD -163 and -158 mL, 95% CI -308.65 to -17.35 and 95% CI -277.57 to -39.03, respectively) compared to participants who received lidocaine injections. Results at one month for $P_{det.max}$ on voiding, EUS activity in electromyography, and maximal urethral pressure were inconclusive and consistent with benefit of either BTX-A or lidocaine injections.

Finally, one small trial consisting of five men with SCI compared weekly BTX-A injections with normal saline as placebo. The placebo had no effect on DSD in the two participants allocated to the placebo treatment. Their urodynamic parameters were unchanged from baseline values until subsequent injections with BTX-A once a week for three weeks. These subsequent injections resulted in similar responses to those of the three participants who were allocated to the BTX-A treatment. Unfortunately, the report presented no data on placebo treatment.

Only the trial that compared sphincterotomy with stent placement reported outcome measures renal function and urologic complications related to DSD. Results for renal function at 12 and 24 months, and urologic complications related to DSD at three, six, 12, and 24 months were inconclusive and consistent with benefit of either sphincteric stent prosthesis or sphincterotomy.

Adverse effects reported were haematuria due to the cystoscopic injection and muscle weakness, of which the latter may be related to the BTX-A dose used.

All trials had some methodological shortcomings, so insufficient information was available to permit judgment of risk of bias. At least half of the trials had an unclear risk of selection bias and reporting bias. One trial had a high risk of attrition bias, and another trial had a high risk of reporting bias.

Authors' conclusions

Results from small studies with a high risk of bias have identified evidence of limited quality that intraurethral BTX-A injections improve some urodynamic measures after 30 days in the treatment of functional bladder outlet obstruction in adults with neurogenic bladder dysfunction. The necessity of reinjection of BTX-A is a significant drawback; a sphincterotomy might therefore be a more effective treatment option for lowering bladder pressure in the long-term.

However, because of the limited availability of eligible trials, this review was unable to provide robust evidence in favour of any of the surgical treatment options. More RCTs are needed, measuring improvement on quality of life and on other types of surgical treatment options for DSD since these are lacking. Future RCTs assessing the effectiveness of BTX-A injections also need to address the uncertainty about the optimal dose and mode of injection for this specific type of urological condition.

BACKGROUND

Description of the condition

The central nervous system controls urination. Normal urination requires a synergic action between the detrusor muscle (smooth muscle) and the external urethral sphincter (striated muscle). To expel urine from the bladder, the external urethral sphincter relaxes, which is followed by a detrusor contraction. The pontine micturition centre controls this synergy between the detrusor muscle and the external urethral sphincter.[1] Disruption of the pathways between the pontine micturition centre and the caudal part of the spinal cord often results in detrusor-sphincter dyssynergia (DSD). In this condition, a detrusor contraction occurs concurrently with an inappropriate contraction of the urethral striated muscle, the periurethral striated muscle, or both, thus, blocking the bladder outlet.[2]

The most common form of bladder outlet obstruction (BOO) in people with neurogenic bladder is DSD. Detrusor-sphincter dyssynergia typically occurs in people with traumatic supra-sacral spinal lesions (spinal cord injury). Other common causes of DSD are multiple sclerosis (MS), acute transverse myelitis, and myelomeningocele.[3-7] Detrusor-sphincter dyssynergia can result in poor bladder emptying and high bladder pressures, which in turn can cause recurrent urinary tract infections, high intravesical pressures, vesico-ureteral reflux, and hydronephrosis. If untreated, progressive renal damage may occur.[8]

Several authors have attempted to classify DSD. For instance, *Blaivas et al.*[9] defined three types of DSD depending on electromyography (EMG) findings. Type three was the predominant type, characterised by a sustained sphincter contraction that coincided with the detrusor contraction. Another classification was proposed by *Yalla et al.*[10] who described three DSD types based on clinical and urodynamic observations. There is a significant overlap between these two classification schemes, and their clinical relevance has been questioned. A simpler way of describing the results of EMG trials is to describe the frequency of external urethral sphincter contraction during detrusor contraction as either intermittent or continuous.[8]

The symptoms associated with DSD represent a functional disability that may result in considerable impairment of a person's quality of life (QoL). Neurogenic bladder problems were associated with lower QoL scores in people with traumatic spinal cord injury.[11] Therefore, QoL is a very important consideration in the management of people with neurogenic bladder dysfunction. Moreover, a relationship between bladder management methods and QoL in people with spinal cord injury was found: Those who were able to void normally had the best QoL in both physical and mental component scores.[12]

Management of DSD is aimed at reducing intravesical pressure and promoting bladder emptying. First-line conservative treatment includes an optimised combination of antimuscarinic agents (anticholinergic drugs) and clean intermittent self-catheterisation. The effect on the bladder pressure should be strictly monitored urodynamically after initiation of antimuscarinic treatment.[13] However, more invasive treatment is necessary in people in whom bladder pressure is pathologically elevated with antimuscarinics, who cannot tolerate antimuscarinic agents, or who are unable to perform clean intermittent self-catheterisation (e.g. people with quadriplegia).

The optimal surgical management of BOO secondary to DSD remains unknown and is the focus of this review. Other causes of BOO, such as benign prostatic enlargement and urethral stricture, are out with the scope of the review.[14-16] Furthermore, we have not addressed the treatment of high bladder pressure in patients with only detrusor overactivity and not DSD. Upper urinary tract diversion is usually reserved as a last resort[17] and was not considered as a part of this review, but we did include suprapubic catheterisation.

Description of the intervention

1. Sphincterotomy

External sphincterotomy is a transurethral treatment of the sphincteric hypertonicity, which is present in DSD by disrupting, either partially or totally, the continuity of the external urethral sphincter. It is performed either with the use of electrocautery[18] or a contact laser.[19,20] The goal is to reduce the intravesical voiding pressure and to lower detrusor leak-point pressure. Sphincterotomy should prevent urologic complications, such as urosepsis and deterioration of renal function; reduce vesico-ureteral reflux; and eliminate the need for chronic indwelling catheterisation. A degree of continence may be maintained if bladder neck function can be preserved. Sphincterotomy can provide an extended period of satisfactory bladder emptying.[21] However, on-going revision may be required and a number of complications have been described, principally postoperative haemorrhage, erectile dysfunction (complete or partial loss of tumescence), urine extravasation, urethral stricture, and fistula formation.[21,22]

2. Implantable urethral stents

Urethral stents mechanically keep open the external urethral sphincter and thereby lower the detrusor leak-point pressure. The stents are either permanent or temporary.

The permanent UroLume® prosthesis (also known as Wallstent in Europe, AMS Medinvent SA, Lausanne, Switzerland) was initially developed as a self-expanding prosthesis used to maintain the patency of stenotic arteries after balloon angioplasty. Milroy et al.[23] first described the use of this stent in the treatment of recurrent urethral strictures. The stent is made of a stainless steel super alloy, which is corrosion-resistant

and non-magnetic. This alloy is woven into a braided, pliable, self-expanding cylindrical mesh. After insertion, the mesh exerts a strong, continuous, outward force against the wall of the urethra (lumen) and maintains a patent diameter of up to 42 F. The mesh becomes epithelialized by urothelium and is considered to be permanent. *Shaw et al.*[24] were the first to use this urethral stent as a successful alternative to external sphincterotomy in the treatment of DSD. Since then, studies have confirmed its long-term clinical benefit and safety, by showing improvements in maximum detrusor pressure and postvoid residual urine volume, alongside unchanged bladder capacity and reduced hydronephrosis.[25,26]

Soni *et al.*[27] first described the use of the Memokath® temporary stent (Engineers & Doctors A/S, Hornbaek, Denmark) to treat DSD. The stent is composed of a nickel-titanium alloy with 'shape memory'. The stent will return to a preformed shape after deformation when heated to 45 ºC or above. When cooled (10 ºC or below), the stent becomes soft and easy to remove. Because of its closed, tight, spiral structure, urothelial ingrowth is prevented, and this allows the stent to be easily removed if required. It has shown short-term success in patients with DSD in terms of decreasing the detrusor pressure and postvoid residual urine volume.[28]

3. Urethral balloon dilatation

Balloon dilatation of the external urethral sphincter was first introduced as a treatment for benign prostatic hyperplasia. *Chancellor et al.*[29] reported on their technique and early experience with balloon dilatation of the external urethral sphincter in seven spinal cord-injured men with DSD. Balloon dilatation of the external urethral sphincter uses placement of the Optilume Prostate Dilator® (American Medical Systems Inc, Minnesota, USA) under fluoroscopic guidance. The balloon is inflated to a diameter of 90 F under a pressure of three to four atmospheres for 10 minutes. Balloon dilatation was effective in significantly reducing postvoid residual urine volume.[30] Balloon dilatation and UroLume® stenting both proved to be as effective as external sphincterotomy in the treatment of DSD.[31] In contrast, *McFarlane et al.*[32] reported a lower success rate than both sphincterotomy and sphincter stenting and did not recommend balloon dilatation for the treatment of DSD.

4. Intraurethral botulinum A toxin (BTX-A) injection

Botulinum A toxin (BTX-A) is a protein neurotoxin produced by a bacterium of the *Clostridium* genus. It is an inhibitor of acetylcholine release at the neuromuscular junction. BTX-A is injected directly into the target muscle, and the clinical effect is to induce relaxation of the injected striated muscle. The clinical effects begin within two to three days and are reversible as terminal nerve resprouting occurs within three to six months. BTX-A has previously been used successfully in the management of muscular

disorders, including strabismus, focal dystonia, skeletal muscle spasms, and spasticity. Application of BTX-A in the lower urinary tract has produced promising results in treating lower urinary tract dysfunction.[33] Its use for the treatment of DSD was first reported by *Dykstra & Sidi*[34] BTX-A was injected once a week for three weeks into the external urethral sphincter of 11 spinal cord-injured men with DSD.

Currently, two preparations of BTX-A are commercially available: onabotulinumtoxinA or Botox® (Allergan Inc., Irvine, California, USA) and abobotulinumtoxinA or Dysport® (Ipsen Ltd, Slough, UK). BTX-A treatment has the advantage of being minimally invasive, can be injected on an outpatient basis, and has a good safety profile. However, it provides only temporary relief of symptoms, because the BTX-A-treated nerve terminals do not degenerate and axonal resprouting and formation of new neuromuscular junctions occurs.[35] As a result of this regeneration, repeat BTX-A sphincter injections are necessary. The duration of effect of a single treatment is two to three months, whereas repeat treatments appear to have cumulative efficacy lasting nine to 13 months.[36]

5. Intrathecal baclofen

Baclofen is a well-recognised option for the treatment of skeletal muscle spasticity.[37] It acts by activating gamma-aminobutyric acid-B receptors, by normalising and decreasing interneuron and motor neuron activity in the spinal cord. Although baclofen has been used for over two decades as an oral preparation, its difficulty in passing through the blood-brain barrier limited its usefulness for the treatment of DSD. Intrathecal baclofen delivery systems were developed to circumvent this problem: Patients receive a continuous intradural administration of baclofen via an implanted pump. Thus, it can be delivered directly into the spinal fluid to allow higher concentrations in the spinal cord. The rationale behind this modality is to minimise the systemic baclofen side-effects from higher oral doses (weakness, dizziness, drowsiness, rash, and hallucinations), while enhancing its therapeutic benefit. After intrathecal application of baclofen, urethral pressure shows urethral relaxation during isovolumetric bladder contractions in spinal cord-injured rats.[38] It has been proposed that baclofen activates inhibitory interneurons that, in turn, inhibit directly external urethral sphincter motoneurons in the nucleus of Onuf.[39] *Steers et al.*[40] showed a 40% decrease of DSD in people with severe spasticity due to spinal cord pathology after intrathecal baclofen.

6. Pudendal nerve block

The pudendal nerve contains the motor axons to the external urethral sphincter as well as other nerve fibres innervating the external anal sphincter and other pelvic floor muscles. By blocking the pudendal nerve, action potential propagation in the nerve is blocked and thus reduces or blocks unwanted external urethral sphincter activity.

Pudendal nerve block using phenol solution has been widely used as a neurolytic agent for the relief of spasticity. Pudendal neurolysis can be done in a relatively non-invasive way and can be easily performed on an outpatient basis. Treatment of DSD with this technique was first described in 1979.[41] Other clinical studies showed that pudendal nerve block performed by phenol solution was safe, easy to perform, and effective as a treatment for DSD in selected people with spinal cord injury.[42,43] However, a number of authors have reported that the duration of the effect of the nerve block was unpredictable.

A relatively recent approach involves the use of high-frequency stimulation to block the pudendal nerve. Several animal studies have demonstrated high-frequency stimulation as a potential method for suppressing DSD and improving effective voiding.[44-47]

7. Suprapubic catheterisation

In a small subset of people with DSD, insertion of an indwelling transurethral or suprapubic catheter is necessary. Insertion of a suprapubic catheter is a simple form of urinary diversion, which involves inserting a catheter directly into the bladder through the abdominal wall. The handling and long-term risks of a suprapubic catheter are often the subject of debate.[48]

Compared to clean intermittent self-catheterisation, the use of an indwelling catheter (either suprapubic or transurethral) significantly increases the risk of bladder and renal stones, complicated urinary tract infections, urethral fistulas, renal failure, strictures, and erosions.[48,49] A controversial issue is the association of long-term use of an indwelling catheter and squamous cell carcinoma of the bladder.[50] There are several advantages of a suprapubic catheter compared to a transurethral catheter: reduced risk of urethral trauma, destruction, or both; less risk of prostatitis or epididymitis; and less urethral pain. However, it requires a minimal 'surgical' intervention to insert the suprapubic catheter, with potential to injure structures adjacent to the bladder, especially the bowel. The preferred insertion technique appears to be quite variable, and there is no evidence of any one best way to insert the suprapubic catheter.[51]

An epidemiological follow-up study found that suprapubic catheters were more frequently used at follow up compared to an initially placed transurethral catheter.[52] This could be due to a shift from the indwelling transurethral catheter towards the suprapubic catheter because of complications related to these, but it is also more convenient as it permits sexual function.[53]

Why it is important to do this review

The wide variety of surgical treatments available for curing or improving BOO in adults with neurogenic bladder dysfunction indicates a lack of consensus for what is optimal treatment. Provided that sufficient numbers of trials of adequate quality have been

conducted, the most reliable evidence is likely to come from the consideration of randomised controlled trials, and this will be the basis for this review. The aim is to help identify optimal practice and to highlight where there is need for further research. Other relevant Cochrane reviews that may be of interest to the reader include the following:

· Intermittent catheterisation for long-term bladder management;[54]
· Which anticholinergic drug for overactive bladder symptoms in adults;[55]
· Catheter policies for management of long term voiding problems in adults with neurogenic bladder disorders;[56]
· Urinary diversion and bladder reconstruction/replacement using intestinal segments for intractable incontinence or following cystectomy;[17] and
· Washout policies in long-term indwelling urinary catheterisation in adults.[57]

OBJECTIVES

To assess the effectiveness of different surgical therapies for the treatment of functional bladder outlet obstruction (i.e. DSD) in adults with neurogenic bladder dysfunction. We considered the following comparisons:

1. Sphincterotomy
   o Sphincterotomy versus no intervention or placebo
   o Sphincterotomy versus non-surgical therapy
   o Sphincterotomy versus other surgical therapy
2. Implantable urethral stents
   o Implantable urethral stents versus no intervention or placebo
   o Implantable urethral stents versus non-surgical therapy
   o Implantable urethral stents versus other surgical therapy
3. Urethral balloon dilatation
   o Urethral balloon dilatation versus no intervention or placebo
   o Urethral balloon dilatation versus non-surgical therapy
   o Urethral balloon dilatation versus other surgical therapy
4. Intraurethral botulinum A toxin (BTX-A) injection
   o Intraurethral BTX-A injection versus no intervention or placebo
   o Intraurethral BTX-A injection versus non-surgical therapy
   o Intraurethral BTX-A injection versus other surgical therapy
5. Intrathecal baclofen
   o Intrathecal baclofen versus no intervention or placebo
   o Intrathecal baclofen versus non-surgical therapy
   o Intrathecal baclofen versus other surgical therapy

6. Pudendal nerve block
    o   Pudendal nerve block versus no intervention or placebo
    o   Pudendal nerve block versus non-surgical therapy
    o   Pudendal nerve block versus other surgical therapy
7. Suprapubic catheterisation
    o   Suprapubic catheterisation versus no intervention or placebo
    o   Suprapubic catheterisation versus non-surgical therapy
    o   Suprapubic catheterisation versus other surgical therapy

METHODS

Criteria for considering studies for this review

Types of studies
Randomised controlled trials (RCT) or quasi-randomised controlled clinical trials in which at least one arm is a surgical method of managing functional BOO in adults suffering from neurogenic bladder dysfunction, including cross-over trials.

Types of participants
All adult men and women with functional BOO due to neurogenic bladder dysfunction, diagnosed either by symptom and history-taking or urodynamic studies. We accepted the trialists' definition of an adult and their diagnosis and classification of DSD.

Types of interventions
At least one arm of the trial included a surgical treatment for functional BOO due to neurogenic bladder dysfunction:
·   sphincterotomy;
·   implantable urethral stents;
·   urethral balloon dilatation;
·   intraurethral BTX-A injection;
·   intrathecal baclofen;
·   pudendal nerve block; or
·   suprapubic catheterisation.
These interventions were compared with no treatment or placebo; non-surgical treatment; or with each other, alone, or in combination.

The review did not address the following:
·   urinary retention as a result of failure of the detrusor muscle to contract (areflexia);

- non-functional causes of BOO (e.g. benign prostatic enlargement and urethral stricture);
- treatment of high bladder pressure in people who do not also have DSD, such as using intravesical botulinum A toxin (BTX-A) with clean intermittent self-catheterisation and bladder augmentation; and
- urinary diversion, which is usually reserved as a last resort and was not considered as a part of this review.

Types of outcome measures
Primary outcomes
1. Clinicians' observations
- Urodynamic measurements/studies (e.g. detrusor leak-point pressure, bladder pressure, postvoid residual urine volume, bladder capacity)
- Renal function
- Adverse effects: number of urologic complications related to DSD (e.g. urinary tract infections)

Secondary outcomes
1. Quantification of symptoms
- Frequency of incontinent episodes from self-report or voiding diary
- Frequency of urinary retention rates
- Clean intermittent self-catheterisation rates
- Use of rescue antibiotics

2. Quality of life
- Acceptability of procedure or satisfaction with outcome (e.g. Patient Global Impression of Improvement (PGI-I)[58])
- Condition-specific health measures (e.g. Qualiveen[59])
- Other condition-specific quality of life questionnaires related to urinary incontinence or voiding symptoms (e.g. Bristol Female Lower Urinary Tract Symptoms (BFLUTS) Questionnaire, Incontinence Impact Questionnaire (IIQ), King's Health Questionnaire (KHQ), Overactive Bladder Questionnaire (OAB-q), International Consultation on Incontinence Modular Questionnaire (ICIQ modules)) or sexual matters (e.g. International index of Erectile Function Questionnaire (IIEF), Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ), ICIQ modules)
- Generic quality of life or health status measures (e.g. Short-Form 36[60], EuroQol[61])
- Psychological outcome measures (e.g. Hospital Anxiety Depression Scale (HADS)[62])

3. Measures of associated symptoms (objective or subjective)
- Bladder symptoms (including symptomatic and occult incontinence)
- Sexual symptoms

4. Surgical outcome measures
- Operating time
- Blood loss
- Need for transfusion
- Additional surgery or other treatment for DSD
- Length of inpatient hospital stay
- Use of antibiotic prophylaxis

5. Adverse effects
- Infection related to the procedure
- Number with perioperative surgical complications (e.g. infection, haemorrhage, etc.)
- Number of urethral strictures due to the procedure with the need of further treatment
- Number with other complications inherent to the procedure

6. Socioeconomic measures
For example, catheter days, inpatient days, days to return to activities of daily living.
- Use of resources
- Cost of interventions or resources
- Resource implications of effects of treatment
- Formal economic evaluations

7. Other outcomes
- Non-prespecified outcomes judged important when performing the review

Search methods for identification of studies

We did not impose any language or other restrictions on the searches, and we identified the trials from the sources listed below.

Electronic searches

Relevant trials were identified from the Cochrane Incontinence Group Specialised Register (date of last search: 20 February 2014). The Register contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL) (1999 onwards), MEDLINE (1966 onwards), MEDLINE In-Process (2001 onwards), and hand searching

of journals and conference proceedings. The methods used to derive this, including the search strategy, are described under the Group's module in *The Cochrane Library*[63]. The terms used to search the Incontinence Group Specialised Register are given below:

((({DESIGN.CCT*} OR {DESIGN.RCT*}) AND {TOPIC.URINE.NEUROGENIC*} AND {INTVENT.SURG*})

All searches were of the keyword field of Reference Manager (Reference Manager Professional Ed. version 2012, New York; Thomson Reuters).

Searching other resources
We searched the reference lists of all relevant reviews and trial reports to identify further relevant trials.

Data collection and analysis
We processed included trial data as described in the *Cochrane Handbook for Systematic Reviews of Interventions.*[64] We resolved any differences of opinion related to trial inclusion, methodological quality, or data extraction by discussion with a third party. We described comparability of trial groups in terms of potential confounding variables, such as use of antimuscarinics, age, and gender.

When appropriate, we undertook meta-analysis. For categorical outcomes, we related the numbers reporting an outcome to the numbers at risk in each group to derive a relative risk (RR). For continuous variables, we used means and standard deviations to derive a mean difference (MD). We used a fixed-effect model for calculation of 95% confidence intervals (95% CI). We had planned to investigate differences between trials if significant heterogeneity was found or appeared obvious from visual inspection of the results.

Where reports included insufficient data for use in the review or where we required further information or clarification on any matters, we made attempts to contact the trial authors.

Selection of studies
Two review authors independently screened the trials identified by the literature search for eligibility by title and abstract, excluding obviously irrelevant reports. For the trials considered eligible, we obtained full-text papers. If there was any uncertainty about the eligibility of the trials based on title and abstract, the same two reviewers reviewed the full paper, resolving any disagreements by discussion and consulting the third review author when disagreement arose. We have listed trials formally consid-

ered for the review but excluded in Table 7.1 'Characteristics of excluded studies' with reasons given for their exclusion.

We used Early Review Organizing Software (EROS 2013, Buenos Aires, Argentina) to perform the selection of the trials. EROS is a web-based program for the initial phases of a systematic review. It facilitates independent revision of references and immediate resolution of discrepancies.

Data extraction and management

Two reviewers independently undertook assessment of methodological quality and data extraction using data extraction forms, based on the Incontinence Group's assessment criteria, which include quality of random allocation and concealment, description of dropouts and withdrawals, analysis by intention-to-treat, and 'blinding' during treatment and at outcome assessment. Extracted data and quality assessment were cross-checked and any disagreements discussed and, if necessary, resolved by a third reviewer.

RESULTS

Description of studies

The characteristics of included studies are described in Table "Characteristics of included studies" which is available online http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004927.pub4/full at *The Cochrane Library*.[65]

The characteristics of excluded studies are described in Table 7.1.

Results of the search

The search strategy (first run in October 2011) identified 43 records. An updated search run in December 2012 retrieved five additional records, and another updated search run in February 2014 retrieved four additional records. This resulted in a total of 52 records (Figure 7.1). After examination of the titles and abstracts of these references, we removed one duplicate and excluded 33; thus, we accessed 18 trials for eligibility. We obtained full-text copies of these trials, which we subjected to further assessment.
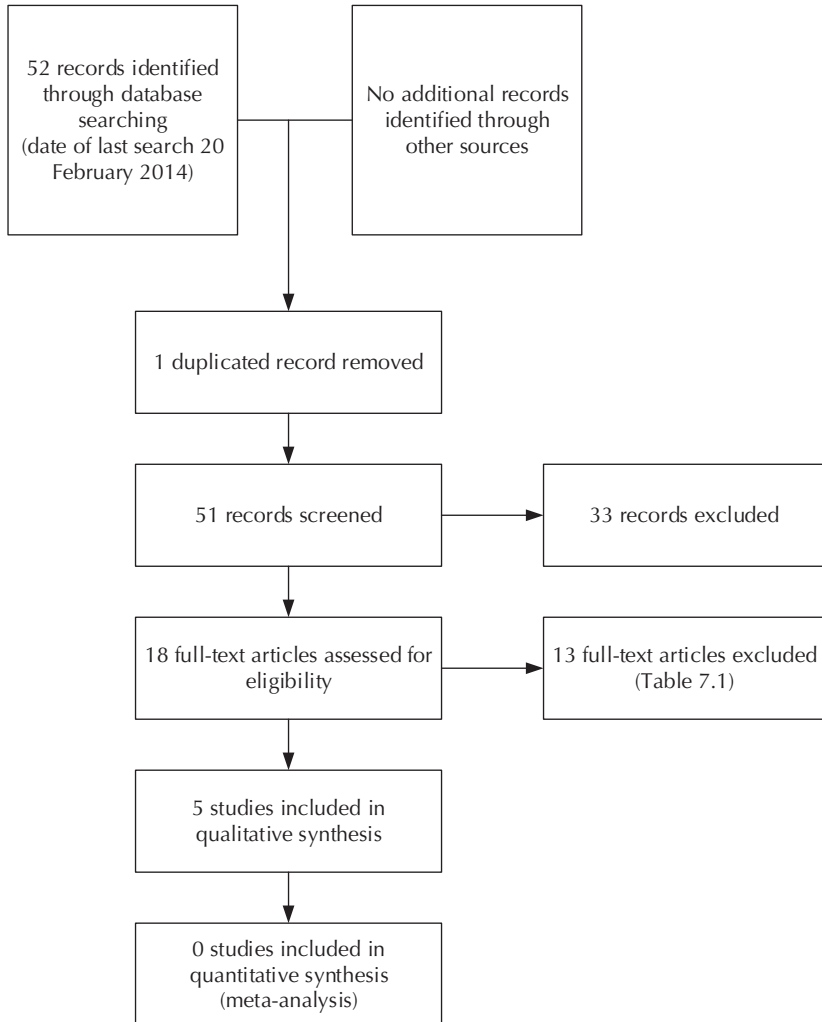
Included studies

The further assessment of the 18 full-text reports identified five trials evaluating surgical management of functional BOO in adults with neurogenic bladder dysfunction.[66-70] One trial was published in Chinese[67] and translated by a native Chinese urologist-in-training with Dutch as a second language. We have provided further details in the 'Characteristics of included studies' which is available online.[65]

Table 7.1   Characteristics of excluded studies

Study	Reasons for exclusion
Chancellor MB, Rivas DA, Abdill CK, *et al*[31]. *Arch Phys Med Rehabil. 1994 Mar;75(3):297-305*	Not a RCT. Quote: "Each patient selected his own form of treatment"
Dunn MD, Portis AJ, Kahn SA Yan Y, *et al*.[81] *J Endourol. 2000 Mar;14(2):195-202.*	Not urethral stents, but ureteral pigtail stents. Not on functional BOO in adults with neurogenic bladder dysfunction
Herschorn S, Gajewski J, Ethans K, et al.[72] *Neurourology and Urodynamics 2009;28(7):608–9*	Not intraurethral BTX-A injection but intradetrusor injection for the treatment of neurogenic urinary incontinence
Herschorn S, Gajewski J, Ethans K, *et al*.[71] *Neurourology and Urodynamics 2009;28(2):138–9.*	Not intraurethral BTX-A injection but intradetrusor injection for the treatment of neurogenic urinary incontinence
Loubser PG, Narayan RK, Sandin KJ, *et al*.[77] *Paraplegia 1991;29(1):48–64.*	7 participants underwent urodynamics in this trial, 1 participant continued to have detrusor hyperreflexia with DSD, but this 1 participant cannot be randomised
Mehta S, Hill D, Foley N, *et al*[78] *Arch Phys Med Rehabil. 2012 Apr;93(4):597-603.*	Non-randomised: review paper for the treatment of incomplete voiding after SCI. The authors reviewed 2 studies on DSD,[68,69] which we already included
Meythaler JM, Guin-Renfroe S, Brunner RC, *et al*[80] *Stroke 2001;32(9):2099–109.*	Treatment of spasticity of extremities with intrathecal baclofen; no evaluation of lower urinary tract function
Naumann M, So Y, Argoff CE, *et al*.[79] *Neurology 2008;70(19):1707–14.*	Non-randomised; review paper on BTX-A for the treatment of autonomic disorders and pain. They reviewed 3 studies on DSD,[68-70] which we already included
Schurch B, de Seze M, Denys P, *et al*.[74] *Neurourology and Urodynamics. 2004; Vol. 23, issue 5/6:609–10.*	Not intraurethral BTX-A injections but intradetrusor injections for the treatment of neurogenic urinary incontinence
Schurch B, de Sèze M, Denys P, *et al*.[73] *Neurourology and Urodynamics 2005;24(5/6):545–6.*	Not intraurethral BTX-A injections but intradetrusor injections for the treatment of neurogenic urinary incontinence
Schurch B, Denys P, Kozma CM, *et al*.[75] *European Urology 2007;52(3):850–8.*	Not intraurethral BTX-A injections but intradetrusor injections for the treatment of neurogenic urinary incontinence
Steers WD, Meythaler JM, Haworth C, *et al*.[40] *Journal of Urology 1992;148(6):1849–55.*	Not a RCT
Thavaseelan JT, Burns-Cox N, Jordan K, *et al*.[76] *BJU International 2005;95 (Suppl 1):4–5.*	RCT. However, no intra-urethral BTX-A injections but intra-detrusor injections for the treatment of neurogenic urinary incontinence

The characteristics of included studies are described in Table "Characteristics of included studies" which is available online at http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004927.pub4/ full at *The Cochrane Library*.[65]

Figure 7.1 PRISMA study flow diagram

The surgical treatments studied in the included trials were as follows:
- sphincterotomy[66] ;
- placement of sphincteric stent prosthesis[66] ;
- BTX-A injection into the external urethral sphincter[67-70] ; and
- lidocaine injection in the external urethral sphincter.[68]

Two trials included placebo as a comparator,[69,70] and two added oral medication to the surgical intervention.[67,70]

Erasmus University Rotterdam

Design

All included trials were RCTs with two arms, of which two trials[66,70] were parallel-arm trials of two interventions. In *Cui et al.*[67] all included participants received the same surgical intervention, and on the second day, only a randomised subgroup received a pharmaceutical treatment. In *de Sèze et al.*[68] participants who reported a negative result at the end of the trial received treatment from the other arm, and in *Dykstra & Sidi*[69] the participants who were allocated to the placebo arm received the actual intervention after completion of the study.

Setting

Care was provided in a hospital setting in four trials: in a urology department in China,[67] at the physical medicine unit of two different centres in France,[68] in a university clinic on an outpatient basis in the United States,[69] and in an outpatient setting of five university hospitals and one rehabilitation clinic in France.[70] One trial provided care at three spinal cord injury centres in the United States.[66]

Participants

The trials enrolled a total of 199 participants. The number of participants in individual trials ranged from five to 86.
· One trial only enrolled participants with DSD due to MS.[70]
· Three trials[66,67,69] only enrolled participants with DSD due to traumatic spinal cord injury.
· One trial[68] included participants with different reasons for cord lesion (traumatic, MS, and congenital malformation).

<u>Duration of neurological disease</u>

The average duration of onset of underlying neurological disease was 10 years[66-70] and ranged from 2.5[67] to 16 years.[70] The presence of DSD was urodynamically confirmed in all trials,[66-70] of which two added needle-electrode EMG to diagnose DSD,[68,69] and *de Sèze et al.*[68] added also voiding cystourethrography to confirm DSD.

<u>Age and gender</u>

The average age of the study participants overall was 40 years, ranging from 32[69] to 50[70] years. Two trials[66,69] enrolled only men. In one trial[67], we found a discrepancy between the reported gender in the abstract and in the main text: The abstract reported 31 men and seven women, while the main text reported 28 men and seven women. The remaining trials included either more men (92%)[68] or more women (67%).[70]

Other concurrent treatment

Two trials[68,70] made statements about the use of other treatments or medication during the trial. Participants from *de Sèze et al.*[68] discontinued use of forms of treatment that interfered with bladder function during the trial, except in two participants for whom oral antispastic medication (baclofen) was maintained at a constant dose throughout the study. Participants from *Gallien et al.*[70] were excluded if they took any treatment that could have altered neuromuscular transmission.

Interventions

There were no trials evaluating urethral balloon dilatation, intrathecal baclofen, pudendal nerve block, or suprapubic catheterisation. The trials tested the following surgical interventions.

Sphincterotomy
· External urethral sphincterotomy versus implantable urethral stent placement[66]

Intraurethral botulinum A toxin (BTX-A) injection
· BTX-A injection into the external urethral sphincter with and without oral baclofen[67]
· BTX-A injection versus lidocaine injection into the external urethral sphincter[68]
· BTX-A injection versus placebo (saline) injection into the external urethral sphincter[69]
· BTX-A injection versus placebo (saline) injection into the external urethral sphincter with all participants also having oral alpha blockers[70]

Intraurethral botulinum A toxin (BTX-A) injection protocols

The variety in single and repeat injections and mode of BTX-A injection differed between trials:
· *De Sèze et al.*[68] and *Gallien et al.*[70] administered BTX-A injections one time with a single injection transperineally;
· *Cui et al.*[67] also administered BTX-A injections one time, but with a cystoscope transurethrally at eight different sites into the external urethral sphincter; and
· *Dykstra & Sidi*[69] administered BTX-A injections once a week for three weeks, using a cystoscope transurethrally to inject at three to four different sites into the external urethral sphincter.

Cui et al.[67] used BTX-A produced in China (Lanzhou Biotechnology). The other three trials used onabotulinumtoxinA.[68-70]

Also, the dose in units (U) of BTX-A differed between trials:

Table 7.2 Adverse effects

Included studies	Reported adverse events	Details of reported adverse events
Chancellor et al.[66]	1. device removal (stent) 2. additional insertion procedures (stent) 3. requirement of repeat sphincterotomy due to restenosis of the sphincter 4. bladder neck obstruction 5. no alterations in erectile function or ejaculation in both groups	1. Stent explantation in 6 of 31 participants (19%) due to the following: - stent migration detected at 3-month follow up (n =3); - incorrect placement of stent at insertion (n = 1); - participant's own request because he did not like using the condom catheter to collect urine (n = 1); and - pain and symptoms of dysreflexia during reflex voiding (n = 1) 2. Additional insertion procedures of stent (i.e. more than 1 insertion procedure) in 7 participants (23%): - 2 procedures (n = 6); and - 3 procedures (n = 1) 3. Repeat sphincterotomy in 2 of 26 participants (8%) 6 months postoperatively 4. Of all participants, 9% required urethrotomy because of a urethral stricture (Analysis 1.14*), and 21% were treated for bladder neck obstruction (Analysis 1.12*)
Cui et al.[67]	1. haematuria 2. muscle weakness and central nervous system symptoms in BTX-A with oral baclofen group	Toxic and adverse events were recorded between 2 to 9 months postoperatively 1. all participants in both groups had varying degrees of haematuria 2. after 1 week of oral baclofen, 3. participants reported muscle weakness and central nervous system symptoms like dizziness, malaise, and weakness
De Sèze et al.[68]	1. faecal incontinence after lidocaine injection 2. transitory exacerbation of urinary incontinence for 2 weeks after BTX-A 3. no complications involving haemorrhaging or infection 4. no systemic side-effects (e.g. nausea, vomiting, dry mouth, dysphagia, weakness in the respiratory muscles, or paresis of the extremities) in both groups	Adverse effects were evaluated at the end of the study (30 days)
Dykstra and Sidi[69]	1. mild, generalised upper extremity weakness 2. mild haematuria after cystoscopic injections 3. no urinary tract infections due to cystoscopic injections 4. no adverse effects, such as nausea, vomiting, dry mouth, diplopia, blurred vision, photophobia, dysphonia, dysarthria, dysphagia, or subjective weakness of the respiratory muscles	1. mild generalised upper extremity weakness in 3 participants, of which in 1 participant - 3 weeks after the last injection single-fiber electromyography studies revealed increased fiber density and a small increase in jitter at slow-firing rates (3 Hz) in the left deltoid 2. haematuria resolved within 24 hours

Consequences for participants	Trial author's conclusions
1. stents were removed without difficulty (despite epithelialisation) or longterm complications; prosthesis migration was easily diagnosed in all cases **2**. consequences not mentioned **3**. consequences not mentioned **4**. consequences not mentioned	No author's conclusions concerning adverse effects
1. haematuria resolved without additional treatment after 2 to 3 days in all but 1, who received haemostatic agents and required hospitalisation for observation **2**. discontinued the use of baclofen after 1 week but continued follow up	BTX-A with baclofen is relatively safe with few complications, which are easily accepted by the participants; however, the long-term toxicity is unknown
1. consequences not mentioned **2**. consequences not mentioned	BTX-A is safe because of the very scarce side-effects reported by the participants
1. caused difficulty with transfers and some activities of daily living; these gradually subsided over a 2- to 3-week period, after which the strength returned to normal **2**. consequences not mentioned	The transient weakness suffered by 3 participants was probably caused by receiving a too-large toxin dose in a 3-week period. An initial dose of 140 units of toxin was injected, followed by 2 doses of 240 units each week. To prevent weakness from the initial 3 injections, the trial authors now wait 2 weeks between injections

Table 7.2 Adverse effects (continued)

Included studies	Reported adverse events	Details of reported adverse events
Gallien et al.[70]	Serious adverse events: 1. multiple sclerosis attack 2. pyelonephritis 3. lumbar radicular pain 4. femoral fracture 5. uterine leiomyoma 6. drug-induced confusion 7. dyspnoea Non-serious adverse events: 8. urinary tract infections 9. multiple sclerosis attack 10. urinary leakages 11. faecal incontinence	12 serious adverse events in 11 different participants during follow-up: 1. 2 and 4 participants in the placebo and BTX-A group, respectively 2. 1 participant in placebo group 3. 1 participant in placebo group 4. 1 participant in placebo group 5. 1 participant in BTX-A group 6. 1 participant in BTX-A group 7. 1 participant in BTX-A group 64 non-serious adverse events were reported in 45 participants during follow-up: 8. urinary tract infections in 38 participants (placebo n = 12; 29%, and BTX-A n = 16; 36%; RR 1.24, 95% CI 0.67 to 2. 29, Analysis 2.11.1) 9. multiple sclerosis attack in 9 participants (placebo n = 3; 7%, and BTX-A n = 6; 13%; RR 1.86, 95% CI 0.50 to 6.95, Analysis 2.8*) 10. urinary leakages in 4 participants (placebo n =2; 5%, and BTX-A n = 2; 4%; RR 0.93, 95% CI 0.14 to 6.30, Analysis 2.11.2*) 11. 1 participant in BTXA group (placebo n = 0, and BTX-A n = 1; RR 2.80, 95%CI 0.12 to 66.70, Analysis 2.11.3*)

*) The details of the statistical data analyses are available online at *The Cochrane Library*.[65]
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004927.pub4/full

- 100 U[68,70] ;
- 200 U[67] ; and
- 140 U initially, and subsequent injections of 240 U.[69]

Outcomes

Primary outcomes

All trials reported urodynamics measurements, including the postvoid residual urine volume - either measured urodynamically or using catheterisation. Other reported urodynamic outcomes were as follows: detrusor pressure, bladder capacity, bladder compliance, uroflow rate, voided volume, urethral pressure profile, and EMG of external urethral sphincter activity.

The urodynamic outcomes were all measured at different time points. Three trials[67,68,70] measured primary outcomes one month after injection and one trial,[69] a week after each injection. *Chancellor et al.*[66] considered primary outcomes at three, six, 12, and 24 months postoperatively.

Consequences for participants	Trial author's conclusions
All 11 participants with a serious adverse event were declared in the context of hospitalisation	No serious adverse event could be attributable to BTX-A

Only one trial[66] reported renal function, in terms of hydronephrosis and vesico-ureteric reflux, and urologic complications related to DSD (e.g. urinary tract infection).

Secondary outcomes
Chancellor et al.[66] quantified DSD symptoms by reporting the catheterisation rates. Four trials reported quality of life,[66-68,70] using different instruments to measure satisfaction rate[67,68] and condition-specific quality of life.[66,67,70] However, no trial reported if the instruments (questionnaires) were validated measures. Only *Chancellor et al.[66]* described associated symptoms, such as alterations in erectile function or ejaculation. Four trials reported associated symptoms of the underlying neurologic disease, such as autonomic dysreflexia symptoms[66,68,69] or MS attacks.[70] All trials reported surgical outcomes, consisting of blood loss, infection related to the procedure, hospital-stay length, occurrence of urethral strictures, complications, toxic effects, adverse events, tolerance, and side-effects.[66-70] Further details on adverse effects can be found in Table 7.2.

No trial reported socioeconomic measures, and therefore we did not describe these measures in the results. Other important outcomes reported were the need for re-intervention[68] and participant-reported days of effect.[68,69]
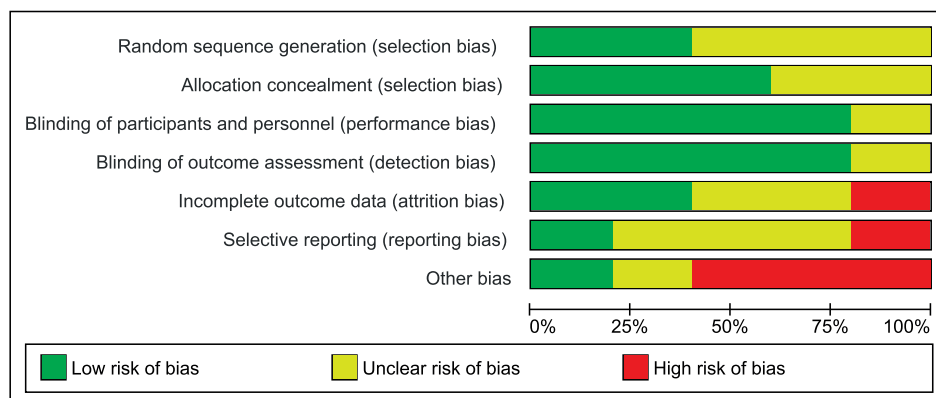
Excluded studies

We excluded 13 trials after further assessment of the 18 full-text reports.

- Six trials compared surgical interventions on detrusor overactivity but not functional BOO.[71-76]
- Five trials were not randomised.[31,40,77-79]
- *Meythaler et al.*[80] determined the effect of intervention on spasticity of extremities, but not on the urological tract.
- *Dunn et al.*[81] compared stents for the upper urinary tract (ureteric stents) instead of the lower urinary tract (urethral stents).

We provide further details in the 'Characteristics of excluded studies' tables (Table 7.1).

Risk of bias in included studies

We present specific characteristics, details of assessment, methodological quality, and risk of bias of the included trials in the 'Characteristics of included studies' tables available online[65] and in Figure 7.2 and Figure 7.3.

**Figure 7.2** Risk of bias graph
review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies

Allocation (selection bias)

Random sequence generation (selection bias)

The method used for random sequence generation was unclear in three of five trials[66-68]: All three trials simply stated the trial was randomised, but provided no further
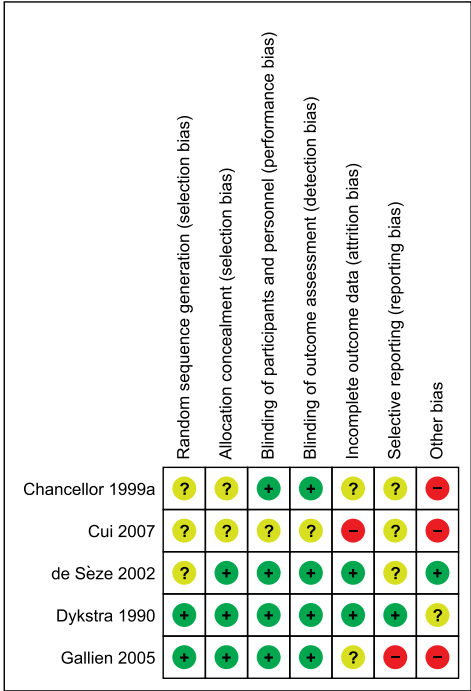
Figure 7.3   Risk of bias summary
review authors' judgements about each 'Risk of
bias' item for each included study

details about the sequence generation process. We judged two trials to be at low risk:
both *Dykstra & Sidi*[69] and *Gallien et al.*[70] used a computer random number generator.

Allocation concealment (selection bias)

We judged three of five trials[68-70] as having an adequate method of concealment of al-
location prior to assignment since they used central allocation. The remaining two[66,67]
did not provide details about allocation concealment; hence, we judged them as
'unclear' risk of bias.

Blinding (performance bias and detection bias)

We judged the performance bias due to knowledge of the allocated interventions by
participants and personnel during the study and the detection bias during outcome
assessment as 'low' risk of bias in four of five trials: Three trials[68-70] stated that they were
'double-blind' and provided a clear description of the blinding of the participants and
personnel and outcome assessment, whereas due to specific surgical approaches,
blinding in *Chancellor et al.*[66] was not possible. However, the review authors judged
that the outcomes of *Chancellor et al.*[66] were not likely to be influenced by lack of
blinding.

One trial[67] did not provide details about blinding of participants and personnel, nor about blinding of outcome assessment, so we therefore judged as 'unclear' risk of performance and detection bias.

Incomplete outcome data (attrition bias)

Two trials[68,69] did not contain missing data; therefore, we judged them to be at low risk of attrition bias. Two trials[66,70] did not provide a satisfactory explanation for the missing of data, and therefore there was insufficient information available to permit judgement of 'low' or 'high' risk of attrition bias. We judged one trial to be at high risk of bias because there was dropout due to adverse events only in the experimental group.[67] Only one trial[70] reported that they had performed an intention-to-treat analysis. However, they did not report how they handled missing values. The other trials[66-69] did not report how they handled data from participants who deviated from the protocol, but we assumed that they were analysed in the groups to which they were randomised.

Selective reporting (reporting bias)

It was unclear if there was selective reporting of the outcomes in three trials, because the protocols were not available.[66-68] However, it has to be noted that the trials reported the outcomes of all study parameters mentioned in the Methods section. Even though no trial protocol was available for *Dykstra & Sidi*,[69] the review authors judged the risk of selective reporting as 'low' since correspondence with a trial author assured that all of the trial's prespecified outcomes were reported in the prespecified way. We judged one trial[70] as high risk for reporting bias since the report provided no result for an outcome of interest mentioned in the methods section.

Effects of interventions

The details of the following statistical data analyses are available online at *The Cochrane Library*.[65] http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004927.pub4/full

Comparison 01: implantable urethral stent versus sphincterotomy

One small trial addressed this comparison.[66] All participants had traumatic spinal cord injury with urodynamically verified DSD. *Chancellor et al.*[66] compared implantation of the UroLume® sphincteric stent prosthesis with conventional external sphincterotomy.

Primary outcome measures
Urodynamic measurements

Postvoid residual urine volume (Analysis 1.1) and cystometric bladder capacity (Analysis 1.2) were not statistically significantly different between the interventions at either time-point.

The maximum detrusor pressure measured at three, six, or 12 months (Analysis 1.3) was relatively stable and low in both groups without statistically significant differences between the groups. However, at 24 months, the maximum detrusor pressure significantly increased in the participants who received an implantable stent, compared to the participants after sphincterotomy (MD 30.00 cmH$_2$O, 95% CI 8.99 to 51.01, Analysis 1.3.4).

Renal function

The occurrence of vesico-ureteral reflux was not statistically significantly different between the groups at 12 and 24 months (Analysis 1.4).

Hydronephrosis using radiography was reported per renal unit, although we have strong indications that the reported number of evaluated renal units was incorrectly reported. The report describes an evaluation of 52 renal units in the sphincterotomy group and 69 renal units in the stent group. Further in the report, 59 renal units were evaluated in the stent group. We assumed 59 units was correct since this could be confirmed by the associated reported percentage. The occurrence of hydronephrosis was not statistically significantly different between the groups at 12 and 24 months (Analysis 1.5). The confidence intervals were wide, reflecting few events and small groups.

The occurrence of urinary tract infections as a complication related to DSD was more common, but also not statistically significantly different between the groups at three, six, 12, and 24 months, neither in terms of positive urine culture (Analysis 1.6), nor in terms of symptomatic urinary tract infections (Analysis 1.7).

Secondary outcome measures

Quantification of symptoms

The participant-reported disappearance of autonomic dysreflexia symptoms was not statistically significantly different between groups at 24 months (Analysis 1.8). The catheterisation rates also were not statistically significantly different between groups at three, six, 12, and 24 months (Analysis 1.9).

Quality of life

The trial did not report which questionnaires it used to evaluate bladder emptying and quality of life with respect to the urological condition and if these questionnaires were validated. Exact data of the number of participants worrying about DSD, noticing bothersomeness with urination, the number who were hampered in their daily activities, and the participants reporting that the urological condition interfered with social life were lacking. We were therefore not able to analyse the effect of the intervention on quality of life.

Measures of associated symptoms (objective or subjective)

Participants reported their bladder-emptying ability as "much better", "somewhat better", "no change", "somewhat worse", and "much worse". For the current review, "much better" and "somewhat better" defined improvement, while "no change", "somewhat worse", and "much worse" defined no improvement. No statistically significant difference of the improvement rate of the bladder-emptying ability was observed between groups at three, six, 12, and 24 months (Analysis 1.10).

The report stated that no alterations in erectile function or ejaculation were noted in men who underwent sphincterotomy or stent placement at any time. The report provided no data.

Surgical outcome measures

Surgical measures were reported in all 26 participants who underwent sphincterotomy and in 30 of 31 participants who underwent stent placement.

More participants after sphincterotomy (23/26, 88.5%) than after stent placement (19/30, 63.3%) were hospitalised for two days or longer after the surgical intervention, in favour of stent placement (RR 0.72, 95% CI 0.53 to 0.97, Analysis 1.11). There were no statistically significant differences between groups in the number of participants with bladder neck obstruction requiring treatment (Analysis 1.12).

Adverse effects

(See Table 7.2.)

There were no statistically significant differences between groups in outcomes of haemorrhaging (one-day postoperative bleeding as quantified by haemoglobin value, Analysis 1.13) or number of participants with urethral strictures requiring surgical treatment (Analysis 1.14). Re-stenosis of the sphincter in two participants who underwent sphincterotomy required repeat sphincterotomy six months postoperatively.

Comparison 02: botulinum A toxin injection versus placebo

Two trials addressed this comparison.[69,70]

The extremely small trial from *Dykstra & Sidi*[69] in five men with spinal cord injury compared sphincter injections with either a dose of BTX-A (n = 3) or normal saline as placebo (n = 2), applied once a week for a total of three weeks. The initial dose of BTX-A was 140 U on a botulinum A toxin, with subsequent injections of 240 U. In the three participants allocated to the BTX-A treatment, an average decrease of 25 cmH_2O was seen in the maximal urethral pressure, an average decrease of 125 mL was seen in their postvoid residual urine volume, and an average decrease of 30 cmH_2O was found in the maximum bladder pressure during voiding. After completion of the study, participants who had received placebo were offered the opportunity to undergo the same

injections with BTX-A. The report mentions that in participants who received placebo injections, all outcomes were unchanged from baseline values until the subsequent injection with BTX-A once per week for three weeks. This resulted in similar responses to those of the other three participants who initially received BTX-A. The effects of the BTX-A injection lasted an average of 60 days in all five participants. All participants continued to use condom catheters after injection. Three participants had suffered from autonomic dysreflexia symptoms during voiding, of which all reported a noticeable improvement in their autonomic dysreflexia symptoms after toxin injections. Unfortunately, the report presented no data on placebo treatment, and therefore we could not make quantitative comparison between active and placebo treatment.

Gallien et al.[70] compared a single transperineal injection of BTX-A (Botox®, Allergan Inc.) into the external urethral sphincter with a single placebo (saline) transperineal injection into the external urethral sphincter in MS patients. In addition, participants in both groups were prescribed an alpha blocker (5 mg tablet slow-release alfuzosin twice a day) over four months. All results mentioned below in this comparison originate from *Gallien et al.*[70]

Primary outcome measures
Urodynamic measurements
The postvoid residual urine volume measured using catheterisation at 30 days did not differ statistically significantly between groups (Analysis 2.1). However, the voiding volume at 30 days was statistically significantly larger in the BTX-A group (MD 69 mL, 95% CI 11.87 to 126.13, Analysis 2.2).

At 30 days, the BTX-A group had a statistically significant lower pre-micturition detrusor pressure (MD -10.00 cmH$_2$O, 95% CI -17.62 to -2.38, Analysis 2.3.2) and maximum detrusor pressure (MD -14.00 cmH$_2$O, 95% CI -25.32 to -2.68, Analysis 2.3.3) compared to the placebo group. All other urodynamic outcomes at 30 days did not differ statistically significantly between groups: basal detrusor pressure (Analysis 2.3.1), maximal bladder capacity (Analysis 2.4), maximal urinary flow (Analysis 2.5), bladder compliance at functional bladder capacity (Analysis 2.6), and maximal and closure urethral pressure (Analysis 2.7).

Renal function
No data were available for analysis of any of the outcomes relating to renal function.

Secondary outcome measures
Quantification of symptoms
The occurrence of MS attacks was reported in both groups and did not differ statistically significantly between groups (Analysis 2.8).

Quality of life
The International Prostate Symptoms Score (IPSS) was measured as a condition-specific quality of life questionnaire related to lower urinary tract symptoms. This IPSS score did not differ statistically significantly between groups (Analysis 2.9). The variables assessing the quality of voiding (obstructive symptoms, urinary frequency, urgency, and incontinence) were assessed using 10 cm visual analogue scales (VAS). The VAS scores were not statistically significantly different between groups (Analysis 2.10).

Measures of associated symptoms (objective or subjective)
No data were available for analysis of any of the outcomes relating to symptoms associated with DSD.

Surgical outcome measures
The trials reported no relevant data regarding any surgical outcome measures.

Adverse effects
(See Table 7.2.)

   Outcomes reported that related to the surgical intervention were the number of people with urinary tract infections, urinary leakage (incontinence), and faecal incontinence. There were no statistically significant differences between groups (Analysis 2.11). Serious adverse events and non-serious adverse events were reported, though exact data were not available.

Comparison 03: botulinum A toxin injection combined with non-surgical therapy
We identified one small trial[67] comparing a single 200 U BTX-A injection combined with oral baclofen versus a single 200 U Chinese-manufactured BTX-A injection without oral baclofen, in patients after spinal cord injury.

Primary outcome measures
Urodynamic measurements
The study measured the postvoid residual urine volume, though no data were available from the report to analyse the effect of intervention on postvoid residual urine volume.

   Urodynamics were performed in both groups one month after the injections. The maximum uroflow rate (Analysis 3.1), maximal cystometric capacity (Analysis 3.2), and volume per voiding (Analysis 3.3) were not significantly different between groups. The bladder compliance was significantly higher (better) in the BTX-A group without oral baclofen group than in the BTX-A group with oral baclofen. Participants after BTX-A with baclofen had a lower (worse) compliance with a MD of -7.50 mL/cmH$_2$O, 95% CI

-10.74 to -4.26 (Analysis 3.4), compared to participants after BTX-A without baclofen. The report does not describe at which bladder volume the compliance was calculated. This is important because the bladder compliance describes the relationship between change in bladder volume and change in detrusor pressure. Furthermore, this trial did not report the detrusor pressure, which is a shortcoming since it is an important urodynamic measure when evaluating renal function. Therefore, the value of compliance as an outcome in this report may be limited.

Renal function
No data were available for analysis of any of the outcomes relating to renal function.

Secondary outcome measures

Quantification of symptoms
No data were available for analysis of any of the outcomes that quantifies symptoms. The report describes the measurement of the urinary frequency per 24 hours, though no data were available.

Quality of life
The amelioration degree was not statistically significantly different between groups (Analysis 3.5). The report did not describe how the amelioration degree was measured. The IPSS was administered in men, and the Urogenital Distress Inventory (UDI) was administered in women, though no data were available from the report. We were therefore not able to analyse the effect of intervention regarding the quality of life.

Measures of associated symptoms (objective or subjective)
No data were available for analysis of any of the outcomes relating to associated symptoms of DSD.

Surgical outcome measures
No data were available for analysis of any of the outcomes relating to surgical outcome measures.

Adverse effects
Reported adverse events were haematuria and muscle weakness (Table 7.2). However, no data were available for analysis of any of the outcomes relating to adverse effects.

Comparison 04: botulinum A toxin injection versus other surgical therapy

One very small trial[68] addressed this comparison; participants with spinal cord lesions (due to traumatic spinal cord injury, MS, or congenital malformation) received either a single 100 U BTX-A injection (Botox®, Allergan Inc.) or a lidocaine injection into the external urethral sphincter via the transperineal route. Participants who had a negative result at the end of the trial (30 days) received the other treatment. The results presented below only include data from the first period, since only this information was available from the report.

Primary outcome measures

Urodynamic measurements

The postvoid residual urine volume measured by catheterisation was significantly lower (better) after seven days (MD -163 mL, 95% CI -309 to -17, Analysis 4.1.2) and 30 days (MD -158 mL, 95% CI -278 to -39, Analysis 4.1.3) in favour of the group who received BTX-A injections. These differences were not quite statistically significantly different in the short-term (one day after treatment) (Analysis 4.1.1).

Reported urodynamic outcomes 30 days after injection were maximal detrusor pressure on voiding (Analysis 4.2), maximal urethral pressure (Analysis 4.3), and improvement in Blaivas classification of DSD (Analysis 4.4). None of these urodynamic outcomes were statistically significantly different between groups.

Renal function

No data were available for analysis for any of the outcomes relating to renal function.

Secondary outcome measures

Quantification of symptoms

No data were available for analysis of any of the outcomes that quantified symptoms of DSD.

Quality of life

The satisfaction score with treatment, using a question ("Do you find this treatment to be efficacious?") with response options from 0 (no efficacy) to 10 (maximal efficacy), was measured 30 days after injection. This was statistically significantly higher (better) in the participants who received BTX-A injections (MD 3.41, 95% CI 0.93 to 5.89, Analysis 4.5).

Measures of associated symptoms (objective or subjective)

The disappearance of symptoms of autonomic dysreflexia was not statistically significantly different between groups (Analysis 4.6). The report described the assessment of

the participant's personal opinion about the evolution of the voiding difficulties (time to induce voiding), but no data were available from the report for quantitative analysis. All participants in the BTX-A group reported an improvement in voiding difficulties, whereas the voiding difficulties remained unchanged in the lidocaine group.

Surgical outcome measures

At the end of the trial (30 days), one of five participants from the BTX-A group and all eight participants from the lidocaine group required another injection. The difference did not however reach statistical significance (Analysis 4.7).

Tolerance assessed by a quantitative tolerance score was not significantly different between groups (Analysis 4.8). Forty-six per cent of the participants reported that the BTX-A injection was efficacious for three months, and in 23% of the participants, the effect lasted longer than three months. The efficacy was shorter than three months in 31% of participants.

Adverse effects

There were no events of haemorrhaging or infections related to the procedure in either group and no systematic side-effects. One participant in each group reported side-effects, involving faecal incontinence after lidocaine and transitory exacerbation of urinary incontinence for two weeks after BTX-A (Table 7.2).

DISCUSSION

Summary of main results

In patients with neurogenic bladder dysfunction, the first aim of any therapy is protection of the upper urinary tract.[13] In patients with detrusor-sphincter dyssynergia (DSD), a high detrusor pressure during the voiding phase can result in a pathologic high-pressure bladder, which needs to be converted into a low-pressure reservoir. In patients for whom conservative treatment (i.e. clean intermittent self-catheterisation and pharmaceutical treatment (e.g. antimuscarinics)) is not possible or feasible, surgical treatment options should be considered. According to the European Association of Urology Guidelines,[13] sphincterotomy is the standard surgical treatment for DSD. Since the introduction of sphincterotomy in 1958 as a treatment of obstruction at the level of the external urethral sphincter in people suffering from neurogenic bladder,[82] improvements in surgical care and the development of new surgical options have been developed. However, consensus on what defines optimal surgical management seems to be lacking. This was the background of the current systematic review.

Only a limited number of small randomised controlled trials (RCTs) comparing a surgical approach with any other intervention in the treatment of functional bladder outlet obstruction (BOO) in adults with neurogenic bladder dysfunction was available. Also, the most recent included trial was performed no less than six years ago.[67]

Primary outcomes: urodynamic measurements

In the only trial comparing sphincterotomy with urethral stent placement,[66] the maximum detrusor pressure was lower (mean difference (MD) of -30.00 cmH$_2$O, 95% confidence interval (CI) 8.99 to 51.01, Analysis 1.3.4) in the sphincterotomy group compared to the stent group, but only at two years.

Interestingly, this was due to an increase of maximum detrusor pressure in the stent group, rather than because of a decrease in the sphincterotomy group. Results for maximum detrusor pressure were inconclusive at three, six, and 12 months. Results for postvoid residual urine volume and cystometric bladder capacity were inconclusive and consistent with benefit of either sphincteric stent prosthesis or sphincterotomy at three, six, 12, and 24 months.

Four of five included trials assessed intraurethral botulinum A toxin (BTX-A) injections as a surgical option. Unfortunately, we could not combine these in a meta-analysis as the comparator treatment differed in these trials. Comparing a single intraurethral 100 U BTX-A injection (Botox®, Allergan Inc.) with a placebo injection, while administering concomitant alfuzosin in multiple sclerosis (MS) patients,[70] voiding volume was higher after BTX-A (MD of 69.00 mL, 95% CI 11.87 to 126.13, Analysis 2.2). Also, both pre-micturition and maximal detrusor pressure were lower after BTX-A. A mean difference of -10.00 cmH$_2$O, 95% CI -17.62 to -2.38 and -14.00 cmH$_2$O, 95% CI -25.32 to -2.68, respectively, was found after 30 days (Analysis 2.3). However, postvoid residual urine volume as measured by catheterisation, basal detrusor pressure, maximal bladder capacity, maximal urinary flow, bladder compliance at functional bladder capacity, maximal urethral pressure, and closure urethral pressure at 30 days were inconclusive and consistent with benefit of either BTX-A or placebo injections. *Cui et al.*[67] compared 200 U intraurethral BTX-A injection (Lanzhou Biotechnology, China) with or without concomitant oral baclofen in spinal cord injury patients. Bladder compliance was better in patients who received BTX-A injections without oral baclofen, compared to the patients who received BTX-A injections with oral baclofen. Compared to the BTX-A group without baclofen, the BTX-A group with baclofen had a MD of -7.50 mL/cmH$_2$O, 95% CI -10.74 to -4.26 after one month (Analysis 3.4). Results for maximum uroflow rate, maximal cystometric capacity, and volume per voiding were all inconclusive and consistent with benefit of either BTX-A injection or BTX-A injection with the addition of oral baclofen. We believe that the relevance of bladder compliance as an outcome measure in this setting should be questioned. First, the authors did not report at which

bladder volume the compliance was calculated. Second, the trial authors did not provide data for comparison of detrusor pressure, which is a more important parameter for the effectiveness of treatment. Third, the trial authors did not provide a theoretical explanation of why particularly the addition of oral baclofen - which is supposed to act as an antispasticity agent - is not favoured in this trial.

The trial of *de Sèze et al*[68] compared a single 100 U intraurethral BTX-A injection (Botox®, Allergan Inc.) with a single intraurethral lidocaine injection in participants with DSD of mixed aetiology (i.e. traumatic spinal cord injury, MS, or congenital malformation). Botulinum A toxin injections resulted in lower postvoid residual urine volumes with MDs of -163.00 mL, 95% CI -308.65 to -17.35 and -158.30 mL, 95% CI -277.57 to -39.03 after seven and 30 days, respectively (Analysis 4.1), though not yet after one day. Results at one month for maximal detrusor pressure on voiding, EUS activity in electromyography, and maximal urethral pressure were inconclusive and consistent with benefit of either BTX-A or lidocaine injections. In addition, participants were significantly more satisfied 30 days after BTX-A injections (Analysis 4.5).

Finally, *Dykstra & Sidi*[69] performed a trial involving five men with spinal cord injury. These men were injected with either BTX-A (initial dose of 140 U onabotulinumtoxinA with subsequent injections of 240 U) or placebo (saline) once a week for three weeks at three or four sites in the external urethral sphincter. The placebo had no significant effect on DSD in the two participants allocated to the placebo treatment. Their urodynamic parameters were unchanged from baseline values until subsequent injections with BTX-A once a week for three weeks. These subsequent injections resulted in similar responses to those of the three participants who were allocated to the BTX-A treatment.

However, it is unclear how relevant changes in urodynamic parameters, such as postvoid residual urine volumes, are to participants' satisfaction with treatment and particularly whether beneficial urodynamic changes translate into reduced effect on damage to the kidneys, as none of the trials reported this crucial outcome.

Primary outcomes: renal function and urologic complications related to DSD
The remaining two primary outcome measures, renal function and urologic complications related to DSD, were only reported in the trial that compared sphincterotomy with stent placement. Results for renal function vesico-ureteric reflux and hydronephrosis, Analysis 1.4; Analysis 1.5) at 12 and 24 months, and urologic complications related to DSD (e.g. urinary tract infection, Analysis 1.6; Analysis 1.7) at three, six, 12, and 24 months were inconclusive and consistent with benefit of either sphincteric stent prosthesis or sphincterotomy.

Participant-reported outcomes and quality of life

Despite the major impact of neurogenic bladder dysfunction on quality of life (QoL), only two trials[67,70] used questionnaires as a patient-reported outcome measure. Both used the International Prostate Symptom Score (IPSS), which is a seven-item symptom score originally developed for men with benign prostatic hyperplasia,[83] the addition of a QoL question. Where *Gallien et al.*[70] used this prostate symptom score in both male and female patients, *Cui et al.*[67] used the Urogenital Distress Inventory (UDI)[84] in female participants, which lacks a specific QoL question. Since both trials did not report the data of the QoL question of the IPSS separately, we were not able to draw any conclusions regarding the improvement of QoL after intervention. *Chancellor et al.*[66] reported surveying participants regarding the QoL with respect to the urogenital condition, but the lack of data and information regarding if and which questionnaires were used does not provide us with any meaningful data. In the trial of *de Sèze,*[68] a treatment satisfaction score was determined using a single question. However, this single question ("Do you find this treatment to be efficacious?") may not be specific enough and can be interpreted as an improvement in symptoms as well as an improvement in QoL.

Duration of effect

The findings of the aforementioned trials evaluating BTX-A injections suggest that BTX-A may be useful in the treatment of DSD in adults with neurogenic bladder dysfunction. The duration of effectiveness of BTX-A injections is however limited. *Dykstra & Sidi*[69] reported an effect of BTX-A of an average of 60 days after the third (last) injection, and *de Sèze et al.*[68] reported BTX-A was efficacious for at least three months in the majority of participants (69%).

Adverse effects

See Table 7.2 on adverse effects.

Twenty-three per cent of participants needed more than one stent insertion procedure, and 19% of participants required a stent explantation. This was in contrast to the adverse effects of sphincterotomy, where a repeat sphincterotomy after six months was required in only 8% of participants. Treatment for bladder neck obstruction was necessary in one out of five of all participants.

Concerning the adverse events in the BTX-A trials, haematuria was reported in two trials,[67,69] but this was due to the cystoscopic injection and not necessarily due to the injected agent. More important are the effects of BTX-A on muscle weakness. This seem related to the dose of BTX-A used.

Two trials using more than 100 U BTX-A reported muscle weakness;[67,69] this was in contrast to the two trials using 100 U (single dose) BTX-A, in which no muscle weakness was observed[68] or reported.[70] However, the last two trials reported both incontinence

for faeces[68] and urine.[68,70] The serious adverse events as reported by *Gallien et al.*[70] were not attributable to BTX-A.

Quality of the evidence

In general, the included trials were small, diversely designed, and reported outcomes were defined in different ways. Therefore, due to paucity of evidence, the results should be interpreted cautiously. The risk of selection bias and reporting bias (Figure 7.3) is certainly present, mainly because of insufficient information to permit judgement. Contacting trial authors resulted in additional information for one trial,[69] though initially three of five trials did not provide enough information in their report.[66,67,69] These potential risks may be related to inadequate reporting common in older trials,[66,69] or to publication in a non-English language journal,[67] rather than to methodological shortcomings.

Potential biases in the review process

We applied no language or other restrictions in the search for trials. Despite the comprehensive search, we may still have missed unreported trials or trials only reported in conference abstracts, causing publication bias.

We added the following non-prespecified outcomes in the protocol to the review as secondary outcomes, since we judged these important during this review:
·   The occurrence of autonomic dysreflexia symptoms and MS attacks as associated symptoms of neurogenic lower urinary tract dysfunction.
·   The need for reinjection of intraurethral BTX-A.
·   Participant-reported days of effect

This may have introduced unintentional outcome reporting bias in the review process with the possibility of biased and misleading interpretation of the results.[85] However, we added these outcomes because of knowledge of studies that existed, not necessarily because of knowledge of the results.

Agreements and disagreements with other studies or reviews

We identified two systematic reviews that systematically reviewed surgical treatment options in the treatment of DSD.[78,79]

   Mehta et al.[78] conducted a systematic review and meta-analysis to assess the effect of intraurethral BTX-A injections on improving bladder emptying in patients with spinal cord injury. They pooled data from two RCTs[68,69] and six uncontrolled trials, and concluded that BTX-A was effective in significantly reducing postvoid residual urine volume, detrusor pressure, and urethral pressure after one month. They made no statements about the clinical utility of BTX-A. Because this review included non-

randomised controlled trials, the data used for meta-analysis were pre-intervention versus postintervention.

Naumann et al.[79] conducted an evidence-based review of the safety and efficacy of BTX-A in the treatment of autonomic and urologic disorders and low back and head pain. The conclusions and recommendation of the safety and efficacy of BTX-A in the treatment of DSD were based on the quality of the trials.[86] *Gallien et al.*[70] received the highest classification based on the quality of the trial, and *de Sèze et al.*[68] and *Dykstra & Sidi*[69] received the second best classification. Based on these three trials, *Naumann et al.*[79] recommended that BTX-A should be considered for DSD in people with spinal cord injury with a level B rating for recommendations.[86] No effects of interventions were analysed.

AUTHORS CONCLUSIONS

Implications for practice

At present, there are insufficient data available to determine the optimal surgical treatment of BOO in adults with neurogenic bladder dysfunction. Four out of five of the trials focused on BTX-A treatment. This review has found evidence of limited quality that BTX-A injection - either administered by itself or in combination with another treatment - confers benefit with regard to increasing voided urine volume, lowering detrusor pressure, and decreasing postvoid residual bladder urine volume. In addition, one small study found that it appears to lead to a higher satisfaction than lidocaine injection. However, the necessity of regular reinjection of BTX-A is a significant drawback. A sphincterotomy might be a more effective treatment option for lowering bladder pressure in the long-term; however, results from one small study comparing sphincterotomy versus sphincteric stent prosthesis on urodynamic measures were inconclusive.

Implications for research

Unfortunately, this review failed to provide robust evidence in favour of any of the surgical treatment options, because of the limited availability of eligible trials, the variability in the interventions (e.g. dose and mode of injection of BTX-A) of the included trials, and particularly because of their small size (ranging from five to 86 participants). Also, the duration of follow-up of the included trials was limited, with an average of eight months.

Therefore, more and larger RCTs are needed to evaluate the most effective surgical intervention for functional BOO in adults with neurogenic bladder dysfunction. Furthermore, RCTs of specific surgical treatment options for DSD (i.e. urethral balloon

dilatation, intrathecal baclofen, pudendal nerve block, suprapubic catheterisation) are lacking. Randomised controlled trials assessing the effectiveness of BTX-A need to address the remaining uncertainty about the optimal dose and mode of injection, keeping in mind the possible dose-related adverse events.

Trials should use standardised terminology and outcomes in accordance with International Continence Society (ICS) standards[2] and the Consolidated Standards of Reporting Trials (CONSORT) statement[87] improve the quality of the reports and draw meaningful conclusions. In addition, further trials are advised to select outcomes that really matter to patients and practitioners, which is facilitated by the Core Outcome Measures in Effectiveness Trials (COMET) initiative.[88]

The lack of trials assessing QoL from the patient's point of view as an outcome is worrying, as the medical (technical) success does not necessarily correspond with the emotional judgement of success reported by the patient. Health-related QoL should receive much more attention in future trials. Furthermore, none of the included trials addressed socioeconomic outcomes. In future trials, the duration of effectiveness of BTX-A injections should be considered as a socioeconomic outcome.

This systematic review included only RCTs and quasi-RCTs. However, because of the limited availability of eligible trials, future reviews should consider including evidence from non-randomised trials for outcomes, although this will introduce bias.

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