

# A review of prospective Clinical Trials for neurogenic bladder: The place of surgery, experimental techniques and devices

Cristian Persu<sup>1</sup>, Emmanuel Braschi<sup>2</sup>, John Lavelle<sup>3</sup>

<sup>1</sup>Department of Urology, Carol Davila University of Medicine, Romania

<sup>2</sup>Instituto Nacional de Rehabilitacion Psicofisica del Sur. Mar del Plata, Argentina

<sup>3</sup>Stanford University & Staff Physician VA Palo Alto Health Care System, Department of Urology, Palo Alto, California, USA

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## Correspondence

Cristian Persu  
Carol Davila University of  
Medicine  
Department of Urology  
Dr Cretestilor Nr 3K,  
Sector 4  
042183 Bucharest,  
Romania  
phone: +40 722 302 225  
cpersu@clicknet.ro

**Introduction** The neurogenic urinary bladder has been known for at least 30 years now and the concepts behind it are continuously evolving, but there is actually not much work that has been done to accumulate solid clinical evidence in this field. We review the surgical and experimental techniques used in the management of this condition.

**Material and methods** To achieve our goal, we performed Internet searches using the same search string: Urinary bladder, neurogenic. In each case, the search was limited to clinical trial, subjects were human and the language was English. After duplicate removal, we obtained a final number of 580 papers. Data was extracted from each paper into a database file and was analyzed separately for adult and pediatric populations.

**Results** A total of 70 full text papers were reviewed and analyzed according to the previously mentioned algorithm. The first prospective, randomized surgical trials were published less than 20 years ago, starting with 1994, and the number of papers published each year since then has remained in the range of 1–3. The oldest prospective clinical trial for this indication dates back to 1975. The total number of patients included in surgical trials is 3453, out of which 59% are males. The papers include a total of 369 children (21.2%), essentially looking at all the techniques that are also used in adults.

**Conclusions** There is still a lot of work to be done in order to obtain a significant level of evidence in the field of surgical procedures used in neurogenic bladder patients.

**Key Words:** neurogenic bladder ◊ clinical trial ◊ surgery, devices ◊ experimental technique

## INTRODUCTION

The neurogenic urinary bladder is defined as a dysfunctional bladder associated with a known neurological injury, which can be spinal cord injury (SCI), multiple sclerosis (MS), spina–bifida, etc. [1]. Although the term has been known for at least 30 years now and the concepts behind it are continuously evolving, there is actually not much work that has been done to accumulate solid clinical evidence in this field.

The choices of treatment for the patients with a neurogenic bladder include surgery, electrical stimula-

tion, or physical exercise, many of them being still in an experimental phase. While drugs are the single most used element that is found, at least temporarily, in the therapeutic approach of all these patients, surgery gets the role of salvaging the situation when all other treatments failed or are considered inappropriate. Whether it is indicated to improve storage capacity, relieve outlet obstruction, cure incontinence or treat complications such as stones or tumors, surgery is a strong weapon in the armamentarium of the urologist that deals with neurogenic bladders.

In the era of evidence-based medicine, it is quite often realized that there simply isn't enough data to support a particular technique or indication, and the surgical field of the neurogenic bladder is one of the best possible examples [2]. Everyone knows that bladder augmentation is a good option to improve storage or that bulking agents are a reasonable option for stress urinary incontinence, but is there enough evidence out there to support what we sometimes tend to take for granted?

The aim of our work is to review the clinical trials looking at surgical treatments, devices and experimental techniques for urinary related conditions in patients that have a neurogenic bladder, to outline the general results of major techniques used and to consider the principles of management that are most commonly used, as reported in the literature. We consider that every device, technique or new approach that is reported for the first time in the literature should be considered as experimental until it is validated by multiple clinical trials of good quality. The accepted methods of validation nowadays are the prospective clinical trials, which start with a very clear protocol that covers diagnosis, treatment and follow-up.

## METHODS

To achieve our goal of reviewing as many relevant papers as possible we performed searches on both PubMed and OVID databases, using the same search string: Urinary Bladder, neurogenic [MESH]. The option for the Medical Subject Heading (MESH) vocabulary was based on the idea of standardization of terminology and reporting, supported by the International Continence Society (ICS) and many other scientific organizations [3].

In each case, the search was limited to clinical trials, subjects were limited to human and the language of the paper had to be English. There was no year limit for our search, so even older papers were considered. The search on PubMed returned 478 results in total, while from OVID we were able to get only 425 papers. The results of the two searches were saved into two different files, containing title, abstract, authors, keywords, and the relevant data on the journal that published the paper. Data was then imported into the reference manager software and combined for easier processing.

The next step was duplicate removal, which led to a final number of 580 papers that needed to be considered for the purpose of our work. The entire reference was exported to a Microsoft Access database, which allowed for greater flexibility in sorting and indexing the data by different criteria.

The inclusion criteria a paper had to meet simultaneously to be evaluated by our research were:

- Clinical trial using at least one surgical technique, device or experimental technique for a urinary related condition
- Primarily looking at the management/treatment of neurogenic bladder (papers were not excluded if also dealing with non-neurogenic conditions)
- Main paper (not abstract) in English
- Use surgery as main therapy
- Results clearly stated (numbers, statistics, etc)

If the abstract was not enough to clearly identify all the inclusion criteria, the full text paper was retrieved and analyzed. After applying these criteria, a total number of 73 papers were selected for in-depth analysis.

Data was extracted from each paper into a database file, where we recorded the main subject of the paper, its objectives, the total number of subjects and the number of males and females that were enrolled. Other headers included results, conclusions, personal remarks, main technique used, source of funds for study and year of publication. Data was analyzed separately for adult and pediatric populations.

We did not consider it important to sort the papers according to their country of origin, since the results are published in internationally recognized journals. However, there could be some differences in the approach to the patient, or even in the results of similar procedures, that are region or race related, but we think that this is not the main topic of our work.

The final step of the analysis consisted of grouping together all studies looking at similar procedures (bladder augmentation, outlet obstruction treatment, stress incontinence, etc), pointing out the main causative neurological condition and then, according to the source of funds used, sorting into four groups: *government*, *pharmaceutical industry*, *private sources* or *not stated*. We documented the adherence of each journal to the *Uniform Requirements for Manuscripts (UMS)* issued by the International Committee of Medical Journal Editors (ICMJE) in 2001 [4].

## RESULTS

A total of 73 full text papers were reviewed and analyzed according to the previously mentioned algorithm. The first prospective, randomized surgical trials were published less than 20 years ago, starting with 1994, and the number of papers published each year since then has remained in the range of one to three. The oldest prospective clinical trial looking at medical devices for this indication dates back to 1975.

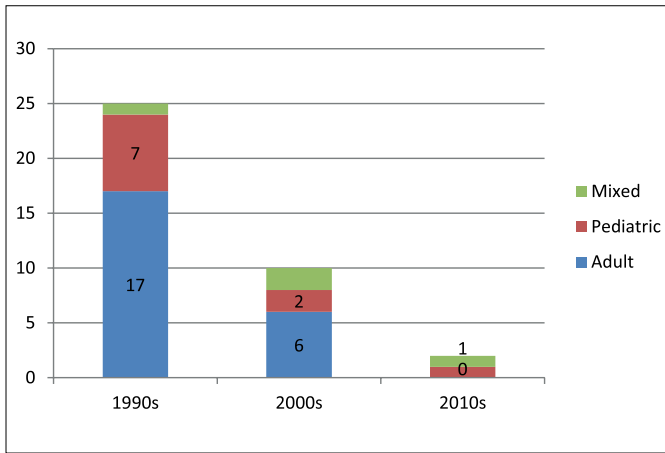


Figure 1. Number of trials for each ten year period.

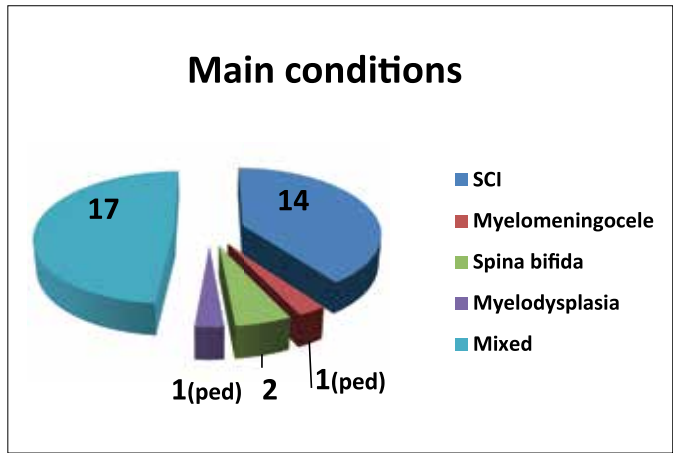


Figure 2. Main conditions behind the neurogenic bladder.

The total number of patients included in surgical trials is 3453, out of which there are 2037 male patients (59%). There are two papers that do not state the sex of the patients and a third paper that, although it does not clearly state this, seems to include only males as it looks at a urethral stent for relieving outlet obstruction. The papers include a total of 369 children (21.2%), essentially looking at all the techniques that are also used in adults. In fact, four trials are based on mixed populations, with patients' ages ranging between 3 months and 62 years old.

The oldest randomized trial for a pediatric population was published in 1995, and there is a mean value of one paper published every 1.5 years since then. The male:female ratio in the pediatric trials is about 1.4:1, although some trials do not describe the series from this point of view.

The largest series of patients included in one trial is 183 cases for adults and 107 for children, while the smallest trials included only 4 adults or 11 children. The median size of the series is of 30 and 19 cases respectively (Figure 1).

About half of the trials included patients with various neurological conditions considered responsible for the urinary disorder, while most of the trials including only SCI patients were looking at the treatment of bladder outlet obstruction (BOO). The main conditions being looked at are (Figure 2):

1. Spinal cord injury – 14 trials
2. Spina bifida – 3 trials
3. Myelomeningocele – 1 trial (pediatric)
4. Myelodysplasia – 1 trials (pediatric)
5. Mixed conditions – 17 trials

Only nine trial authors (24.3%) declare having received financial help for their work. One-third of them were funded by governmental institutions,

three artificial sphincter trials were supported by the company that manufactures the device, and the other three were supported by non-governmental funds. The vast majority of trials do not acknowledge any form of financial support. No evolution trend could be observed in this matter. There is an obvious lack of implication of governmental institutions in a field where spending some money now may reduce health care cost while improving health-related quality of life in the long run. At the same time, we appreciate that ultimately the health care system is actually paying for the surgeries, depending on the way the system is organized in each country, and, with the same budget but more implication towards a systematic approach, more valuable data could be obtained (Table 1).

We identified 11 surgical trials looking at various types of urinary diversion aiming to treat storage symptoms, seven of them evaluating the ileovesicostomy and four assessing the results of bladder augmentation. There are seven trials evaluating urethral stents aimed to relieve BOO due to detrusor-sphincter dyssynergia (DSD). Stress urinary incontinence was the subject of six clinical trials, three of them evaluating the artificial urinary sphincter produced by AMS. Another three trials are evaluating sacral roots neuromodulation for neurogenic

Table 1. Number of trials by main source of funding

	Sponsor	N
1.	Medical company	3 (8.1%)
2.	Government organization	3 (8.1%)
3.	Non-government / private	3 (8.1%)
4.	Not stated	28 (75.7%)

detrusor overactivity. Other trials are aimed toward sacral rhizotomies, stones treatment, sphincterotomy or nerve rerouting.

The ileovesicostomy trials included a total number of 180 cases, about 10% being children. The follow-up time ranges from one month to 3 years. In all series, patients are satisfied with the results and the urodynamic parameters improve. The reported continence per urethra rate ranges between 0 and 100% depending on the particular aspects of the technique, and the continence procedure seems to associate a higher incidence of complications. The most common complication reported is stomal stenosis, occurring in about 12% of cases after 6 to 32 months. Stones are reported in less than 5% of the cases and about 20% of the patients require another procedure in the first two years. No author reports deterioration of the upper urinary tract or *de novo* hydronephrosis. One author reports a 100% re-intervention rate after two years and complications in all cases.

The bladder augmentation using bowel segments was evaluated in 275 patients, out of which more than 40 were children. The longest follow-up in this category is 15 years. The results demonstrate an average of 3 times increase of bladder capacity and more than 7 times increase in bladder compliance on urodynamics. Reflux and hydronephrosis disappear in the first year after the intervention in most cases. The failure rate is about 12% overall, a little lower in pediatric populations. Overall, the technique proved safe, with a complication rate ranging from 1 to 10%. One study on the pediatric population demonstrates no metabolic consequences of the procedures during a follow up period of up to 13 years. Auto-augmentation seems to offer good results, but it may take one year before any improvement is seen.

Bladder outlet obstruction is a serious condition in neurogenic patients, but none of the trials we reviewed actually deal with differentiating functional DSD from mechanical obstruction (enlarged prostate, bladder neck obstruction, strictures, etc). There are seven trials evaluating different aspects of stents for DSD, including patients aged between 16 and 79 years old. Data proves that urethral stents are safe to use and lead to an overall improvement in voiding and storage parameters in up to 95% of the patients, while significant improvement is seen only in about 76% of cases. Storage pressure lowers in all cases, but not necessarily to safe levels. Spontaneous voiding is reported in up to 100% of the patients which were unable to void before the intervention, with a decrease of the PVR with a mean value of 225 ml. The number of episodes of auto-

nomic dysreflexia decreases by 50% and the rate of dramatic episodes decreases even more. The rate of UTIs lowers by 25% at one year after placing the stent. There is no impact on erectile or renal function, and the effects are completely reversible if the stent is no longer needed. When the stent is not efficient, it is usually not necessary to take it out as it is well tolerated. One trial proves that stents could significantly improve voiding in patients with failed sphincterotomy. The overall complication rate is in the range of 17%, the most common situation being migration of the device and a subsequent need for repositioning. Other complications include incrustation (0 to 16% incidence reported), urethral erosion with fistula (one case reported) or urethritis (two cases reported).

All the studies are evaluating only one type of stent, so there is no actual comparison between various models that are available and which have very different shapes or composition. The longest follow-up is less than three years, which might be inconclusive in the aspect of long-term safety and efficacy.

Sphincterotomy offers improvements regarding voiding parameters, with a significant reduction of the PVR in 69% of the cases, important decrease of the rate and intensity of autonomic dysreflexia episodes. VUR is improved in about 60% of cases and disappears completely in 40%, while recurrent UTIs are cured or have a significantly lower incidence in 74% of the patients. There are no reported complications of the procedure. The procedure is irreversible and has a failure rate of about 19%.

Stress urinary incontinence is another condition in which all the trials we reviewed fail to make a clear connection with the neurological disease. Bulking agents trials offer contrasting data, depending on the actual agent used and the time of follow-up. There is no trial comparing two or more bulking agents or a bulking agent versus another procedure aimed to improve continence. One trial evaluates a bulking agent for the treatment of VUR, and the results show improvement in all cases and cure in 63%, with no complications and a follow-up of 5 years.

The artificial urinary sphincter offers continence in about two-thirds of the cases, and the number can be improved by further fine-tuning of the device. The mean period of life for the sphincter is about 56 months, but up to 20% of them need to be removed earlier due to patient-related situations. A good capacity and no previous surgery in the area seem to be key factors in improving success rates for the artificial sphincter. There are reports of *de novo* VUR in up to 10% of the patients, with chances of renal failure. The results look similar in adult and pedi-

atric populations, although no comparative study exists. All authors agree that the patient should be informed up-front about the high rate of mechanical and surgical complications associated with the implantation of an artificial sphincter.

Electrical stimulation of the sacral roots, with or without rhizotomies is a hot subject, with many techniques and a couple of devices that aim to improve both storage and voiding, and even other conditions possibly related to the neurological injury. Neuromodulation has been evaluated in both adult and pediatric populations, on series ranging from 5 to 33 patients, with follow-up periods of up to 5 years. The initial stimulation test fails in about 33% of the patients, and another 16% show no response despite the positive outcome of the first stage. The main benefit of neuromodulation seems to be the increase in bladder capacity, with actual values that vary in a very wide range. Urinary continence is obtained by about 40% of the responsive patients, while a significant reduction is observed in all the others. Autonomic dysreflexia decreases both as incidence and as amplitude of signs and the other urodynamic parameters are improved overall, but reported data is inconsistent between trials. The use in pediatric population showed similar results. There are no safety concerns related to neuromodulation, the only major reported issue being the poor overall response rate due to the many cases that fail to respond to testing or final implantation.

The neurostimulation device is evaluated by studies that only included adult patients, mainly with SCI. In all papers, the results underline the beneficial effects including bladder function but also extend to improve erection and bowel function. The longest follow-up data available extends to two years, showing an increase in bladder capacity of at least 340 ml, with significant decrease in the PVR and improvement or cure of VUR. Autonomic dysreflexia episodes are still present in all cases, but with decreased values of blood pressure and lower incidence. The high initial cost of the procedure is reportedly balanced by the improved health status after 8 years, although one author reports that overall quality of life is unchanged by this procedure.

Nerve rerouting aimed to restore both bladder and bowel function proved effective in 78% of the cases of a mixed adult and pediatric series of nine patients. The novel reflex may take up to one year to become active and the surgical technique is not yet standardized. The results show that continence cannot be achieved by this technique, but the improvement in storage and voiding parameters may be sufficient to completely replace antimuscarinics or other treatments.

The treatment of detrusor overactivity continues to be a hot area for research, and the papers we reviewed report the use of electrical stimulation (5 papers), different drugs (4 papers) or a particular technique of rhizotomy in children. Electrical or magnetic stimulation of the bladder did not prove effective, and for many authors, the targeted pathways were unclear. There are two papers reporting improvement of enuresis episodes and an increase of bladder capacity with subsequent decrease in pressure in two thirds of the population. Event-driven stimulation of the dorsal penile or clitoral nerve was able to suppress urgency and increase bladder capacity in two thirds of the cases, with no adverse events, but the author concludes that the technique is not suitable in a chronic setting.

A selective rhizotomy technique was able to resolve NDO in all cases and to improve other urodynamic parameters subsequently, with results lasting for the entire follow-up period. The author notes that the results are better in children under 9 years old. The use of cranberry extract has overall inconclusive results. There are no adverse effects reported, and the efficacy data ranges from ineffective to very good. One recent study suggests that a better renal function improves the chances of preventing symptomatic UTIs.

## DISCUSSION

Although good quality studies are available and the evidence offered is relevant for the subject in discussion, there is actually no trial looking at the very core of the management of the neurogenic bladder. We all seem to accept that by reducing storage pressure and treating VUR our patient will be better, but in fact we cannot describe the improvement in the long run. In many cases, the reported positive evolution of one parameter is considered as a step forward in the management of the patient, although the implication on other parameters of storage and voiding are not known [5].

The implication of the industry in financing surgical trials is beneficial as it allows for more data to come out as support for a specific device or technique. On the other hand, these studies usually extend over short periods of time and generally evaluate the device itself, not comparing it to other similar devices that might be available. Such an approach is leading to results that are looking good overall, without clearly stating pros and cons over similar procedures.

The number of trials financed by governmental institutions is surprisingly low and we were unable to find a comprehensive explanation for the situation.

Although in some countries the governments are not paying for health care, this is not the case for the vast majority of countries, where governmental institutions pay for the care of neurogenic bladder patients, if not in full at least for a significant part of the total cost. Since the health care system, public or private, ultimately covers the expenses related to surgical interventions for the management of the neurogenic bladder patients [6], it seems obvious that only little effort is required in the direction of proper standardization of the approach, procedure and reporting so that all data in the system could be eventually used in the direction of obtaining good clinical evidence, on large series of patients and techniques, spanned over long periods of time. Such an approach would offer data on what really happens with the patient after his surgery and the true benefits could be evaluated not only as improved storage or voiding parameters, but as the evolution of the health status of the urinary tract over time.

When speaking about clinical trials looking at the surgical management of the neurogenic bladder, the general perception is that there is a lot of data available, covering every possible aspect of this field. Our research demonstrates the opposite, by pointing out a very low total number of trials, many of which have design issues that might alter the final results [7]. For example, many studies include patients with different neurological conditions, or mix adult and pediatric populations but analyze the results all together. The size of the series is another important issue for many trials, as a low number of patients is known to alter significantly the statistical analysis. Finally, there are studies that lack a power calculation, offering only basic information about the outcomes of the proposed treatment [8].

Summarizing what we know so far from the literature, we can state that bladder augmentation is a safe and effective procedure, both in adult and pediatric populations, with an associated complication rate of about 10%. Ileovesicostomy, considered less invasive, associates higher re-intervention rates, low continence rate per urethra and an overall higher complication rate compared to augmentation techniques. The treatment of BOO caused by DSD can be either by sphincterotomy or by using a stent. Sphincterotomy has the advantage of the lower cost while the main disadvantage is the irreversible character of the intervention. Taking into account the significant failure rate, it seems that the stents will completely replace this procedure, at least in those systems that can afford this change. There are many stents available today, and there is

no comparative data to help. We know that a stent is safe, effective and can be removed without any subsequent implication. There is no clear data concerning the treatment of SUI in the neurogenic bladder patient, as there is no clear etiology of the condition defined in the available trials. The artificial urinary sphincter offers continence for at least two-thirds of the patients and the life expectancy of the device is less than 6 years. The complication rate is significant. Electrical stimulation of the neural pathways involved in the micturition cycle looks very promising, with a great deal of studies already available or in progress. The results show improvement that can extend beyond the urinary tract and lasting benefits. The cost of the procedure remains high and the success rate still needs to be improved.

We notice that, with only one exception, all trials report positive results of the therapy for most of the included patients. All trials sponsored by the industry show significant benefits of using the device produced by the sponsor and none is offering comparative data with a similar technique or device [9]. In the end, this type of data might lead to confusion and indecision when choosing the most appropriate treatment for a particular patient, since the literature supports every single technique possible in that case [10].

## CONCLUSIONS

There is still a lot of work to be done in order to obtain a significant level of evidence in the field of surgical procedures used in neurogenic bladder patients. Available data is more of the *expert opinion* type, and the results are often confusing or contrasting, so a meta-analysis cannot lead to the development of guidelines for management.

Surgeries for different urinary conditions related to a neurological injury are a common practice in centers all over the world, and the first step toward acquiring reliable data is to standardize some methods and procedures, which will eventually lead to results that can be put together and analyzed on large number of patients.

A greater implication and support from the health care systems would contribute to studies on a larger, national scale and the patients could be followed longer and more comprehensively. Although the ultimate benefit of a better knowledge and understanding of the procedures is for the patient, the financial implications might be of great importance for the medical system that has an increased awareness of the real problems associated with the neurogenic bladder.

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