# W5: Neurogenic detrusor overactivity: What to do after 15 years of Botulinum toxin?

**Workshop Chair:** Michele Spinelli, Italy  
**13 September 2016 11:00 - 12:30**

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<td>Michele Spinelli</td>
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<td>On label Botox: revision of data and reinjection rate</td>
<td>Julien Renard</td>
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<td>Carlos D’Ancona</td>
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## Aims of course/workshop

Neurogenic bladder is a term applied to a malfunctioning urinary bladder due to neurologic dysfunction or insult emanating from internal or external trauma, disease, or injury. Symptoms of neurogenic bladder range from detrusor underactivity to overactivity (depending on the site of neurologic insult), sphincter underactivity or overactivity and loss of coordination with bladder function. Treatment options have evolved rapidly in the last 20 years. The aim of this workshop will be to give participants the most complete overview (features, diagnosis and management) of neurogenic bladder focusing especially on therapeutical options and their latest trends.

## Learning Objectives

After this workshop participants should be able to:
1. Have an overview of the management of neurogenic bladder
2. Know what current treatment options are available
3. Learn about current research and potential new therapeutical approaches

## Target Audience

Urologists, Neurourologists, Neurologists

## Advanced/Basic

Advanced

## Suggested Reading

- European Association of Urology- Guidelines
- Textbook of the neurogenic bladder- J. Corcos; D. Ginsberg; G. Karsenty, Taylor and Franc

## Michele Spinelli

In last 20 years urologists involved in study and treatment of neurogenic bladder had the occasion to assist at a revolution of care.

Starting from reflex voiding in neurogenic bladder by means of different triggers, introduction of larger use of intermittent catheterization has permitted to resolve voiding difficulties at low pressure and complete.

The concept of restoring micturition cycle in a “physiological approach”, with conservation of anatomy became in last decades the goal. In the field of pharmacological and medical modulation we assisted to possibility of escape surgical approaches using less invasive and reversible approaches as second line treatment.

The era of Botulinum toxin injection and the era of electrical neurostimulation and modulation are today considered main revolutions in functional urology.
But what we are looking for future?

We have a population long term treated with botulinum toxin asking something different and in this population we have patients becoming less responder.

On the other hand in last ten years we assisted to nothing new in term of treatment, only to the on labelling of botulinum toxin with a low dosage.

Are we going back to necessity of augmentation surgery?

What is going on in neuromodulation?

Is precocious approach in neuromodulation one of the new target?

TBC

Julien Renard

One of the main complaints of neurological patients, whatever the main etiology might be (medullar lesion, Parkinson’s disease, Multiple Sclerosis, Myelomeningocele...) is often linked to urological symptoms. In fact profound alterations of lower urinary tract control cause various symptoms. Among these, urinary incontinence is often the only apparent sign since urgency can be reduce or absent because of sensory deficits (1). Type of incontinence is in most of cases urge and due to neurogenic detrusor overactivity which requires a specific management. Antimuscarinic drugs often offer the first line of treatment but unfortunately can either be of insufficient effect for symptom management or cause side effects which are too much of a burden for patients (dryness of mouth, constipation). In this context, the advent of botulinum toxine has changed the game. Approved in 2011 by the Food and Drug Administration, the main indication for detrusor injection of botulinum toxin is the treatment of neurogenic detrusor overactivity in patients who have an inadequate response or intolerance to antimuscarinics. Recently the range of BoNT-A injections has increased, in some cases however in course of evaluation, to patients with painful bladder symptoms, idiopathic detrusor overactivity and voiding dysfunction. Its mechanism of action involves the motor nervous system including the inhibition of neuromuscular jonctions by blocking acetylcholine release. However its action is not only limited to this aspect. Botulinum toxin injection, in fact, also regulated the sensory nerve function by blocking neurotransmitter release and reducing receptor expression in the urothelium. In addition recent studies revealed an anti-inflammatory effect and globally in an improvement of urothelium function helping restore bladder function (2)

From a technical point of view, injections require a cystoscopic (rigid or flexible) intervention that needs to be repeated every 6-9 months. The procedure can be performed in local anesthesia in most patients.

In terms of effect, intradetrusor injection determines in neurogenic detrusor overactivity patients, an improvement in daily incontinence and catherization episodes, in maximum cystometric capacity, reflex volume and maximum detrusor pressure. In overactive bladder patients, it leads to significant improvement in bladder diary (daily frequency and urgency) and daily incontinence. (3)

Today two types of toxins are available on the market:
- Onabotulinumtoxin A ( Botox, Allergan Inc, Irvine, Ca)
- Abobotulinumtoxin A ( Dysport , Ipsen biphasmaceuticals, Inc, BAsking Ridge, NJ)

Botox has been in the last years the main product used in larger studies. However some authors have challenged its superiority by comparative studies which concluded to similar effects between the two products but longer intervals between injections for Dyspo (4)

One other open debate lies in the required dose necessary for management of neurogenic detrusor overactivity which range in the literature form 50 U to 300 U. Nowadays guidelines however recommend doses of 200 U for correct management.

Michele Spinelli / Julien Renard

Surgical management of patients with neurogenic bladders represents the last line of treatment for neurological patients. In fact, usually these procedures represent a heavy surgery which is not facilitated by the general condition of patient. However, if followed regularly and correctly, if patient is compliant there is usually no need for this management. In fact Urinary diversions, although once frequently employed are only required in special circumstances ( S. Herschorn) and that is in the case of failure of conservative management and medical management ( intermittent catheterization, anticholinergic medications, beta3 agonist
therapy) which leads to complications of the upper urinary tract (hydronephrosis, uretero-renal reflux, bladder wall thickening and concomitant progressive renal deterioration, urosepsis). Indications is found also in the case of unmanageable incontinence, inability to catheterize per urethra or in the cases of infectious complications linked to lower urinary tract (bladder diverticula).

After posing a correct indication, the main burden for physician and patient will be to choose a urinary diversion suitable. Two main types can be offered. Non continent diversion such as ileal conduit or colon conduit, or ileo vesicostomy. Continent diversions such as continent catheterizable pouch (Indiana, Koch, T pouch, Duke pouch, others) or catheterizable continent stoma with or without augmentation cystoplasty (Mitrofanoff, Hemi-Koch).

The main advantages of these diversions will be to restore low pressure urinary storage and protect the upper tract. Furthermore it should improve the quality of life providing a reliable state of continence.
Stoke Mandeville
Retrospective study on 150 pts.
1945-1963

WS: Neurogenic detrusor overactivity: What to do after 15 years of Botulinum toxin?
Workshop Chair: Michele Spedini, Italy
10 September 2016 11:05 - 12:30

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Long-term survival in spinal cord injury: a fifty year investigation

The aim of this study was to examine long-term survival in a population-based sample of spinal cord injury (SCI) survivors in Great Britain, identify risk factors contributing to death and explore trends in some of death over the decades following SCI. Current survival status was successfully identified in 92.7% of the study sample. Standardized mortality ratios (SMR) between SCI patients and the general population were calculated for the period 1945-1963 and 1964-2003 and showed a significant decrease over time (p<0.05). The excess mortality risk was associated with higher average age and completeness of spinal cord injury. While mortality declined in the last five decades, male sex and lower levels of injury remained significant predictors for death. The study also shows that the completeness of the injury at presentation was not a significant predictor of survival. The findings provide important information for future research and clinical care.

Keywords: mortality; spinal cord injury; survival analysis

'60 treatment of complications

'70 Quantity of life
UUT safety
early treatment

Not only Plumbers

The Normal Micturition Cycle

Storage phase

Emptying phase

Bladder filling

Normal desire to void

Normal desire

>99% of the cycle is spent filling

alberto zanollo center

for study and treatment of neurogenic bladder and sacral area dysfunctions
goals
permit adequate storage at low intravesical pressure
realize emptying at low intravesical pressure
preservation of upper urinary tract
control of infections
continence control without catheter or stoma

Treatment modalities to facilitate bladder emptying
• external compression
• initiation of reflex contraction
• pharmacological manipulation
• bladder neck incision or resection
• external sphincterotomy
• alpha-sympathetic drugs
• relaxants of striated muscle

• intermittent catheterization

Sir Ludwig Guttmann
Intermittent catheterization: history
• 1st February 1944: opening of the National Spinal Injuries Centre in Stoke Mandeville
  – From the author’s personal observations it would appear that neither urethral catheterisation (indwelling) nor suprapubic cystotomy had yet proved a safeguard against ascending urinary infection
  
  • Non-touch intermittent catheterization
  – Sterile, by MD, every 6 hours
  – First publication in 1947: decrease of UTI, no urethral stenosis, no urethral fistulae
  – Earlier return to micturition

Lapides J, Diokno AC, Silber SJ, Lowe BS.

• Antimuscarinic agents
• Surgery
- Lifestile modifications
- Bladder retraining FES
- Antimuscarinic agents
- Pharmacological "modulation"
- Intravesical vanilloids
- Botulinum toxin
- Electrical "modulation"
- Surgery

Antimuscarinics

<table>
<thead>
<tr>
<th>Antimuscarinic</th>
<th>Oxybutynin</th>
<th>Tolterodin</th>
<th>Propiverin</th>
<th>Trospiumchlorid</th>
<th>Solifenacin</th>
<th>Darifenacin</th>
<th>Fesoterodin</th>
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</thead>
<tbody>
<tr>
<td>CNS penetration</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Metabolisation via cytochrome system</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>CNS penetration and elimination unchanged</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
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</tbody>
</table>

Limited by the high incidence of side effects and lack of selectivity:
- dry mouth
- constipation
- blurry vision

Spinelli M. Citeri M. Zanollo L. Guerrer C. Rizzato L.
EAU 2013
Augmentation Cystoplasty

- Enlargement of the bladder using an intestinal segment
  - Increase bladder capacity and compliance
  - Eliminate or decrease involuntary contractions
  - Increase threshold volume at which involuntary contractions occur

Augmentation Cystoplasty Technique

- Create a large opening in the bladder
  - Clam
  - Anterior flap (posterior incision)
  - Posterior flap (anterior incision)
- Addition of a bowel segment
  - Ileum
  - Cecum (ileo-cecal), sigmoid
  - Stomach
- Can be combined with a catheterizable stoma

Augmentation Cystoplasty Technique

- Bowel segment must be detubularized
  - Increase surface area
  - Eliminate peristalsis
- Ileal cystoplasty
  - 25 - 30 cm. of ileum
  - Detubularized into “U” or “S” shape
  - “W” for larger segments

\[ V = \pi r^2h \]

110 pts.

81 EC
10 EC + AS
6 EC + MIT

Augmentation Cystoplasty Complications

- Recurrent UTI
- Persistent mucus
- Stone formation
  - 35% for large and 13% for small intestine (Flood)
- Incomplete emptying
  - Requires intermittent catheterization
  - All patients should be willing to accept this

Augmentation Cystoplasty Complications

- Metabolic disturbances
  - Hyperchloremic metabolic acidosis with small and large intestine
- Perforation
  - 5% in long term
  - More common in patients who catheterize
- Tumor
  - Minimal risk in detubularized, effectively emptied, uninfected cystoplasty
Autoaugmentation

• Detrusor myotomy
  - No addition of bowel segment
  - Detrusor muscle dissected off of the anterior, superior and lateral surfaces of the bladder to create a large diverticulum

• Stohrer, et al.
  - 52 pts with NVD
  - Mean 1.5 ± 0.4 yrs (min 4 yrs)
  - MCC 132 to 320 ml
  - Compliance 9 to 25 ml/cmH2O
  - Pdetmax 95 to 48 cmH2O
  - PVR 45 to 163 ml
  - 4 failures, 9 LTFU
  - Level 4 evidence

Don’t modify the anatomy!

Try to modulate neurogenic dysfunction
Vanilloids

- Capsaicin and Resiniferatoxin
- Activate nociceptive sensory nerve fibers via vanilloid receptor (VR1)
  - Transducer of painful thermal stimuli and acidity
- Activation of VR1 selectively excites and subsequently desensitizes C-fibers

• Antimuscarinic agents
• Surgery
• Pharmacological “modulation” Intravesical vanilloids
• Electrical stimulation and modulation

Vanilloids

• Interesting concept
• Many small series
• Best concentrations and delivery methods for each not established
• No interest by companies

• Antimuscarinic agents
• Surgery
• Pharmacological “modulation” Intravesical vanilloids
Sacral anterior roots stimulation for bladder control in paraplegia
Paraplegia 20:365-381, 1982

- Lifestyle modifications
- Bladder retraining FES
- Antimuscarinic agents

- Pharmacological "modulation"
- Intravesical vanilloids

- Electrical "modulation"
- Botulinum toxin
  - Surgery

Botulinum toxin A

- Botox (Allergan)
  - Vacuum dried
  - 100U vials
- Dysport (Ipsen)
  - Freeze dried
  - More disruptive
  - 500U vials
- Come from different bacterial strains
  - clostridium botulinum
- Dose comparison depending on indication
  - 1 Botox unit = 2-5 Dysport units !!!

Effects of Botulinum Toxin Type A on Detrusor-Sphincter Dyssynergia in Spinal Cord Injury Patients
Dennis D. Dykstra
University of Minnesota, Minneapolis, Minneapolis, Minnesota

primi 5 pazienti 1988
1994 BFA in the sphincter

- Detrusor external sphincter dyssynergia
- Neurogenic detrusor overactivity
- Pelvic floor spasticity in women
- Non-neurogenic overactive bladder
- Benign prostatic hyperplasia
- Interstitial cystitis

are there systemic side effects?
how many times to repeat?
where is the position in algorithm?

Injection technique
- Rigid or flexible scope
- Feasible under local anesthesia
- Trigone sparing or including the trigone?
  - No induction of VUR at 6 weeks
  - No local or systemic side effects
  - Efficacy remains to be evaluated
new technologies

Radiofrequency rizotomy


microanastomosi intradurale tra radici lombari sane e radici motorie sacrali

Xiao technique, nerve rerouting......

thank for your attention
Sacral Rhizotomy

Carlos D’Ancona
Division of Urology, School of Medical Sciences
State University of Campinas – UNICAMP
Campinas, Sao Paulo, Brazil

Affiliations to disclose†:

- Astellas
- Ache

Funding for speaker to attend:

- Self-funded
- Institution (non-industry) funded

Sponsored by:

† All financial ties (over the last year) that you may have with any business organisation with respect to the subjects mentioned during your presentation.

• Munro (1945) - anterior rhizotomy with occasional improved vesical function
• Mieroviski (1950) - sacral rhizotomy S2 to S5, detrusor areflexia, sexual dysfunction, urethral and anal sphincter dysfunction
• Misak et al. (1962) – comparative study between rhizotomy and alcohol injection in subarachnoid space with advantage of rhizotomy
• Heimburger et al. (1948) – improved vesical capacity after lycodaine injection in the sacral foramen
• Rockswold et al. (1974) – anesthetic unilateral S3 block decrease detrusor contraction

• Tockzek et al. (1975) – identification of sacral roots by electrical stimulation and cystometry
• Törrens & Griffith (1976) – good results with selective sacral rhizotomy
• Gasparini et al. (1992) - selective sacral rhizotomy 94% increase vesical capacity

• Mulcahy & Young (1978) – first study in percutaneous radiofrequency
• Ferreira & D’Ancona (2011)*
• Cho & Lee (2012)
• Kim JH et al. (2015)

Prospective study
n = 12 SCI patients
Percutaneous radiofrequency sacral rhizotomy is performed in 8 patients
Follow-up: 12 months


Inclusion criteria
- SCI and NDO, refractory to antimuscarinic drug
- ASIA score A
- Age ≥18
- Positive S3 bilateral anesthetic blockage

Exclusion criteria
- Negative of S3 bilateral anesthetic blockage response
- Presence of ulcer pressure in sacral region

Results
- Increased bladder capacity
- Reduced maximum detrusor pressure
- Reduced autonomic dysreflexia
- Erectile dysfunction (1 patient)
- Detrusor overactivity after 12 months


Urodynamic parameters at baseline and after S3 bilateral anesthetic blockade

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>30' after S3 bilateral anesthetic blockade</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC (mL)</td>
<td>100.2 (+57.9)</td>
<td>313.7 (+103.1), p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>PdetMCC (cm H2O)</td>
<td>82.4 (+31.77)</td>
<td>64.5 (+18.8), p &lt; 0.01</td>
<td></td>
</tr>
</tbody>
</table>


Demographic data.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Neurological level of injury</th>
<th>ASIA score</th>
<th>Voiding method</th>
<th>Time since injury (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>27</td>
<td>T8</td>
<td>A</td>
<td>CIC</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>28</td>
<td>C6/C7</td>
<td>A</td>
<td>CIC</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>40</td>
<td>T9</td>
<td>A</td>
<td>CIC</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>41</td>
<td>C5/C6</td>
<td>A</td>
<td>CIC</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>22</td>
<td>C5/C6</td>
<td>A</td>
<td>CIC</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>37</td>
<td>T12</td>
<td>A</td>
<td>CIC</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>33</td>
<td>L1</td>
<td>A</td>
<td>CIC</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>23</td>
<td>C5</td>
<td>A</td>
<td>CIC</td>
<td>24</td>
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</tbody>
</table>


Urodynamic parameters at baseline, 6 and 12 months after percutaneous radiofrequency sacral rhizotomy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (n = 8)</th>
<th>6 mo (n = 8)</th>
<th>12 mo (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC (mL)</td>
<td>100.2 (+57.1)</td>
<td>313.7 (+103.1)</td>
<td>280.2 (+133.4)</td>
</tr>
<tr>
<td>PdetMCC (cm H2O)</td>
<td>82.4 (+31.77)</td>
<td>64.5 (+18.8)</td>
<td>69.9 (+28.7)</td>
</tr>
</tbody>
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Conclusion

Safe procedure
Low incidence of morbidity
Good results up to 12 months of follow-up
Decrease autonomic dysreflexia
However, further studies are needed with greater number of patients


Prospective study
n = 12 SCI patients
Percutaneous radiofrequency sacral rhizotomy
Follow-up: 4 weeks


Results

Characteristics of the Patients with Spinal Cord Injury

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/ Sex</th>
<th>AIS Impairment Scale</th>
<th>Time since injury (months)</th>
<th>Volding method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34/F C4 (B)</td>
<td>60 C3</td>
<td>12</td>
<td>Se/vodling</td>
</tr>
<tr>
<td>2</td>
<td>50/M C4 (A)</td>
<td>7 C3</td>
<td>32</td>
<td>Diaper vodling</td>
</tr>
<tr>
<td>3</td>
<td>50/M C4 (A)</td>
<td>7 C3</td>
<td>32</td>
<td>C4 (B)</td>
</tr>
<tr>
<td>4</td>
<td>50/M C4 (A)</td>
<td>7 C3</td>
<td>32</td>
<td>T4 (B)</td>
</tr>
<tr>
<td>5</td>
<td>50/M C4 (A)</td>
<td>7 C3</td>
<td>32</td>
<td>T10 (A)</td>
</tr>
<tr>
<td>6</td>
<td>50/M C4 (A)</td>
<td>7 C3</td>
<td>32</td>
<td>T14 (B)</td>
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<tr>
<td>7</td>
<td>50/M C4 (A)</td>
<td>7 C3</td>
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<tr>
<td>8</td>
<td>50/M C4 (A)</td>
<td>7 C3</td>
<td>32</td>
<td>T22 (B)</td>
</tr>
<tr>
<td>9</td>
<td>50/M C4 (A)</td>
<td>7 C3</td>
<td>32</td>
<td>T26 (B)</td>
</tr>
<tr>
<td>10</td>
<td>50/M C4 (A)</td>
<td>7 C3</td>
<td>32</td>
<td>T30 (B)</td>
</tr>
<tr>
<td>11</td>
<td>50/M C4 (A)</td>
<td>7 C3</td>
<td>32</td>
<td>T34 (B)</td>
</tr>
<tr>
<td>12</td>
<td>50/M C4 (A)</td>
<td>7 C3</td>
<td>32</td>
<td>T38 (B)</td>
</tr>
</tbody>
</table>

ASIA: American Spinal Injury Association
CIC: Clean intermittent catheterization


Comparison of urinary volume and incontinence

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average CIC volume of each time (ml)</td>
<td>304±108</td>
<td>467±134*</td>
</tr>
<tr>
<td>Total amount of incontinence (ml)</td>
<td>255±59</td>
<td>66±191*</td>
</tr>
</tbody>
</table>

Values are mean±standard deviation
*P<0.05


Comparison of cystometrogram findings before and after RSDR

<table>
<thead>
<tr>
<th>Patient</th>
<th>Maximal bladder capacity (ml)</th>
<th>Trabeculation (times)</th>
<th>Maximal bladder capacity (ml)</th>
<th>Trabeculation (times)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>300</td>
<td>1</td>
<td>300</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>400</td>
<td>1</td>
<td>500</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>500</td>
<td>1</td>
<td>700</td>
<td>1</td>
</tr>
<tr>
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<tr>
<td>12</td>
<td>140</td>
<td>1</td>
<td>2500</td>
<td>1</td>
</tr>
</tbody>
</table>


Conclusion

It is safe
There are few complications
Decreases the incontinence
Increases bladder volume
Limitation – long term effects on the detrusor
Further studies are needed with greater number of patients and longer follow-up

• Prospective and randomized study
• n = 10 SCI patients
• Percutaneous bipolar continuous radiofrequency sacral rhizotomy
• Follow-up: 12 weeks


Percutaneous bipolar continuous radiofrequency on sacral nerves

Theory:
• bipolar RF is more effective than monopolar
• bipolar RF generates current between two closely placed electrode tips
• generates a high RF electric field
• more rapid tissue heating
• ability to generate larger lesions than monopolar


Results

Percutaneous bipolar continuous radiofrequency on sacral nerves

Patient’s demographic and clinical data

<table>
<thead>
<tr>
<th>Patient’s demographic and clinical data</th>
<th>Frequency of UI</th>
<th>Volume of UI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>M53, C5 (28)</td>
<td>58, 63, 48</td>
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<tr>
<td>2</td>
<td>M30, C5 (22)</td>
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<td>M26, C5 (28)</td>
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<tr>
<td>5</td>
<td>M39, C5 (28)</td>
<td>57, 62, 48</td>
</tr>
<tr>
<td>Intervention</td>
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<td></td>
</tr>
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<td>58, 63, 48</td>
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<td>M39, C5 (28)</td>
<td>57, 62, 48</td>
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</table>


Results

Values of UDS parameters at baseline and follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>Intervention group</th>
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</thead>
<tbody>
<tr>
<td>Frequency of UI</td>
<td>Baseline</td>
<td>3 mo</td>
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<tr>
<td>Rosenberg</td>
<td>104.89±81.91</td>
<td>86±50±20.30</td>
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<tr>
<td>MDC (nitro)</td>
<td>64.68±45.97</td>
<td>77.89±39.82</td>
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<tr>
<td>Volume of MDC (nitro)</td>
<td>332.4±184.38</td>
<td>232.8±184.38</td>
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<tr>
<td>QoL</td>
<td>318.4±64.62</td>
<td>351.3±64.62</td>
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</tbody>
</table>

Values are presented as mean±standard deviation. UDS, urodynamic study; MDC, maximum detrusor pressure during filling; MOC, maximum onsympygmatic capacity; UI, urinary incontinence.

Percutaneous is more cost-effective

Percutaneous RF & neuromodulation therapy:
- $1,800 test sacral nerve stimulation
- $23,000 sacral nerve stimulation implant
- $300 - $400 bipolar RF


Sacral Rhizotomy

Advantages
- Minimally invasive
- Outpatient procedure
- Low cost
- High success rate in short and mid-term follow-up

Disadvantages
- Erectile dysfunction
- Lower limb atrophy
- Urethral and anal sphincter dysfunction
- Recurrent NDO in long-term follow-up

Houle, AM et al., J Urol, 160:1088-1091, 1998

Thank you
どうもありがとうございました
Neurostimulation and neuromodulation: Are we waiting something new?

Caldwell: direct stimulation of the sphincter

Direct stimulation of reservoir

Sacral roots stimulation

Sacral Root Stimulation: Brindley Approach

The Brindley era
The Brindley era

Sacral anterior root stimulation (SARS) with posterior sacral rhizotomy (PR)

PR to avoid neurogenic detrusor overactivity

SARS with intradural book electrode SARS with extratradural cuff leads

ELECTRICAL STIMULATION
NORMAL VOIDING ACT

Detrusor contraction (Stimulus)

S2 direct stimulation to obtain erection

S3-S4 direct stimulation to obtain bowel contraction

effect parameters related

effects on all sacral area dysfunctions with 3 different programs

only SCI complete lesion invasive

PR non accepted long term wallerian degeneration
anatomical and functional knowledge of “sacral box”

The electrical box of “pelvic area”

anatomical studies

primary somatic contributor of pudendal nerve for external sphincter leg, foot

all pelvic autonomic functions and striated muscles

pelvic autonomic and somatic no leg or foot
from neurostimulation to neuromodulation

- contraction of levator ani, external anal sphincter muscle (Pudendal nerve)
- sensation in labia majora, vagina, penis, scrotum (perineal branch of Pudendal nerve) and into rectum (inferior rectal nerve)
- flexion of the toes (tibial branch of sciatic nerve)

sacral neuromodulation indications
- urge incontinence
- voiding difficulties
- urgency frequency
- faecal incontinence
- pelvic pain
- idiopathic ?

Paradox 1

How does sacral neuromodulation suppress voiding in patients with incontinence, but promote voiding in patients with “non-obstructive” urinary retention?

De Groat ISPIN 2003

Paradoxe 2

treatment for everything!

“If I enter in an “electrical system” and I have success with a modulation it means that I have an undisclosed neurogenic situation”

Spinelli 2003
Electrical stimulation of peripheral nerves

• to cause muscle contraction
• to produce sensation
• to activate reflexes
• to modulate some function of central nervous system (neuromodulation)
Working model: normal function

- Afferents synapse in PAG
- Sensation registered in RI
- Decision to void in PFC
- Motor output in ACG
- For voiding, motor output activates PMC (via PAG)
- PMC sends motor output to bladder and urethra

Sacral neuromodulation indications

LUTS
motor and sensory

Selection of patients
predictive factors
- psychological evaluation
- neurophysiological evaluation

Method
from PNE and one stage implant to SPI two stage
- tined lead
- sacral and pudendal

Outcome
parameters?
First description of the minimally invasive technique
Sacral Neuromodulation (Interstim®)

- Frequency / Urgency ≤ 50-80%
- Urinary Incontinence ≤ 50-80%
- Urinary Retention > 80%
- Chronic constipation > 70%
- Faecal incontinence > 90%

SNM Concerns

- Not approved for neurogenic LUTS
  - ? of indications/studies
  - ? of financial reimbursement if done
  - ? about MRI safety

Literature data thanks to Dr. Elneil

SNM Concerns literature

van Vosskuilen AC, et al., Eur Urol 2008; 42:560-72
Interstim for Neurogenic LUTS

- Review of neurogenic patients tested with SNS
- 33 patients tested, 28 implanted

Wallace et al, AJOG, 2007

SNM for Neurogenic LUTS Meta-analysis

- 26 studies (357 patients) as of April 15, 2010
- Pooled success rates
  - 68% for test phase
  - 92% for permanent SNS
- Mean follow-up of 26 months


Interstim for Neurogenic LUTS

- N = 62 trialed
  - DO = 34
  - Retention = 28
  - DSD = 9
- 41/62 had > 50% improvement, 37 implanted
  - Follow up avg 4.3 years
- 76% of those implanted maintained outcomes
  - 8% results partially altered
  - 16% loss of efficacy

Chaabane, et al, Neurourol Urod, 2011

| Reference | Year of publication | Type of evidence | Study No. | No. of patients | No. of patients (%) | Mean follow up | Study includes data on
<table>
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<td>6 (60)</td>
<td>28</td>
<td>T-Y-P</td>
</tr>
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</table>

LUTS = lower urinary tract dysfunction; MS = multiple sclerosis; CVA = cerebrovascular accident; CP = cerebral palsy.
Patients with Retention

Patients with NDO

### Issues with SNM for Neurogenic LUTS

- Potential loss of efficacy in patients with progressive disease

- MRI issues: “MRI is not recommended for a patient who has any implanted component of a neurostimulation system. Exposing a patient with an implanted neurostimulation system or component to MRI may potentially injure the patient or damage the neurostimulator...”

[Medtronic website, 2006]

### Chronic Pudendal Nerve Stimulation

- \( N = 15 \) with neurogenic DO (8M, 7F)
- Tined leak placed near pudendal nerve
- 12/15 had successful trial stage and implanted
  - 8 became continent
  - Remainder had significant improvement
- Many had improvement in bowel function
- At 6 mo follow-up improvements maintained

[Spinelli et al, Neurourol Urod, 2005]
Genital Nerve Stimulation

- N = 67 (41 M, 26 F; 56 SCI)
  - 17 had sensation and completed all 3 cycles
- Clitoral or Penile stimulation
- Automatic or Patient controlled stimulation
  - 3 cystometrygrams
    - 1 - no stim
    - 2 - automatic stim
    - 3 - patient controlled stim

Opisco et al, J Urol, 2008

Neuromodulation for Neurogenic LUTS

- Large number of studies on commercially available neuromodulation devices
- SNM – studied on a plethora of neurogenic etiologies
  - OAB and Retention
  - Results similar to idiopathic


The “dark side”:
what efforts for future

What’s the real aim of our efforts in the future?

- to find out an answer for non-responder patients
- to improve the clinical outcome in therapeutic options
- to open new fields in modulation and direct stimulation of sacral area

Early Sacral Neuromodulation Prevents Urinary Incontinence After Complete Spinal Cord Injury

- Placement of bilateral S3 leads soon after SCI
  - during flaccid stage
- At 2 years fu prevented progression to high pressure overactive bladder

method monitoring

Objective responses

size recharge

sacral and pud monolateral bilateral

easy for pts and ph

Neuromodulation

Neurophysiological Assessment During Implant Of Sacral Neuromodulation Lead (SPI technique)

EAS direct efferent and reflex responses

spinal SEPs D10-D12 afferent response

S3 stimulation
Activation of afferent innervation over up to three sacral segments

Efferent stimulation also provides direct activation of the external urethral sphincter, the external anal sphincter, and levator ani muscles, which may be of some benefit in sacral area control.
method
monitoring
objective responses
monolateral bilateral
size recharge
sacral and pud
easy for pts and ph

Unilateral versus bilateral neuromodulation in a rat rhythmic bladder contraction model

Bilateral stimulation abolished bladder contractions.

BILATERAL IMPLANT BIPOLAR EACH SIDE

BILATERAL IMPLANT CROSS OVER STIMULATION

The stimulation is not trans-foramen rather anterior to sacrum

method
monitoring
objective responses
IPG size recharge

sacral and pud
monolateral bilateral

Restore Prime
Two octapolar lines
Weight 67 g
H:65mm
L:49mm
Thickness 15 mm
Socket A: 0-7

bifurcated extension lead
sacral epidural approach

thank to Prof. Raz

Sacral Hiatus

bilateral caudal epidural

thank to Prof. Raz

simultaneous pudendal and sacral stimulation

bilateral pudendal nerve stimulation
new strategies of pelvic nerve stimulation for recovery of pelvic sexual functions and locomotion in paraplegics

current practice
future concepts

predictive factors
selective stimulation
bioengineering
neuropasticity and precocious modulation

device and leads

different parameters related to symptoms?
cycling to avoid nerve abutment?
Tai C.
voiding reflex in chronic spinal cord injured cats induced by stimulating and blocking pudendal nerves
Neuourology Urodynamic 2008

What to choose?
• Constant voltage vs constant current
• High frequency tonic stimulation
  • Burst stimulation
  • Current fractionalization
  • kHz tonic stimulation with complete current conduction blockage
  • Different waveforms
  • Independent power sources

Round the corner?
• Axonics
• Bioness
• Biowave
• Bluewind
• Stimguard

Sacral
Tibial
Pudendal
Cavernous
Implantable
Wireless
cutaneous
Multiple channel independent programming IPG
Low and high frequency
More flexible leads
Selective stimulation settings
Close loop

precocious modulation

precocious modulation!

CARE
↓
CURE
Thanks for your attention
Augmentation Cystoplasty

Remains an option

- in neurogenic bladder dysfunction
- non-neurogenic bladder dysfunction

when conservative management, pharmacological methods and minimally invasive treatments have been unsuccessful and exhausted

Augmentation Cystoplasty

- used for the small capacity, high-pressure, poorly compliant or overactive bladder

- The technique aims to
  - provide urinary storage
  - protect the upper urinary tract and preserve renal function
  - provide continence
  - resistance to infection
  - offer a convenient method of voluntary and complete emptying.

History

- first described in the canine model by Tizzoni and Foggi in 1888
- first described in humans by von Mikulicz in 1889
- The technique was popularised by Couvelaire in the 1950s, as a treatment for small contracted tuberculous bladders
- The introduction of clean intermittent self-catheterisation (CISC) contributed to the wider use of AC,

Techniques

<table>
<thead>
<tr>
<th>Type of AC</th>
<th>No. of Patients</th>
<th>Initial Procedure</th>
<th>Final Result</th>
<th>Bladder Capacity</th>
<th>Bladder Compliance</th>
<th>Bladder Pressure</th>
<th>Outcome</th>
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<td>Simple AC</td>
<td>50</td>
<td>Transplantation</td>
<td>Success</td>
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<td>Good</td>
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<td>Couvelaire AC</td>
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<td>Bladder Augmentation</td>
<td>Success</td>
<td>500 cc</td>
<td>40</td>
<td>20</td>
<td>Good</td>
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<td>Couvelaire AC</td>
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<td>Success</td>
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<td>40</td>
<td>20</td>
<td>Good</td>
</tr>
</tbody>
</table>
Techniques

Ileum
- most widely used bowel segment
- Ideally 25–40 cm from the ileocaecal
- detubularized into "U" or "S" shape
- "W" for larger segments

Sigmoid
- is generally detubularised as a straight patch or a cup patch
- most common alternative to ileum

Advantages: Its thick muscular wall, large lumen and abundant mesentery guarantee adequate bladder capacity and manoeuvrability

Potential disadvantages:
• the higher risk of UTI (secondary to colonic commensal bacteria)
• larger amounts of mucus production
• theoretically higher long-term risk of malignancy

Indications

Caecum
- can be used in its original tubular shape more
- as a detubularised patch to prevent spontaneous colonic contractions and avoid associated rises in bladder pressure
- most commonly used in conjunction with the terminal ileum as an ileo-caecocystoplasty

It has great mobility, which permits tension-free ureteric anastomosis;
however, the diarrhoea and malabsorption associated with resection of the ileo-caecal valve is often

GASTROCYSTOPLASTY
Where bowel is unavailable or unsuitable, and in patients with metabolic acidosis, stomach is an alternative to bowel.

Advantages
• reduced secretion of mucus
• reduced infection risk
• reduced absorption of electrolytes.

Disadvantages
include the haematuria-dysuria syndrome in particular, are less commonly used

Complications

EARLY COMPLICATIONS
• wound infection (5–6.4%)
• small bowel obstruction (3–5.7%)
• bleeding requiring re-operation (0–3%)
• infection of ventriculo-peritoneal shunt where present (0–20%)
• Regular CISC is needed in 6–39%
• The mortality rate from AC is reported to be 0–2.7%
Stone Formation

- formation of urinary tract stones common complication of cystoplasty’ 3-40%
  - 2% of patients who void spontaneously and efficiently
  - 5-times as common in augmented patients who need to perform CISC when the bladder is catheterised urethrally
  - up to 10-times as common in patients with Mitrofanoff-type channels when the bladder is emptied from above,

*stasis as an important factor in stone formation*

Stone Formation

- usually triple phosphate
  - implying that bacteriuria with urease-producing bacteria (Proteus, Providencia and Klebsiella) may be a causative factor
  - Other risk factors are the presence of intravesical foreign bodies
  - staples
  - mesh
  - mucus
  - hypocitraturia.

Carcinoma

- risk of bladder cancer is higher for patients with congenital bladder dysfunction over the normal population
- controversy as to whether enterocystoplasty is an independent risk factor for carcinogenesis
- Approximate risk of 1.2%
- Many associated with urogenital TB or with other risk factors tobacco use
- long latency period between augmentation and the occurrence (mean of 19–22 years in some series)

Carcinoma

Risk factors
- urinary stasis
- Nitrosamines
- infection
- bladder calculi
- chronic patch inflammation
- immunosuppression

Tumours are generally adenocarcinomas of the bladder or bowel,
- most commonly located in the region of the anastomosis

Incontinence

Nocturnal enuresis

- attributed to a reduction in urethral closing pressure
- relaxation of the pelvic floor muscles,
- increased urine output
- failure of the sphincter to increase in tone in response to contractions from the bowel patch during sleep

*combination of anticholinergic medication, CISC and bladder neck surgery*

Incontinence

Surgical correction usually required only for selected patients with either congenital sphincter deficiency or neuropathy.
Incontinence

- AUS is the outlet procedure that offers the maximum chance of spontaneous voiding.

- performed concomitantly with AC without any increased morbidity, infection rate or change to success rates of either procedure

- theoretical concern that urethral trauma due to CISC in patients with both an AC and an AUS may introduce bacteria into the urine and risk infective complications: not been a concern identified in published studies

Conclusions

There remains a role for AC in the 21st century, greater competition from less invasive procedures

It remains an essential component of the full armamentarium of 1 interventions required to treat bladder overactivity,

Excellent and sustained continence rates, and acceptable morbidity.