Innovations in Neuromodulation

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and

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London
Conflicts of Interest

Medtronic Consultant/Speaker

astellas Consultant/Speaker
Principles of Neuromodulation

• The electrical activities in nerves play a central role in cell-to-cell communication effecting:
  – Sensory, motor, organ functions

• Neuromodulators modulate these electrical activities in the targeted nerve
  – They effect this by changing transmembrane potential (voltage difference inside-outside of membrane)
NEUROMODULATION SITES

- OCD\(^1\)
- Parkinson's Disease
- Essential Tremor
- Dystonia\(^1\)
- Severe Spasticity
- Chronic Pain
- Gastroparesis\(^1\)
- Overactive Bladder Retention Fecal Incontinence

- Depression\(^2\)
- Epilepsy\(^2\)
- Neurodegenerative Diseases (drug-device)\(^3\)
- Migraine Headache Pain\(^3\)

1. Humanitarian Device Exemption (HDE), 2. Investigational Use Only (IDE), 3. Research
VOIDING DYSFUNCTION
AND
CHRONIC URINARY RETENTION
<table>
<thead>
<tr>
<th>Psychological causes of urinary retention in women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysteria</td>
</tr>
<tr>
<td>Psychosis</td>
</tr>
<tr>
<td>Rape</td>
</tr>
<tr>
<td>Incest</td>
</tr>
<tr>
<td>Abortion</td>
</tr>
<tr>
<td>Pelvic surgery</td>
</tr>
<tr>
<td>Sterility</td>
</tr>
<tr>
<td>Marriage</td>
</tr>
<tr>
<td>Death in the family</td>
</tr>
<tr>
<td>Intrafamilial conflict</td>
</tr>
</tbody>
</table>
Aetiology

Primary
- Congenital neurological disease
- Congenital muscular disorders

Secondary
- Neurological disease
- Inflammation
- Endocrine (hypothyroidism, diabetes)
- Psychogenic (anxiety, depression, hysteria)
- Iatrogenic (bladder/bowel/gynaecological surgery)
- Idiopathic (failure of urethral sphincter relaxation)
Classification of VD and CUR

Asymptomatic Voiding Dysfunction
   Recurrent UTI, Frequency, Urgency

Symptomatic Voiding Dysfunction
   Poor stream, Straining, Incomplete emptying

Acute Retention
   Painless/Painful, Sudden onset

Chronic Retention
   Reduced sensation, Frequency/Urgency, Nocturia, UTI

Acute-on-chronic Retention
   Painful/Painless, Sudden onset, Chronic retention incontinence
Maximal Urethral Closure Pressure

Maximal Urethral Closure Pressure = 166 cm H₂O
Expected [92 – age(21)] = 71 cm H₂O

> 50% expected value for age

2-D and 3-D USS Sphincter Volume

> 1.8 cm³

EMG
Lifestyle and Behavioural Changes

Catheterisation

Problems with UTI, Compliance, etc

Urethral Dilatation

Efficacy

Neuromodulation

Major Reconstructive Surgery e.g. Clam Ileocystoplasty
Neuromodulation or Bladder ‘Pacemaker’
### Outcomes of Stage-1 SNM in relation to investigations performed

N=175

<table>
<thead>
<tr>
<th></th>
<th>Success</th>
<th>Failure</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>37.1±11.1</td>
<td>34.8±12.0</td>
<td>0.389</td>
</tr>
<tr>
<td>(n=142)</td>
<td>(n=33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UPP (cmH2O)</strong></td>
<td>102.47±26.8</td>
<td>105.4±22.2</td>
<td>0.643</td>
</tr>
<tr>
<td>△ (n=82)</td>
<td>△ (n=22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sphincter volume (cm³)</strong></td>
<td>1.9±0.6 △ (n=69)</td>
<td>2.0±0.4 △ (n=15)</td>
<td>0.381</td>
</tr>
<tr>
<td><strong>EMG Done</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>76</td>
<td>11</td>
<td>0.459</td>
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<tr>
<td>Abnormal (Fowler’s Syndrome)</td>
<td>51</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Equivocal</td>
<td>15</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>△ (n=142)</td>
<td>△ (n=33)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Effect of use of opiates on the outcomes of Stage-1 SNM
SACRAL NEUROMODULATION IN VD and CUR: DETERMINATION OF PROGNOSTIC FACTORS

Study Group:
All patients who underwent SNM 2004-2011
FU for 48.7 months

PROGNOSTIC FACTORS REVIEWED:
Age, Aetiology, UPP, SV, EMG, Opiate use

RESULTS:
Stage-1 outcomes  71% success
Stage-2 outcomes  82% at 3 years

CONCLUSIONS:
No single prognostic factor determined success and opiates had no impact
Larger prospective trials with long-term evaluation are needed
## SNM in Pregnancy

Int Urogynecol J

Table 1 Outcome of 13 pregnancies in ten patients with Fowler’s syndrome treated by sacral neuromodulation

<table>
<thead>
<tr>
<th>Case</th>
<th>Parity</th>
<th>Gestation (weeks)</th>
<th>Mode of delivery</th>
<th>Weight of baby (g)</th>
<th>SNM status during pregnancy</th>
<th>Complications during pregnancy</th>
<th>Co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Multiparous</td>
<td>8</td>
<td>Miscarriage</td>
<td></td>
<td>Off</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Multiparous</td>
<td>32</td>
<td>CS</td>
<td>1,980</td>
<td>Off</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Multiparous</td>
<td>35</td>
<td>CS</td>
<td>3,490</td>
<td>Off</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Multiparous</td>
<td>36</td>
<td>CS</td>
<td>2,300</td>
<td>Off</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Primiparous</td>
<td>36</td>
<td>CS</td>
<td>3,080</td>
<td>Off</td>
<td>rUTI</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Primiparous</td>
<td>36</td>
<td>CS</td>
<td>2,800</td>
<td>Off</td>
<td>rUTI</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Primiparous</td>
<td>37</td>
<td>CS</td>
<td>3,580</td>
<td>Off</td>
<td>rUTI</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Multiparous</td>
<td>38</td>
<td>CS</td>
<td>3,030</td>
<td>On</td>
<td></td>
<td>Breast cancer</td>
</tr>
<tr>
<td>9</td>
<td>Primiparous</td>
<td>38</td>
<td>CS</td>
<td>4,040</td>
<td>On</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Multiparous</td>
<td>39</td>
<td>SVD</td>
<td>3,630</td>
<td>On</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Multiparous</td>
<td>39</td>
<td>SVD</td>
<td>2,820</td>
<td>Off</td>
<td>rUTI</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Primiparous</td>
<td>39</td>
<td>Forceps</td>
<td>2,930</td>
<td>Off</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Multiparous</td>
<td>41</td>
<td>SVD</td>
<td>3,170</td>
<td>Off</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CS* caesarean section, *SVD* spontaneous vaginal delivery, *rUTI* recurrent urinary tract infections

Khunda et al., 2014
Figure 1. The relation between age and SNM successful outcome (%). Note: Median age for cut-off for successful outcome = 43 years.
CUR in Females and Associated Gynaecology Pathology
*Implanted with SNM Device*

Karmarkar et al., 2015
> 150,000 Patients Treated Worldwide
1996-2004 Historically SNM in 30 patients with urinary retention

2004  Appointed consultant at UCLH and NHNN in August

2004  10 patients implanted

2005-2010  Service expansion in SNM therapy with 20-35 patients per year
            Training of colleagues from around the UK, South Africa and Europe

2010-2011  European Pudendal Neuromodulation study with Medtronic

2010 to date  Further service expansion of SNM at NHNN
               > 300 implanted patients (Local)

2012 to date  Working with NICE/BSUG/IUGA/INS to develop guidelines
               for SNM use in the UK, Europe and Worldwide
               (National and International)
               Working with MEDTRONIC to make NHNN an International
               training centre

2014  MOU for SNM research

2016  > 500 implanted patients
Challenges

Leads
Fixation
Mechanical stress
Design and Material
Electromagnetic interference

Implantable Neuromodulators
Power management or Battery Life
  • Wireless Technology
  • Design and size
Programming
  • Parameters definition
  • Security
Electromagnetic interference
  • MRI

Programmers
Wireless communication
Electromagnetic interference
  • MRI
> 150,000 Patients Treated Worldwide
Challenges

**Leads**
- Fixation
- Mechanical stress
- Design and Material
- Electromagnetic interference

**Implantable Neuromodulators**
- Power management or Battery Life
  - Wireless Technology
  - Design and size
- Programming
  - Parameters definition
  - Security
- Electromagnetic interference
  - MRI

**Programmers**
- Wireless communication
- Electromagnetic interference
  - MRI
Solutions
Identify our Neuromodulation Needs

- Accepted by patient and doctor
- Easy implantation and programming
- Reduce cost
- Multiple anatomical locations
What are our problems?

Lead Issues
- Fixation
- Mechanical stress
- Design and Material
- Electromagnetic interference

Current leads can ‘unfix’
Current leads can ‘fracture’
Suitable
Not MRI compatible

Current solutions 2015
R & D
- New leads with modified tines, design and greater flexibility
- Not MRI compatible
- Awaiting CE mark
What are our problems?

Implantable Neuromodulators
Power management or Battery Life
  • Wireless Technology
  • Design and size
Programming
  • Parameters definition
Electromagnetic interference
  • MRI

- Needs to change every 3-7 years
- Not fully available
- Patients can feel battery in-situ
- Needs special technical input
- Some compatibility

Current solutions 2015
R & D
- Rechargeable, small battery lasting up to 15 years, with better external communication
- Technical input minimal and can be done remotely
- MRI compatible
What are our problems?

Programmers
• Technical expertise required  Mandatory
• Wireless communication  Not available currently
• Electromagnetic interference  Not MRI compatible
  • MRI

Current solutions 2015
R & D
- Tablet interface, so can be programmed by anyone once taught
- Remote programming
Review our Research and Development Stance

- Preclinical Research
- Clinical Feasibility
- Product Development
- Clinical Trials re Safety
- Regulatory approval
- Clinical Trials re Efficacy
- Clinical Uptake

Clinically Established

Usually 5 years → Usually 5-10 years
New Companies

BlueWind Medical

FemPulse

StimGuard

Axonics

NUVIANT Medical
Vaginal Neuromodulation Technology
FemPulse®

• Target: OAB, Multiple pelvic floor disorders

• Vaginal approach neuromodulation delivery

• Targets the plexuses that serve as the "gateway" between pelvic visceral organs and the central nervous system (autonomic plexus which resides adjacent to the apex of the vagina near its junction with the cervix)

• Continuous and targeted treatment without surgery or an implant

• Ease-of-use may make all the difference in treatment compliance
Modified Sacral Neuromodulation Technology
Axonics®

Target: OAB, Multiple pelvic floor disorders

Quadripolar tined flexible lead for sacral neuromodulation

External Pulse Generator (EPG)
  • Disposable trial “patch” used to evaluate suitability of patients for a permanent implant

Implantable Pulse Generator (IPG)
  • Miniature and rechargeable
  • Capable of monopolar and bipolar stimulation options
  • Rechargeable wireless puck allowing patient mobility

Patient remote
  • Small handheld user-friendly device used by the patient to adjust therapy settings

Clinician programmer
  • Tablet supporting implantation procedure and customized settings of the implant
Implantable Tibial Nerve Neurmodulation Systems
Implantable Tibial Nerve Device
‘Gecko’

- Target: OAB, Multiple pelvic floor disorders
- Thin implantable neuromodulator
- Can modulate of a variety of neural structures, and thus multiple neural targets including OAB
- Bi-directional wireless link with neural-physiological measurements allows reprogramming and updating
- Rechargeable battery with capacity exceeding 2 weeks
StimGuard®

- Target: OAB, Multiple pelvic floor disorders
- StimGuard is a 1.3mm microchip neuromodulator implanted with a needle, under the skin.
- The device communicates with a small external transmitter (requires no physical contact with the skin).
- Device contains no batteries or upgrade components
- Compatible with MRI scans.
Research and Development Stage

- Target: OAB, Multiple pelvic floor disorders
Introduction: RENOVA™ System components

Passive Implant

External Control Unit

Physician Programmer
### Introduction: OPTIMIST Study design

<table>
<thead>
<tr>
<th>Patients &amp; Clinical sites</th>
<th>36 implanted patients at 4 centers in The Netherland and UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Population</td>
<td>Patients with OAB with or without urge incontinence</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Incidence of SAE (system and/or procedure related)</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td>• Six-month clinical improvement</td>
</tr>
<tr>
<td></td>
<td>o Number of voids/day</td>
</tr>
<tr>
<td></td>
<td>o Volume voided/void</td>
</tr>
<tr>
<td></td>
<td>o Degree of urgency prior to void</td>
</tr>
<tr>
<td></td>
<td>o Number of leaks per day</td>
</tr>
<tr>
<td></td>
<td>In the presence of urge incontinence:</td>
</tr>
<tr>
<td></td>
<td>o Leakage episodes/day</td>
</tr>
<tr>
<td></td>
<td>o Severity of leaking episodes</td>
</tr>
<tr>
<td></td>
<td>o Absorbent pads used due to leaking/day</td>
</tr>
<tr>
<td></td>
<td>• Quality of Life Questionnaire – OAB-q</td>
</tr>
</tbody>
</table>
Methods: Implantation procedure

Mean “skin to skin” duration: 34 min

First skin cut
Fascia cut
Identifying bundle

Implant placement
Last implant suture
Last Skin suture

Intra-operative sensory/motor response is tested to confirm accurate location.
Results - Demographics

**Gender**
- Female, 31, 86%
- Male, 5, 14%

**OAB diagnosis**
- Wet OAB, 31, 86%
- Dry OAB, 5, 14%
Results: Clinical Performance in OAB Symptoms

<table>
<thead>
<tr>
<th>Month</th>
<th>Percent of OAB subjects %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1 (n=33)</td>
<td>54.5/15.2</td>
</tr>
<tr>
<td>Month 3 (n=34)</td>
<td>64.7/17.6</td>
</tr>
<tr>
<td>Month 6 (n=34)</td>
<td>70.6/17.6</td>
</tr>
</tbody>
</table>
Discussion & Conclusion

The RENOVA™ novel peripheral nerve stimulator is feasible & safe

- 70.6% of all subjects (n=34) show >50% improvement at 6m
- 27.6% of UI subjects were dry at 6 months
- There is a trend toward improvement of the responders over time
- OAB-q results demonstrated significant improvements

Advantages:

- Miniature leadless implant
- Battery-less
- Wireless

**Simple and safe** implantation procedure achieving objective and subjective improvement for patients suffering from OAB
Where next with implantables?

• Pudendal neuromodulation
  – Current systems do not specifically support pudendal
    neurmodulation, but extend sacral neurmodulation
    technology to the pudendal nerve

• Why is it important to consider alternative technology?
  – The pudendal nerve is a good alternative to sacral
  – It stimulates S2, S3, and S4 better (increased afferent
    stimulation through the sacral nerve roots)
  – It is more desired than sacral
  – It salvages >90% of sacral failures

Alternative ‘wearable efficacious’ technology

Current stance

– Safety is good

– But, cutaneous technology does not demonstrate long term efficacy currently

– Device delivery is a problem as it requires adhesives (not always tolerated) and may impact on daily living
Conclusion

Emerging Technology

- Technology is only part of the picture
  - We need more nerves and sites to modulate
  - We need more innovation
  - We need efficacy, safety and longevity

Hospital Admin

- Patients
  - Selection is key
  - Self-management is essential
  - Outcomes
    - Efficacious and safe
    - Responsive to multiple conditions: OAB, CPPS, Sexual dysfunction
  - Better data

Patient

Funding

Healthcare Professionals

- Cost to Hospital Admin and Funders
  - Align to cost needs, quality and utilization goals
  - Look at lower cost settings: outpatients, day-case

- Healthcare Professionals
  - Ease of use encourages uptake
  - Longevity of device and battery system
  - Treats multiple conditions
Thank-you