Bladder Control and Electrical Stimulation

Neurogenic Bladder and SNS

Overactive Bladder and SNS

Fowler, Griffiths and de Groat, Nat Neurosci, 2008
Elkelini, Abuzgaya and Hassouna, IUGA J, 2010
Sacral Neuromodulation (SNM) and Tibial Nerve Stimulation for Neurogenic Bladder Control


EFFICACY OF NEUROSTIMULATION USING A NOVEL TRANSDERMAL AMPLITUDE MODULATED SIGNAL (TAMS) IN A PRE-CLINICAL DETRUSOR OVERACTIVITY (DO) RAT MODEL

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Methods

- Continuous infusion of 0.25% acetic acid to generate bladder hyperreflexia
- Ag/AgCl Electrodes
- Collect data on bladder pressure and void volume

Animal Model

- NeuroStimulation “Patch”
- Bladder catheter
- Pressure transducer
- Infusion pump
- Urinary bladder
- Pelvic nerve
- Pudendal nerve
- Urethra
- Collection cup
- LabVIEW function generator for SNS waveform generation

Signal

- Amplitude-modulated waveform
- 210 kHz carrier frequency

T=1/f = Low (amplitude-modulating) stimulation frequency
PW = Pulse width
Tc=1/fc = Carrier frequency
Intravesical Pressure (mm Hg)

<table>
<thead>
<tr>
<th>Priority</th>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pulse Width</td>
<td>50, 100-800 µs in 100 µs increments</td>
</tr>
<tr>
<td>2</td>
<td>Pulse Frequency</td>
<td>5, 15-55 Hz in 10 Hz increments</td>
</tr>
<tr>
<td>3</td>
<td>Pulse Amplitude</td>
<td>-2 to -10 V in 2 V increments</td>
</tr>
<tr>
<td>4</td>
<td>Orientation</td>
<td>Lateral/Longitudinal</td>
</tr>
<tr>
<td>5</td>
<td>Pulse Polarity</td>
<td>Negative/Positive</td>
</tr>
<tr>
<td>6</td>
<td>Geometry</td>
<td>Triangle/Square/Sine</td>
</tr>
</tbody>
</table>
Results and Conclusions

- TAMS waveform reduced contraction frequency in an NDO rodent model
- Further work required to evaluate the potential of this technology for the treatment of urge incontinence
Transdermal amplitude-modulated signal (TAMS): Pre-clinical efficacy

- Control
- Breakthrough at 18 cc

17 V, 10 Hz, 2 ms SNS Stimulation
- Breakthrough at 25 cc
- TAMS Stimulation

- Shen, Roppolo, Subbaroyan et al., Neurourol Urodyn, 30 (4), Apr 2011
- Tai, Shen, Wang et al., BJU 2011
Transdermal amplitude-modulated signal (TAMS): Safety

• Single site, N=12 (Healthy normal)
• 3-day of stimulation and diary
• Signal: 6 V, 1 ms, 35 Hz
• No serious or significant AEs
• Minimal or no pain or discomfort from the stimulation
• Minimal changes in urinary or fecal patterns
• Minimal changes in vital signs
Clinical trial to investigate the efficacy of acute sacral neurostimulation using a novel transdermal amplitude-modulated signal (TAMS) in subjects with neurogenic detrusor overactivity

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The authors would like to acknowledge Mr. Peter Guy, Consultant Urologist at Duke of Cornwall Spinal Injuries Unit for participating in the study as an investigator.
Objective

Demonstrate safety and efficacy of an acute exposure to non-invasive sacral neurostimulation using a novel transdermal amplitude modulated signal (TAMS) to treat neurogenic detrusor overactivity (NDO) in a randomized, sham controlled study.
Signal

Electrode Hydrogel Epidermis

\[ Z = C_e + R_h + C_s = 10 + 25 + 40 = 75 \, \Omega \]

\[ Z = R_e + R_h + R_s = 500 + 25 + 10k = \sim 10 \, k\Omega \]

R – Resistance
C – Capacitance
Study Design

Single blind, randomized, crossover design (N=20, 3 sites)

- 5 Hz, 1 ms or 10 Hz, 1 ms TAMS
- 3 CMGs performed: Baseline, Active/Sham, Sham/Active
- Pain and discomfort VAS

All CMGs performed at 40 cc/min
Study Equipment

- **Signal Generator**
  - Frequency Adjustment (Disabled)
  - Voltage Adjustment
  - ON/OFF button
  - Bicolor LED
  - Connection Jacks (Lead / Data Cable)

- **Resistance Cable**

- **Commercial TENS Electrode**
Methods: Electrode Locations

PERINEAL  S2/S3 DERMATOME  S3 FORAMEN

Figure Source: www.backpain-guide.com
Significant increase in bladder capacity at first leak for 5 Hz signal

- Baseline
- 5 Hz, 1 ms
- Sham

Volume (mL)

All Subjects: 20, 15, 20
MS Subjects: 9, 5, 9
ASIA D Subjects: 4, 3, 4
ASIA A Subjects: 7, 7, 7

* Indicates significant difference.
Significant increase in bladder volume at start of detrusor contraction in ASIA ‘A’ subjects

**Volume (mL)**

- **Baseline**
- **5 Hz, 1 ms**
- **Sham**

*Significant increase in bladder volume at start of detrusor contraction in ASIA ‘A’ subjects*
Volume at first contraction: 182 ml
Pves: 85 cm/H2O
Duration: 3’ 31”
Volume at first contraction: 365 ml
Pves: 70 cm/H2O
Duration: 1’ 58”
Adverse events (AEs)

- 9 AEs reported
- All AEs mild and resolved spontaneously
- 3-Definitely related to the study device/procedure
- 2-Possibly related
Conclusions

• 5 Hz, 1 ms TAMS significantly increased bladder capacity at first leak and volume at first detrusor contraction in ASIA ‘A’ subjects

• Stimulation with TAMS with these parameters in the MS was not found to be effective

• Further clinical work is required to evaluate the potential of this technology for the treatment of NDO
4 Week Safety and Efficacy Evaluation of Patient Managed Neuromodulation System (PMNS) via a Transdermal Amplitude Modulated Signal (TAMS) for Treatment of Overactive Bladder

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¹Southampton Univ. Hosp. Trust, Hampshire, United Kingdom,
BACKGROUND

• Faulty communication between CNS and bladder plays a role in OAB
• Antimuscarinic medications remain a mainstay of treatment
• Side effects may limit their usefulness
• Transcutaneous or implanted electrical stimulation devices have been shown to relieve symptoms of OAB

PURPOSE OF TRIAL

Assess safety and efficacy of a novel, noninvasive PMNS, administered via a self-contained patch, in patients who had previously failed other therapies, including at least one anti-cholinergic drug, for OAB.

DEVICE

PMNS transmits transdermal amplitude-modulated signal (TAMS), (carrier signal and pulse envelope), through patch applied to skin with aid of placement tool

Controlled by wireless handheld remote control
Study Design

• Multi-center, prospective, randomized, self-controlled clinical study including males and females at least 18 years of age with documented OAB symptoms for at least 6 months
• Must have failed conservative therapy for OAB
  – Behavior modification, fluid management and at least one anti-cholinergic drug prescribed to treat OAB.
• Must have mean of 8 or more voids AND 1 urgency (urinary) incontinence episode per day, measured over a 3-day period

• Randomized to 1 of 2 PMNS patch placement groups
  – Investigator Placement group
  – Subject Placement group
• 7-day washout period from anti-cholinergic medications prescribed for treatment of OAB, if applicable
• 3-day baseline voiding diary during run-in period, used to help confirm eligibility
Study Design

• All subjects undergo 4 weeks (wk 1-4) of treatment
  – Investigator places PMNS patch on all subjects for wk 1 of treatment
  – Three-day voiding diaries are completed at wk 1 & 4

• Investigator Placement group
  – return to study site at wks 2, 3 & 4 for PMNS patch replacement

• Subject Placement group
  – return to study site at wk 2, trained/observed in self-patch placement, using placement tool.
  – Replaced own PMNS patch during wk 3 & 4
Primary Objective/Efficacy Variable

Change in mean urgency (urinary) incontinence episodes (leaks) between baseline and Week 4 of active treatment

Secondary Objectives

Evaluate change from baseline to week 4 of active treatment:

• mean urinary frequency
• mean urgency episodes
• mean volume per void

Study Success

Success criteria of 50% reduction in leaks in at least 50% of subjects; chosen prior to start of study
Demographics (Per Protocol)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Description</th>
<th>Investigator Placement</th>
<th>Subject Placement</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean (SD)</td>
<td>59.6 (10.6)</td>
<td>62.1 (14.6)</td>
<td>60.8 (12.7)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>30 to 84</td>
<td>31 to 88</td>
<td>30 to 88</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>34 (91.9)</td>
<td>35 (94.6)</td>
<td>69 (93.2)</td>
</tr>
<tr>
<td>Race</td>
<td>Black or African American</td>
<td>7 (18.9)</td>
<td>1 (2.7)</td>
<td>8 (10.8)</td>
</tr>
<tr>
<td></td>
<td>White or Caucasian</td>
<td>30 (81.1)</td>
<td>36 (97.3)</td>
<td>66 (89.2)</td>
</tr>
<tr>
<td>BMI</td>
<td>Mean (SD)</td>
<td>27.4 (5.2)</td>
<td>27.8 (5.8)</td>
<td>27.6 (5.5)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>20 to 39</td>
<td>18 to 40</td>
<td>18 to 40</td>
</tr>
</tbody>
</table>

n=64
Results

• No significant differences found between subject or investigator applied groups for any of 4 endpoints at baseline or 4 weeks

• 74 subjects enrolled
  – Per Protocol population = 64 patients
    • 8 major protocol violations, 2 withdrawals

• Results represent Per Protocol population
  – no significant differences found between ITT or PP population for any endpoint at any time point
Safety Results (n=74)

65 Adverse Events in 30 patients

- **Mild**: 58 (91%)
- **Moderate**: 6 (9%)

Types of AEs

- **Skin Irritation**: 15 (23%)
- **All Other**: 49 (77%)

No Severe AEs

100% of AEs resolved
Primary Endpoint:
Change in mean urgency incontinence episodes (over 24 hours) – Per Protocol

<table>
<thead>
<tr>
<th></th>
<th>Investigator</th>
<th>Self</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>4.8 (3.3)</td>
<td>4.9 (3.2)</td>
<td>4.9 (3.2)</td>
</tr>
<tr>
<td>4 week</td>
<td>2.3 (2.6)</td>
<td>2.1 (2.5)</td>
<td>2.2 (2.5)</td>
</tr>
</tbody>
</table>

% change:
- Investigator: -52%
- Self: -57.1%
- All: -55.1%

p<0.0001
Standard deviations in parentheses
% changes based on total patient mean change

n=64
Results: Success criteria
50% reduction in leaks in at least **50% of subjects**
(Per Protocol)

**Total population**

- N=40 (62.5%)
- N=24 (37.5%)

95% CI (50.6%, 74.4%)  n=64
Secondary Endpoint:
Change in mean voiding frequency (over 24 hours) – Per Protocol

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline (Standard Deviation)</th>
<th>4 Week (Standard Deviation)</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator</td>
<td>11.1 (2.8)</td>
<td>9.2 (2.6)</td>
<td>-17.1%</td>
</tr>
<tr>
<td>Self</td>
<td>11.5 (3.3)</td>
<td>9.7 (2.8)</td>
<td>-15.7%</td>
</tr>
<tr>
<td>All</td>
<td>11.3 (3.1)</td>
<td>9.4 (2.7)</td>
<td>-16.8%</td>
</tr>
</tbody>
</table>

p<0.0001
Standard deviations in parentheses
% changes based on total patient mean change
n=64
Secondary Endpoint: 
Change in mean # of urgency episodes (over 24 hours) – Per Protocol

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>4 week</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator</td>
<td>9.8 (3.4)</td>
<td>7.6 (3.1)</td>
<td>-22.4%</td>
</tr>
<tr>
<td>Self</td>
<td>10.3 (3.8)</td>
<td>8.0 (3.4)</td>
<td>-22.3%</td>
</tr>
<tr>
<td>All</td>
<td>10.0 (3.6)</td>
<td>7.8 (3.3)</td>
<td>-22.0%</td>
</tr>
</tbody>
</table>

% changes based on total patient mean change

p<0.0001

Standard deviations in parentheses

n=64
Secondary Endpoint: Change in mean volume per void* (over 24 hours) – Per Protocol

<table>
<thead>
<tr>
<th></th>
<th>Per Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator</td>
<td>171.6 (68.8)</td>
</tr>
<tr>
<td>Self</td>
<td>186.2 (65.1)</td>
</tr>
<tr>
<td>All</td>
<td>179.4 (66.7)</td>
</tr>
</tbody>
</table>

% change: 3.6% vs. 4.6%

p<0.0371

Standard deviations in parentheses

% changes based on total patient mean change

*mean volume per void with reported volume

n=64
Conclusions

• No differences existed between investigator applied and subject applied patch usage groups

• Significant reductions in urinary frequency, urgency, and urge incontinence were found after 4 weeks of treatment with the PMNS patch

• The PMNS patch appears to be an effective, noninvasive treatment for the symptoms of OAB