Lumbar to Sacral Nerve Rerouting to Restore Voiding in Spina Bifida

Kenneth M. Peters, MD
Chairman, Department of Urology
Peter & Florine Ministrelli Distinguished Chair in Urology
William Beaumont Hospital, Royal Oak, Michigan

Disclosures

- No relevant financial disclosures

Myelomeningocele

- The neurologic lesion produced by this condition can be variable, depending on what neural elements, if any, have everted with the meningocele sac. The bony vertebral level often provides little or no clue to the exact neurologic level or lesion produced.
- The neurologic lesion produced by this condition influences lower urinary tract function in a variety of ways and cannot be predicted just by looking at the spinal abnormality or the neurologic function of the lower extremities.

Phenotypes

- Synergic (26%)
- Dyssynergic with and without poor detrusor compliance (37%)
- Complete denervation (36%)
Specific Concerns

1) Safety
   - Obstruction
   - Pressure
   - Emptying

2) Social function
   - Continence

Phenotypes

- Categorization of lower urinary tract function in this way has been extremely useful because it reveals:
  - which children are at risk for urinary tract changes
  - who should be treated prophylactically
  - who need close surveillance
  - who can be monitored at greater intervals

Spina Bifida - State of the Art

- Low Pressure Storage
- Continence
- Function

Neuromodulation

InterStim®

The Bion
Botox ... ?

Presynaptic Nerve Terminal

ACh Vesicles
BT
SNAP-25

Blocks ACh Fusion & Release


Lumbar to Sacral Nerve Rerouting: The Xiao Procedure

L5 Dermatome

Scratch
**Xiao Animal Studies**

- **Bench to Bedside**
  - Rat Studies – Late 1980s
    - L4 to L6 Anastomosis
    - Bladder contraction with electrical stimulation
    - Neural Tracing (HRP)
      - Somatic motor axons regenerated successfully into the pelvic nerve
      - Bladder was reinnervated by the L4 motor neurons
  - New concept: the impulse delivered by the efferent neurons of a somatic reflex arc can be transferred to initiate responses of an autonomic effector

- **Higher animal experiments:**
  - Continued experiments focused on the underlying mechanism of the somatic-autonomic reflex pathway for micturition
  - Pharmacological studies:
    - New nerve pathway mediated by cholinergic transmission
      - Nicotinic and Muscarinic Receptors
    - Because the same neurotransmitter is released, somatic reflex activity can be transferred to the bladder smooth muscle and cause a detrusor contraction
    - Can induce reflex in intact animal and after acute spinal cord injury

**Xiao Human Studies – Spinal Cord Injury**

  - 15 Males – Hyperreflexic Bladder and DESD
  - 67% success
  - Synergistic Voiding

**Expanding the Xiao Concept to Spina Bifida Bladder Leg**
Beaumont Experience

- Patient selection
- Pre-operative evaluation
- Surgical approach
- Post-operative care
- Post-operative follow-up
- Potential complications
- Definition of success

Xiao Human Studies – Spina Bifida

- Spina Bifida - J Urology 2005
  - 20 Children - 14 Areflexic, 6 Hyperreflexic NGB
  - 85% success
- Update - European Urology 2006
  - 92 Spinal Cord Injury, 88% success
  - 110 Spina Bifida, 87% success

Beaumont Experience

- Patient selection
  - Age 6 or greater
  - Neurogenic bladder on CIC
  - Intact lumbar nerve roots based on EMG testing
  - Upper extremity motor function
Study Design

- Lower Extremity
  - Neurological Exam
  - EMG / Nerve Conduction Studies
- Bladder
  - Questionnaires
  - CMG / Pressure-Flow
  - Cystoscopy / RBUS / Labs
  - Reflex Arc Stimulation
- Bowel
  - Questionnaires

Beaumont Experience

Pre-operative evaluation
- MRI
- Neurological Exam
- EMG / Nerve Conduction Studies
- Cystoscopy
- Urodynamics
- BUN/Creat

Difficult Surgical Approach

Spinal Cord Injury
Below spinal cord at level of cauda equina
Laminectomy performed to access the dura
Dura opened allowing access to the cauda equina nerve roots
**Spina Bifida**

- Much more challenging
- Often tethered cord
- Approach is different

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**Beaumont Experience: Operation**

- 9 spina bifida patients treated
  - OR time
    - Mean: 183 ± 49 minutes
    - Range: 127 – 278 minutes
  - Blood loss
    - Mean: 57 ± 43 cc
    - Range: 10 – 100 cc
  - Perioperative complications:
    - Wound drainage: 3 patients
    - Lower extremity weakness

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**Beaumont Experience**

- Post-operative care
  - Perioperative antibiotics (Amp / Gent)
  - Bedrest x 48 hours
  - Monitor for dural leak
  - Neurovascular checks
  - Advance diet as tolerated
  - Home on oral pain medication, stool softener and oral antibiotics

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**Beaumont Experience**

- Post-operative follow-up
  - Neurological Examination
    - 1 month, 1 year
  - Urodynamic Testing / Dermatome Stimulation
    - 3, 6, 9, 12, 18, 24, 36 Months
  - Ultrasound
  - Laboratory Monitoring
**Patient Characteristics**

- 9 Patients
  - 3 males
  - 6 females
- Spina Bifida
- Age
  - Median: 8 years
  - Range: 6 to 37 years
- Ambulatory Status
  - AFOs: 5 patients
  - Forearm crutches: 2 patients
  - No assistance: 4 patients
- No prior major bladder surgery

**Baseline Characteristics**

<table>
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<tr>
<th>Pt</th>
<th>Age yrs</th>
<th>Ht. in</th>
<th>Wt lbs</th>
<th>Level</th>
<th>Closed VP</th>
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**Outcomes**

- Hospitalization
  - Mean Length of Stay: 3.4 (2-7) days
  - Perioperative Complications (30 days):
    - Foot Drop - 1 Patient
    - Wound Drainage - 3 Patients
    - Prolonged Inability to Bear Weight - 1 Patient

**Perioperative Data**

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Early Outcomes

- Interesting Stories...
  - Bowel/Bladder Neurological Changes
    - Sudden Worsening of Urinary and/or Fecal Incontinence
    - Improved Continence
    - Ability to Initiate Voiding

Outcomes: Lower Extremity

- Early
  - 8/9 weak
- 1 Year
  - 8/9 at or near baseline
  - 1/9 with foot-drop

Assistive Devices For Ambulation

<table>
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Voiding and Urodynamic Data

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Outcomes: Bladder

Bladder Capacity (MCC) Comparison

- Baseline
- 12 Months

P = 0.18

Involuntary Detrusor Contractions

- Baseline
- 12 Months

P = 0.13

Presence of Novel Reflex Arc with Stimulation

- Months Postoperative

Number Voiding
- Preoperatively: n=2
- 12 Month Urodynamic Testing
  - Voided: n=7
  - Mean Voided Volume = 133 ± 75 cc (50-250)
  - Mean PVR = 119 ± 125 cc (10-380)
  - Mean Qmax = 10 ± 8 cc/sec (4-25)

Number Catheterizing
- 12 Month Questionnaire:
  - 7/9 still using catheter
Outcomes: Bowel

Change In Ability to Move Bowel

Number of Patients

Markedly Markedly Slightly Slightly Markedly Markedly Markedly Markedly Markedly
Worse Worse Worse Worse

6 Months 12 Months

Global Response

Patients

Markedly Markedly Slightly Slightly Markedly Markedly Markedly Markedly Markedly
Markedly Markedly Slightly Slightly Markedly Markedly Markedly Markedly Markedly
Worse Worse Worse Worse

Since having surgery how has the ability to move your bowels changed?

Since having surgery how has the ability to void changed?

Since having surgery how has your quality of life changed?

Knowing what you know now, would you undergo the surgery again?

Lessons Learned

Patient Selection:
- Intrauterine closure of myelomeningocele associated with:
  - Longer operative times
  - Worse intraoperative scar tissue
  - Greater lower extremity weakness postoperatively

Pre-operative neurological testing
- Requires intact lumbar donor nerve
  - Patients using crutches may be at increased risk of conversion to chair
  - Higher lesions may require nerve graft

UPDATE

- Recently finished 2 year follow-up
- Currently 4 of 9 off catheterization
- Bowels improved in most
- Incontinence still problem in some
- Recently performed the rerouting procedure on 4 more children
- Dr. Gilmer joined our research team and was integral in performing the procedure in May 2009

Lessons Learned

- Intrauterine closure of myelomeningocele associated with:
  - Longer operative times
  - Worse intraoperative scar tissue
  - Greater lower extremity weakness postoperatively

- Requires intact lumbar donor nerve
  - Patients using crutches may be at increased risk of conversion to chair
  - Higher lesions may require nerve graft
Conclusions

- First North American trial in spina bifida demonstrating return of bladder and bowel function with nerve rerouting
- Early results show improvement in bladder and bowel function that may have a major impact on quality of life in patients with spina bifida
  - No patient on anticholinergic
  - 2/9 off catheterization at 1 year, 4 of 9 off cath at 2 years
  - 7/9 with novel reflex present
  - 9/9 voiding and/or have a novel reflex
- Foot drop present in 1 patient
- Follow-up ongoing for 3 years
- Crucial to do this under rigorous research protocol given the potential risks. Should not be offered as standard of care until more data is available!

Future Directions

- Novel Micturition Centers
  - Functional MRI
- Preventing Lower Extremity Complications
  - Donor rootlet separation and identification
  - End-to-side anastomosis
- Nerve Growth Factor
  - Can be administered by injection stem cells at the time of the anastomosis

Questions?

Special Thanks to:
- CG Xiao, MD - Nerve Rerouting Pioneer
- Benjamin Girdler, MD - Resident
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- Gary Trock MD - Neurology
- Cindy Turzewski - Study Coordinator
- Our Patients