

A PHASE 2 STUDY - TENGION AUTOLOGOUS NEO-BLADDER AUGMENT (NBA) FOR AUGMENTATION CYSTOPLASTY IN SUBJECTS WITH NEUROGENIC BLADDER SECONDARY TO SPINA BIFIDA

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ABSTRACT:

Introduction: The ability to use an autologous cell-seeded biodegradable scaffold for bladder augmentation was demonstrated in patients with neurogenic bladder (NB) due to spina bifida (SB) at Children's Hospital Boston (CHB)¹. We conducted a confirmatory prospective multicenter Phase 2 study of the Tengion NBA in a similar population.

Methods: Male or female subjects, 3 to 21 years, with NB due to SB, were eligible if they required augmentation cystoplasty for bladder pressure ≥ 40 cm H₂O and/or new onset of upper tract changes. Eligibility was confirmed by a Steering Committee. Bladder neck sling was the only concomitant surgical procedure permitted. Since biomechanical stimulation (cycling) promotes tissue regeneration, patients were required to bladder cycle postoperatively. Following an open bladder biopsy, urothelial and smooth muscle cells were grown *ex vivo* for 5 - 7 weeks, then seeded onto a biodegradable scaffold (the NBA). The implanted NBA served as a template for bladder tissue regeneration. The primary endpoint was urodynamic (UDS) compliance 1 year post implantation. Evaluations included cystograms, renal ultrasounds, physicals and labs.

Results: Four centers enrolled 11 subjects; 10 (6 females) were implanted. Mean age was 8.2 [3-16] years. The procedure was generally well tolerated. Six patients able to bladder cycle showed clinical improvement. Overall, UDS changes were consistent with those from CHB. Hydronephrosis and/or reflux improved/resolved in 4/5 patients. Patients unable to cycle (3 concomitant bladder neck slings, 1 low pressure high grade reflux) showed no UDS improvement at 12 months.

Discussion: The study supports the potential of regenerative medicine in bladder augmentation. Long term follow-up is ongoing. Additional studies are needed to confirm the benefits of this promising technology.

I. OBJECTIVE:

A prospective, multicenter Phase 2 study in the United States was undertaken to evaluate the efficacy and safety of an autologous NBA for bladder augmentation in subjects with neurogenic bladder secondary to spina bifida who are refractory to medical treatment.

II. METHODS:

ENTRY CRITERIA:

- Male or female 3-21 years old
- Presence of either or both of the following despite maximally-tolerated dose of anticholinergic agents:
 - decreased and inadequate bladder compliance with a bladder pressure ≥ 40 cm H₂O at or below the predicted bladder capacity for age
 - new-onset of upper urinary tract changes (hydronephrosis, vesicoureteral reflux [VUR]) in the last 12 months
- Eligibility confirmed by a Steering Committee

ENDPOINTS:

- Primary endpoint: compliance at 12 months after augmentation
 - Mean of 2 reflective consecutive UDS runs as read by a central reader
- Safety
- Continenence
 - Assessed by a post-hoc qualitative analysis of patient/parent-reported assessment of voiding habits
- Radiographic evaluation of hydronephrosis and/or VUR
- Long term follow-up 60 months after augmentation

Reference cited:
1. Atala A, Bauer SB, et al. (2006) Lancet 367, 1241-1246.

PROCEDURES:

- Open biopsy of bladder for procurement of autologous bladder cells
 - At time of biopsy, laparoscopic evaluation of adequacy of the omentum for wrapping of NBA during implantation
 - Isolation and propagation of autologous urothelial and smooth muscle cells *ex vivo* for 5 - 7 weeks by Tengion
- Cells seeded onto a biodegradable scaffold for implantation
- Surgical attachment of the NBA to the dome of the native bladder (Figure 1)
- Vascularization enhanced through mobilization and wrapping of omentum around the NBA (Figure 2)
- Bladder neck sling was performed concomitantly if deemed necessary during screening
- Subjects were required to cycle (intermittently fill and empty their bladder) post op to promote regeneration
- Urodynamic, clinical and radiographic assessments at 6, 9 and 12 months post implantation

Figure 1: Implant of NBA at dome of native bladder

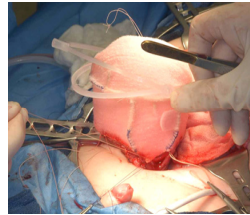
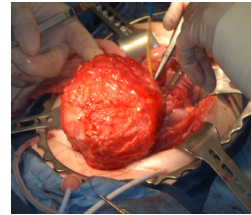


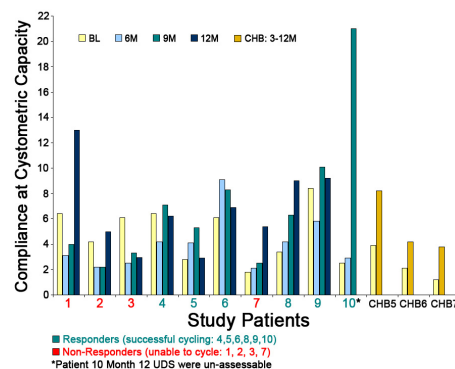
Figure 2: Wrapping of omentum around NBA for vascularization



III. RESULTS:

- Four centers participated:
 - Boston Children's Hospital
 - Children's Hospital of Los Angeles
 - The Children's Hospital of Alabama
 - Wake Forest Baptist Medical Center
- 11 subjects enrolled
 - 10 implanted with NBA
 - 6 females; 4 males
 - Mean age was 8.2 [3-16] years

Figure 3: Compliance at Cystometric Capacity (central reader) over time in 10 patients, compared with original CHB results



- Compliance at cystometric capacity did not reliably correlate with patient-reported outcome:
 - Patient 1: despite improved compliance (Figure 3) patient showed no clinical improvement, urodynamic curve as a whole unchanged from baseline
 - Patient 5: despite an unremarkable compliance at 12M (Figure 3) patient has reported improvement in continence, capacity, urodynamic curve as a whole demonstrates a generally improved pressure volume relationship

Table 1: Cystometric Capacity (central reader) over time in 10 patients

Patient	Baseline (mL)	Month 6 (mL)	Month 9 (mL)	Month 12 (mL)
1	296	168	208	188.5
2	209	105	87.5	50
3	189	49	60	50
4	310	228	310	273.5
5	75	94	123.5	125
6	301.5	304	252	281
7	44	128	86	116
8	117.5	225	275	225
9	361.5	334.5	319	423
10	119	115	86	N/A

RESULTS OF RESPONDERS:

- 6 patients showed UDS and/or clinical improvement (Figure 3)
- Per patient/parent-reported assessment, continence improved in 5/5 with baseline incontinence
 - 1 with baseline continence: stable
- Hydronephrosis and/or reflux improved/resolved in 4/5 patients

RESULTS OF NON-RESPONDERS:

- 4 patients had at least one concomitant anatomic abnormality that could interfere with their ability to cycle effectively:
 - 1 patient had severe low pressure, high grade reflux, impeding her ability to retain urine in her bladder in order to cycle
 - 3 patients had open bladder necks (all underwent bladder neck slings at NBA implantation)
 - 2 of the 3 bladder neck slings failed
- Incontinence improved only in the 1 patient undergoing bladder neck closure. No change was reported for the other 3 patients
- Hydronephrosis: improved in 1 patient with baseline hydronephrosis
- VUR: unchanged in the 2 patients with baseline VUR

IV. CONCLUSIONS:

- **Feasibility of Tengion NBA demonstrated by improved UDS, continence, radiographics, and clinical assessments**
- **This study replicates the results of the original neo-bladder augment reported by investigators from CHB¹**
- **Cycling is an important determinant for successful regeneration**
 - Patients with anatomic barriers to bladder cycling (e.g., open bladder necks) may have challenges with successful bladder regeneration
- **Urodynamic Endpoint:**
 - Compliance at cystometric capacity as a single endpoint is not reflective of the success or failure of this technology
 - Evaluation of the Pressure-Volume relationship at multiple predetermined pressure-specific bladder capacities may be a more clinically meaningful endpoint
- **Subjective patient/parental assessment (e.g., voiding diary) is critical to accurate evaluation of outcome**
- **Safety: 12 month data support generally well-tolerated technology**
 - Adverse events are as expected for this patient population
- **Long-term follow up of these patients is ongoing**

- Central reader's determination of cystometric capacity was based on the first occurrence of one of the following: uninhibited contraction, intravascular pressure ≥ 60 cmH₂O, sensation/pain, leak, or end of filling
- In some cases, the criteria used to determine cystometric capacity at different time points varied within a given patient
 - Example: In patient 1, cystometric capacity at 6M was measured at pressure ≥ 60 cmH₂O and at 12M it was measured at the first contraction
- In most runs cystometric capacity as assessed by the central reader was lower than the total volume infused by the investigator

SAFETY:

Table 2: Treatment Emergent Adverse Events occurring in ≥ 2 patients up to 12 months post-implantation

Adverse Event	N (%)*
Urinary Tract Infection	10(100)
Pyrexia	6(60)
Nausea	5(50)
Vomiting	4(40)
Cough	2(20)
Diarrhea	2(20)
Headache	2(20)
Nasopharyngitis	2(20)
Pruritis	2(20)
Rash	2(20)

*N= number of patients experiencing event
% = percent of patients experiencing event

Most events were reported as mild or moderate and unrelated to the procedure or NBA