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ORIGINAL RESEARCH ARTICLE

A pilot study assessing the feasibility and effectiveness of amniotic bladder therapy in patients with neurogenic detrusor overactivity

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Abstract

Neurogenic detrusor overactivity (NDO) is characterized by involuntary detrusor contractions that often occur following spinal cord injury (SCI). In addition, patients with SCI above T6 are at risk for autonomic dysreflexia (AD). Amniotic membranes (AM) are used for the management of wound healing in multiple medical disciplines. Thus, this study aims to evaluate the efficiency of amniotic bladder therapy (ABT) in managing NDO, specifically in patients with SCI. The patients received intra-detrusor injections under general anesthesia of 100 mg micronized AM (Clarix Flo) diluted in 10 mL 0.9% preservative-free sodium chloride. Clinical evaluations, including maximum detrusor pressure, maximum cystometric capacity, and frequency of AD, were conducted, alongside the completion of questionnaires (Qualiveen questionnaire) preoperatively and postoperatively at weeks 2, 4, 8, and 12. Eight consecutive patients with an average age of 39.6 ± 13.6 years were included. After ABT, a significant decrease in the severity of urinary tract symptoms was observed based on the Qualiveen questionnaire: 3.9 ± 0.17 at baseline to 2.9 ± 0.21 at week 2, 2.1 ± 0.53 at week 4, and 1.4 ± 0.20 at week 8 ($P < 0.01$). Improved clinical symptoms were associated with a decreased maximum detrusor pressure, increased maximum cystometric capacity, and reduced frequency of AD. In conclusion, we investigated ABT as a potential treatment option for NDO associated with SCI. Further investigations are warranted to validate the effectiveness of ABT in this patient population and determine treatment durability.

Keywords: Neurogenic bladder; Neurogenic detrusor overactivity; Autonomic dysreflexia

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1. Introduction

Neurogenic detrusor overactivity (NDO) after spinal cord injury (SCI) is a common complication, generally characterized by urinary urgency and incontinence, significantly impacting normal daily activities and reducing the patient's quality of life (QoL). In patients with NDO, achieving a state of low storage bladder pressure along with an increase in maximum cystometric bladder capacity can improve symptoms of incontinence.

However, the loss of supraspinal neuronal connections to the bladder after SCI can induce a series of complex reactions, namely urothelial cell death, inflammation, urinary tract infection (UTI), urinary incontinence, bladder hypertrophy, and fibrosis, which impair the contractile properties of the bladder and make it difficult to maintain low bladder pressures while storing urine.[1] Subsequently, as the bladder pressure increases, the risk of more serious complications (e.g., upper urinary tract deterioration and autonomic dysreflexia [AD] incidence) increases. Hence, the treatment of NDO primarily aims to protect the upper tract from damage by decreasing bladder pressure, which can be achieved by impeding the processes of bladder inflammation, fibrosis, urothelial cell death, neural sensitization, detrusor dyssynergia, incontinence, UTI, and AD. NDO after SCI is often managed with intermittent catheterization as well as indwelling catheters (often the q4 to q6 hour regimen) and potentially reflex voiding.

The amniotic membrane (AM) is the inner part of the placenta that forms a sac around the fetus during pregnancy. This biological tissue is inherently known to provide therapeutic properties for the treatment of different pathologies. It has been used clinically over the last century for applications such as dermal wound covering and ocular surface reconstruction to promote apoptosis of pro-inflammatory cells, prevent differentiation of pro-fibrotic cells, and promote expedited wound healing.[2] Based on these properties, the use of AM in amniotic bladder therapy (ABT) may overcome the limitations in the current management of NDO. We have previously evaluated ABT in patients with interstitial cystitis/bladder pain syndrome, idiopathic detrusor overactivity (IDO), and radiation cystitis (RC), and we observed symptomatic improvement as early as 2-week post-injection without any complications.[3] This observed that symptomatic improvement was associated with an improvement in urodynamic assessments, including a significant increase in maximum cystometric capacity. In addition, we evaluated the use of ABT in the management of NDO, specifically in patients with SCI, based on the safety profile and potential benefits in recalcitrant patients with limited treatment options.[2,4] Herein, ABT was applied intraoperatively directly into the detrusor based on the anti-inflammatory and anti-fibrotic properties of AM and the inflammatory and fibrotic processes in the pathophysiology of NDO.

2. Methods

The patients enrolled in this study had terminal NDO, defined as those who experienced involuntary detrusor contractions (IDC) near or at the maximum cystometric capacity (MCC) in the setting of a clinically relevant neurologic disease and who had failed previous treatment modalities, including oral therapies with anticholinergics, beta-3 adrenergic agonists, and intravesical therapy with botulinum toxin injections.[5] All patients had traumatic SCI and were using intermittent self-catheterization to empty the bladder. The study was approved by the local institutional review board committee (IRB-22-12-5277). We excluded patients with evidence of upper urinary tract damage, pregnancy, prior radiotherapy, intravesical stones, acute UTI, and a history of bladder and/or pelvic cancers. We also excluded the patients who had used intravesical botulinum toxin (Botox) within 6 months before the commencement of the study to avoid interference with the results. The patients did not receive additional anticholinergics or beta-3 agonists after ABT.

Baseline evaluation included history, physical examination, serum chemistries, urinalyses, urine culture, urine cytology, cystoscopy, renal ultrasound, urodynamic examination (i.e., cystometry by filling the bladder at a rate of 20 mL/min and recording storage pressures), and symptom assessment as measured by the Qualiveen questionnaire. The urodynamic parameters were analyzed according to the standardization report of the International Continence Society. The assessments conducted included maximum detrusor pressure (MDP; cmH_2O) and volume (mL) for the first IDC, as well as MCC corresponding to the volume (mL) at which involuntary voiding occurred and/or filling was stopped. In the absence of involuntary voiding bladder and without spontaneous bladder contractions, filling was stopped at 500 mL. To calculate detrusor compliance (as measured by the change in volume over the change in detrusor pressure), detrusor pressure was measured when the bladder was empty and at MCC. Clinical evaluation and questionnaires were repeated at weeks 2, 4, 8, and 12. Urodynamics were repeated at weeks 4 and 12. Local or systemic side effects were evaluated during and after treatment. AD was evaluated at baseline and repeated at weeks 2, 4, 8, and 12 by asking the patients the following questions: "do you have episodes of AD (a condition where blood pressure rises very fast, usually because of a painful stimulus below the level of your lesion, resulting in symptoms such as headaches, sweating, goosebumps)? If so, how many?"

ABT was standardized among all patients. In brief, patients were given intra-detrusor injections of 100 mg micronized AM (Clarix Flo; BioTissue, USA) diluted in 10 mL 0.9% preservative-free sodium chloride. Injections were performed through a cystoscope using a 23-gauge Williams needle into the lateral and posterior bladder walls, sparing the dome (to avoid intraperitoneal injection) and the trigone (because of the possible risk of reflux) under general anesthesia. A standardized procedure was followed for all patients, with twenty 0.5 mL injections delivered into two rows of ten throughout the lateral and posterior bladder

walls. Clarix Flo is a sterile, micronized human AM product that is derived from the placenta and umbilical cord and is aseptically processed and manufactured from donated human birth tissues according to regulations established by the US Food and Drug Administration. The micronized AM is terminally sterilized through gamma irradiation and does not contain live cells but retains the natural extracellular matrix components innate to the AM tissue.[6]

Descriptive statistics for continuous variables are reported as the mean ± standard deviation (SD), and statistical analysis was performed using the R software version 4.1.3 (R Core Team, Austria). The differences between parameters before and after treatment were analyzed with paired *t*-tests. A *P*-value < 0.05 was considered statistically significant.

3. Results

Eight consecutive patients (female [n = 5] and male [n = 3]) with an average age of 39.6 ± 13.6 years (23 – 65 years) met the inclusion criteria and were included in the current study. On average, the patients experienced symptoms of the neurogenic bladder (NGB) for 9.4 (6.2 – 13.8) years and had tried multiple therapies, including anticholinergics (n = 7), beta-3 adrenergic agonists (n = 8), and Botox injection (n = 8). All patients initially responded to intravesical botulinum toxin A but had a decreased response after 3 – 4 years. All patients had SCI with lesions at or above the T-6 level (Table 1). In addition, before treatment with AM, none of the included patients were completely continent on clean intermittent catheterization (CIC), although all used self-catheterization to empty their bladders. After ABT, all patients were completely continent between CIC and continued to use self-catheterization to empty their bladders every 4 – 6 h. The severity of the injury, as evaluated by the American Spinal Injury Association impairment scale, was grade A in 100% of patients.

Before micronized AM treatment, all the patients reported a high symptomatic impact on their daily lives based on their responses to the Qualiveen questionnaire (Figure 1). After injection, all eight patients reported a significant decrease in the severity of their urinary tract symptoms as the average Qualiveen score decreased from 3.9 ± 0.17 at baseline to 2.9 ± 0.21 at post-ABT week 2 (P < 0.01), 2.1 ± 0.53 at post-ABT week 4 (P < 0.01), and 1.4 ± 0.20 at post-ABT week 8 (P < 0.01). A considerable decrease in symptomatic impact on their daily lives was noted in all four categories of the Qualiveen. Furthermore, their symptoms remained relatively stable when measured at post-ABT week 12 with a reported embarrassment score of 1.39 ± 0.08, a constraint score of 1.42 ± 0.09, a fear score of 1.45 ± 0.09, and a QoL score of 1.3 ± 0.19 (Figure 1, all P < 0.01 as compared to baseline).

In addition, all eight patients included in the current study reported a significant increase in their first volume IDC and MCC and a decrease in MDP for at least 3 months following treatment. The patient's pre-treatment MCC was 208.63 ± 34.98 mL, and MDP was 67.38 ± 2.88 cmH_2O. At 4 weeks following micronized AM treatment, MCC was increased to 430.25 ± 32.4 mL (P < 0.01), and MDP was decreased to 33 ± 1.2 cmH_2O (P < 0.01). At 12 weeks following treatment, MCC and MDP remained relatively the same at 427.25 ± 24.9 mL and 33.38 ± 1.85 cmH_2O, respectively. The post-treatment mean detrusor compliance increased from 27.5 ± 10.6 mL/cm water to 65 ± 15.2 mL/cm water at week 4 and subsequently to 63 ± 14.4 mL/cm water at week 12 (Table 2). Furthermore, at 12 weeks following injection, all patients were completely continent on CIC.

We also evaluated the frequency of AD in all eight patients at baseline and weeks following treatment with micronized AM. Before treatment, all eight patients experienced symptoms either daily or every other day. All patients reported improvements in their symptoms by week 2, and at week 12, all eight patients reported no symptoms of AD (Table 3).

Table 1. Patient demographics

Patient	Age (years)	Neurological level	Upper motor neuron bladder dysfunction
1	37	T6	Complete
2	29	T3	Complete
3	31	T6	Complete
4	35	C7	Complete
5	47	C6	Complete
6	23	T4	Complete
7	50	C5/6	Complete
8	65	C2	Complete

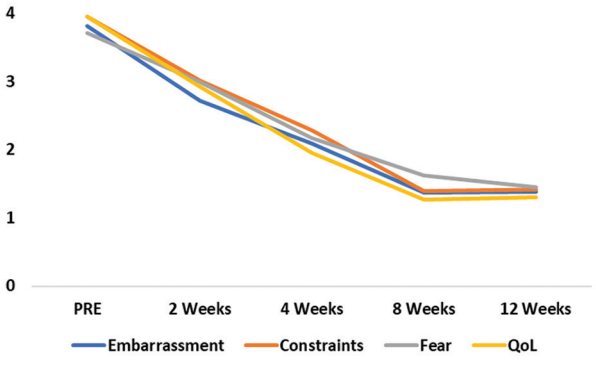


Figure 1. Qualiveen questionnaire scores before and after amniotic bladder therapy.

Table 2. MCC, MDP, and volume at first IDC (mL) at baseline, week 4, and week 12

Patients	MCC (mL)			MDP (cmH_2O)			Volume at first IDC (mL)		
	Baseline	Week 4	Week 12	Baseline	Week 4	Week 12	Baseline	Week 4	Week 12
NGB #1	217	402	422	66	34	33	75	165	175
NGB #2	260	442	404	71	32	30	88	170	190
NGB #3	226	451	472	63	35	32	96	185	180
NGB #4	236	472	450	69	32	34	79	182	180
NGB #5	180	390	400	69	32	36	68	130	140
NGB #6	160	405	410	67	33	33	62	120	140
NGB #7	220	470	440	64	32	34	81	165	170
NGB #8	170	410	420	70	34	35	58	158	160

Abbreviations: IDC: Involuntary detrusor contraction; MCC: Maximum cystometric capacity; MDP: Maximum detrusor pressure; NGB: Neurogenic bladder.

Table 3. Frequency of autonomic dysreflexia at baseline and weeks following treatment

Patients	Baseline	Week 2	Week 4	Week 8	Week 12
NGB #1	Daily	Once in week 2	None	None	None
NGB #2	Daily	None	None	None	None
NGB #3	Every other day	Twice in week 2	None	None	None
NGB #4	Daily	None	None	None	None
NGB #5	Daily	Every other day	Once a week	Once a week	None
NGB #6	Every other day	Once a week	None	None	None
NGB #7	Daily	None	None	None	None
NGB #8	Daily	Every other day	None	None	None

Abbreviations: NGB: Neurogenic bladder. Two patients had an acute UTI 2-week post-injection and were successfully treated with oral antibiotics. No other adverse events related to micronized AM injections occurred throughout the study.

4. Discussion

NDO is caused by a neurologic lesion, such as SCI, which results in aberrant and disorganized neuronal pathways controlling micturition. These patients generally have abnormal alterations of the bladder tissue, including disruption of the uroepithelium, decreased transepithelial resistance, and increased urea permeability. This can further lead to urothelial tissue inflammation, urothelial cell apoptosis, and the release of a cascade of pro-inflammatory cytokines that increase the excitability of bladder nerve fibers. Subsequently, this affects the ability of the patient to store urine and to empty the bladder efficiently, thereby resulting in urinary urgency, retention, and incontinence. With the progression of the disease, NGB patients exhibit varying degrees of thickening and hardening of the bladder wall caused by fibrosis, thereby further impacting bladder functions, which include decreased bladder capacity, increased bladder pressure during the storage phase, and poor compliance.[7] The high bladder pressure may then lead to reflux of urine into the kidney and cause renal scarring and chronic renal insufficiency.

The primary aim of treating NDO is to protect the upper tract from damage by decreasing bladder pressure to <40 cmH_2O in the storage phase. The secondary aim is to maintain urinary continence and improve QoL.[8] Current pharmacological NDO treatments, such as antimuscarinics or beta-3 adrenergic receptor agonists, induce bladder muscle relaxation, thereby improving bladder storage parameters.[9] However, these treatments have reported side effects, including constipation and dry mouth. Intra-detrusor injections of botulinum toxin A are the gold standard option for refractory patients to conventional medications, which aim to induce muscle paralysis and inhibit urothelial sensory nerve function.[10] However, the available therapies often carry significant side effects and may lose efficiency over time.[11] Furthermore, these treatment options may relieve the clinical symptoms of patients but have limited effects on the underlying pathophysiology and prevention of recurrence. Notably, there is currently no effective treatment for lower urinary tract symptoms associated with bladder fibrosis. To enhance the management of NDO, it is paramount to target the molecular mechanisms involved in NDO, including the perpetuating cycle of inflammation, fibrosis, urothelial cell death, and neural sensitization.[12,13]

AM is known to contain anti-scarring and anti-inflammatory properties and has been used in the treatment of many clinical indications.[14] The therapeutic applications of AM are diverse, and the mechanisms of action are multimodal. The immunomodulatory function is related to the apoptosis of pro-inflammatory cells and the suppression of pro-inflammatory cytokines such as

IL-12, TNF-α, and NO synthase 2.[15] The anti-scarring effect stems from preventing the expression of α-smooth muscle actin (α-SMA) by pro-scarring myofibroblasts through the suppression of TGF-β1 promoter activity and canonical TGF-β signaling.[2] Recent studies have also displayed that the key component within AM, i.e., HC-HA/PTX3, can reprogram and de-differentiate pro-scarring myofibroblasts, which was mediated by SDF1-CXCR4 signaling followed by the activation of canonical BMP signaling.[16] These functions are especially relevant in patients with NDO wherein pathologic processes, such as chronic inflammation, unabated fibroblast proliferation, and persistent myofibroblast activation, coupled with excessive extracellular matrix deposition, can disrupt the normal healing cascade and promote the development of contractile fibrosis.[17] Hence, the use of ABT and other similar modalities in patients with NDO is a promising therapeutic concept to reduce pathologic bladder inflammation and scarring in SCI patients.

In this study, we evaluated the ability of ABT to promote rapid symptomatic improvements and long-term benefits in recalcitrant NGB patients with high-level SCI. We have previously evaluated ABT in patients with interstitial cystitis/bladder pain syndrome, IDO, and RC and found symptomatic improvements as early as 2 weeks post-injection.[3] Specifically, the RC and IDO patients also exhibited increased bladder capacity based on voided volume and MCC up to 12 weeks after ABT. Similarly, in the current study, we reported the promising effects of ABT for NDO with improvements in patient-reported outcomes and functional data. The severity of urinary tract symptoms improved by 32% at 2-week post-injection and 64% at 3-month post-injection based on the total Qualiveen score. This was associated with a 50% reduction in MDP and a 105% improvement in MCC at 3-month post-injection. More importantly, the MDP was <40 cmH_2O in all patients after treatment, thereby reducing the potential for upper urinary tract damage. The study also reported long-term implications as the patients were predominantly young, with an average age of 39.6 ± 13.6 years, and had a full life ahead of them.

Aside from preserving renal function, urinary continence is also a significant factor affecting the patient's QoL and long-term independence. The decreased bladder compliance and increased pressure in these patients can lead to persistent incontinence that ultimately damages the tissue integrity of the skin, which leaves patients susceptible to skin breakdown, such as pressure injuries and incontinence-associated dermatitis.[18] Hence, increasing bladder compliance in these patients can directly affect their overall QoL. Likewise, a better understanding and promotion of long-term psychological and social well-being may facilitate advances in medical care to further extend the individual life spans of people with SCI.[19]

An additional problem frequently encountered by these patients is AD, a potentially life-threatening condition of the autonomic nervous system with an exaggerated reflexive increase in blood pressure. This occurrence is associated with severe headaches, bradycardia, facial flushing, lower extremity sweating, and a significantly increased risk of stroke by 300% to 400%.[20] It is well known that NDO can increase afferent stimulation and trigger AD episodes in patients with high-level lesions.[21] Thus, the peripheral stimulation after high bladder pressures must be resolved to prevent AD occurrence. Although the effect of constipation on AD was not investigated in our study, it is well known that this can also be a factor leading to AD and its consequences in patients. In future studies, we will exclude patients with heavy constipation or document methods of bowel evaluation. In our study, we found all patients had decreased episodes of AD at 12 weeks post-ABT, likely due to their high bladder pressures being resolved. Patients progressed from experiencing ADs daily before injection to none after injection. While the immediate impact on QoL is clear, future studies are warranted to monitor the prevention of longer-term complications (e.g., stroke) through the utilization of ABT.

This was the first study to investigate ABT for the management of NDO in SCI patients, and this study was not without limitations, which included the lack of randomization, the small number of participants, and the absence of a control group. Further studies to investigate the physiologic mechanism and duration of improvement, as well as randomized placebo-controlled trials, should be performed to validate the promising results obtained in this study for ABT in neurogenic patients with SCI.

5. Conclusion

We investigated ABT as a potential treatment option for SCI-associated NDO. Further investigations are needed to validate the effectiveness of ABT in this patient population and determine treatment durability. More research is required to develop a better understanding of the mechanisms through which ABT treats these complex disorders.

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Conflict of interest

The authors have no relevant conflict of interest to disclose.

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Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Wayne State University Institutional Review Board (WSU IRB# 22-12-5277). Informed consent was obtained from participants included in the study.

Consent for publication

Verbal consent and permission were obtained from participants included in the study to publish their data.

Availability of data

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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