Botulinum Toxin Type A (Botox) Injection in Bladder Dysfunction in Patients with Multiple Sclerosis (Ain Shams experience)

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ABSTRACT

Background: Bladder dysfunction is very common in patients with multiple sclerosis (MS), affecting up to 60-90% of patients with MS at any stage during the course of their disease. Bladder dysfunction in MS patients can be classified into (a) Detrusor hyperreflexia or overactivity and (b) Detrusor external sphincter dyssynergia (DESD). Aim of the study: To evaluate the effect of botulinum toxin type A (BTX-A) (BOTOX) in the management of urinary dysfunction in MS patients. Methods: Fifteen (15) clinically definite MS patients, according to Poser criteria, of the relapsing–remitting type (RR) were admitted in Ain Shams University Specialized Hospital (ASUSH) during one year period, from October 2004 to October 2005 and assessed: clinically, neurophysiologically and radiologically by MRI brain and spinal cord. Urodynamic study was done to classify the type of bladder dysfunction. Patient were treated with either 300 units of botulinum toxin type A (BTX-A) (botox) injected in the bladder base and trigone in cases of detrusor hyperreflexia or 100 to 200 units of botox injection divided in equal doses into the four quadrants of the external sphincter in cases of DESD. Results: Nine patients (60%) had detrusor hyperactivity (hyperreflexia) “Group A” and 6 patients (40%) had detrusor external sphincter dyssynergia, DESD “Group B”. The maximum efficacy of BTX-A injection occurred between 7 and 21 days following the injection. Follow up duration ranged from 3-6 months with continuous symptoms improvement. In bladder wall treatment group (group A) with bladder wall hyperreflexia there were highly significant decrease in the number of micturations per 24 hours and highly significant increase in the cystometric capacity (p<0.001) after injection. In urethral treatment group (group B) with DESD there were highly significant decrease in the mean postvoid residual urine volume and in the maximum voiding pressure (P<0.001). Conclusion: Our finding showed that the urodynamic study is an essential tool in diagnosing bladder dysfunction in MS patients and botulinum toxin type A is a promising tool of management of the urinary dysfunction in patients with MS. More study should be done on the use of BTX-A in other neurological disorder with urinary disturbances. (Egypt J. Neurol. Psychiat. Neurosurg., 2006, 43(1): 539-551).

INTRODUCTION

Bladder problems are commonly encountered in patients with multiple sclerosis (MS). Surveys have indicated that between 60-90% of MS patients can be affected at any stage, with different urinary symptoms and do not correlate well with the underlying pathology. There are three important reasons why neurologists need to focus on neurogenic bladder dysfunction in multiple sclerosis (MS):

A- Urinary symptoms are disruptive, interfering with critical life areas such as social, vocational and sexual activities.
B- Complications from urinary dysfunction can cause morbidity and mortality, and
C- Bladder symptoms can be managed and urinary complications prevented.

At 1964 review of autopsies of MS patients, attributed 55% of deaths to hydronephrosis or pyelonephritis. However a more recent study reports only 5% deaths related to urinary tract involvement. This dramatic decrease in mortality related to
urologic factors is attributed to improved diagnostic methods and intermittent catheterization.

For urination to occur two events must take place simultaneously: the bladder detrusor muscle must contract at the same time that the sphincter muscle relaxes and opens, permitting a free flow of urine out. Bladder dysfunction develops because MS blocks or delays transmission of nerve signals in areas of the central nervous system that controls the bladder and urinary sphincter. These symptoms may be caused by a "spastic" bladder that is unable to hold the normal amount of urine, or by a bladder that does not empty properly, and thus always retains some urine in it. Retaining urine may lead to complications such as repeated infections or kidney damage.

So, broadly, there are three types of bladder disturbances seen in MS:

1- **Failure to store urine.** (Storage dysfunction, detrusor hyperreflexia, or overactivity). This is the pattern seen most frequently in MS and is the result of an overactive detrusor muscle. The symptoms associated with this condition are: a- Urgency (the bladder must empty immediately). b-Frequency of micturation c- Nocturia (the need to empty the bladder during the night) d- Incontinence.

2- **Failure to empty urine.** (Emptying dysfunction, detrusor external sphincter dyssynergia, DESD). The 'failure to empty' type is one where the bladder is unable to empty completely and is usually the result of the sphincter failing to remain open while the detrusor muscle contracts. The symptoms associated with this type of bladder are: a- Hesitancy, (difficulty commencing the flow of urine), b- Incontinence due to overflow of the full bladder, c- The feeling of incomplete emptying which can lead to frequency, urgency and sometimes nocturia. Thus it may mimic the 'Failure to store' bladder. So, with similar symptoms occurring with different types of bladder dysfunction, it is difficult to diagnose the actual problem on history alone.

3- A combination of the previous two types.

Botulinum toxin, first isolated by van Ermengem in 1897, is the most potent biological toxin known to human. Toxin acts by inhibiting acetylcholine release at the presynaptic cholinergic junction resulting in muscle relaxation and has been shown to be safe and effective in the treatment of conditions caused by increased muscle tonicity and spasticity. One study documented that more than 70% of MS patients with bladder problems treated on the basis of history and physical examination alone received inappropriate therapy.

**Aim of the study:** To evaluate the effect of botulinum toxin type A (BTX-A)(BOTOX) in the management of urinary dysfunction in MS patients.

**Patients and Methods**

**Patients:**
Fifteen (15) clinically definite MS according to Poser criteria, were admitted in Ain Shams University Specialized Hospital (ASUSH) during one year period, from October 2004 to October 2005 and assessed: clinically, neurophysiologically and radiologically by MRI brain and spinal cord. All were of the relapsing–remitting type (RR)

All patients were complaining of urinary symptoms and failed medical management for at least 3 months, which include:

1- Diet modification.
2- Fluid intake planning.
3- Bladder and bowel training.
4- Caffeine restrictions.
5- Medications.

**Methods:** All patients were submitted to the following steps:

1- A bladder diary. Times and amounts recording.
2- Urine analysis.
3- Urine culture and sensitivity.
4- Residual urine assessment through pelvi-abdominal ultrasound examination.
5- Plain abdominal X-ray.
6- Urodynamic study: a mean of assessing actual bladder and sphincter function by measuring volumes and pressures during filling and emptying.

According to the urodynamic study, the patients were injected in the bladder wall in cases of detrusor hyperactivity (hyperreflexia) or in the urethral sphincter in cases of DESD.

**Urodynamic study:**

A urodynamic study is a series of tests and X-rays that provides a detailed look at the functioning of the bladder and sphincter and help to diagnose problems with storing or voiding. Performing urodynamic study involves placing two small catheters, one in the bladder and the other in the rectum (for abdominal pressure measuring). The catheter in the bladder, which are pressure sensitive, provide readings about how the bladder reacting to being filled.

Bladder pressure is measured as the bladder is filled with normal saline at a rate of 10-100 /minute with the patient lying down. The urinary catheter contain two channels. One channel is used for filling and pressure can be recoded through the other.

Sphincter electromyography (EMG) was assessed using perineal surface electrodes in order to determine the urethral sphincteric activity.

A "volume versus pressure" graph, (cystometrogram, CMG), is produced.

The urodynamic study was done using Dantec machine, DUET, MG/UD/225.

**Vesical pressure (P ves):** is the pressure that is measured inside the bladder, which is a combination of the pressure being exerted on the bladder by the abdominal contents, pressure of any urine in the bladder and the force that the detrusor muscle is exerting on that fluid.

**Abdominal pressure (P abd):** is measured by placing a special catheter in the rectum. It is significant because the bladder is contained in the floor of the abdominal cavity and it is important to isolate pressures and activity occurring in the bladder itself.

**The detrusor pressure (P det):** is a subtracted pressure that is calculated by subtracting the abdominal pressure from the vesical pressure.

The second portion of the test involves having the patient urinate while the catheter is still in place. The entire test takes approximately 30-40 minutes.10,11

**Bladder injection technique:** The bladder injection was done by 300 U of botox diluted in 30 ml saline injected into the bladder wall, where 30 injections were given in equal distribution all around the bladder wall. A rigid cystoscope and standard cystoscopic collagen injection needle were used to inject the botox submucosally. We focused on placing most of the injection directly into the bladder base and trigone.

**Urethral injection technique:** BTX-A urethral sphincter injection was done by mixing 100-200 U of botox with 4 ml saline just before injection.

A rigid cystoscope and standard cystoscopic collagen injection needle were used to inject the botox deeply into the external sphincter at 3-O'clock, 6-O'clock, 9-O'clock, & 12-O'clock positions in approximate equal amounts.

Follow up consisted of patient clinic visit and postvoid noninvasive residual urine measurements by bladder U/S.

Patients were asked whether the voiding complaints were improved and answered using a three-point scale: 1, excellent response. 2, fair response. 3, no improvement.

Collection of voiding diaries to document alterations in frequency of urination and incontinence. Follow up urodynamic study done after 3 months from the first injection.

**Statistical analysis:**

SPSS statistical software package (V. 9.02, Echosoft Corp., USA, 1998) was used for data
analysis. The methods used for statistical analysis were the following:
1. Comparison between 2 dependent groups for parametric data using Paired t test.
2. Comparison between 2 independent groups for parametric data using Student t test.

The probability (p) value were then obtained from all these tests with (n1+n2-2) degrees of freedom. P-values less than 0.05 were considered significant, while at 0.01 or 0.001 were highly significant.

Data were summarized using mean and standard deviation for quantitative data and percent for qualitative data.

**RESULTS**

The age of our patient group ranged from 21 to 39 years. Nine patients were females and 6 were males.

EDSS of our patients ranged from 2-5. Duration of the disease range from 2 years to 7 years.

Nine patients (60%) had detrusor hyperactivity (hyperreflexia) "Group A", (5 females and 4 males) and 6 patients (40%) had detrusor external sphincter dysynergia, DESD (3 females and 3 males). "Group B"

The maximum efficacy of BTX-A injection occurred between 7 and 21 days following the injection.

Follow up duration ranged from 3-6 months with continuous symptoms improvement.

**Bladder wall treatment outcome in the 9 patients (group A) with bladder wall hyperreflexia:**
1. 66.5% reported excellent response (response 1) (6 patients), and 33.5% reported fair response (response 2) (3 patients).
2. Decreased number of micturations per 24 hours from 15.7 to 9.67, with highly significant difference, (p<0.001).
3. Increased cystometric capacity from 146 to 248 ml H2O with highly significant difference (p<0.001).
4. No statistically significant change was found in the mean postvoid residual urine volume (P>0.05) and in the maximum voiding pressure (P>0.05).
5. No patient developed urinary retention.

**Urethral treatment outcome in the 6 patients (group B) with DESD:**
1. The mean postvoid residual urine volume decreased from 226 to 92.8 ml after the procedure with highly significant difference (P<0.001).
2. Maximum voiding pressure decreased from 85.5 to 52.2 cm H2O with highly significant difference (P<0.001).
3. Cystometric capacity increased from 199 ml to 217.8 ml. (but non-significant) (p>0.05).
4. The incidence of retention requiring catheterization decreased by 75%.
5. Patients reported decreased infection rates.

In urethral treatment group only one patient complained of temporary stool incontinence lasting for 3 weeks and improved.

In both group, no systemic complications (like respiratory depression) were recorded in the follow up period. Also complications due to vesicouretal reflux (local complications) were not recorded in the 6 months follow up period.

There is no correlation between the pattern of urinary disturbance and duration of the disease and degree of disability (P >0.05).

Table 1. The urinary symptoms in the 15 MS patients were as the following:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Urgency</td>
<td>12/15</td>
<td>80%</td>
</tr>
<tr>
<td>2- Frequency</td>
<td>11/15</td>
<td>73%</td>
</tr>
<tr>
<td>3- Urge incontinence</td>
<td>10/15</td>
<td>66.5%</td>
</tr>
</tbody>
</table>

Table 542
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<tr>
<th>Bladder treatment(n=9)</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>t value</th>
<th>P value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Postvoid residual urine volume (ml)</td>
<td>23±7.21</td>
<td>29±8.41</td>
<td>-1.62</td>
<td>P&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>2-Maximum voiding pressure (cmH₂O)</td>
<td>56.7±10.2</td>
<td>53.4±6.9</td>
<td>0.8</td>
<td>P&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>3-Cystometric capacity (cm H₂O)</td>
<td>146±10.8</td>
<td>248±11.2</td>
<td>-19.67</td>
<td>P&lt;0.001</td>
<td>HS</td>
</tr>
<tr>
<td>4-Number of micturation/24 hours</td>
<td>15.7±2.29</td>
<td>9.67±2</td>
<td>12.73</td>
<td>P&lt;0.001</td>
<td>HS</td>
</tr>
</tbody>
</table>

HS: highly significant
NS: non significant

**Fig. (1):** Cystometric capacity (CC) in patients with detrusor hyperreflexia before and after bladder wall injection.

**Table 2.** The outcome of bladder wall injection.

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<thead>
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<td>12.73</td>
<td>P&lt;0.001</td>
<td>HS</td>
</tr>
</tbody>
</table>
Fig. (2): Number of micturitions/24 hours before and after bladder wall injection in patients with detrusor hyperreflexia.

Fig. (3): Normal urodynamic study, filling phase.
**Fig. (4):** Filling phase of urodynamic study in case of detrusor hyperreflexia (overactivity) before injection, showing the rising of detrusor and vesical pressure early during filling with early first desire (FD), normal desire (ND), severe desire (SD) and urge desire (UD) with low cystometric capacity.

**Fig. (5):** Filling phase of urodynamic study in case of detrusor hyperreflexia (overactivity) after injection showing improvement of the cystometric capacity (CC) with no rise of the vesical and detrusor pressure during filling.

**Table 3.** Shows the outcome of urethral injection of patients with DESD.

<table>
<thead>
<tr>
<th>Bladder treatment (n=9)</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>t</th>
<th>P value</th>
<th>significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Postvoid residual urine volume(ml)</td>
<td>226±19.8</td>
<td>92.8±7.25</td>
<td>15.47</td>
<td>P&lt;0.001</td>
<td>HS</td>
</tr>
<tr>
<td>2- Maximum voiding pressure (cmH₂O)</td>
<td>85.5±5.36</td>
<td>52.2±3.49</td>
<td>12.75</td>
<td>P&lt;0.001</td>
<td>HS</td>
</tr>
<tr>
<td>3- Cystometric capacity (cm H₂O)</td>
<td>199±16.8</td>
<td>217.8±22.1</td>
<td>-1.66</td>
<td>P&gt;0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

HS: highly significant  
NS: non significant

**Fig. (6):** Pre and post injection PVRUV in patient with DESD.
Fig. (7): Maximum voiding pressure in patients with DESD.

Fig. (8): Urodynamic study, empty phase, in case of DESD, before treatment showing excessive EMG activity of the urethral sphincter during micturation.
Fig. (9): Urodynamic study, empty phase, in case of DESD, after treatment showing diminished of the EMG activity during micturation.

DISCUSSION

The physiologic alterations that accompany MS can lead to significant bladder dysfunction. These disturbances are known to have a major impact on overall morbidity and patient's quality of life. In MS patients bladder dysfunction can be categorized as upper motor neuron (UMN) dysfunction. The UMN syndrome presents as a disruption of the descending pathways providing the inhibitory input to the sacral micturation centre. Loss of supraspinal control leads to involuntary, reflexive bladder contraction and to neurogenic incontinence. Additionally, in most cases an impaired coordination of the detrusor and sphincter system (EDSD) can result in elevated bladder pressures during micturation which leads to structural bladder damage, vesicourethral reflux and subsequent renal insufficiency. One study documented that more than 70% of MS patients with bladder problems treated on the basis of history and physical examination alone received inappropriate therapy. Urodynamic study is so important tool in detecting the type of abnormality and to localize the site of injection.

From the patient's point of view the most important goals are continence and a good tolerability of the therapy which can be achieved, as we conclude from our results, with BTX-A injection.

The long lasting effect of the injection up to 6 months in some cases also encourage the use of BTX-A in selected patient group, but the reversibility of treatment might raise controversies. The controversy came from the opinion that in cases of high complete tetraplegic patients with complete spinal cord injury, the surgical sphincterotomy might appear more secure and appropriate. But in cases of MS, where the recovery of function might be expected, the BTX-A remains a good option.

Neurogenic detrusor overactivity is characterized by involuntary detrusor contractions during bladder filling that cannot be consciously suppressed.

A number of therapeutic options are available for the treatment of neurogenic detrusor overactivity, but undesirable side effects can limit their use. Most patients with neurogenic detrusor overactivity and incontinence are treated with anticholinergic medication. Other treatments
include sacral root rhizotomy with anterior root stimulator implants\textsuperscript{17,18}, phenol injection into the subtrigonal region\textsuperscript{19}, and pudendal nerve stimulator.\textsuperscript{20}

Botulinum toxin type A injection appear to offer a new and promising alternative to other nonsurgical treatments for neurogenic detrusor overactivity.

For detrusor muscle injection, we choose to inject 30 spots, predominantly targeting the bladder base and trigone areas. Our strategy with injection is to target the neural influx into the bladder at the point of highest concentration to maximize our results. This includes afferent nerve populations, especially c-fibers, which demonstrate significant innervation in the bladder neck and trigone areas.\textsuperscript{21}

Our results showed significant improvement of the voiding complaints with excellent and fair response in all nine patients who received injection in the bladder wall with significant decreased number of micturation per day and less nocturia which will improve the quality of life of the patients.

Follow up urodynamic study for this group of patients showed increased capacity of urinary bladder with its impact on improvement of the symptomatology of the patients.

This study demonstrated also that their was no risk of developing urinary retention after relaxing the bladder wall with BTX-A with no significant change in the volume of post void residual urine which was clinically evident from lack of symptoms of lower urinary tract infection and no observed episodes of clinical pyelonephritis.

So we have both subjective and objective evidence for beneficial effect of Botulinum toxin in the management of patients with detrusor overactivity.

The other options at the time of injection for this group of patients were sacral neuromodulation or bladder augmentation/diversion\textsuperscript{22}, both of which are invasive. So BTX-A injections appear to offer a new and promising alternative tool to other surgical and non-surgical management for the hyperreflexic bladder with encouraging results.

Regarding urethral - injected group (6 patients) who had DESD were physically unable or refuse intermittent catheterization. This group of patient showed improvement of their ability to empty their bladders more effectively as evidenced by the decrease in the mean post void residual urine volume and significantly decreased maximum voiding pressure, which was high before injection due to the resistance of the contracted detrusor external sphincter which become less contracted and relaxed during voiding after BTX-A injection in the urethral sphincter. Also the beneficial effect was evident from decreased incidence of retention requiring catheterization by 75%.

Although the risk of developing or worsening stress urinary incontinence (SUI) was low (4\%) in the study done by Smith et al.\textsuperscript{21}, no patients in our group developed this side effect most probably due to small number of patients and high selection of patients with no evidence of any sign or symptoms of stress incontinence.

So, patients should be counseled about this potential temporary side effect before injection, particularly if they already have symptoms or signs of SUI.

Thus, urethral BTX-A injections in patients with MS appear to be a practical and valuable alternative to clean intermittent catheterization, especially in patients who cannot perform self-catheterization for any reason.

In all patients no systemic side effect were observed, this also goes with the results of Reitz et al.\textsuperscript{23} and Schulte –Baukloh.\textsuperscript{24} On the other hand, Wyndaele and Van Dromme reported severe generalized muscle weakness in two patients treated with botulinum toxin for neurogenic bladder overactivity.\textsuperscript{25} In their study, one patient developed the generalized weakness after 300 and 1000 units Dysport at 3 months interval, and the second patient after injection with 300 units of Botox. The higher diffusion ability of the English toxin (Dysport) might explain the observed generalized weakness in their study. Also too high
dilution or false injection technique might also explain the systemic diffusion of the toxin with consecutive general side effect in their patients.

On the other hand, we have one patient developed temporary stool incontinence which may be explained by the local diffusion of the toxin to the anal sphincter.

Lastly, one cannot deny the skillfulness and cleverness of humans in transforming the lethal toxin of Clostridium botulinum into a modern day therapeutic medicine.

**Conclusion and Recommendation:**

1. Urodynamic study is an essential tool in diagnosing bladder dysfunction in MS patients and other neurological disorders with urinary disturbances.
2. Botulinum toxin type A is a promising tool of management of the urinary dysfunction of patient with MS.
3. More study should be done on the use of BTX-A in other neurological disorder with urinary disturbances like post stroke, spinal cord injury, transverse myelitis, cauda equina lesion and autonomic neuropathy.
4. Further studies aiming at studying the histological aspects of the detrusor muscle before and after the injections are necessary to understand the effect of the botulinum toxin type A injections on the smooth muscle and to exclude any injections induced fibrosis.

**REFERENCES**


الملخص العربي

حقق اليوتوكس في مرضى التصلب اللوحي الذين يعانون من اضطراب في المثانة

اضطراب المثانة من الأعراض شائعة الحدوث في مرضى التصلب اللوحي، حيث يحدث في حوالي 20-90% في هؤلاء المرضى في أي مرحلة من مراحل المرضى.

1-النموذج الأول: حيث يوجد زيادة في نشاط عضلة جدار المثانة.
2-النموذج الثاني: حيث يوجد عدم تناسق في نشاط العضلة القاعية الخارجية للمثانة.

الهدف من البحث:

تقييم تأثير حقن اليوتوكس في علاج اضطرابات المثانة في مرضى التصلب اللوحي.

طريقة البحث:

تم دراسة 5 أمراض من مرضى التصلب اللوحي من النوع المنتكس - المتتنس هذه ممارسات بوص - خلال سنة أثناء دخل المرضى في مستشفى عين شمس التخصصي حيث تم دراسة المرضى إكلينيكيًا والاستجابة الفييولوجيًا العصبية (الودم الاضطرابات المستفرزة) وعن طريق الانتقاة المغناطيسية على المخ والدماغ الشوكي والمنطقة العنقية والصدرية، وكما تم دراسة ديناميكية الفيول لتحديد نوع اضطراب المثانة. وتم علاج المرضى عن طريق حقن اليوتوكس. حيث تم حقن

551
300 وحدة بيونتوكس في جدار المثانة في النوع الأول حيث يوجد زيادة في نشاط عضلة جدار المثانة. وتم حن من 100 إلى
200 وحدة بيونتوكس في العضلة القاعية الخارجية بجرعات متساوية في الأركان الأربعة. وقد أظهرت النتائج أن تسع
مرضى كانوا من النوع الأول و ستة مرضى كانوا من النوع الثاني. وقد ظهرت فاعلية الحقن ما بين سابع يوم حتى 3 أسابيع
بعد الحقن. وتمت متابعة المرضى لمدة تتراوح من 3 إلى 6 سنة شهر حيث استمر تحسن الأعراض و فاعلية الحقن طوال
فترة المتابعة.
في المجموعة الأولى أظهرت النتائج نقص عدد مرات النبول في اليوم مع زيادة سعة المثانة زيادة مؤقتة. أما بالنسبة
لمجموعة الثانية، فقد أظهرت النتائج نقص متوسط كمية البول المتبقي بالمثانة بعد النبول مع نقص الحد الأقصى للضغط
اللازم للنبول.
من هذه الدراسة يمكن استنتاج أهمية دراسة ديناميكية للبول لتشخيص نوع اضطراب البول في مرضى التصلب
اللويحي وأن عقار البيونتوكس من الوسائل الوضعية لعلاج اضطرابات المثانة في هؤلاء المرضى. ونصح بمزيد من الدراسات
على عقار البيونتوكس في مختلف أمراض الجهاز العصبي التي تصاحب اضطرابات في المثانة.