بسم الله الرحمن الرحيم

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بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

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The Effect of Intravesical OnabotulinumtoxinA (Botox) Injections on Urinary Bladder Functions in Children

Thesis

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By

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Abd El-Wahed Mohammad

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List of Abbreviations

Abb.	Full term
AC	*Augmentation Cystoplasty*
Ach	*Acetyl Choline*
AUA	*American Urologic Association*
BBD	*Bladder and Bowel Dysfunction*
BNC	*Bladder Neck Closure*
BNR	*Bladder Neck Reconstruction*
BTX	*Botox*
CIC	*Clean Intermittent Catheterization*
CNS	*Central Nervous System*
DLP	*Detrusor Leak Pressures*
DO	*Detrusor Overactivity*
DSD	*Detrusor Sphincter Dyssynergia*
DUD	*Detrusor Underutilization Disorder*
DV	*Dysfunctional Voiding*
DV	*Dysfunctional Voiding*
DVSS	*Dysfunctional Voiding Symptom Score*
EAU	*European Association of Urology*
EDOUF	*Extraordinary Daytime Only Urinary Frequency*
EUS	*External Urethral Sphincter*
FDA	*US Food and Drug Administration*
FI	*Flow Index*
FVC	*Frequency/Volume Chart*
GI	*Gastrointestinal*

List of Abbreviations (Cont...)

Abb.	Full term
IAP	*Intraabdominal Pressure*
ICCS	*International Children's Continence Society*
IDOD	*Idiopathic Detrusor Overactivity Disorder*
IUS	*Internal Urethral Sphincter*
LUT	*Lower Urinary Tract*
MRI	*Magnetic Resonance Imaging*
OAB	*Overactive Bladder*
PAG	*Periaqueductal Grey*
PBND	*Primary Bladder Neck Dysfunction*
PMC	*Pontine Micturition Center*
PTNS	*Percutaneous Tibial Nerve Stimulation*
PUV	*Posterior Urethral Valve*
PVR	*Post Void Residual*
SPSS	*Statistical Package for Social Science*
TENS	*Transcutaneous Electrical Nerve Stimulation*
US	*Ultrasonography*
VCU	*Voiding Cystourethrography*
VUR	*Vesico-Ureteric Reflux*
WBNA	*Wide Bladder Neck Anomaly*
ΔV	*Volume Change*

Abstract

Background: Children with overactive bladder and urinary incontinence are probably the most difficult to manage because of the serious effects on kidney functions and social life. Botulinum toxin has shown its effectiveness in lowering the bladder pressure and obtain adequate continence with nearly no complications.

Objective: To evaluate clinical and urodynamic efficiency of intravesical OnabotulinumtoxinA (Botox) injections in children with lower urinary tract symptoms and overactive bladder. These pediatric patients were resistant to the urotherapy and the anticholinergic treatment.

Patients and Methods: Eleven patients aged from 5 to 13 years old (median age 8.5 years old), 6 males and 5 females with daytime and or nighttime urinary incontinence with lower urinary tract symptoms and detrusor overactivity detected by urodynamic study. five cases have idiopathic detrusor overactivity , four cases with neurogenic overactive bladder and two cases have detrusor sphincter dyssynergia (DSD), were treated with onabotulinumtoxinA (Botox) injections after failure of the urotherapy and anticholinergic treatment and followed up in urology clinic 3 , 6 , 9 , 12 months post injection . Assessment the patients were obtained clinically through the bladder diary and the dysfunctional voiding scoring system and by urodynamic study before and after Botox injections. We used onabotA (Botox) in 10 units / kg with maximal dose 300 units via cystoscopy into 21 different sites.

Results: We noted improvement of the urgency in all patients (totally disappeared) and frequency, in the patients with voluntary voiding who didn't require intermittent catheterization**.** Absence leakage during the daytime between CIC in (6 patients) and in the patient with voluntary voiding (5 patients) after Botox injections. All patients were having a daily episodes of nocturnal enuresis before Botox injections and totally disappeared in 2 patients (40%), three patients (60%) were having two episodes of nocturnal enuresis / week. after Botox injections. Remaining 6 patients, the urinary catheter was inserted during sleep. Dysfunctional voiding system score (DVSS) has been significantly decreased (marked improvement) after Botox injections, the mean was 16.73 before Botox and decreased to 6.18 after Botox (p -value < 0.001). The maximal detrusor pressure was significantly decreased in 9 patients after Botox injections, the mean was 88.67 cmH_2O before Botox and decreased to 50 cmH_2O after Botox (p-value= 0.022). The micturating cystometric capacity (MCC) was increased after Botox injections also in those 9 patients. The mean was 136.11 before Botox and was increased to 162.78 ml after Botox (p-value=0.137). The post voiding residual volume was decreased after Botox injections in 5 patients who were having voluntary voiding, the mean was 64 ml before Botox and decreased after improving the emptying function of the bladder to 24 ml after Botox injections i.e**.**59.6% the mean decrease in PVR after Botox injections (p-value=0.014). The detrusor leakage pressure was decreased after Botox injections in 4 patients. The mean was 80.5 cmH_2O before Botox injections and decreased to 46.5 cmH_2O after Botox injections. (P-value =0.281)

Conclusion: onabotulinumtoxinA (Botox) is an adequate alternative to more invasive surgical interventions in children with lower urinary tract symptoms and incontinence who failed medical treatment.

Keywords: onabotulinumtoxinA, children, Botox, neurogenic bladder, lower urinary tract dysfunction, incontinence.

INTRODUCTION

Children with urinary incontinence with idiopathic overactive bladder (OAB) as well as neurogenic bladder often experience inadequate storage and emptying of urine and result in serious effects on kidney functions and quality of their social lives. Prevalence of OAB varies between 15–20% and decreases with age and is reduced to levels as low as 12% in adolescent period ***(Kajiwara et al., 2006).***

Overactive bladder (OAB) is a voiding dysfunction related to filling phase of the urinary bladder and defined by International Children's Continence Society (ICCS) as "urinary urgency, usually accompanied by frequency and nocturia, with or without urinary incontinence, in the absence of urinary tract infection or any other obvious pathology ***(Austin et al., 2016).***

Finding a solution for making the bladder more compliant, reduced pressure, increasing the bladder capacity, avoiding renal compromise and upper urinary tract deterioration is an essential aspect in treatment plan as well as making the ability for children to reach an improved degree of urinary continence with adequate social life through a minimally invasive approach. Nonetheless some patients respond to the usual initial treatment of overactive bladder that includes behavioral modifications, timed voiding, double voiding with clean intermittent catheterization (CIC) and approved oral medications at recommended doses ***(Uçar et al., 2018).***

Children with no response to urotherapy or medical therapy or those with no tolerance to oral therapy due to side effects (dry mouth, blurred vision, constipation) are prone to the more invasive treatment methods.

Botulinum-A toxin injection was first used in urology by ***Dykstra et al. in (1998)*** for treatment detrusor sphincter dyssynergia (DSD) observed in patients having spinal injury. Later, application to the detrusor was described for the first time ***by Schurch et al. in (2000).*** The US Food and Drug Administration (FDA) approved Botox (BTX) in 2011 for neurogenic and idiopathic detrusor overactivity and both the American Urologic Association (AUA) and the European Association of Urology (EAU) guidelines recommended intravesical onabotulinumtoxinA (Botox) injections for the patients with urgency urinary incontinence refractory to anticholinergic therapy ***(Gormley et al., 2015).***

OnabotulinumtoxinA is a two-chain polypeptide neurotoxin protein produced by the bacteria Clostridium botulinum. The onabotulinumtoxinA is one of the seven serotype neurotoxins and inhibits acetylcholine and adenosine triphosphate release from parasympathetic presynaptic nerve terminals and causes flaccid muscle paralysis. Disruptions in the autonomic nervous system are also common where symptoms such as dry mouth, postural hypotension, and constipation can occur ***(Uçar et al., 2018).***

In present study, the experience concerning the use of onabotulinumtoxinA (Botox) in children with urinary incontinence and overactive bladder to delay or avoid the need for augmentation cystoplasty, the more invasive and permanent procedure among the invasive surgical therapies, is reported. Additionally, the transient nature of onabotulinumtoxinA has allowed the option of discontinuation if results are not satisfactory or an alternative treatment is more suitable.