Review Article

Detrusor External Sphincter Dyssynergia (DESD) and Botulinum Toxin A (BoNT-A): A Meta-analysis of Efficacy

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Abstract

Botulinum toxin A injection into the detrusor can reduce detrusor contractility, improve bladder compliance, and resume urinary continence. While a urethral injection of BoNT-A may reduce the urethral resistance and facilitate bladder emptying reducing postvoid residual (PVR) and frequent urinary tract infections. This work aims to provide cumulative data about the efficacy of Botulinum Toxin A (BoNT-A) in treating patients with Detrusor External Sphincter Dyssynergia (DESD). A systematic search was performed of PubMed, Cochrane library Ovid, Scopus & Google scholar to identify Urology RCTs, clinical trials, and comparative studies, which studied the outcome of Baseline assessment versus Follow-up assessment of DESD patients. A meta-analysis was done using fixed and random-effect methods. The main outcome measures were average PVR (postvoid residual), MDP (mean detrusor pressure), dLPP (detrusor leak point pressure), and MUP (mean urethral pressure). A total of 8 studies were identified involving 500 patients. Regarding outcome measures, the random-effects model of the meta-analysis study showed a highly significant decrease in mean PVR and MUP in follow up assessment compared to baseline assessment ($p=0.001$). The fixed-effects model showed a highly significant decrease in mean MDP in follow up assessment ($p<0.001$). The random-effects model of the meta-analysis study showed a non-significant difference in mean dLPP in follow up assessment ($p>0.05$). To conclude, Botulinum toxin A injection proved its efficacy through reducing mean PVR, MDP, and MUP in the follow-up assessment, but we didn't find a significant change in mean dLPP in the follow-up assessment.

Keywords: Detrusor External Sphincter Dyssynergia; Botulinum Toxin A

Introduction

Detrusor sphincter dyssynergia (DSD) is a urodynamic description of a dysregulation of the micturition reflex, wherein an attempted voiding, the external urethral sphincter contracts involuntarily during detrusor contraction. [1,2] The Blaivas classification categorizes DSD into 3 subtypes. Type one is a crescendo increase in sphincter activity during detrusor contraction with sudden complete relaxation of the sphincter as the detrusor pressure begins to decline. Type two is clonic contractions of the external sphincter causing interrupted urinary stream. Type three is persistent sphincter contraction through the detrusor contraction, leading to the inability to void through the urethra. [1]

DSD can be diagnosed via several modalities, including EMG recordings during the voiding phase of urodynamic studies -which is the most commonly used modality-, voiding cystourethrograms, and urethral pressure monitoring. [1]

This condition affects mainly patients with suprasacral cord lesions, such as spinal cord injury (SCI), multiple sclerosis, and spina bifida. [1,3]

Whilst DSD is a frequent problem, its complications can greatly impact the quality of life (QoL) of patients affected if it is not identified and treated properly. DSD can lead to post-void residual urine (PVR), recurrent urinary tract infections (UTIs), upper urinary tract dysreflexia, and autonomic dysreflexia (AD). [4]

Because of its great effects on QoL, several medical and surgical procedures have been introduced to treat DSD. Oral anti-muscarinic agents, urethral stents, external sphincterotomy, and augmentation enterocystoplasty have been used. These modalities have had varying outcomes and side effects. [3]

The oral agents have been reported to have limited efficacy. The conventional external sphincterotomy was reported to be associated with many complications, including, hemorrhage,

How to Cite this Article: Alshammari MB, et al. Detrusor External Sphincter Dyssynergia (DESD) and Botulinum Toxin A (BoNT-A): A Meta-analysis of Efficacy. Ann Med Health Sci Res. 2021;11: 1212-1216.

erectile dysfunction, and revision, although the new endoscopic and minimally invasive techniques have developed. [4]

The use of urethral injections of botulinum toxin type A (BoNT-A) as an alternative treatment of DSD. This modality has since become a common treatment for these patients. [4]

Botulinum toxin A injection into the detrusor can reduce detrusor contractility, improve bladder compliance, and resume urinary continence. While a urethral injection of BoNT-A may reduce the urethral resistance and facilitate bladder emptying reducing PVR and frequent UTIs. However, the use of these is not without complications, as the use of Botulinum toxin A can trigger detrusor under-activity, and the use of BoNT-A will trigger an undesired exacerbation of urinary incontinence. [3]

This work aims to provide cumulative data about the efficacy of Botulinum Toxin A (BoNT-A) in treating patients with Detrusor External Sphincter Dyssynergia (DESD).

Literature Review

Our review came following the (PRISMA) statement guidelines. [5]

Identification of studies

- Basic searching was done over the Cochrane library, PubMed, Ovid, Scopus, and Google scholar using the following keywords: Detrusor External Sphincter Dyssynergia, Botulinum Toxin A.
- Published, English, full-text studies were included.

Criteria of accepted studies

Types of studies:

The review will be restricted to RCTs, clinical trials, and comparative studies, prospective follow-up studies, which studied the outcome of Baseline assessment versus Follow-up assessment of DESD patients.

Types of participants

DESD patients

Types of outcome measures

Average PVR (postvoid residual)

Average MDP (mean detrusor pressure)

Average dLPP (detrusor leak point pressure)

Average MUP (mean urethral pressure)

Inclusion criteria

- English literature.
- Journal articles.
- Describing DESD patients with either Baseline assessment or Follow-up assessment.
- Human studies.

Exclusion criteria

- Articles of retrospective nature.
- Case reports and case series.

Locating studies

Original articles, abstracts appear to fulfill inclusion criteria will be retrieved in full, with another reviewer assessment and consensus will be reached.

Data extraction

Using the following keywords: Detrusor External Sphincter Dyssynergia, Botulinum Toxin A, data will be independently extracted by two reviewers and cross-checked.

Statistical analysis

Statistical analysis using MedCalc (Ostend, Belgium). The pooling of data, standard mean differences (SMDs), with 95% confidence intervals (CI) done. Meta-analysis was performed to calculate a direct estimate of each outcome. According to heterogeneity status across trials using the I^2-statistics; a fixed-effect model ($P \geq 0.1$) or random-effects model ($P<0.1$) were used.

Study selection

This is explained in Figure 1.

Results

Descriptive analysis of all studies included [Table 1] and [Table 2]. [6-12]

The included studies were published between 2002 and 2020. Regarding patients' characteristics, the total number of patients in all the included studies was 500 patients, while their average follow-up time was (3 months). The average age of all patients was (41.9 years), and all patients had 100 IU Botulinum Toxin A.

A meta-analysis of outcome measures:

Data were divided into two groups:

- Baseline assessment

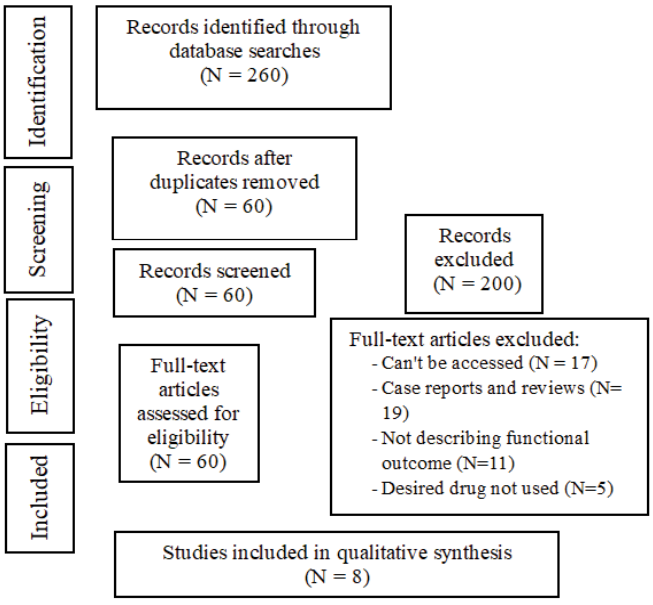

Figure 1: Study selection algorithm.

Table 1: Patients and study characteristics

N	Author	Number of patients Total	Initiating disease	Age (average years)	Dose (IU)
1	De Sèze et al. [6]	13	SCI, MS, myelitis	45.5	100
2	Gallien et al. [7]	86	MS	50	100
3	Chen et al. [8]	20	SCI	37.9	100
4	Chen et al. [9]	18	SCI	36.7	100
5	Yang et al. [10]	15	SCI	40.5	100
6	Soler et al. [11]	99	SCI	38.4	100
7	H. Chen et al. [12]	54	SCI	32	100
8	Chow et al. [13]	195	SCI	54.5	100

#Studies were arranged according to the publication year. SCI: spinal cord injury. MS: multiple sclerosis.

Table 2: Summary of outcome measures in all studies

N	Author	Outcome measures							
		PVR		MDP		dLPP		MUP	
		Baseline assessment	Follow-up assessment	Baseline assessment	Follow-up assessment	Baseline assessment	Follow-up assessment	Baseline assessment	Follow-up assessment
1	de Sèze et al. [6]	264	105	74	77	--	--	109	78
2	Gallien et al. [7]	220	186	67	55	--	--	83	69
3	Chen et al. [8]	355	243	90	80	79	64	139	105
4	Chen et al. [9]	292	198	76	67	85	78	134	101
5	Yang et al. [10]	347	155	82	78	71	60	101	63
6	Soler et al. [11]	227	98	77	70	68	64	135	130
7	H. Chen et al. [12]	--	--	--	--	62	23.7	--	--
8	Chow et al. [13]	108.4	110.4	47.2	36.8	--	--	--	--

- Follow-up assessment

A meta-analysis study was done on 8 studies that described and compared the 2 different groups of patients; with an overall number of patients (N= 500).

Patients who achieved outcome measures were pooled:

Each outcome was measured by:

Standard Mean Difference (SMD)

- Average PVR (postvoid residual)
- Average MDP (mean detrusor pressure)
- Average dLPP (detrusor leak point pressure)
- Average MUP (mean urethral pressure)

Regarding the outcome measures, we found 7 studies reported PVR. I^2 (inconsistency) was 88.6% with highly significant Q test for heterogeneity ($p<0.0001$), so random-effects model was carried out; with overall SMD= -0.77 (95% CI -1.241 to -0.316). The random-effects model of the meta-analysis study showed a highly significant decrease in mean PVR in Follow up assessment compared to Baseline assessment ($p=0.001$) [Figure 2].

We found 7 studies reported MDP. I^2 (inconsistency) was 0% with non-significant Q test for heterogeneity ($p>0.05$), so fixed-effects model was carried out; with overall SMD= -0.343 (95% CI -0.475 to -0.212).

The fixed-effects model of the meta-analysis study showed a highly significant decrease in mean MDP in Follow up assessment compared to Baseline assessment ($p<0.001$) [Figure 3].

We found 5 studies reported dLPP. I^2 (inconsistency) was 93.9% with highly significant Q test for heterogeneity ($p<0.0001$), so

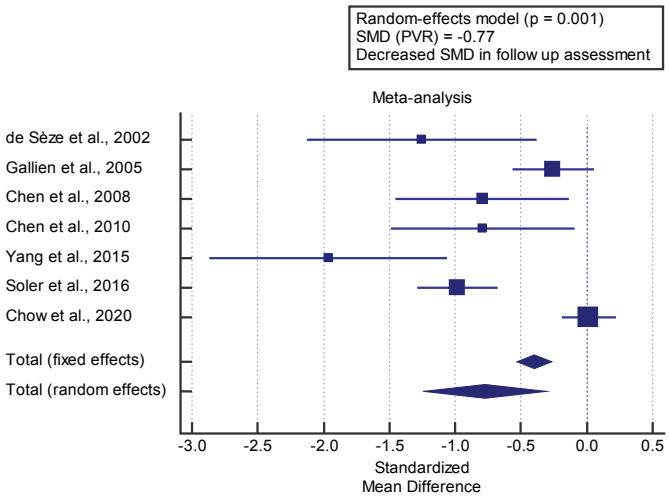

Figure 2: Forest plot of (PVR) – SMD.

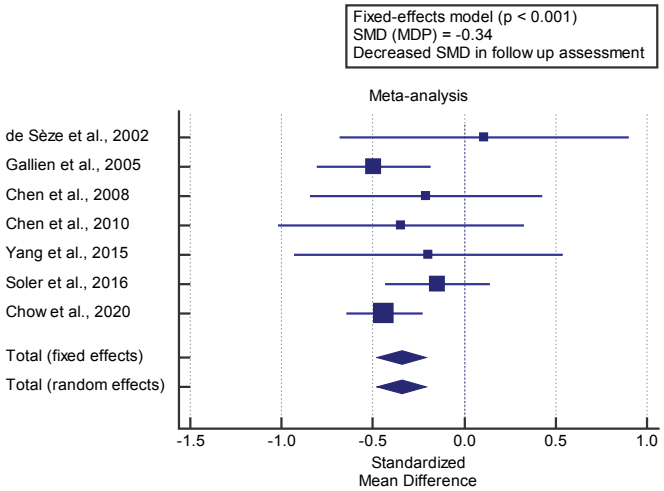

Figure 3: Forest plot of (MDP) – SMD.

random-effects model was carried out; with overall SMD= -0.776 (95% CI -1.705 to 0.153).

The random-effects model of the meta-analysis study showed a non-significant difference in mean dLPP in Follow up assessment compared to Baseline assessment (p>0.05) [Figure 4].

We found 6 studies reported MUP. I^2 (inconsistency) was 73.5% with highly significant Q test for heterogeneity (p<0.0001), so random-effects model was carried out; with overall SMD= -0.73 (95% CI -1.129 to -0.330).

The random-effects model of the meta-analysis study showed a highly significant decrease in mean MUP in Follow up assessment compared to Baseline assessment (p<0.001) [Figure 5].

Discussion

This work aims to provide cumulative data about the efficacy of Botulinum Toxin A (BoNT-A) in treating patients with Detrusor External Sphincter Dyssynergia (DESD). The included studies published between 2002 and 2020 only the RCTs, clinical trials, and comparative studies, prospective follow up studies were included.

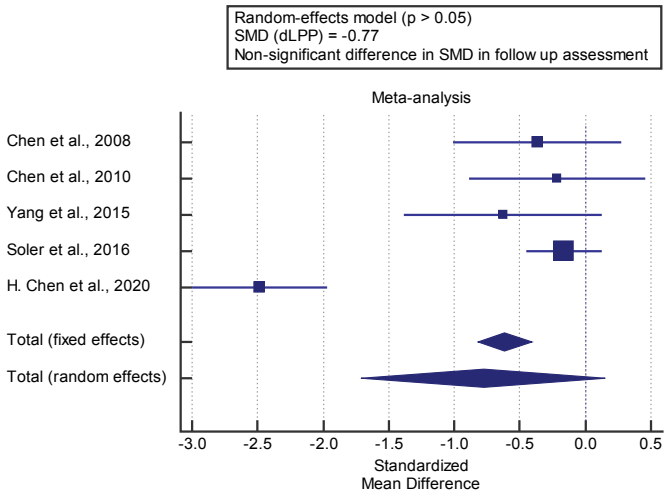

Figure 4: Forest plot of (dLPP) – SMD.

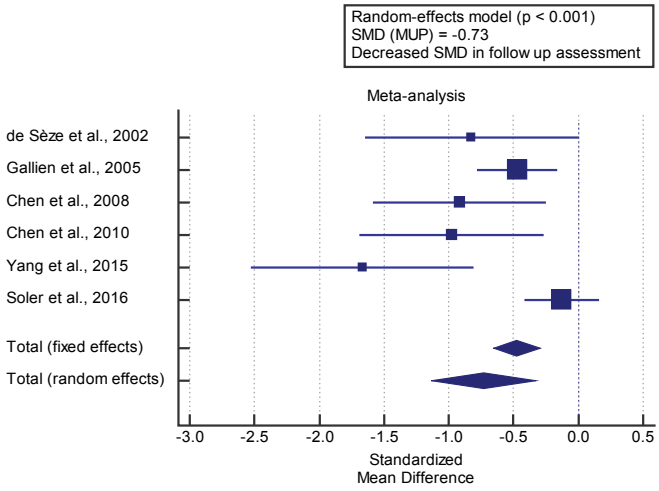

Figure 5: Forest plot of (MUP) – SMD.

Regarding patients' characteristics, the total number of patients in all the included studies was 500 patients, while their average follow-up time was (3 months). The average age of all patients was (41.9 years), and all patients had 100 IU Botulinum Toxin A.

A meta-analysis study was done on 8 studies that described and compared the 2 different groups of patients; with an overall number of patients (N= 500).

Regarding the outcome measures, we found 7 studies reported PVR. The random-effects model of the meta-analysis study showed a highly significant decrease in mean PVR in Follow up assessment compared to Baseline assessment (p=0.001).

Our results came in agreement with, Kuo and Ng, a retrospective review was conducted in 9 patients with DESD with the purpose of outcome discussion after the injection of BTX-A to the external sphincter. They compared the PVR before and after the injection. It showed a statistically significant reduction, as the mean pre-operative PVR was 179.2 ± 86.8 ml, turn into 45.7 ± 44.4 ml postoperatively. [13]

Besides, Mehta et al. pooled meta-analysis was conducted in 2012, aimed to examine the effect of BTX-A injection into the detrusor sphincter in individuals suffering from incomplete voiding after SCI. It showed a statistically significant reduction in PVR, 1-month post-injection has observed an average decrease from 252 to153 ml (99 ml). [14]

We found 7 studies reported MDP. The fixed-effects model of the meta-analysis study showed a highly significant decrease in mean MDP in Follow up assessment compared to Baseline assessment (p<0.001).

Similar results were reported by Huang et al. In a study conducted on 59 patients to measure the effect of botulinum toxin A injection in spinal cord injury patients with detrusor overactivity and detrusor external sphincter dyssynergia. Comparing the urodynamic parameters at baseline, all patients experienced a significant mean reduction MUP by 29.61%. [15]

Another recent study done by Goel et al. on 353 patients found that patients had a lower MUP after BoNT-A treatment compared to their baseline mean MUP value (pooled random-effects effect size=-0.83; 95%CI=-1.48, -0.18; P=.0119). This improvement led to the increased quality of life of these patients. [16]

We found 5 studies reported dLPP. The random-effects model of the meta-analysis study showed a non-significant difference in mean dLPP in Follow up assessment compared to Baseline assessment (p>0.05).

Our results came in disagreement with the study done by Goel et al. which found significantly lower DLPP compared to their baseline mean DLPP value (pooled random-effects effect size=-0.55; P=.028). [16]

Tsai et al. reported that a 37cm H_2O reduction in the leak point pressure with a clinical success rate of 72% (p<0.05). Despite that, the post-op value was still more than 40 cm H2O which may predispose to subsequent renal damage. [17]

We found 6 studies reported MUP. The random-effects model of the meta-analysis study showed a highly significant decrease in mean MUP in Follow up assessment compared to Baseline assessment ($p<0.001$).

Tsai et al. conducted a prospective study on the treatment of detrusor sphincter dyssynergia (DSD) with BoNT-A via a transperitoneal injection, they reported that 45 cm H2O reduction in the detrusor pressure when comparing pre to post BoNT-A injection with a mean of a 106.3 to 61.4 respectively ($p<0.05$). They also addressed that the detrusor pressure decreases later than the urethral pressure and this is probably because the BoNT-A predominantly affects skeletal muscle thus, contraction of the detrusor muscle could persist even post-injection. [17] This fact is supported by Goel et al. meta-analysis in which 3 out of 13 included study observe the slower reduction in the detrusor pressure comparing to urethral pressure. [16]

According to Kuo which investigates the satisfaction and urodynamic parameter after the injection with BoNT-A in patients with DSD, a reduction from 45.7 pre-injection to 30.7 post-injection in the detrusor pressure was observed ($p=0.01$). However, they also reported that BoNT-A is not the most appropriate method for the treatment of DSD since it may increase the incontinence grade. [18]

In a Goel et al. meta-analysis which is about the usage of BoNT-A in DSD, they supported the fact that has been reported by Tsai and Kuo study that there is a significant reduction in MDP after BoNT-A injection comparing to the baseline value observed in 10 studies included in the review. [16]

Conclusion

To conclude, Botulinum toxin A injection proved its efficacy through reducing mean PVR, MDP, and MUP in the follow-up assessment, but we didn't find a significant change in mean dLPP in the follow-up assessment.

Competing Interests

The authors declare that they have no competing interests. All the listed authors contributed significantly to the conception and design of study, acquisition, analysis, and interpretation of data and drafting of the manuscript, to justify authorship.

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