



Trigonal-Sparing vs. Trigonal-Involved OnabotulinumtoxinA Injection for the Treatment of Overactive Bladder: A Systematic Review and Meta-Analysis

OPEN ACCESS

Edited by:

Rizwan Hamid, Royal National Orthopaedic Hospital, United Kingdom

Reviewed by:

Matthew O. Fraser, Duke University, United States Luke Grundy, Flinders University, Australia

*Correspondence:

Yongqiang Wang doctorcuiys@163.com Liying Dong Doctorliying@163.com

[†]These authors have contributed equally to this work and share first authorship

Specialty section:

This article was submitted to Autonomic Neuroscience, a section of the journal Frontiers in Neurology

Received: 10 January 2021 Accepted: 06 September 2021 Published: 08 October 2021

Citation:

Cui Y, Cai T, Dong T, Zhang X, Zhou Z, Lu Y, Zhang Y, Wu J, Gao Z, Wang Y and Dong L (2021) Trigonal-Sparing vs. Trigonal-Involved OnabotulinumtoxinA Injection for the Treatment of Overactive Bladder: A Systematic Review and Meta-Analysis. Front. Neurol. 12:651635. doi: 10.3389/fneur.2021.651635 Yuanshan Cui^{1,2†}, Tong Cai^{3†}, Tiantian Dong^{1†}, Xiaoyi Zhang⁴, Zhongbao Zhou², Youyi Lu¹, Yong Zhang², Jitao Wu¹, Zhenli Gao¹, Yongqiang Wang^{1*} and Liying Dong^{1*}

¹ Department of Urology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, China, ² Department of Urology, Beijing Tian Tan Hospital, Capital Medical University, Beijing, China, ³ Yangzhou University, Yangzhou, China, ⁴ People's Liberation Army of China Rocket Force Characteristic Medical Center, Department of Urology, Beijing, China

Objective: Overactive bladder (OAB) is a disease characterized by the presence of urinary urgency. We carried out a meta-analysis to assess the effectiveness and safety of trigonal-involved injection of onabotulinumtoxinA (BoNT-A) in comparison with the trigonal-sparing technique in cases with OAB [neurogenic detrusor overactivity (NDO) and idiopathic detrusor overactivity (IDO)].

Methods: Randomized controlled trials (RCTs) of BoNT-A injection for OAB were searched systematically by using EMBASE, MEDLINE, and the Cochrane Controlled Trials Register. The datum was calculated by RevMan version 5.3.0. The original references of relating articles were also reviewed.

Results: In total, six RCTs involving 437 patients were included in our analysis. For OAB, the trigone-including group showed a different patient symptom score (p = 0.03), complete dryness rate (p = 0.002), frequency of incontinence episodes (p = 0.01), detrusor pressure at maximum flow rate (p = 0.01), and volume at the first desire to void (p = 0.0004) compared with the trigone-sparing group. Also, a trigone-including intradetrusor injection demonstrated a significant improvement in the patient symptom score (p = 0.0004), complete dryness rate (p = 0.0002), frequency of incontinence episodes (p = 0.0004), complete dryness rate (p = 0.0002), frequency of incontinence episodes (p = 0.0004), detrusor pressure at maximum flow rate (p = 0.0002), and volume at the first desire to void (p = 0.0003), detrusor pressure at maximum flow rate (p = 0.01), and volume at the first desire to void (p = 0.0006) compared with the trigone-sparing group for treatment of NDO. The adverse events rates were similar in both groups.

Conclusions: The meta-analysis has demonstrated that trigone-including BoNT-A injection was more effective compared with the trigone-sparing injection for the treatment of OAB, especially for NDO.

Keywords: onabotulinumtoxinA (BoNTA), overactive bladder (OAB), neurogenic detrusor overactivity (NDO), idiopathic detrusor overactivity, randomized controlled trials (RCT), meta-analysis

1

INTRODUCTION

According to the International Continence Society (ICS), overactive bladder (OAB) is a disease characterized by the presence of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI), in the absence of urinary tract infection (UTI) or other clear pathology (1). OAB is a common disease that threatens the quality of human life severely. The symptoms of OAB were disturbing chronic disease and imposed an economic burden in many patients (2). The incidence of OAB increased significantly with age from 11% up to 20% between the ages of 40 and 60 years for both men and women (3, 4). OAB was considered as a symptom complex, and it includes idiopathic detrusor overactivity (IDO) or neurogenic detrusor overactivity (NDO). According to the ICS, IDO was defined as the occurrence of involuntary detrusor contractions during filling cystometry without infected and pathological changes. NDO was detrusor overactivity (DO) caused by various neurologic diseases such as brain tumors, dementia, and spinal cord injury (SCI) (5). Although the causes of NDO and IDO are different, they show many similar symptoms and treatment methods.

For treating this disease, there are many methods, including bladder and behavioral training, drug treatment, onabotulinumtoxinA (BoNT-A), neuromodulation, and surgical therapies. Bladder and behavioral training was the first-line treatment for OAB, and drug treatment, such as the use of anticholinergics, was the second-line treatment; low compliance can affect the treatment result in the mentioned two treatments (3). In these circumstances, onabotulinumtoxinA has been advised as an alternative treatment for patients.

BoNT-A is a poisonous potent neurotoxin produced by the anaerobic bacterium clostridium botulinum and related species (6). According to antigenic and serological classification, there are eight distinguishable exotoxins of BoNT (A, B, C₁, C₂, D, E, F, and G), and type A had a better effect in durative time (7). BoNT-A inhibits muscle contractions on muscle by binding strongly to presynaptic cholinergic nerve terminals at the neuromuscular junction to inhibit acetylcholine release.

According to the American Urological Association and European Association of Urology guidelines recommendations, BoNT-A has been recommended as an alternative treatment (8, 9). Intravesical BoNT-A injections have achieved the satisfactory clinical effect; it could increase bladder capacity, decreased sense of urgency, and improved other symptoms in patients with NDO or IDO (10–13). In the past 10 years, the drugs were injected into different sites of the bladder wall with a cystoscope. The most common adverse reactions following the administration of the toxin reported in the clinical research were urinary retention and urinary tract infection (14). The trigone of the bladder has a large number of sensory nerve fibers (15), which might

improve effectiveness with trigonal injections. Recent research also showed that trigonal BoNT-A injection had a less adverse effect and shorter treatment time compared to that of bladder body injections (16).

BoNT-A injection is an effective alternative treatment. Unfortunately, there is no standardized way of injecting BoNT-A for the treatment of OAB. Therefore, a systematic review and a meta-analysis of randomized controlled trials (RCTs) were performed to assess the effectiveness and safety of trigonalinvolved injection of BoNT-A comparison with the trigonalsparing technique in cases with OAB (NDO and IDO).

MATERIALS AND METHODS

Study Design

A systematic review of RCTs was carried out using the preferred reporting items for the meta-analyses (PRISMA) checklist (17). Main analyses included trigonal-including vs. trigonal-sparing. The subgroup analysis was IDO vs. NDO.

Search Strategy

We searched relevant RCTs looking at the use of BoNT-A intravesical injection for patients with OAB on PubMed (1997 to Oct. 2020), EMBASE (1997 to Oct. 2020), and the Cochran Central Register for Controlled Trials. Keywords and medical subjects were as follows: "onabotulinumtoxinA (BoNT-A)," "overactive bladder," "neurogenic detrusor overactivity," "idiopathic detrusor overactivity," "randomized controlled trials," and "meta-analysis." Two authors completed the whole screening process independently, and if there was any dispute, articles would be sent to another author for evaluation. Relevant reference articles were also included. Furthermore, we reviewed original references of included texts.

Inclusion Criteria

All of the included RCTs meet the following criteria: (a) the studies should have a connection with the topic "The effect of BoNT-A injections for patients with overactive bladder"; (b) the full useful texts are on RCTs; (c) accurate data could be obtained, and there are similar indicators between the trigone-including group and trigone-sparing group in every RCT. The following studies were excluded: (a) the data were incomplete; (b) the type of study was an abstract, review, comment, case-control, and cohort study. Furthermore, we included the most recently published studies if they described identical experiments. Every study was included if different measures were evaluated.

Quality Assessment

We used the Cochrane risk of bias tool to determine the quality of the retrieved RCTs (18). The quality items were selective outcome reporting, blinding, allocation concealment, incomplete outcome data, random sequence generation, and other sources of bias. A graph summarizing the risk of bias was generated based on discussions among the authors (shown in **Figure 1**). Then, according to the guidelines published in the Cochrane Handbook for Systematic Reviews of Interventions v.5.3.0, the studies were classified qualitatively (19). All of the authors

Abbreviations: OAB, overactive bladder; UUI, urgency urinary incontinence; UTI, urinary tract infection; NDO, neurogenic detrusor overactivity; DO, overactivity; SCI, spinal cord injury; BoNT-A, onabotulinumtoxinA; IDO, idiopathic detrusor overactivity; RCT, randomized controlled trial; MD, mean difference; SE, standard error; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom; OR, odds ratio.



participated in the quality assessment of all RCTs and agreed with the results. Meanwhile, the differences between each RCT were bridged through discussion among authors. All authors participated in the evaluation process and reached a consensus on the final results.

Data Extraction

The following information was collected for RCTs: (a) the general data in the test; (b) name of the first author; (c) published time; (d) the design of study and size of the sample; (e) the efficacious data in every article that changes in the following parameters, such as the impact on patient symptom score; impact on complete dryness rate; impact on change in the number of incontinence episodes; impact on detrusor pressure at maximum flow rate; impact on volume at the first desire to void; impact in maximum cystometric capacity; impact on post-void residual volume. Finally, another author checked the data extracted from the text. Meanwhile, our team cross-checked references and data for each included study to ensure there were no overlapping data and to maintain the meta-analysis integrity.

Statistical Analysis and Meta-Analysis

The abstracted data were analyzed with Review Manager 5.1.0 (The Cochrane Collaboration, London, UK) (19). The mean difference (MD) with a 95% confidence interval (CI) was utilized to analyze the continuous data and the odds ratio (OR), and 95% CI was applied to analyze the dichotomous data among the different groups. The chi-square based on Q statistic was performed to check the heterogeneity among the studies, and the result was recognized as significant at P < 0.05. The fixedeffects model was used and considered to be homogeneous if the result was p-value > 0.05. We utilized the I^2 statistic to analyze inconsistent results, and it can reflect the proportion of heterogeneity across trials. In this meta-analysis, it is not necessary to have ethical approval and patient consent because all the data were acquired from articles that have already been published. When the $I^2 < 50\%$, this indicated that there was no significant heterogeneity and the fixed-effects model (Mantel-Haenszel method) would be used. And we performed the random-effects model (DerSimonian and Laird method) when the heterogeneity of the data could not be explained (p < 0.05, $I^2 > 50\%$).



RESULTS

Characteristics of the Individual Studies

Based on the inclusion criteria above, we found 916 articles in the database. After reviewing the abstracts, 578 duplicate articles and 306 studies were removed after reviewing the titles and abstracts of the articles. In total, 26 studies were ruled out for a lack of useful data. Finally, six RCTs (20–25) involving 437 patients were included in our analysis. A detailed flowchart showing the selection process is shown in **Figure 2**. **Table 1** shows the baseline characteristics of studies.

Quality of the Individual Studies

All of the included studies in the systematic review and meta-analysis were high-quality RCTs. **Figure 1** presents a graphical summary of the risk bias. We have found that their randomization process has been developed in all studies. All RCTs were effective and determined the best sample size. The funnel plot displayed the conclusion of a qualitative estimation of publication bias of each RCT (**Figure 3**). **Table 2** showed the specific inclusion and exclusion criteria.

TABLE 1 | Study and patient characteristics.

References	Country	Experimental group	Control group	Sam	ole size	The doses o	f therapy (weeks)	Inclusion criteria	Exclusion criteria
				Experimental group (male/female)	Control group (male/female)				
Hui et al. (21)	China	Include trigone	Exclude trigone	47 (28/19)	44 (23/21)	160 U detrusor + 40 U trigone	200 U detrusor	At least 18 years old with various neurogenic disorders; urodynamic DO with urinary incontinence; an inadequate response or intolerance to oral anticholinergic drugs; participants or their caregiver could perform clean intermittent catheterization.	An allergy to BoNT-A; women were pregnant, lactating or planning to become pregnant during the course of the trial; acute urinary tract infection.
El-Hefnawy et al. (20)	Egypt	Include trigone	Exclude trigone	51 (9/42)	52 (12/40)	100 U at 20 sites onto detrusor and trigone	100 U at 20 sites onto detrusor	All patients had been refractory to treatment with antimuscarinics for 2 months.	Age <18 years old; neurogenic DO; evidence of obstructed urinary flow in absence of prolapse; mixed urinary incontinence; associated urethral pathology; associated bladder pathology; active UTI as evidenced by positive urine culture; and previous intravesical Botox injection.
Huang et al. (22)	China	Include trigone	Exclude trigone	41 (17/24)	39 (13/26)	160 U detrusor + 40 U trigone	200 U detrusor	Presence of DO and DESD; and inadequate response or intolerance to oral anti-muscarinic agent or spasmolytic agents, skeletal muscle relaxant and alpha blockers.	Allergy to BoNT-A; coagulopathy disease and myasthenia gravis; acute urinary tract infection; other causes of bladder outlet obstruction; and previous sphincterotomy.
Kuo (23)	China	Include trigone	Exclude trigone	68 (31/37)	37 (17/20)	75 U detrusor + 25 U trigone	100 U detrusor	Aged 18 years or more, with urodynamic DO and at least one episode of urgency or UUI per day as recorded in the 7-day voiding diary.	Neurogenic bladder, urodynamic ally confirmed bladder outlet obstruction, prior pelvic surgery, anti-incontinence surgery, or urinary tract infection.
Manecksha et al. (24)	Ireland	Include trigone	Exclude trigone	11 (1/10)	11 (2/9)	25 U at 15 sites onto detrusor and 5 sites onto trigone	25 U at 20 sites onto detrusor	Aged \geq 17 yr with urodynamic-confirmed detrusor overactivity, who had failed \geq 6 wk anticholinergic therapy or discontinued therapy due to intolerability	Infection and pregnancy; Patients previously injected with BoNT-A; Patients with any neurologic condition or coagulopathies; as were men with clinical or urodynamic evidence of bladder outflow obstruction.
Abdel-Meguid (25)	ł Egypt	Include trigone	Exclude trigone	18 (17/1)	18 (17/1)	200 U detrusor + 100 U trigone	300 U detrusor	Adults with SCI, neurogenic urinary incontinence and NDO refractory to anticholinergic medications	Patients who refused CIC or refused to discontinue anticholinergics, those who received previous BoNT-A bladder injections and those with uncontrolled urinary tract infection

DO, detrusor overactivity; BoNT-A, botulinum toxin A; UTI, urinary tract infection; DESD, detrusor external sphincter dyssynergia; SCI, spinal cord injury; NDO, neurogenic detrusor overactivity; CIC, clean intermittent catheterization.

Effectiveness

We analyzed the differences in the mean score of each domain for OAB to identify the efficacy of treatment with BoNT-A. Also, we analyzed the differences in treatment effects of BoNT-A for NDO and IDO.

Impact on Patient Symptom Score

Five RCTs involving 401 patients (218 in the trigone-including group and 183 in the trigone-sparing group) recorded the changes in impact on patient symptom score (**Figure 4A**). Since P < 0.05, we employed a random-effects model, which reflected an MD of -1.79 (95 CI%: -3.41 to -0.16, P = 0.03). The results suggest that the trigone-including group showed statistical differences in the impact on patient symptom score compared



with the trigone-sparing group for OAB. A subgroup analysis revealed that trigone-including intradetrusor injection had no marked difference in the impact on patient symptom score compared with the trigone-sparing group for IDO (MD = -0.91, 95% CI: -2.28 to -0.70, P = 0.27). For NDO, it showed a significant difference between the two groups in the change of the impact on patient symptom score (MD = -6.97, 95% CI: -10.83 to -3.11, P = 0.0004).

Impact on Complete Dryness Rate

Four RCTs involving 312 patients (174 in trigone-including group and 138 in trigone-sparing group) recorded the change in impact on complete dryness rate (**Figure 4B**). Since P > 0.05, we employed a fixed-effects model, which reflected an MD of 2.19 (95% CI: 1.32 to 3.63, P = 0.002). The results suggest that the trigone-including group showed statistical differences in the impact on complete dryness rate compared to the trigone-sparing group for OAB. A subgroup analysis revealed that trigone-including intradetrusor injection showed a significantly different impact on patient symptom score compared with the trigone-sparing group for NDO (MD = 3.35, 95% CI: 1.76 to 6.37, P = 0.0002).

Impact on Change in Number of Incontinence Episodes

A total of six RCTs involving 437 patients (236 in the trigoneincluding group and 201 in the trigone-sparing group) recorded the changes in impact on change in the number of incontinence episodes (**Figure 4C**). A random-effects model showed an MD of -0.82 (95% CI: -1.46 to 0.18, P = 0.01). It proved that the trigone-including group showed statistical differences in terms of the impact on change in the number of incontinence episodes for OAB. For IDO, a subgroup analysis revealed that trigoneincluding intradetrusor injection showed no differences in the impact on patient symptom score compared with the trigonesparing group for IDO (MD = 0.12, 95% CI: -0.50 to 0.74, P

TABLE 2 | Criteria for considering studies for the review based on the population, intervention, comparator, outcomes, and study designs (PICOS) structure.

	Population	Intervention	Comparator	Outcomes	Study designs
Inclusion criteria	Aged ≥ 17 years oldwith SCI, neurogenic urinary incontinence and NDO refractory, an inadequate response or intolerance to oral anticholinergic drugs and so on.	BoNT-A into the detrusor and the trigone.	BoNT-A into the detrusor, excluding the trigone.	Impact on patient symptom score; impact on complete dryness rate; impact on change in number of incontinence episodes; impact on detrusor pressure at maximum flow rate; impact on volume at the first desire to void; impact in maximum cystometric capacity; impact on post-viod residual volume.	RCT
Exclusion criteria	Age <17 years old; an allergy to BoNT-A; Infection and pregnancy; mixed urinary incontinence; other causes of bladder outlet obstruction; previous intravesical Botox injection and so on.	Other therapy.	Other therapy.	Qualitative outcomes such as inadequate indicators and others;	Observational study, letters, comments, reviews, and animal experiment.

BoNT-A, onabotulinumtoxinA; RCT, randomized controlled trial; SCI, spinal cord injury; NDO, neurogenic detrusor overactivity.

Cui	i et	al.	

Study or Subgroup I.1.1 IDO El-Hefnawy A 2020 (uo H 2011 Euctom B 2012	Trigone								
Study or Subgroup I.1.1 IDO EI-Hefnawy A 2020 Kuo H 2011 Austom B 2012		*-includ	ling	Trigon	ie-spar	ing		Mean Difference	Mean Difference
I.1.1 IDO El-Hefnawy A 2020 Kuo H 2011 Austom B 2012	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
El-Hefnawy A 2020 Kuo H 2011 Pustom B 2012									_
Kuo H 2011 Ruotom B 2012	-3.5	0.72	51	-4.5	0.76	52	31.0%	1.00 [0.71, 1.29]	
Ductore D 2012	2.42	1.12	68	2.42	1.03	37	30.6%	0.00 [-0.43, 0.43]	
AUSIONIF 2012	9.5	1.13	11	14.1	2.3	11	24.6%	-4.60 [-6.11, -3.09]	
Subtotal (95% CI)			130			100	86.2%	-0.91 [-2.52, 0.70]	-
Heterogeneity: Tau ² = Fest for overall effect: 2	1.83; Chi ² Z = 1.11 (F	° = 60.3 P = 0.27	6, df = 3 7)	2 (P < 0.0)0001);	I ^z = 97	%		
1.1.2 NDO									
C Hui 2016	-26.01	11.56	47	-18.75	15.18	44	6.7%	-7.26 [-12.83, -1.69]	
Huang M 2016	-27.02	10.94	41	-20.32	13.27	39	7.1%	-6.70 [-12.04, -1.36]	
Subtotal (95% Cl)			88			83	13.8%	-6.97 [-10.83, -3.11]	
Heterogeneity: Tau² = Test for overall effect: 2	0.00; Chi² Z = 3.54 (F	² = 0.02, P = 0.00	, df = 1 304)	(P = 0.89	9); I 2 = 0	1%			
otal (95% CI)			218			183	100.0%	-1.79 [-3.41, -0.16]	•
Heterogeneity: Tau ² = 1	2.20; Chi 	² = 74.9	7, df = 4	4 (P ≤ 0.0	00001);	2 = 95	%		
fest for overall effect: 3	Z = 2.15 (F	P = 0.03	3)						-20 -10 0 10 20 Trigone-including Trigone-sparing
Test for subaroup diffe	erences: C	Chi² = 8	.06. df=	= 1 (P = 0).005).1	= 87.6	3%		Angene mendang i rigone spalling
1									
	Trinon	a in alu	diase	Tringer				Odda Datia	Odda Datia
Churche and Churchennessen	Trigone	e-inciu	aing	Trigon	e-spari	ing T-t-l		Odds Ratio	Odds Ratio
study or Subgroup	Even	πs	lotal	Event	S	lotal	weight	M-H, FIXed, 95% CI	M-H, HXed, 95% CI
2.1.1 IDO				_	_				
<uo 2011<="" h="" td=""><td>4</td><td>49</td><td>68</td><td>2</td><td>7</td><td>37</td><td>48.2%</td><td>0.96 [0.39, 2.35]</td><td></td></uo>	4	49	68	2	7	37	48.2%	0.96 [0.39, 2.35]	
Subtotal (95% CI)			68			37	48.2%	0.96 [0.39, 2.35]	
rotal events	l l	49		2	7				
Heterogeneity: Not ap	pplicable								
Fest for overall effect:	: Z = 0.10	(P = 0.	.92)						
2.1.2 NDO									
C Hui 2016	1	13	47		5	44	18.4%	2.98 [0.96, 9.23]	
Huang M 2016	2	22	41	1	0	39	23.4%	3.36 [1.30, 8.64]	
Faha A 2010	1	12	18		6	18	9.9%	4.00 [1.00, 15.99]	
Subtotal (95% CI)			106			101	51.8 %	3.35 [1.76, 6.37]	
Fotal events	L	47		2	1			_	
Heterogeneity: Chi ² =	: 0.10, df =	= 2 (P =	= 0.95);	I²=0%					
Fest for overall effect:	Z = 3.68	(P = 0.	.0002)						
fotal (95% CI)			174			138	100.0%	2.19 [1.32, 3.63]	◆
Fotal events	9	96		4	8				
rotal oronito	: 5.08, df :	= 3 (P =	= 0.17);	l [≈] = 41 %	6				
Heterogeneity: Chi [≥] =	: Z = 3.05	(P = 0.	.002)						U.UI U.I I IU 100
Heterogeneity: Chi ^z = Test for overall effect:	ferences:	∶Chi²=	4.95. (df = 1 (P	= 0.03). I ² = 7	9.8%		ringone-spanng ringone-including
Heterogeneity: Chi ^z = Fest for overall effect: Fest for subaroup diff									
Heterogeneity: Chi² = Fest for overall effect: Fest for subαroup dif									
Heterogeneity: Chi ² = Fest for overall effect: Fest for subdroup dif	Teiner	, inclus	lin	Televe				Mean Diff	Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Fest for subaroup dif	Trigone	a-includ	ling	Trigon	e-spari	ing Tet-l	Mainlet	Mean Difference	Mean Difference
Heterogeneity: Chi [#] = Test for overall effect. Fest for subaroup dif : : : : : : : : : : : : : : : : : : :	Trigone Mean	3-includ SD	ling Total	Trigon Mean	e-spari SD	ing Total	Weight	Mean Difference IV, Random, 95% Cl	Mean Difference IV, Random, 95% Cl
Heterogeneity: Chi ² = Test for overall effect Fest for subdroup dif <u>Study or Subgroup</u> 1.1.1 IDO Hetfnawy A 2020	Trigone Mean	e-includ <u>SD</u> 2.07	ling <u>Total</u> 51	Trigon <u>Mean</u> -1.69	e-spari <u>SD</u>	ing <u>Total</u> 52	<u>Weight</u> 21.7%	Mean Difference IV, Random, 95% Cl	Mean Difference IV, Random, 95% Cl
Heterogeneity: Chi [≠] = Test for overall effect Fest for subaroup dif : : : : : : : : : : : : : : : : : : :	Trigone <u>Mean</u> -1.52 -7 52	e-includ <u>SD</u> 2.07 14 4	ling <u>Total</u> 51 69	Trigon <u>Mean</u> -1.69 -8.6	e-spari <u>SD</u> 1.01 16.2	ing <u>Total</u> 52 37	<u>Weight</u> 21.7%	Mean Difference <u>IV, Random, 95% Cl</u> 0.17 [-0.46, 0.80] 1.08 [-5.16, 7.32]	Mean Difference IV, Random, 95% Cl
Heterogeneity: Chi ^P = Test for overall effect. Test for subdroup dif : : : : : : : : : : : : : : : : : : :	Trigone <u>Mean</u> -1.52 -7.52 -7.9	≥-includ SD 2.07 14.4 4 9	ling <u>Total</u> 51 68 11	Trigon Mean -1.69 -8.6 -4 9	e-spari SD 1.01 16.2 5 9	ing <u>Total</u> 52 37 11	Weight 21.7% 1.0% 1.9%	Mean Difference IV, Random, 95% CI 0.17 [-0.46, 0.80] 1.08 [-5.16, 7.32] -3 00 [-7 53 1 53]	Mean Difference IV, Random, 95% Cl
Heterogeneity: Chi ^P = Test for overall effect Test for subgroup dif Study or Subgroup 3.1.1 IDO EI-Hefnawy A 2020 (Jo H 2011 Rustom P 2012 Subtotal (95% Ch	Trigone <u>Mean</u> -1.52 -7.52 -7.9	≥-includ SD 2.07 14.4 4.9	ting <u>Total</u> 51 68 11 130	Trigon <u>Mean</u> -1.69 -8.6 -4.9	e-spari SD 1.01 16.2 5.9	ing <u>Total</u> 52 37 11 100	Weight 21.7% 1.0% 1.9% 24.5%	Mean Difference IV, Random, 95% CI 0.17 [-0.46, 0.80] 1.08 [-5.16, 7.32] -3.00 [-7.53, 1.53] 0.12 [-0.50, 0.74]	Mean Difference IV. Random, 95% Cl

3.1.2 NDO

 C Hui 2016
 -5.22 0.91 47 -4.08 1.06 44 24.7% -1.14 [-1.55, -0.73]

 Huang M
 -7.19 0.81 41 -6.65 1.02 39 24.8% -0.54 [-0.94, -0.14]

 Taha A 2010
 -4.15 0.63 18 -2.62 0.14 18 25.9% -1.53 [-1.83, -1.23]

 Subtotal (95% CI)
 106
 101
 75.5% -1.08 [-1.66, -0.50]

 Heterogeneity: Tau² = 0.23; Chi² = 14.92, df = 2 (P = 0.0006); P = 87% Test for overall effect: Z = 3.65 (P = 0.0003)

 Total (95% CI)
 236
 201
 100.0% 0.82 [1.46 0.18]

 Total (95% Cl)
 236
 201
 100.0%
 -0.82 [-1.46, -0.18]

 Heterogeneity: Tau² = 0.39; Chi² = 31.75, df = 5 (P < 0.00001); l² = 84%
 -20

 Test for overall effect: Z = 2.52 (P = 0.01)
 -20

 Test for subaroup differences: Chi² = 7.66, df = 1 (P = 0.006), l² = 86.9%

FIGURE 4 | Forest plots showing changes between two groups in the impact on (A) patient symptom score, (B) complete dryness rate, and (C) change in the number of incontinence episodes; NDO, neurogenic detrusor overactivity; IDO, idiopathic detrusor overactivity; SD, standard deviation; IV, inverse variance; Cl, confidence interval; df, degrees of freedom.

20

10

ń.

Trigone-including Trigone-sparing

-10

= 0.71). For NDO, it showed statistical differences between the two groups (MD = -1.08, 95% CI: -1.66 to -0.50, P = 0.0003).

Impact on Detrusor Pressure at the Maximum Flow Rate

A total of six RCTs involving 437 patients (236 in the trigoneincluding group and 201 in the trigone-sparing group) recorded the changes in impact on detrusor pressure at the maximum flow rate (Figure 5A). Since P < 0.05, we employed a random-effects model, which reflected an MD of -4.47 (95% CI: -7.97 to -0.96, P = 0.01). The results suggest that the trigone-including group showed statistical differences in the impact on detrusor pressure at maximum flow rate compared with the trigone-sparing group for OAB. A subgroup analysis revealed that a trigone-including intradetrusor injection showed no marked differences in the impact on detrusor pressure at the maximum flow rate compared with the trigone-sparing group for IDO (MD = -9.01, 95% CI: -19.31 to 1.29, P = 0.09). Also, there were statistical differences in terms of impact on detrusor pressure at the maximum flow rate between the two groups for NDO (MD = -2.82, 95% CI: -4.95to -0.68, P = 0.01).

The Changes in Differences in the Impact on Volume at the First Desire to Void

A total of four RCTs involving 318 patients (117 in the trigoneincluding group and 201 in the trigone-sparing group) recorded the changes in impact on *volume at the first desire to void* (**Figure 5B**). Since P > 0.05, we employed a fixed-effects model, which reflected an MD of 25.07 (95% CI: 11.29 to 38.85, P =0.0004). The results suggest that the trigone-including group showed statistical differences in the impact on the volume of the first desire to void compared with the trigone-sparing group for OAB. For NDO, a subgroup analysis showed statistical differences between the two groups (MD = 24.71, 95% CI: 10.66 to 38.77, P = 0.0006).

Impact in Maximum Cystometric Capacity

A total of four RCTs involving 266 patients (148 in trigoneincluding group and 118 in trigone-sparing group) recorded the changes in impact in terms of maximum cystometric capacity (**Figure 5C**). A fixed-effects model showed an MD of -12.41, 95% CI: -35.16 to 10.33, P = 0.28. It proved that the trigoneincluding group showed no differences in terms of the change in impact in maximum cystometric capacity. A fixed-effects model also showed that the trigone-including group showed no marked differences in the impact in maximum cystometric capacity with the trigone-sparing group for IDO (MD = -5.04, 95% CI: -35.36 to 25.28, P = 0.74).

Impact on Post-void Residual Volume

A total of three RCTs involving 230 participants (130 in the trigone-including group and 100 in the trigone-sparing group) recorded the changes in impact on the post-void residual volume (**Figure 5D**). A fixed-effects model showed an MD of 0.96, 95% CI: -3.72 to -5.63, P = 0.69. There were no statistical differences in terms of impact on post-void residual volume between the two groups.

Safety

Hematuria; General Weakness; Bladder Discomfort; Incidence of Large Post-void Residual; Urinary Tract Infection; Difficulty of Voiding

A total of five RCTs, including 301 participants (152 in the trigone-including group and 149 in the trigone-sparing group) were involved in the research for Hematuria. The OR of the study was 1.34, and the 95% CI was 0.63–2.85 (P = 0.45); three RCTs analyzed the incidence of the general weakness of 207 patients (106 in the trigone-including group and 101 in the trigone-sparing group) (OR = 1.15; 95%CI = 0.36-3.68; P = 0.82); four RCTs including 221 participants (111 in the trigoneincluding group and 110 in trigone-sparing group) were involved in the research for bladder discomfort (OR = 0.85; 95%CI = 0.40–1.79; P = 0.66); four RCTs including 233 patients (115 in the trigone-including group and 118 in the trigone-sparing group) were involved in the research for the incidence of large post-void residual (OR = 1.69; 95%CI = 0.54-5.26; P = 0.37); three RCTs analyzed the incidence of urinary tract infection of 197 patients (97 in the trigone-including group and 100 in the trigone-sparing group) (OR = 1.35, 95%CI = 0.60-3.03 P= 0.47); and three RCTs including 197 participants (97 in the trigone-including group and 100 in the trigone-sparing group) were involved in the research for difficulty of voiding (OR =1.87, 95%CI = 0.88-4.00 P = 0.10). These results indicate that there is no significant difference between the two groups in terms of Hematuria; general weakness; bladder discomfort; incidence of large post-void residual; urinary tract infection; difficulty of voiding. There were no statistical differences in terms of sideeffects between the two groups (Figure 6).

DISCUSSION

OAB is a series of clinical symptoms by urgency frequency with or without UUI that are caused by neurogenic or nonneurogenic factors (4). Behavioral and bladder training, drug therapy, botulinum toxin, electrical stimulation, biofeedback, or surgery can be used to treat patients with OAB. OAB is an illness that greatly compromises the quality of life of patients. Due to less effectiveness and poor adherence to first and second-line treatments, the main objective is the search for new treatments in OAB therapy. Nowadays, literature research reveals that BoNT-A intravesical injection was recommended as a third-line treatment of OAB (26, 27). Intravesical BoNT-A injections may represent a treatment modality for patients with NDO and IDO. Local drug delivery is one of the efficacious ways to lessen the side effects of systemic administration compared with anticholinergic therapy (inadequate efficacy or intolerable side effects).

In summary, for OAB, the trigone-including group showed differences in the patient symptom score (p = 0.03), complete dryness rate (p = 0.002), frequency of incontinence episodes (p = 0.01), detrusor pressure at maximum flow rate (p = 0.01), and volume at the first desire to void (p = 0.004) compared with the trigone-sparing group. A trigone-including injection can improve the patient symptom score. Meanwhile, the higher complete dryness rate and a lower frequency of incontinence



FIGURE 5 | Forest plots showing changes between two groups in (A) impact on detrusor pressure at maximum flow rate, (B) impact on volume at the first desire to void, (C) impact in maximum cystometric capacity, (D) impact on post-void residual volume; NDO, neurogenic detrusor overactivity; IDO, idiopathic detrusor overactivity; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

	Trigone-inc	luding	Trigone-s	sparing		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
C Hui 2016	2	47	1	44	8.4%	1.91 [0.17, 21.85]	
Huang M	5	41	2	39	15.3%	2.57 [0.47, 14.10]	
Kuo H 2011	4	35	6	37	44.1%	0.67 [0.17, 2.60]	
Rustom P 2012	4	11	2	11	10.9%	2.57 [0.36, 18.33]	
Taha A 2010	3	18	3	18	21.3%	1.00 [0.17, 5.77]	
Total (95% CI)		152		149	100.0%	1 34 10 63 2 851	•
Total events	18	152	14	145	100.070	104 [0:00, 2:00]	-
Heterogeneity: Chi ² =	:219 df = 4 (F	P = 0.700	F= 0%				
Test for overall effect:	: Z= 0.76 (P=	0.45)					0.01 0.1 1 10 100
							ingone-sparing ingone-including
В							
	Trinona ina	la colina en	Tringers			Odda Datia	Odda Datia
Study or Subgroup	Frigone-Inc	Total	Frigone-s	sparing Total	Mojet	Udds Ratio	Udds Ratio
C Hui 2018	Evenus	10101	cvents	10101	40.000	0.1010.01.2.021	M-n, rixeu, 95% Ci
Huang M	3	47	2	44	35 0 %	1 46 [0.01, 3.83]	
Taha A 2010	3	18	1	18	15.8%	3 40 10 32 36 271	
1411412010	, i				10.070	0.40 [0.02, 00.27]	
Total (95% CI)		106		101	100.0%	1.15 [0.36, 3.68]	-
Total events	6		5				
Heterogeneity: Chi ² =	= 2.29, df = 2 (F	^o = 0.32);	I²=13%				
Test for overall effect:	: Z = 0.23 (P =	0.82)					Trigone-sparing Trigone-including
C							
	Trigone-inc	ludina	Trigone	sparing		Odds Ratio	Odds Ratio
Study or Subaroup	Events	Total	Events	Total	Weight	M-H, Fixed. 95% CI	M-H, Fixed, 95% Cl
C Hui 2016	0	47	2	44	17.3%	0.18 [0.01, 3.83]	+
Kuo H 2011	13	35	16	37	66.1%	0.78 [0.30, 2.00]	
Rustom P 2012	2	11	2	11	11.1%	1.00 [0.11, 8.73]	
Taha A 2010	3	18	1	18	5.6%	3.40 [0.32, 36.27]	
T-4-1/05/ 00					400		
Total (95% CI)	4.0	111		110	100.0%	0.85 [0.40, 1.79]	$\overline{}$
Tutal events	18 . 1 17 df - 2 m	- 0.500	21				
Test for overall effect:	- 2.37, 01 = 3 (H • 7 = 0 / / /P -	- = 0.50); .0.66)	1 = 0%				0.01 0.1 1 10 100 [°]
, corror overall ellett.	. <u>-</u> - 0.44 (F -	5.50)					Trigone-sparing Trigone-including
D							
-							
Church and C	Trigone-inc	luding	Trigone-9	sparing	10/	Odds Ratio	Odds Ratio
EL Hofpower & 2020	Evenits	<u>rotāi</u> 51	Events	<u>10tal</u>		6 20 10 25 442 22	
Ennemawy A 2020 Kuo H 2011	1	26	U 2	52 27	10.0% 55.1%	1 46 [0 30 7 06]	
	- 			57	33.170	1.40 [0.30, 7.00]	
Rustom P 2012	4	11	1	11	34 9 %	اللاحة فتراجع والمتحد ويهوروا	+
Rustom P 2012 Taha A 2010	4 2 0	11 18	2 0	11 18	34.9%	Not estimable	+
Rustom P 2012 Taha A 2010	4 2 0	11 18	0	11 18	34.9%	Not estimable	
Rustom P 2012 Taha A 2010 Total (95% CI)	4 2 0	11 18 115	0	11 18 118	34.9%	Not estimable	
Rustom P 2012 Taha A 2010 Total (95% CI) Total events	4 2 0 8	11 18 115	2 0 5	11 18 118	34.9%	Not estimable	
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi ² =	4 2 0 = 0.79, df = 2 (F	11 18 115 P = 0.67);	2 0 1²=0%	11 18 118	34.9%	Not estimable	
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	4 2 0 = 0.79, df = 2 (F : Z= 0.90 (P =	11 18 115 [•] = 0.67); 0.37)	2 0 1²=0%	11 18 118	34.9%	Not estimable	0.01 0.1 1 10 100 Trigone-sparing Trigone-including
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	4 2 0 = 0.79, df = 2 (F : Z = 0.90 (P =	11 18 115 P = 0.67); 0.37)	2 0 ²=0%	11 18 118	34.9%	Not estimable	0.01 0.1 1 10 100 Trigone-sparing Trigone-including
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E	4 2 0 = 0.79, df = 2 (F : Z = 0.90 (P =	11 18 115 P = 0.67); 0.37)	2 0 1²=0%	11 18 118	34.9%	Not estimable	0.01 0.1 1 10 100 Trigone-sparing Trigone-including
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E	4 2 0 8 0.79, df = 2 (F : Z = 0.90 (P = Trigone-incl	11 18 115 P = 0.67); 0.37) Iuding	2 0 ²= 0% Trigone-s	11 18 118 sparing	34.9%	Not estimable	0.01 0.1 1 10 100 Trigone-sparing Trigone-including
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E <u>Study or Subgroup</u>	4 2 0 8 0.79, df = 2 (F : Z = 0.90 (P = Trigone-inci Events	11 18 115 P = 0.67); 0.37) Iuding Total	2 0 ²=0% Trigone-s <u>Events</u>	11 18 118 sparing <u>Total</u>	34.9% 100.0% <u>Weight</u>	Not estimable 1.69 [0.54, 5.26] Odds Ratio <u>M-H, Fixed, 95% C</u> 1	0.01 0.1 1 10 100 Trigone-sparing Trigone-including Odds Ratio M-H, Fixed, 95% Cl
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E Study or Subgroup EI-Hefnawy A 2020	4 2 0 = 0.79, df = 2 (F : Z = 0.90 (P = <u>Trigone-incl</u> <u>Events</u> 6	11 18 115 • = 0.67); 0.37) Iuding <u>Total</u> 51	2 0 ² = 0% ² = 0% <u>Frigone-s</u> <u>Events</u> 5	11 18 118 sparing <u>Total</u> 52	34.9% 100.0% <u>Weight</u> 43.1%	Not estimable 1.69 [0.54, 5.26] Odds Ratio <u>M-H, Fixed, 95% C1</u> 1.25 [0.36, 4.40]	0.01 0.1 1 10 100 Trigone-sparing Trigone-including Odds Ratio M-H, Fixed, 95% Cl
Rustom P 2012 Taha A 2010 Total events Heterogeneity: Chi ^P = Test for overall effect: E Study or Subgroup EI-Hefmawy A 2020 Kuo H 2011	4 2 0 : 0.79, df = 2 (F : Z = 0.90 (P = Trigone-incl Events 6 9	11 18 115 9 = 0.67); 0.37) Iuding Total 51 35	2 0 1 ² = 0% Trigone-s <u>Events</u> 5 6	11 18 118 sparing <u>Total</u> 52 37	34.9% 100.0% <u>Weight</u> 43.1% 42.7%	Not estimable 1.69 [0.54, 5.26] Odds Ratio M-H, Fixed, 95% C1 1.25 [0.36, 4.40] 1.79 [0.56, 5.69]	0.01 0.1 1 10 100 Trigone-sparing Trigone-including Odds Ratio M.H. Fixed, 95% Cl
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E Study or Subgroup Ei-Hefnawy A 2020 Kuo H 2011 Rustom P 2012	4 2 0 : Z = 0.90 (P = Trigone-incl Events 6 9 0	11 18 115 0.37) 10.37) 10.037) 10.037) 10.037) 10.037) 10.037) 10.037) 11 10.037 11	2 0 5 1 ² =0% <u>Fvents</u> 5 6 1	11 18 118 118 <u>Total</u> 52 37 11	Weight 43.1% 42.7% 14.2%	Odds Ratio M.H. Fixed, 95% CI 1.25 (0.36, 4.40) 1.79 (0.56, 5.69) 0.30 (0.01, 8.32)	0.01 0.1 1 10 100 Trigone-sparing Trigone-including Odds Ratio M-H, Fixed, 95% Cl
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi [#] = Test for overall effect: E Study or Subgroup EI-Hefnawy A 2020 Kuo H 2011 Rustom P 2012	4 2 0 : Z = 0.90 (P = Trigone-incl Events 6 9 0	11 11 18 115 ² = 0.67); 0.37) 1uding <u>Total</u> 35 11	2 0 5 F= 0% Trigone-s <u>Events</u> 5 6 1	11 18 118 Total 52 37 11	Weight 43.1% 42.7% 14.2%	Not estimable 1.69 [0.54, 5.26] Odds Ratio <u>M-H, Fixed, 95% C1</u> 1.25 [0.36, 4.40] 1.79 [0.56, 5.69] 0.30 [0.01, 8.32]	0.01 0.1 1 10 100 Trigone-sparing Trigone-including Odds Ratio M-H, Fixed, 95% Cl
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E Study or Subgroup EI-Hefnawy A 2020 Kuo H 2011 Rustom P 2012 Total (95% CI)	4 2 0 : 2 - 0,79, df = 2 (F : Z = 0.90 (P = <u>Trigone-incl</u> <u>Events</u> 6 9 0	111 118 115 ² = 0.67); 0.37) 1uding <u>Total</u> 35 11 35 11	2 0 5 F= 0% Trigone-s <u>Events</u> 5 6 1	11 18 118 118 50 52 37 11 100	Weight 43.1% 42.7% 14.2% 100.0%	Not estimable 1.69 [0.54, 5.26] 0dds Ratio <u>M-H, Fixed, 95% CI</u> 1.25 [0.36, 4.40] 1.79 [0.56, 5.69] 0.30 [0.01, 8.32] 1.35 [0.60, 3.03]	0.01 0.1 1 10 100 Trigone-sparing Trigone-including Odds Ratio M-H, Fixed, 95% Cl
Rustom P 2012 Taha A 2010 Total events Heterogeneity: ChP = Test for overall effect: E Study or Subgroup EI-Hefmawy A 2020 Kuo H 2011 Rustom P 2012 Total events	4 2 0 : Z = 0.90 (P = Trigone-inci Events 6 9 0	11 11 18 115 -= 0.67); 0.37) 1uding <u>Total</u> 51 36 11 97	2 0 F= 0% 5 Ference-s 6 1 12	11 18 118 118 <u>Total</u> 52 37 11 100	Weight 43.1% 42.7% 14.2% 100.0%	Not estimable 1.69 [0.54, 5.26] Odds Ratio <u>M-H, Fixed, 95% C1</u> 1.25 [0.36, 4.40] 1.78 [0.56, 5.69] 0.30 [0.01, 8.32] 1.35 [0.60, 3.03]	0.01 0.1 10 100 Trigone-sparing Trigone-including
Rustom P 2012 Taha A 2010 Total events Heterogeneity: Chi ² = Test for overall effect: E Study or Subgroup Ei-Hefnawy A 2020 Kuo H 2011 Rustom P 2012 Total events Heterogeneity: Chi ² = Test for overall effective	4 2 0 : Z = 0.90 (P = Trigone-incl Events 6 9 0 15 : 1.02, df = 2 (F : Z = 0.90 (P =	111 18 115 0.37) 0.37) 1000 115 0.37) 1000 115 11 1000 1100 110000 1100000 110000 110000 110000 11000000	2 0 F= 0% 5 <u>Events</u> 5 6 1 12 F= 0%	11 18 118 Total 52 37 11 100	Weight 43.1% 42.7% 14.2% 100.0%	Not estimable 1.69 [0.54, 5.26] Odds Ratio M-H, Fixed, 95% C1 1.25 [0.36, 4.40] 1.79 [0.56, 5.69] 0.30 [0.01, 8.32] 1.35 [0.60, 3.03]	Odds Ratio M-H, Fixed, 95% Cl 0.01 0.1 1 10 100
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi [#] = Test for overall effect: E Study or Subgroup EI-Hefnawy A 2020 Kuo H 2011 Rustom P 2012 Total (95% CI) Total events Heterogeneity: Chi [#] = Test for overall effect	4 2 0 : Z = 0.90 (P = Trigone-incl Events 6 9 0 15 : 1.02, df = 2 (F : Z = 0.72 (P =	11 18 115 P = 0.67); 0.37) 100 11 35 11 97 P = 0.60); 0.47)	2 0 5 F = 0% Trigone-s <u>Events</u> 5 6 1 12 F = 0%	11 18 118 118 Total 52 37 11 100	Weight 43.1% 42.7% 14.2% 100.0%	Not estimable 1.69 [0.54, 5.26] Odds Ratio <u>M-H, Fixed, 95% C1</u> 1.25 [0.36, 4.40] 1.79 [0.56, 5.69] 0.30 [0.01, 8.32] 1.35 [0.60, 3.03]	Odds Ratio Odds Ratio M-H, Fixed, 95% Cl 0.01 0.1 10 100 Trigone-sparing Trigone-including
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E Study or Subgroup EI-Hefnawy A 2020 Kuo H 2011 Rustom P 2012 Total events Heterogeneity: Chi ² = Test for overall effect:	4 2 0 3 5 0.79, df = 2 (F 2 = 0.90 (P = 7 7 7 7 9 0 15 5 1.02, df = 2 (F 2 = 0.72 (P =	11 18 115 = 0.67); 0.37) 10 10 11 11 97 = 0.60); 0.47)	2 0 F=0% F=0%	11 18 118 Total 52 37 11 100	Weight 43.1% 42.7% 14.2% 100.0%	Not estimable 1.69 [0.54, 5.26] Odds Ratio <u>M-H, Fixed, 95% C1</u> 1.25 [0.36, 4.40] 1.79 [0.56, 5.69] 0.30 [0.01, 8.32] 1.35 [0.60, 3.03]	Odds Ratio M-H, Fixed, 95% Cl 0.01 0.1 10 100 M-H, Fixed, 95% Cl 0.01 0.1 1 10 100 Trigone-sparing Trigone-Including
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi ^P = Test for overall effect: E Study or Subgroup EI-Hefnawy A 2020 Kuo H 2011 Rustom P 2012 Total (95% CI) Total events Heterogeneity: Chi ^P = Test for overall effect:	4 2 0 : 2 - 0,79, df = 2 (F : Z = 0.90 (P = <u>Trigone-incl</u> <u>Events</u> 6 9 0 15 : 1.02, df = 2 (F : Z = 0.72 (P =	11 18 115 = 0.67); 0.37) 100 11 51 35 11 97 = 0.60); 0.47)	2 0 1 ² =0% Trigone-s <u>Events</u> 6 1 1 12 1 ² 1 ² 1 ²	11 18 118 Total <u>Total</u> 52 37 11 100	Weight 43.1% 42.7% 14.2% 100.0%	Not estimable 1.69 [0.54, 5.26] Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.25 [0.36, 4.40] 1.79 [0.56, 5.69] 0.30 [0.01, 8.32] 1.35 [0.60, 3.03]	Odds Ratio M-H, Fixed, 95% Cl 0.01 0.1 10 100 M-H, Fixed, 95% Cl 0.01 0.1 10 100 Trigone-sparing Trigone-including 100
Rustom P 2012 Taha A 2010 Total events Heterogeneity: Chi ^P = Test for overall effect: E Study or Subgroup EI-Hefnawy A 2020 Kuo H 2011 Rustom P 2012 Total (95% CI) Total events Heterogeneity: Chi ^P = Test for overall effect:	4 2 0 : Z = 0.90 (P = Trigone-inci Events 6 9 0 : 15 : Z = 0.72 (P = Trigone-inci	111 18 115 9 = 0.67); 0.37) 1uding 10 11 36 11 97 97 0.47) 1uding	2 0 5 F= 0% Trigone-s <u>Events</u> 6 1 1 12 F= 0%	11 18 118 118 <u>Total</u> 52 37 11 100 \$paring	Weight 43.1% 42.7% 14.2% 100.0%	Not estimable 1.69 [0.54, 5.26] Odds Ratio <u>M-H. Fixed, 95% CI</u> 1.25 [0.36, 4.40] 1.79 [0.56, 5.69] 0.30 [0.01, 8.32] 1.35 [0.60, 3.03] Odds Ratio	Odds Ratio 0.01 0.1 10 100 Trigone-sparing Trigone-including 0.01 0.1 10 0.01 0.1 10 0.01 0.1 10 Trigone-sparing Trigone-including 0.01 0.1 10 0.01 0.1 10 0.01 100 0.01 0.1 10 0.01 0.1 100 0.01 0.1 100 0.01 0.1 100 0.01 0.1 100 0.01 0.1 100 0.01 0.1 100 0.01 0.1 0.1 100 0.01 0.1 0.1 100 0.01 0.1 0.1 0.1 00 0.01 0.0 00 0.00 00
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E Study or Subgroup Ei-Hefnawy A 2020 Kuo H 2011 Rustom P 2012 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E Study or Subgroup	4 2 0 : Z = 0.90 (P = Trigone-incl Events 6 9 0 15 : Z = 0.72 (P = Trigone-incl Events	111 18 115 9 = 0.67); 0.37) 1uding <u>Total</u> 51 36 11 97 9 = 0.60); 0.47) 1uding <u>Total</u>	2 0 5 F = 0% F = 0% 1 F = 0% Trigone-s Events	11 18 118 118 <u>Total</u> 37 11 100 sparing <u>Total</u>	Weight 43.1% 42.7% 14.2% 100.0%	Not estimable 1.69 [0.54, 5.26] Odds Ratio <u>M-H, Fixed, 95% C1</u> 1.25 [0.36, 4.40] 1.77 [0.56, 5.69] 0.30 [0.01, 8.32] 1.35 [0.60, 3.03] Odds Ratio <u>M-H, Fixed, 95% C1</u>	Odds Ratio 0.01 0.1 10 100 Trigone-sparing Trigone-including 0.01 0.1 10 100 Trigone-sparing Trigone-including Odds Ratio 0.01 0.1 10 100 Trigone-sparing Trigone-including
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E Study or Subgroup Ei-Hefnawy A 2020 Kuo H 2011 Rustom P 2012 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: F Study or Subgroup Ei-Hefnawy A 2020	4 2 0 : Z = 0.90 (P = Trigone-incl Events 6 9 0 15 : 1.02, df = 2 (F : Z = 0.72 (P = Trigone-incl Events 10	111 18 115 0.37) 100 115 11 36 111 97 0.47) 0.47) 100 0.47)	2 0 5 F=0% 5 6 1 12 F=0% 7 Trigone-s Events 3	11 18 118 118 <u>Total</u> 52 37 11 100 100 <u>Total</u> 52	34.9% 100.0% Weight 43.1% 42.7% 14.2% 100.0% Weight 24.0%	Not estimable 1.69 [0.54, 5.26] 0.000 Ratio <u>M-H, Fixed, 95% CI</u> 1.25 [0.36, 4.40] 1.79 [0.56, 5.69] 0.30 [0.01, 8.32] 1.35 [0.60, 3.03] Odds Ratio <u>M-H, Fixed, 95% CI</u> 3.98 [1.03, 15.45]	Odds Ratio 0.01 0.1 10 100 Trigone-sparing Trigone-Including Odds Ratio 0.01 0.1 10 100 Trigone-sparing Trigone-Including Odds Ratio 0.01 0.1 10 100 Trigone-sparing Trigone-Including
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E Study or Subgroup Ei-Hefnawy A 2020 Kuo H 2011 Total events Heterogeneity: Chi ² = Test for overall effect: F Study or Subgroup Ei-Hefnawy A 2020 Kuo H 2011	4 2 0 8 5.79, df = 2 (f 2 z = 0.90 (P = 7 7 15 5 1.02, df = 2 (f 2 z = 0.72 (P = 7 7 10 11 10 11	111 18 115 = 0.67); 0.37) 1uding 51 36 11 97 = 0.60); 0.47) 1uding <u>Total</u> 51 35 11 97 = 0.67); 0.37)	2 0 5 F = 0% 7 F = 0% 7 F = 0% F = 0% 7 F = 0% 7 F = 0% 7 12 F = 0% 7 12 F = 0% 7 12 F = 0% 7 12 F = 0%	11 18 118 118 <u>Total</u> 52 37 11 100 <u>Total</u> 52 37 37 37	34.9% 100.0% Weight 43.1% 42.7% 14.2% 100.0% Weight 24.0% 66.9%	Not estimable 1.69 [0.54, 5.26] 0.000 Ratio <u>M-H, Fixed, 95% C1</u> 1.25 [0.36, 4.40] 1.79 [0.56, 5.69] 0.30 [0.01, 8.32] 1.35 [0.60, 3.03] 0.000 Ratio <u>M-H, Fixed, 95% C1</u> 3.98 [1.03, 15.45] 1.24 [0.45, 3.42]	Odds Ratio 0.01 0.1 10 100 Trigone-sparing Trigone-including 0.01 0.1 100 0.01 0.1 100 Trigone-sparing Trigone-including 0.01 0.1 100 0.01 0.1 100 0.01 0.1 100 0.01 0.1 100
Rustom P 2012 Taha A 2010 Total events Heterogeneity: ChP = Test for overall effect: E Study or Subgroup EI-Hefnawy A 2020 Kuo H 2011 Rustom P 2012 Total events Heterogeneity: ChP = Test for overall effect: F Study or Subgroup EI-Hefnawy A 2020 Kuo H 2011 Rustom P 2012	4 2 0 3 5 0.79, df = 2 (F 2 Z = 0.90 (P = 7 7 10 5 5 5 1.02, df = 2 (F 2 Z = 0.72 (P = 7 10 11 11 1	111 18 115 9 = 0.67); 0.37) 100000 111 315 111 97 9 = 0.60); 0.47) 100000 111 315 111 315 111	2 0 5 F = 0% F = 0% F = 0% F = 0% Trigone-s Events 10 1 10 1	11 18 118 118 <u>Total</u> 52 37 11 100 <u>Total</u> 52 37 11	Weight 43.1% 42.7% 14.2% 100.0% ¥24.0% 66.9% 9.1%	Odds Ratio M. 69 [0.54, 5.26] 1.69 [0.54, 5.26] 1.25 [0.36, 4.40] 1.79 [0.56, 5.69] 0.30 [0.01, 8.32] 1.35 [0.60, 3.03] Odds Ratio M-H, Fixed, 95% CI 3.98 [1.03, 15.45] 1.24 [0.45, 3.42] 1.20 [0.05, 18.30]	Odds Ratio 0.01 0.1 10 100 Trigone-sparing Trigone-including 0.01 0.1 10 100 M-H, Fixed, 95% CI 0.01 0.1 1 0 100 Trigone-sparing Trigone-including
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E Study or Subgroup EI-Hefnawy A 2020 Kuo H 2011 Rustom P 2012 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E Study or Subgroup EI-Hefnawy A 2020 Kuo H 2011 Rustom P 2012 Total (95% CI)	4 2 0 8 : Z = 0.90 (P = Trigone-inci Events 6 9 0 15 : Z = 0.72 (P = Trigone-inci Events 10 11 1	111 18 115 = 0.67); 0.37) luding Total 51 355 11 97 = 0.60); 0.47) luding Total 51 355 11 97 = 0.60); 0.47)	2 0 5 F=0% Trigone-s Events 6 1 1 F=0% Trigone-s Events 3 10 1	11 18 118 118 100 100 100 100 100	Weight 43.1% 42.7% 14.2% 100.0% Weight 24.0% 66.9% 9.1%	Odds Ratio 1.69 [0.54, 5.26] 0.0dds Ratio M.H. Fixed, 95% CI 1.25 [0.36, 4.40] 1.79 [0.56, 5.69] 0.30 [0.01, 8.32] 1.35 [0.60, 3.03] Odds Ratio M.H. Fixed, 95% CI 3.98 [1.03, 15.45] 1.24 [0.45, 3.42] 1.00 [0.05, 18.30] 1.87 [0.99 4.60]	Odds Ratio 0.01 0.1 1 10 100 Trigone-sparing Trigone-including 0.01 0.1 1 10 100 0.01 0.1 1 10 100 Trigone-sparing Trigone-including Odds Ratio 0.01 0.1 1 10 100
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi [#] = Test for overall effect: E Study or Subgroup Ei-Hefnawy A 2020 Kuo H 2011 Rustom P 2012 Total (95% CI) Total events Heterogeneity: Chi [#] = Test for overall effect: E Study or Subgroup Ei-Hefnawy A 2020 Kuo H 2011 Rustom P 2012 Total (95% CI) Total events	4 2 0 8 : 0.79, df = 2 (F : Z = 0.90 (P = Trigone-incl Events 6 9 0 15 : 1.02, df = 2 (F : Z = 0.72 (P = Trigone-incl Events 10 11 1 22	111 18 115 = 0.67); 0.37) luding Total 97 = 0.60); 0.47) luding Total 51 35 11 97 51 35 11 97	2 0 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	11 18 118 118 100 502 37 11 100 502 37 11 502 37 11 502 37 11	34.9% 100.0% Weight 43.1% 42.7% 14.2% 100.0% Weight 24.0% 66.9% 9.1% 100.0%	Odds Ratio 1.69 [0.54, 5.26] 1.69 [0.54, 5.26] 1.25 [0.36, 4.40] 1.79 [0.56, 5.69] 0.30 [0.01, 8.32] 1.35 [0.60, 3.03] Odds Ratio M-H, Fixed, 95% CI 3.98 [1.03, 15.45] 1.24 [0.45, 3.42] 1.00 [0.05, 18.30] 1.87 [0.88, 4.00]	Odds Ratio 0.01 0.1 10 100 Trigone-sparing Trigone-including 0.01 0.1 10 100 Trigone-sparing Trigone-including Odds Ratio 0.01 0.1 10 100 Trigone-sparing Trigone-including
Rustom P 2012 Taha A 2010 Total (95% CI) Total events Heterogeneity: Chi [#] = Test for overall effect: E Study or Subgroup Ei-Hefnawy A 2020 Kuo H 2011 Rustom P 2012 Total events Heterogeneity: Chi [#] = Test for overall effect: F Study or Subgroup Ei-Hefnawy A 2020 Kuo H 2011 Rustom P 2012 Total events Heterogeneity: Chi [#] =	4 2 0 8 5.79, df = 2 (f 2 = 0.90 (P = 7 7 10 10 11 1 1 1 22 2 2 01 df = 2 (F 2 2 2 0 10 11 1 1	111 18 115 = 0.67); 0.37) 10 10 11 97 = 0.600; 0.47) 10 10 11 97 = 0.600; 0.47) 11 97 = 0.67); 11 11 97 = 0.67); 11 11 11 11 11 11 11 11 11 1	2 0 5 F = 0% 7 F = 0% 7 F = 0% 7 F = 0%	11 18 118 118 <u>Total</u> 52 37 11 100 <u>Total</u> 52 37 11 52 37 11	34.9% 100.0% Weight 43.1% 42.7% 14.2% 100.0% Weight 24.0% 66.9% 9.1% 100.0%	Not estimable 1.69 [0.54, 5.26] 1.69 [0.54, 5.26] 1.25 [0.36, 4.40] 1.79 [0.56, 5.69] 0.30 [0.01, 8.32] 1.35 [0.60, 3.03] 0.45 [0.60, 3.03] 0.45 [0.60, 3.03] 1.24 [0.45, 3.42] 1.24 [0.45, 3.42] 1.24 [0.45, 3.42] 1.27 [0.88, 4.00]	Odds Ratio 0.01 0.1 10 100 Trigone-sparing Trigone-Including Odds Ratio M-H, Fixed, 95% Cl Odds Ratio 0.01 0.1 10 100 Trigone-sparing Trigone-including
Rustom P 2012 Taha A 2010 Total events Heterogeneity: ChP = Test for overall effect: E Study or Subgroup EI-Hefmawy A 2020 Kuo H 2011 Rustom P 2012 Total events Heterogeneity: ChP = Test for overall effect: F Study or Subgroup EI-Hefmawy A 2020 Kuo H 2011 Rustom P 2012 Total events Heterogeneity: ChP = Total events Heterogeneity: ChP = Test for overall effect	$\begin{array}{c} & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & $	111 18 115 = 0.67); 0.37) 100 115 11 97 = 0.60); 0.47) 100 11 97 = 0.60); 0.47) 11 97 = 0.60); 0.47) 11 11 97 = 0.67); 11 11 15 15	2 0 7 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1	11 18 118 118 <u>Total</u> 52 37 11 100 <u>Total</u> 62 37 11 100	Weight 43.1% 42.7% 14.2% 100.0% 24.0% 66.9% 9.1% 100.0%	Not estimable 1.69 [0.54, 5.26] 1.69 [0.54, 5.26] 1.25 [0.36, 4.40] 1.25 [0.36, 4.40] 1.79 [0.56, 5.69] 0.30 [0.01, 8.32] 1.35 [0.60, 3.03] 0.dds Ratio M-H, Fixed, 95% C1 3.98 [1.03, 15.45] 1.24 [0.45, 3.42] 1.20 [0.05, 18.30] 1.87 [0.88, 4.00]	Odds Ratio 0.01 0.1 10 100 Trigone-sparing Trigone-including 0.01 0.1 10 100 M-H, Fixed, 95% Cl 0.01 0.1 10 100 Odds Ratio M-H, Fixed, 95% Cl 0.01 0.1 10 100

FIGURE 6 | Forest plots showing changes between two groups in (A) hematuria, (B) general weakness, (C) bladder discomfort, (D) incidence of large post-void residual, (E) urinary tract infection, and (F) difficulty of voiding; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

episodes in patients with a trigone-including intradetrusor injection can also increase the quality of life of patients. At the same time, the analysis demonstrated that the trigone-including group showed a similar result to the trigone-sparing group in terms of the aspects of maximum cystometric capacity (p = 0.28) and post-void residual volume (p = 0.69).

The dose of BoNT-A can affect the therapeutic effect. In this study, the high dose (150-300 U) of BoNT-A was used for the treatment of NDO, and it showed marked differences between the trigone-including group and trigone-sparing group. At the same time, there were no differences between the groups for treatment of IDO when a low dose (25-150 U) of BoNT-A was used. The dose of BoNT-A was different for the treatment of NDO and IDO, and we cannot be sure which one dose of BoNT-A was suitable for the treatment of OAB. The dose of 50 U demonstrated consistently lower non-sustained efficacy than doses of 100 U or higher (28). Meanwhile, the 150 U does or higher had the same clinical curative effect and not provided additional effect. Previously research can also show the high doses of BoNT-A can increase the risk of post-void residual(PVR) and associated urinary tract infection(UTI) in patients with OAB (29). Thus, we recommend to use a dose of 100 U for treatment of unexplained OAB.

In subgroup analyses, a trigone-including intradetrusor injection demonstrated significant improvement in patient symptom score (p = 0.0004), complete dryness rate (p = 0.0002), frequency of incontinence episodes (p = 0.0003), detrusor pressure at maximum flow rate (p = 0.01), and volume at the first desire to void (p = 0.0006) compared with the trigone-sparing group for treatment of NDO. That, the two methods did not differ for the treatment of IDO. This result showed that the trigone is potentially the optimal region where therapy should be directed.

BoNT-A, a potent neurotoxic protein, is a kind of neurotoxin that comes from the aerobic bacterium botulinum. There are several types of botulinum toxin, and type A is the most effective regarding duration. There are two influencing mechanisms: (a) it can regulate acetylcholine release from presynaptic neurons and inhibit the contractions of the detrusor or urethral sphincter; (b) it also regulates sensory nerve function by blocking the release of various noxious neurotransmitters, including adenosine triphosphate, calcitonin gene-related peptide, calcitonin generelated peptide, and substance P (14). The BoNT-A consists of two pieces: 50-kDa light chain and a 100-kDa heavy endocytosis (30). The light chain of BoNT-A has biological activities. It cleaves the synaptosome-associated protein in the presynaptic nerve terminal and inhibits the release of acetylcholine by disrupting the fusion of vesicles with the neuron's cell membrane. This could finally lead to flaccid paralysis of muscles (31, 32). BoNT-A was injected into multiple sites within the bladder wall directly by cystoscopy. The most common adverse reactions following the administration of the toxin are urinary retention and urinary tract infection.

NDO was considered in relation to neural dysfunction. The motor neurons of the bladder include: (a) the sympathetic nerves, which are associated with an increment of bladder outlet obstruction during the storage phase of the micturition cycle; and (b) the parasympathetic nerves, which can produce spontaneous action potential and initiating spontaneous contraction of the bladder. New research indicates that the trigone was most densely innervated in the bladder. These nerves respond to passive distension and active contraction of the bladder and are the sensory component during a normal micturition cycle (33). Botulinum toxins have a direct role in the sensory nerve endings as well as the synaptic nerve junctions. Intravesical injections of BTX-A are useful for the treatment of bladder overactivity without the systemic adverse effects associated with pharmacotherapy (34). Thus, using trigonal injection might play a central role in treating NDO.

This meta-analysis found that the inclusion of the trigone in the injection pattern improves the outcome. Moreover, other studies reported that pressure directly on the trigone results in sensations of urgency, and trigonal injection of lidocaine or surgical denervation of the trigone relieved urgency in patients with OAB (35). This makes sense, as it is known that there is a rich source of afferent innervation in the trigone. These afferents originate primarily via the hypogastric nerve, suggesting a sympathetic nerve origin for the afferents responsible for urgency sensation arising from the trigone, whereas filling sensations arising from the bladder body are likely mixed in origin (parasympathetic and sympathetic) (36). Also, this metaanalysis revealed a greater effect in NDO than IDO, where it well-known that sensory nerve function is altered. We know that the sensory nerves innervate the bladder and are tuned to be mechanosensitive and that this signal activates areas of the spinal cord responsible for relaying sensation (37). Furthermore, studies have shown that the vortex infused into the bladder lumen is able to significantly attenuate this mechanosensitive bladder nerve activity without affecting the pressure/volume relationship during bladder filling (38). Thus, the analysis and conclusions of this meta-analysis are consistent with previous anatomical and physiological findings.

The incidence of adverse events between the trigone-including group and trigone-sparing group included hematuria (p = 0.45) and general weakness (p = 0.82); bladder discomfort (p = 0.66); incidence of large post-void residual (p = 0.37); urinary tract infection (p = 0.47); and difficulty of voiding (p = 0.10). The adverse events rates were similar in both groups. It is worth mentioning that trigone-including injections of BoNT-A may cause vesicoureteral reflux in theory; however, Mascarenhas et al. showed it did not cause vesicoureteral reflux in patients with OAB (39, 40). Meanwhile, the single injection of BTX-A only inflicts minor damage and does not induce bladder fibrosis or cause bladder tissue damage. The adverse reactions from longterm treatment remain to be elucidated (41).

One final but important point is that the results of injecting BoNT-A for treatment of OAB are affected by the dose of BoNT-A and the depth of injection. The work of Jo et al. presents a subgroup analysis according to the dose of BoNT-A. When a dosage of 200–300 units of BoNT-A was used, the endpoints of the symptom score, complete dryness, and frequency of incontinence episodes improved significantly in the trigoneincluding group. The depth of injection was determined by the surgeon with flexible or rigid cystoscopy. Jo et al. also reported that the depth of injection had no significant impact on the efficacy and safety between submucosal and detrusor injection (42). Submucosal injections have some advantages. It is easy to operate, does not require deep injection of the needle, and reduces the damage of the blood vessel. Thus, we recommend submucosal injection as a standard approach for the treatment of OAB (43).

This meta-analysis included six RCTs and concentrating on the efficacy and safety of BoNT-A for the treatment of overactive bladder. Compared with previous studies, our study had some advantages; the data were derived from randomized, double-blind controlled trials. Meanwhile, we also separately analyze the differences between IDO and NDO. However, this study also has some limitations, which reflect the common limitations of other systematic reviews and meta-analyses. This article did not include numerous patients and RCTs, which may affect our meta-analysis quality. Meanwhile, we will need more appropriate high-quality trials to improve the accuracy of results.

CONCLUSIONS

In summary, our meta-analysis has demonstrated that trigoneincluding BoNT-A injection was more effective compared with the trigone-sparing injection for the treatment of OAB, especially for NDO. There had been similar safety between the two methods.

REFERENCES

- Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn*. (2002) 21:167–78. doi: 10.1002/nau.10052
- Onukwugha E, Zuckerman IH, McNally D, Coyne KS, Vats V, Mullins CD. The total economic burden of overactive bladder in the United States: a disease-specific approach. *Am J Managed Care*. (2009) 15(4Suppl.):S90–7.
- Garely AD, Burrows LJ. Current pharmacotherapeutic strategies for overactive bladder. *Expert Opin Pharmacother*. (2002) 3:827–33. doi: 10.1517/14656566.3.7.827
- 4. Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol.* (2003) 20:327–36. doi: 10.1007/s00345-002-0301-4
- Hagen EM Eide GE, Rekand T, Gilhus NE, Gronning M. Traumatic spinal cord injury and concomitant brain injury: a cohort study. *Acta neurologica Scandinavica Supplementum.* (2010) 190:51–7. doi: 10.1111/j.1600-0404.2010.01376.x
- Montecucco C, Molgó, J. Botulinal neurotoxins: revival of an old killer. Curr Opin Pharmacol. (2005) 5:274–9. doi: 10.1016/j.coph.2004.12.006
- Nigam PK, Nigam A. Botulinum toxin. Indian J Dermatol. (2010) 55:8–14. doi: 10.4103/0019-5154.60343
- Gormley EA, Lightner DJ, Burgio KL, Chai TC, Clemens JQ, Culkin DJ, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. J Urol. (2012) 188(6Suppl.):2455–63. doi: 10.1016/j.juro.2012.09.079
- Lucas MG, Bosch RJ, Burkhard FC, Cruz F, Madden TB, Nambiar AK, et al. EAU guidelines on assessment and nonsurgical management of urinary incontinence. *Eur Urol.* (2012) 62:1130–42. doi: 10.1016/j.eururo.2012.08.047
- Reitz A, Stöhrer M, Kramer G, Del Popolo G, Chartier-Kastler E, Pannek J, et al. European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

TC and TD: conceptualization and methodology. ZZ: data curation. TC and YW: writing—original draft preparation. YL: visualization. ZG: investigation. XZ: supervision. YZ: software. JW and LD: validation. YC: writing—reviewing and editing. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the National Nature Science Foundation of China (Nos. 81870525; 81801429; and 81572835), Taishan Scholars Program of Shandong Province (No. tsqn201909199), Beijing Municipal Administration of Hospitals' Ascent Plan (Code: DFL20190502), and Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (Code: ZYLX201820).

due to neurogenic detrusor overactivity. *Eur Urol.* (2004) 45:510–5. doi: 10.1016/j.eururo.2003.12.004

- Cui Y, Zhou X, Zong H, Yan H, Zhang Y. The efficacy and safety of onabotulinumtoxinA in treating idiopathic OAB: a systematic review and meta-analysis. *Neurourol Urodyn*. (2015) 34:413–9. doi: 10.1002/nau.22598
- Yuan H, Cui Y, Wu J, Peng P, Sun X, Gao Z. Efficacy and adverse events associated with use of onabotulinumtoxina for treatment of neurogenic detrusor overactivity: a meta-analysis. *Int Neurourol J.* (2017) 21:53–61. doi: 10.5213/inj.1732646.323
- Zhou X, Yan HL, Cui YS, Zong HT, Zhang Y. Efficacy and safety of onabotulinumtoxinA in treating neurogenic detrusor overactivity: a systematic review and meta-analysis. *Chinese Med J.* (2015) 128:963–8. doi: 10.4103/0366-6999.154318
- Duthie JB, Vincent M, Herbison GP, Wilson DI, Wilson D. Botulinum toxin injections for adults with overactive bladder syndrome. *Cochrane Datab Syst Rev.* (2011) 12:CD005493. doi: 10.1002/14651858.CD005493.pub3
- Andersson KE. Bladder activation: afferent mechanisms. Urology. (2002) 59(5Suppl.1):43–50. doi: 10.1016/S0090-4295(01)01637-5
- Kuo HC. Comparison of effectiveness of detrusor, suburothelial and bladder base injections of botulinum toxin a for idiopathic detrusor overactivity. J Urol. (2007) 178:1359–63. doi: 10.1016/j.juro.2007.05.136
- Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg.* (2010) 8:336–41. doi: 10.1016/j.ijsu.2010.02.007
- Vader JP. Randomised controlled trials: a user's guide. *BMJ*. (1998) 317:1258. doi: 10.1136/bmj.317.7167.1258
- DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. (1986) 7:177–88. doi: 10.1016/0197-2456(86)90046-2
- El-Hefnawy AS, Elbaset MA, Taha DE, Wadie BS, Kenawy M, Shokeir AA, Badry ME. Trigonal-sparing versus trigonal-involved Botox injection for treatment of idiopathic overactive bladder: a randomized clinical trial. Lower urinary tract symptoms. *Adv Onl Publ.* (2020) 13:22–30. doi: 10.1111/luts.12321

- Hui C, Keji X, Chonghe J, Ping T, Rubiao O, Jianweng Z, et al. Combined detrusor-trigone BTX-A injections for urinary incontinence secondary to neurogenic detrusor overactivity. *Spinal Cord.* (2016) 54:46–50. doi: 10.1038/sc.2015.143
- Huang M, Chen H, Jiang C, Xie K, Tang P, Ou R, et al. Effects of botulinum toxin A injections in spinal cord injury patients with detrusor overactivity and detrusor sphincter dyssynergia. J Rehabil Med. (2016) 48:683– 7. doi: 10.2340/16501977-2132
- Kuo HC. Bladder base/trigone injection is safe and as effective as bladder body injection of onabotulinumtoxinA for idiopathic detrusor overactivity refractory to antimuscarinics. *Neurourol Urodyn*. (2011) 30:1242– 8. doi: 10.1002/nau.21054
- 24. Manecksha RP, Cullen IM, Ahmad S, McNeill G, Flynn R, McDermott TE, et al. Prospective randomised controlled trial comparing trigone-sparing versus trigone-including intradetrusor injection of abobotulinumtoxinA for refractory idiopathic detrusor overactivity. *Eur Urol.* (2012) 61:928–35. doi: 10.1016/j.eururo.2011.10.043
- Abdel-Meguid TA. Botulinum toxin-A injections into neurogenic overactive bladder-to include or exclude the trigone? A prospective, randomized, controlled trial. J Urol. (2010) 184:2423–8. doi: 10.1016/j.juro.2010.08.028
- Kasman A, Stave C, Elliott CS. Combination therapy in overactive bladderuntapped research opportunities: A systematic review of the literature. *Neurourol Urodyn.* (2019) 38:2083–92. doi: 10.1002/nau.24158
- Huang AJ, Grady D, Mendes WB, Hernandez C, Schembri M, Subak LL, et al. Randomized controlled trial of device guided, slow-paced respiration in women with overactive bladder syndrome. *J Urol.* (2019) 202:787–94. doi: 10.1097/JU.00000000000328
- Dmochowski R, Chapple C, Nitti VW, Chancellor M, Everaert K, Thompson C, et al. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. J Urol. (2010) 184:2416–22. doi: 10.1016/j.juro.2010.08.021
- Cohen BL, Barboglio P, Rodriguez D, Gousse AE. Preliminary results of a dose-finding study for botulinum toxin-A in patients with idiopathic overactive bladder: 100 versus 150 units. *Neurourol Urodyn.* (2009) 28:205–8. doi: 10.1002/nau.20611
- Franciosa G, Floridi F, Maugliani A, Aureli P. Differentiation of the gene clusters encoding botulinum neurotoxin type A complexes in *Clostridium botulinum* type A, Ab, and A(B) strains. *Appl Environ Microbiol.* (2004) 70:7192–9. doi: 10.1128/AEM.70.12.7192-7199.2004
- Dolly JO, O'Connell MA. Neurotherapeutics to inhibit exocytosis from sensory neurons for the control of chronic pain. *Curr Opin Pharmacol.* (2012) 12:100–8. doi: 10.1016/j.coph.2011.11.001
- 32. Rummel A. The long journey of botulinum neurotoxins into the synapse. *Toxicon*. (2015) 107:9–24. doi: 10.1016/j.toxicon.2015.09.009
- Purves JT, Spruill L, Rovner E, Borisko E, McCants A, Mugo E, et al. A three dimensional nerve map of human bladder trigone. *Neurourol Urodyn.* (2017) 36:1015–9. doi: 10.1002/nau.23049
- 34. Chancellor MB, Elovic E, Esquenazi A, Naumann M, Segal KR, Schiavo G, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of urologic conditions. *Toxicon.* (2013) 67:129–40. doi: 10.1016/j.toxicon.2013.01.020
- 35. Westney OL, Lee JT, McGuire EJ, Palmer JL, Cespedes RD, Amundsen CL. Long-term results of Ingelman-Sundberg denervation procedure for

urge incontinence refractory to medical therapy. J Urol. (2002) 168:1044–7. doi: 10.1016/S0022-5347(05)64571-5

- Yamaguchi K, Kobayashi M, Kato T, Akita K. Origins and distribution of nerves to the female urinary bladder: new anatomical findings in the sex differences. *Clin Anat.* (2011) 24:880–5. doi: 10.1002/ca.21186
- Grundy L, Harrington AM, Caldwell A, Castro J, Staikopoulos V, Zagorodnyuk VP, et al. Translating peripheral bladder afferent mechanosensitivity to neuronal activation within the lumbosacral spinal cord of mice. *Pain.* (2019) 160:793–804. doi: 10.1097/j.pain.000000000001453
- Collins VM, Daly DM, Liaskos M, McKay NG, Sellers D, Chapple C, et al. OnabotulinumtoxinA significantly attenuates bladder afferent nerve firing and inhibits ATP release from the urothelium. *BJU Int.* (2013) 112:1018–26. doi: 10.1111/bju.12266
- Mascarenhas F, Cocuzza M, Gomes CM, Leão N. Trigonal injection of botulinum toxin-A does not cause vesicoureteral reflux in neurogenic patients. *Neurourol Urodyn.* (2008) 27:311–4. doi: 10.1002/nau.20515
- Karsenty G, Elzayat E, Delapparent T, St-Denis B, Lemieux MC, Corcos J. Botulinum toxin type a injections into the trigone to treat idiopathic overactive bladder do not induce vesicoureteral reflux. J Urol. (2007) 177:1011-4. doi: 10.1016/j.juro.2006.10.047
- Apostolidis A, Jacques TS, Freeman A, Kalsi V, Popat R, Gonzales G, et al. Histological changes in the urothelium and suburothelium of human overactive bladder following intradetrusor injections of botulinum neurotoxin type A for the treatment of neurogenic or idiopathic detrusor overactivity. *Eur Urol.* (2008) 53:1245–53. doi: 10.1016/j.eururo.2008. 02.037
- Jo JK, Kim KN, Kim DW, Kim YT, Kim JY, Kim JY. The effect of onabotulinumtoxinA according to site of injection in patients with overactive bladder: a systematic review and meta-analysis. *World J Urol.* (2018) 36:305– 17. doi: 10.1007/s00345-017-2121-6
- Mehnert U, Boy S, Schmid M, Reitz A, von Hessling A, Hodler J, et al. morphological evaluation of botulinum neurotoxin A injections into the detrusor muscle using magnetic resonance imaging. *World J Urol.* (2009) 27:397–403. doi: 10.1007/s00345-008-0362-0

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Cui, Cai, Dong, Zhang, Zhou, Lu, Zhang, Wu, Gao, Wang and Dong. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.