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ORIGINAL ARTICLE

The effect of onabotulinumtoxinA according to site of injection in patients with overactive bladder: a systematic review and meta-analysis

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Abstract
Purpose This study assessed the efficacy and safety of onabotulinumtoxinA according to injection site for treatment of overactive bladder.
Methods A systematic literature review located randomized controlled trials of onabotulinumtoxinA treatment for neurogenic detrusor overactive bladder and idiopathic overactive bladder in adults. We searched MEDLINE, EMBASE, and the Cochrane Controlled Trials Register using the Ovid platform. Meta-analysis was based on Cochrane Review Methods.
Results Eight studies (419 participants) were included. Trigone-including injection demonstrated a significant improvement in symptom score (SMD = − 0.53, 95% CI − 1.04 to − 0.02, $P = 0.04$, $I^2 = 78\%$), higher complete dryness rates (OR = 2.19 patients, 95% CI 1.32–3.63, $P = 0.002$, $I^2 = 41\%$), and lower frequency of incontinence episodes (WMD = − 0.85 per day, 95% CI − 1.55 to − 0.16, $P = 0.02$, $I^2 = 87\%$) in patients. Comparing trigone-including injection to trigone-sparing injection, lower detrusor pressure (WMD = − 2.55 cm H_2O, 95% CI − 4.16 to − 0.95, $P = 0.002$, $I^2 = 0\%$) and higher volume at first desire to void (WMD = 17.54 ml, 95% CI 1.00–34.07, $P = 0.04$, $I^2 = 0\%$) were observed with trigone-including injection. Between intradetrusor and suburothelial injection sites, there were no differences in efficacy or safety regarding the incidence of vesicoureteral reflux, hematuria, general weakness, bladder discomfort, large post-void residual, and urinary tract infection.
Conclusion Trigone-including onabotulinumtoxinA injection has superior efficacy to trigone-sparing injection without increased complications. The depth of injection does not influence the efficacy or safety of onabotulinumtoxinA.

Keywords Neurogenic detrusor overactive bladder · Idiopathic overactive bladder · Meta-analysis · OnabotulinumtoxinA

Introduction

Overactive bladder (OAB), defined by the International Continence Society (ICS) as a condition characterized by urinary urgency, usually affects frequency and nocturia with or without urinary incontinence [1]. Overactive bladder (OAB) is a common health disorder of multifactorial origin. It affects quality of life and imposes an economic burden [2, 3], and its prevalence is approximately 12–19% in both men and women [4–6].

The primary treatment for OAB is behavior therapy according to ICS guidelines. Although antimuscarinic agents are currently a treatment option for OAB [7, 8], their use in certain patients can be discontinued due to inadequate efficacy or side effects [9, 10]. In such situations, onabotulinumtoxinA (BoNT/A) has been suggested as an alternative treatment. There is evidence of the efficacy and tolerability of BoNT/A injections in patients with OAB [11, 12]. This drug acts to prevent the release of acetylcholine, adenosine triphosphate (ATP), and substance P. Moreover,

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it down-regulates capsaicin receptors and purinergic receptors on afferent neurons. These mechanisms are related to the pathophysiology of OAB [12, 13].

However, there is no standard method of injecting BoNT/A for treatment of OAB. Accordingly, we performed a systematic review and meta-analysis to evaluate the efficacy and safety of BoNT/A in patients with OAB according to injection site.

Materials and methods

We used a systematic approach to locate publications comparing the efficacy and safety of BoNT/A in patients with OAB according to injection site. The study is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and on Cochrane Review Methods [14].

Data and literature sources

We searched MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE (R) Daily, and Ovid MEDLINE (R) 1946 to the present (OVID platform), EMBASE (from 1974) (OVID platform), the Cochrane Controlled Trials Register (OVID platform), and the Cochrane Database of Systematic Reviews (OVID platform) from inauguration to February 22, 2017. A literature search of the Web of Science and Google Scholar was additionally performed to search all relevant studies. We manually searched the reference lists of the retrieved studies, ClinicalTrials.gov, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) for additional unpublished/published studies. The main keywords were idiopathic overactive bladder, urinary urgency, urinary urgency incontinence, neurogenic bladder, onabotulinumtoxinA, and randomized controlled trial.

Study selection

All selected studies were independently identified by two reviewers (KNK and JYK) based on predefined selection criteria, and disagreements on primary study selection were arbitrated by a third reviewer (JKJ). Studies were included in our meta-analysis if they fulfilled the following criteria: (1) randomized controlled trial in any published international journal without language restriction, (2) adult patients undergoing treatment for idiopathic detrusor overactivity or neurogenic detrusor overactivity with BoNT/A, (3) studies comparing the effects of BoNT/A according to injection site, and (4) primary outcomes of bladder symptoms, such as incontinence-specific quality of life (I-QOL), and overactive bladder symptom score (OABSS). Secondary outcomes were complete dryness rate; change in the number of incontinence episodes; and urodynamic variables of detrusor pressure at maximum flow rate, volume at first desire to void, post-void residual volume, maximum cystometric bladder capacity, and adverse events. The outcome variables were mean differences or incidences of events between the groups at designated times.

Data extraction

After the two reviewers (JKJ and DWK) independently extracted data using a pre-specified data extraction form, the third reviewer (KNK) confirmed the extracted data. The following variables were extracted: (1) number of patients and patient characteristics, (2) means and standard deviations or incidences of events regarding outcome data, (3) protocol for administration and dosage, (4) follow-up time for outcome data, and (5) adverse events in patients. If the above variables were not mentioned in a study, then the data was requested via email.

Assessment of methodological quality

The reviewers (JKJ and DWK) independently estimated the risks of bias in the studies using the Cochrane risk-of-bias tool. This tool evaluates randomized controlled studies by assessing the methods for generating random sequences, concealing allocations, blinding participants, and assessing outcomes, as well as evaluates any incompleteness in outcome data, selective outcome reporting, and other possible sources of risk of bias.

Quality of evidence

We used GRADE assessments to determine the quality of evidence [14]. Two reviewers (JKJ and KNK) assessed the quality of each outcome independently. The five categories, based on GRADE quality assessment, were limitations of design, inconsistency, indirectness, imprecision, and publication bias. “Summary of findings” tables were presented by a GRADE profiler (GRADEpro) and included the following outcomes: (1) changes in patient symptom score, (2) complete dryness rate, (3) change in number of incontinence episodes among patients, (4) detrusor pressure at maximum flow rate, (5) volume at first desire to void, (6) incidence of hematuria, and (7) incidence of large post-void residual.

Statistical analysis

Continuous data were reported as mean differences and 95% confidence intervals (CIs) and were analyzed using weighted mean differences (WMDs) and the generic inverse variance method. For the analysis of bladder symptom scores, we used the standardized mean difference in the reported

severity of symptoms between injection methods. Binary outcomes were analyzed to compare the odds ratio with a 95% CI. Heterogeneity between studies was evaluated by the χ^2 test and I^2 statistics [15]. An I^2 statistics > 50% and χ^2 tests with P values < 0.10 were regarded as statistically significant. When significant clinical or statistical heterogeneity was found, random-effects models were applied.

A subgroup analysis was conducted according to the dose of BoNT/A administered in patients. We performed all statistical analyses with RevMan version 5.3. If the number of included studies was less than 10, we did not evaluate publication bias because of the low statistical power.

Results

Identification of studies

Initial searches of the databases identified 863 publications. In addition to removing 578 duplicate articles, 285 publications were eliminated as their titles and abstracts showed that they did not fulfill the selection criteria. For the remaining 14 publications, we obtained full manuscripts for scrutiny, subsequently identifying eight publications with potentially relevant studies. The other six publications were excluded, because they used a different study design (one publication), the study design was not randomized (one publication), the patients were not adults (one publication), or the articles reported the same data (three publications). Thus, eight studies and 419 participants were included in this meta-analysis (Fig. 1) [16–23].

Study characteristics and patient populations

The included articles were published in five countries: Czech Republic (two), Ireland (one), Saudi Arabia (one), Taiwan (two), and China (two) between 2007 and 2016. Of these, five studies compared the effects of trigone-sparing and trigone-including intradetrusor injection of BoNT/A [16–20], and three compared the effects of inradetrusor and suburothelial BoNT/A injections [21–23]. The characteristics of the studies are summarized in Table 1.

Quality of included studies

All eight studies used a random allocation method, and four studies described blinding methods in detail [16, 18–20]. The risk-of-allocation concealment was high in four studies [17, 21–23]. The risks of allocation concealment and blinding were unclear in the other studies, and the risks of selective reporting and incomplete outcome data were low. Risk-of-bias graphs and summaries are presented in Fig. 2a, b.

Trigone-sparing versus trigone-including intradetrusor injection

Scores that assess bladder symptoms were incontinence-specific quality of life (I-QOL) [16, 17], overactive bladder symptom score (OABSS) [19], QOL using the International Prostate Symptom Score-QOL subset [20], and urgency severity score (USS) [18]. Our meta-analysis revealed significant improvements in patient symptom scores for the trigone-including intradetrusor injection of BoNT/A (SMD = − 0.53, 95% CI − 1.04 to − 0.02, P = 0.04, I^2 = 78%) (Fig. 3a). A subgroup analysis according to dose of BoNT/A revealed that trigone-including intradetrusor injection significantly improved symptom scores when 200-300 units of BoNT/A were used (SMD = − 0.44, 95% CI − 0.73 to − 0.15, P = 0.003, I^2 = 8%).

There was a significantly higher complete dryness rate in patients (OR = 2.19 patients, 95% CI 1.32–3.63, P = 0.002, I^2 = 41%) (Fig. 3b) with trigone-including intradetrusor injection. A subgroup analysis revealed that trigone-including intradetrusor injection had a significantly higher complete dryness rate when 200–300 units of BoNT/A were used (OR = 3.35 patients, 95% CI 1.76–6.37, P = 0.0002, I^2 = 0%).

There was a significantly lower frequency of incontinence episodes in patients (WMD = − 0.85 per day, 95% CI − 1.55 to − 0.16, P = 0.02, I^2 = 87%) with trigone-including intradetrusor injection (Fig. 3c). A subgroup analysis also revealed that trigone-including intradetrusor injection demonstrated a significantly lower frequency of incontinence episodes when 200–300 units of BoNT/A were used (WMD = − 0.88 per day, 95% CI − 1.59 to − 0.18, P = 0.01, I^2 = 91%).

Urodynamic variables were extracted from four randomized trials [16, 18–20]. We found a lower detrusor pressure at maximum flow rate following trigone-including intradetrusor injection than the measure following trigone-sparing injection (WMD = − 2.55 cm H_2O, 95% CI − 4.16 to − 0.95, P = 0.002, I^2 = 0%) (Fig. 4a). In addition, following trigone-including intradetrusor injection, we found a higher volume at the first desire to void (WMD = 17.54 ml, 95% CI 1.00–34.07, P = 0.04, I^2 = 0%) (Fig. 4b). The two methods of trigone-including and trigone-sparing injection did not differ in maximum cystometric capacity (WMD = − 19.54 ml, 95% CI − 44.87–5.80, P = 0.13, I^2 = 0%) (Fig. 4c) or post-void residual volume (WMD = 20.14 ml, 95% CI − 2.25–45.52, P = 0.08, I^2 = 0%) (Fig. 4d).

In five studies [16–20] representing 334 patients, the incidence of vesicoureteral reflux was not reported in either group of patients receiving trigone-including injections or trigone-sparing injections. The rates of hematuria were 11.3 and 9.4% after the trigone-including injections

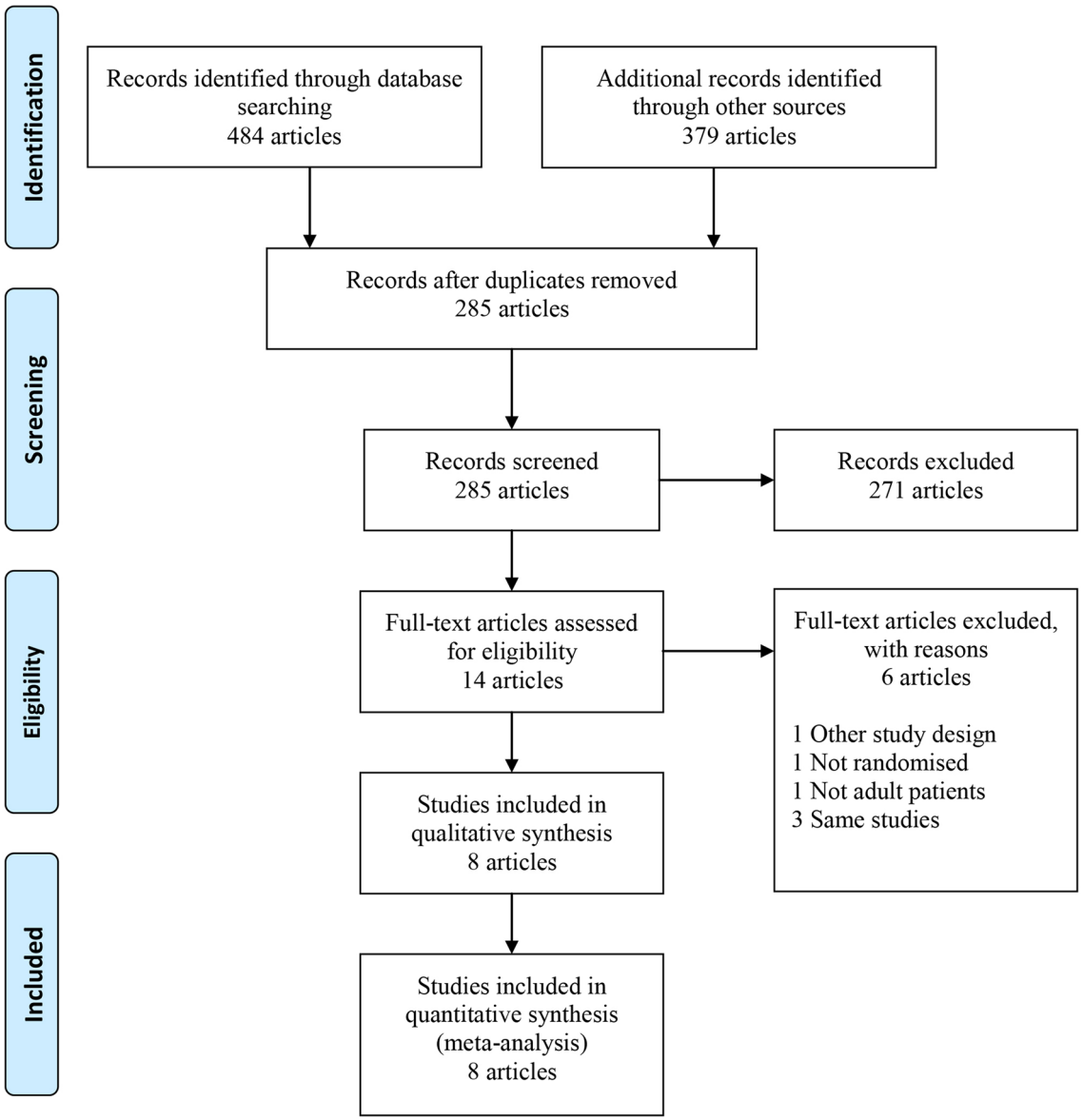


Fig. 1 Flow chart of the literature search strategy

and trigone-sparing injections, respectively, and there was no statistical difference between the groups (OR = 1.21, 95% CI 0.59–2.50, $P = 0.60$, $I^2 = 0\%$) (Fig. 5a). There were also no differences between the patient groups in bladder discomfort (OR = 1.15, 95% CI 0.36–3.68, $P = 0.82$, $I^2 = 13\%$) (Fig. 5b), incidence of large post-void residual volume (> 150 ml) (OR = 0.98, 95% CI 0.46–2.09, $P = 0.96$, $I^2 = 0\%$) (Fig. 5c), general weakness (OR = 1.09, 95% CI 0.19–6.27, $P = 0.92$) (Fig. 5d), or urinary tract infection (OR = 0.85, 95% CI 0.34–2.13, $P = 0.72$, $I^2 = 0\%$) (Fig. 5e).

Intradetrusor versus suburothelial injection

Our meta-analysis demonstrated that detrusor pressure did not differ between intradetrusor and suburothelial injection (WMD = − 5.21 cmH_2O, 95% CI − 12.65–2.23, $P = 0.17$, $I^2 = 3\%$) (Fig. 6a). In addition, there were no differences in maximum cystometric capacity (WMD = − 35.24 ml, 95% CI − 73.90–3.42, $P = 0.07$, $I^2 = 0\%$) (Fig. 6b), detrusor compliance (WMD = 4.22 ml/cmH_2O, 95% CI − 20.14–28.58, $P = 0.73$, $I^2 = 74\%$) (Fig. 6c), or reduction

Table 1 Characteristics of included randomized controlled trials

Study	Year	Underlying disease	Administration method	Pts (*n*)	Gender male/female	Dosage (U) injection procedure	Follow-up period (weeks)	Anticholinergic drugs use
Hui [16]	2016	NDO after SCI	Include trigone	47	28/19	160U detrusor + 40U trigone	Baseline, 4 and 12	91% use
			Exclude trigone	44	23/21	200U detrusor	weeks	95% use
Huang [17]	2016	DO after SCI	Include trigone	41	17/24	160U detrusor + 40U trigone	Baseline, 4 and 12	100% use
			Exclude trigone	39	13/26	200U detrusor	weeks	100% use
Kuo [18]	2011	IDO	Include trigone	68	31/37	75U bladder body + 25U trigone, 50U bladder body + 50U trigone	Baseline and 3 months	Use more than 3 months before study, discontinue on the
			Exclude trigone	37	17/20	200U bladder body		day of screening
Rustom [19]	2012	IDO refractory to	Include trigone	11	1/10	160 U at 20 sites into the bladder wall	Baseline, 6, 12, and 26 weeks	More than 6 weeks before study,
		anticholinergics	Exclude trigone	11	2/9	160 U at 15 sites into the adder wall + 5 sites into the trigone		discontinue 2 weeks before injection
Taha [20]	2010	NDO after SCI	Include trigone	18	17/1	200U detrusor + 100U trigone	Baseline, 2, 8, 12, and 18 weeks	Discontinue 2 weeks before
			Exclude trigone	18	17/1	300U detrusor		injection
Krhut [21]	2012	NDO refractory to	Intradetrusor	14	9/5	300U at 30 sites into the detrusor	Baseline, and 3 months	No data
		anticholinergics	Suburothelial	18	17/1	300U into the submucosa suburothelial		
Kuo [22]	2007	DO refractory to anticholinergics	Intradetrusor	15	8/7	100U at 40 sites into the detrusor	Baseline, 1, 2, and 4 weeks	Discontinue 1 week before injection
			Suburothelial	15	10/5	100U into the submucosa suburothelial		
Samal [23]	2013	NDO after SCI	Intradetrusor	11	10/1	300U at 30 sites into the detrusor	Baseline, 6, and 12 weeks	Discontinue 1 week
			Suburothelial	12	11/1	300U at 30 sites into the submucosa suburothelial		before injection

NDO neurogenic detrusor overactivity; *SCI* spinal cord injury; *IDO* idiopathic detrusor overactivity; *DO* detrusor overactivity; *Pts* patients

in incontinence episodes (WMD = − 1.32 per day, 95% CI − 5.69–3.06, $P = 0.56$, $I^2 = 78\%$) (Fig. 6d).

Adverse events were reported in all of the included studies [21–23]. Of these adverse events, loss of muscle strength was extracted from two studies [21, 23], and there was no difference in loss of muscle strength between groups of patients with intradetrusor and suburothelial injection (OR = 0.26, 95% CI 0.03–2.67, $P = 0.26$, $I^2 = 0\%$). One study reported the adverse events of dysuria, acute urinary retention, urinary tract infection, and gross hematuria [22], and the events did not differ between patient groups.

Quality of evidence

The quality of each outcome was evaluated by GRADE approach and "summary of findings" data is shown in

Table 2. As a result, the quality of evidence in this meta-analysis ranged from very low to moderate. Most studies had problems with risk of bias, inconsistency, and imprecision. The number of included studies was fewer than 10, demonstrating low statistical power, so publication bias was not assessed.

Discussion

To our knowledge, this is the first study of botulinum injection for OAB-based meta-analysis to assess treatment effects according to injection site and depth of injection. We observed significant differential effects in trigone-including injection versus trigone-sparing injection and no different effects according to injection depth. Trigone-including injection provides greater improvements in patient symptom scores, higher complete dryness rates, and lower frequency of incontinence episodes. Trigone-including injection also provides lower detrusor pressure at maximum flow rate and higher volume at first desire to void. In terms of safety, trigone-including injection showed no increase of adverse effects.

Fig. 3 Effects of trigone-including and trigone-sparing intradetrusor injection. **a** Impact on patient symptom score; **b** impact on complete dryness rate (patient number); **c** impact on change in number of incontinence episodes (number per day) ▶

The work of Purves et al. presents a three-dimensional nerve map of the human bladder including the trigone [24]. The authors found traversing myelinated neural pathways in the trigone of the bladder, showing striking neural density. As a key component in vesical deactivation, the trigone plays a crucial role in detrusor overactivity. Other previous study also reported that trigone has rich sensory neural fibers [25]. In addition, trigonal muscles are sensitive to small amount of pressure changes; it has a crucial role of initiation of involuntary contraction of bladder [26]. Therefore,

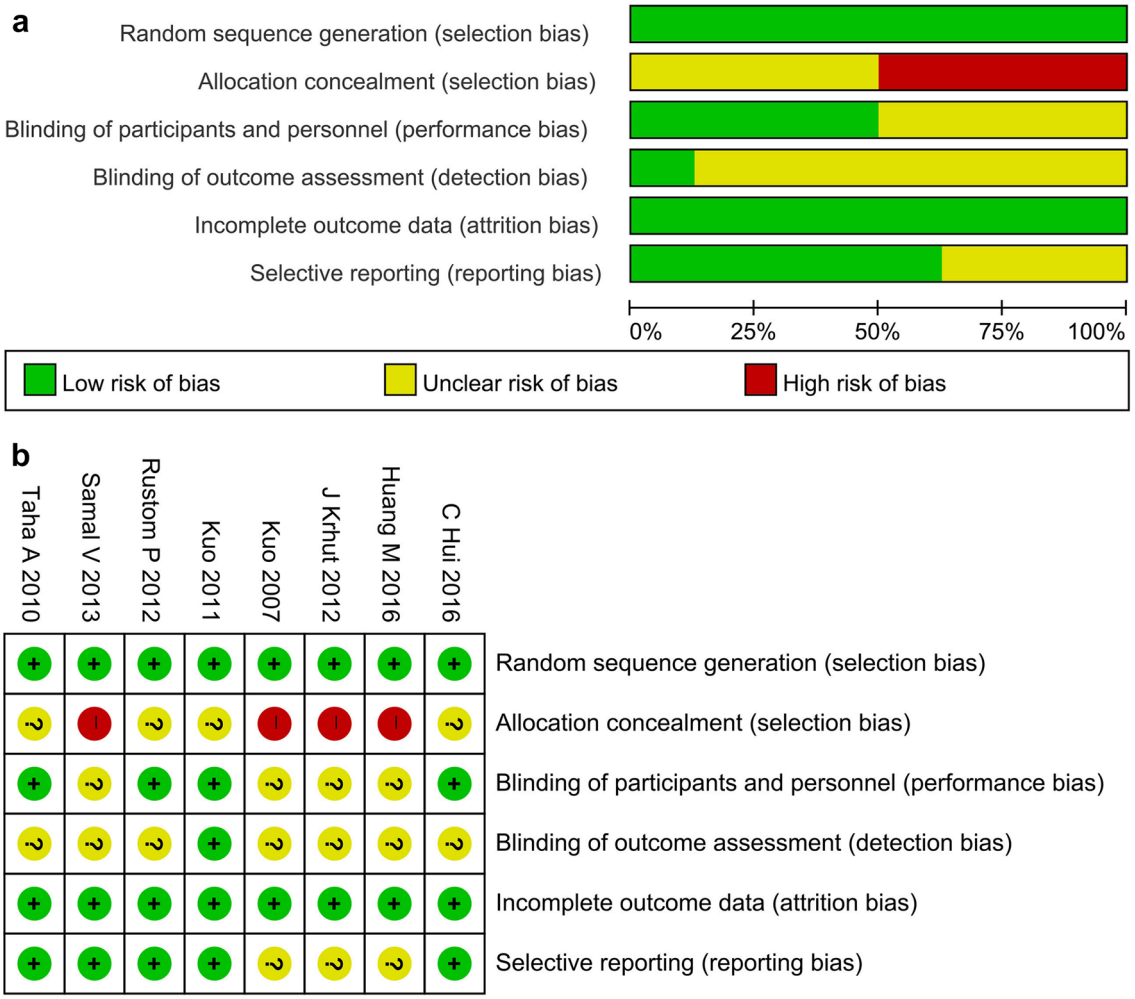
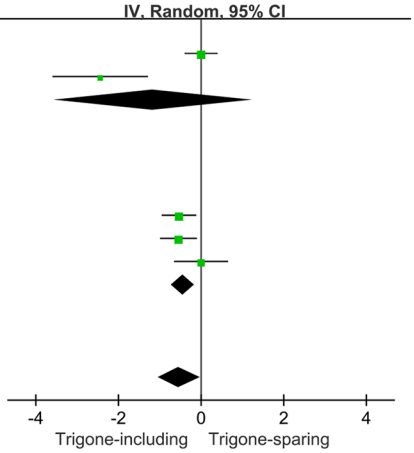


Fig. 2 **a** Risk-of-bias graph for all included randomized controlled trials. **b** Risk-of-bias summary for all trials

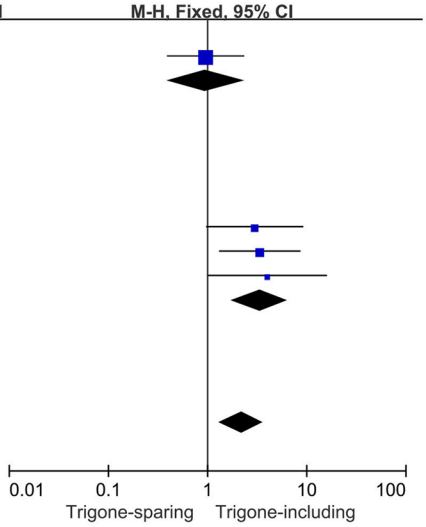
a

Study or Subgroup	Trigone-including Mean	SD	Total	Trigone-sparing Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
6.1.1 BoNT/A 100-200 Unit								
Kuo 2011	2.42	1.12	68	2.42	1.03	37	23.6%	0.00 [-0.40, 0.40]
Rustom P 2012	9.5	1.13	11	14.1	2.3	11	11.4%	-2.44 [-3.60, -1.29]
Subtotal (95% CI)			**79**			**48**	**35.0%**	**-1.16 [-3.55, 1.23]**
Heterogeneity: Tau² = 2.79; Chi² = 15.35, df = 1 (P < 0.0001); I² = 93%								
Test for overall effect: Z = 0.95 (P = 0.34)								
6.1.2 BoNT/A 200-300 Unit								
C Hui 2016	-26.01	11.56	47	-18.75	15.18	44	23.3%	-0.54 [-0.95, -0.12]
Huang M 2016	-27.02	10.94	41	-20.32	13.27	39	22.8%	-0.55 [-0.99, -0.10]
Taha A 2010	2.22	0.65	18	2.22	0.55	18	19.0%	0.00 [-0.65, 0.65]
Subtotal (95% CI)			**106**			**101**	**65.0%**	**-0.44 [-0.73, -0.15]**
Heterogeneity: Tau² = 0.01; Chi² = 2.16, df = 2 (P = 0.34); I² = 8%								
Test for overall effect: Z = 2.97 (P = 0.003)								
Total (95% CI)			**185**			**149**	**100.0%**	**-0.53 [-1.04, -0.02]**
Heterogeneity: Tau² = 0.25; Chi² = 18.09, df = 4 (P = 0.001); I² = 78%								
Test for overall effect: Z = 2.03 (P = 0.04)								
Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%								



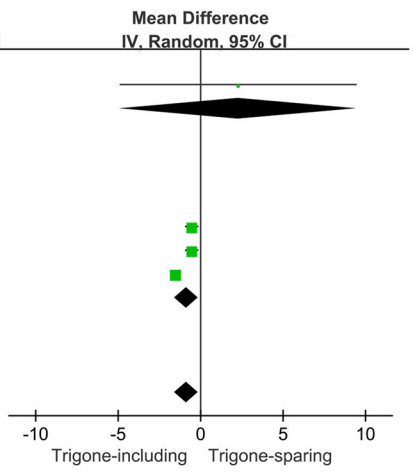
b

Study or Subgroup	Trigone-including Events	Total	Trigone-sparing Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
6.2.1 BoNT/A 100 Unit						
Kuo 2011	49	68	27	37	48.2%	0.96 [0.39, 2.35]
Subtotal (95% CI)		**68**		**37**	**48.2%**	**0.96 [0.39, 2.35]**
Total events	49		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
6.2.2 BoNT/A 200-300 Unit						
C Hui 2016	13	47	5	44	18.4%	2.98 [0.96, 9.23]
Huang M 2016	22	41	10	39	23.4%	3.36 [1.30, 8.64]
Taha A 2010	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]**
Total events	47		21			
Heterogeneity: Chi² = 0.10, df = 2 (P = 0.95); I² = 0%						
Test for overall effect: Z = 3.68 (P = 0.0002)						
Total (95% CI)		**174**		**138**	**100.0%**	**2.19 [1.32, 3.63]**
Total events	96		48			
Heterogeneity: Chi² = 5.08, df = 3 (P = 0.17); I² = 41%						
Test for overall effect: Z = 3.05 (P = 0.002)						
Test for subgroup differences: Chi² = 4.95, df = 1 (P = 0.03), I² = 79.8%						



c

Study or Subgroup	Trigone-including Mean	SD	Total	Trigone-sparing Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
6.3.1 BoNT/A 100 Unit								
Kuo 2011	-6.95	20.8	68	-9.23	16.2	37	0.9%	2.28 [-4.91, 9.47]
Subtotal (95% CI)			**68**			**37**	**0.9%**	**2.28 [-4.91, 9.47]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.62 (P = 0.53)								
6.3.2 BoNT/A 200-300 Unit								
C Hui 2016	-5.22	0.91	47	-4.68	1.06	44	32.4%	-0.54 [-0.95, -0.13]
Huang M 2016	-7.19	0.81	41	-6.65	1.02	39	32.5%	-0.54 [-0.94, -0.14]
Taha A 2010	-4.15	0.63	18	-2.62	0.14	18	34.2%	-1.53 [-1.83, -1.23]
Subtotal (95% CI)			**106**			**101**	**99.1%**	**-0.88 [-1.59, -0.18]**
Heterogeneity: Tau² = 0.35; Chi² = 21.98, df = 2 (P < 0.0001); I² = 91%								
Test for overall effect: Z = 2.45 (P = 0.01)								
Total (95% CI)			**174**			**138**	**100.0%**	**-0.85 [-1.55, -0.16]**
Heterogeneity: Tau² = 0.35; Chi² = 22.78, df = 3 (P < 0.0001); I² = 87%								
Test for overall effect: Z = 2.40 (P = 0.02)								
Test for subgroup differences: Chi² = 0.74, df = 1 (P = 0.39), I² = 0%								



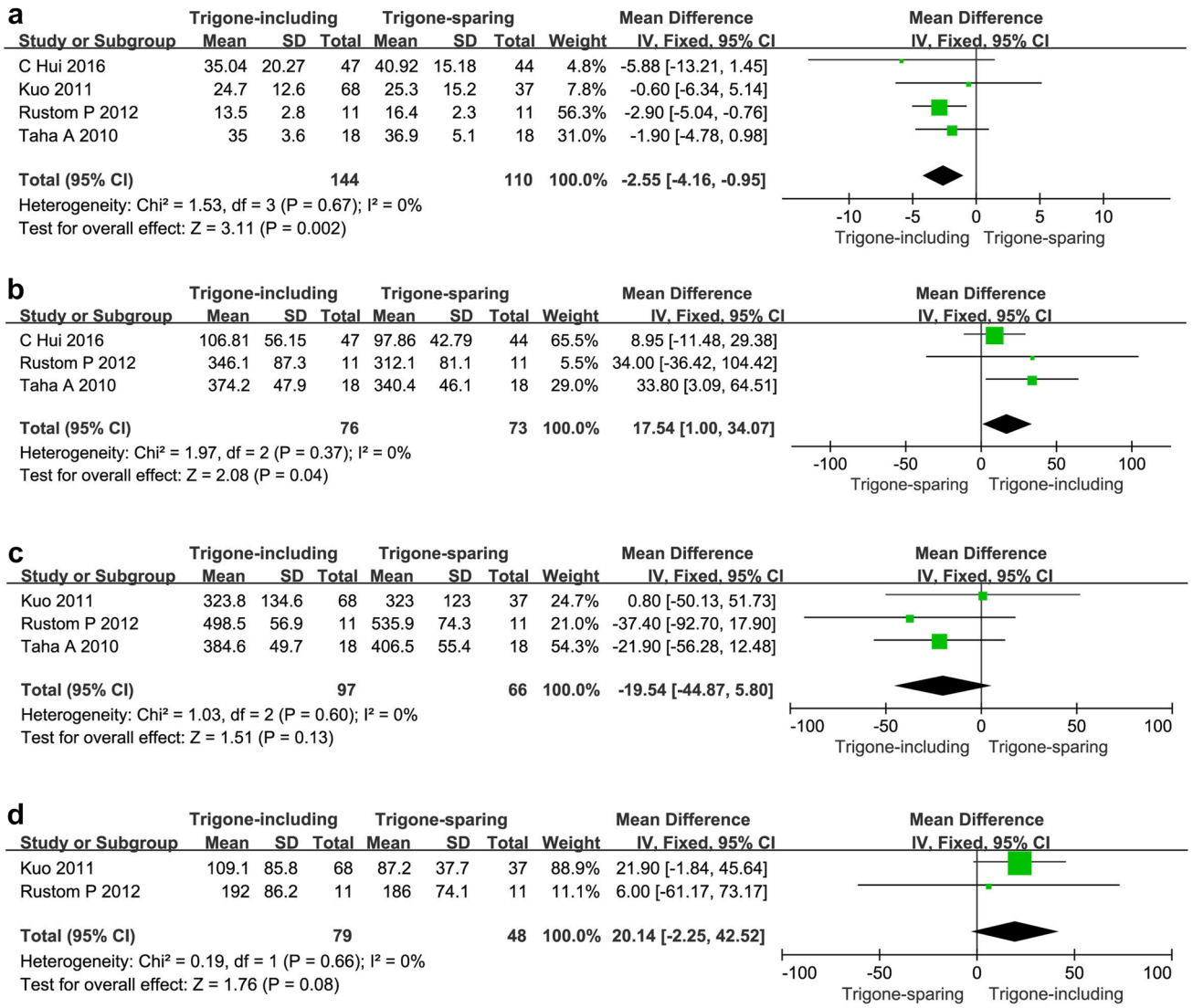


Fig. 4 Effects of trigone-including and trigone-sparing intradetrusor injection. **a** Impact on detrusor pressure at maximum flow rate (mmHg); **b** impact on volume at the first desire to void (ml); **c** impact on maximum cystometric capacity (ml); **d** impact on post-void residual volume (ml)

trigonal injection for denervation can reduce involuntary detrusor contractions. These findings suggested the key role of trigonal denervation using trigonal injection with considering myogenic and neurogenic effect. Our meta-analysis demonstrated the importance of trigonal deactivation. Trigone-including intradetrusor injection was found to yield lower detrusor pressure than trigone-sparing injection, and it led to fewer episodes of incontinence. In our meta-analysis, superior quality of life (QOL) was observed in patients with trigone-including injection than in patients with trigone-sparing injection. There was significantly higher complete dryness rate and lower frequency of incontinence episodes in patients with trigone-including intradetrusor injection, with these factors leading to increased QOL due to trigonal injection. Moreover, the two methods did not differ in post-void residual volume. Consequently, trigone-including intradetrusor injection is more effective than trigone-sparing intradetrusor injection for treatment of OAB.

A subgroup analysis according to dose of BoNT/A revealed that trigone-including intradetrusor injection demonstrated significantly improvement in symptom scores, higher complete dryness rate, and lower frequency of incontinence episodes when 200–300 units of BoNT/A were used. In spite of dose-dependent response in efficacy, a dose-dependent increase in adverse effects precluded using higher dose of BoNT/A, and 100 units of BoNT/A is recommended for the treatment of OAB [27, 28]. Therefore, more extensive, well-controlled, randomized studies using different dose according to site of injection are needed to assess the incidence of adverse effects.

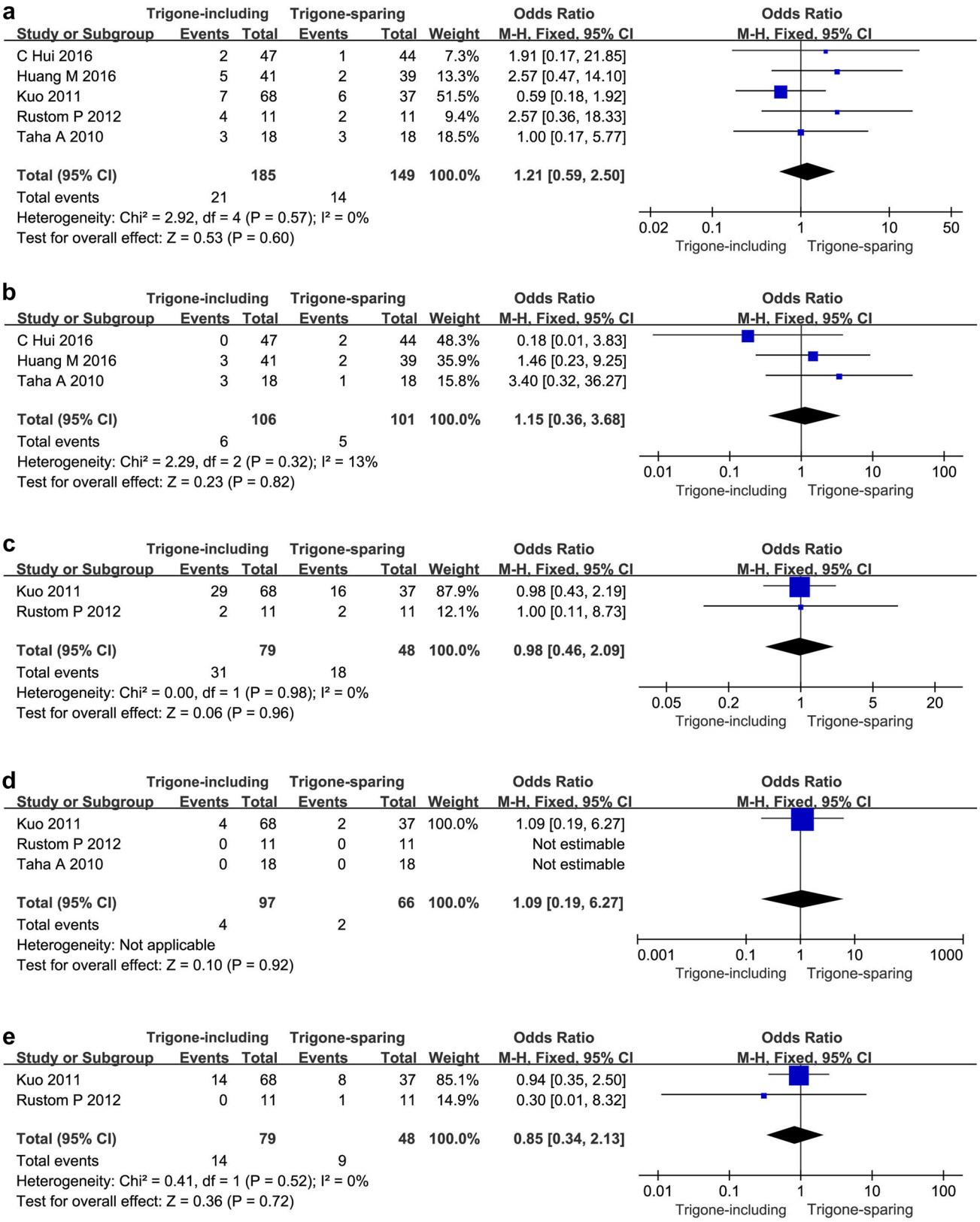


Fig. 5 Complications of trigone-including and trigone-sparing intradetrusor injection. **a** Hematuria; **b** general weakness; **c** bladder discomfort; **d** incidence of large post-void residual; **e** urinary tract infection

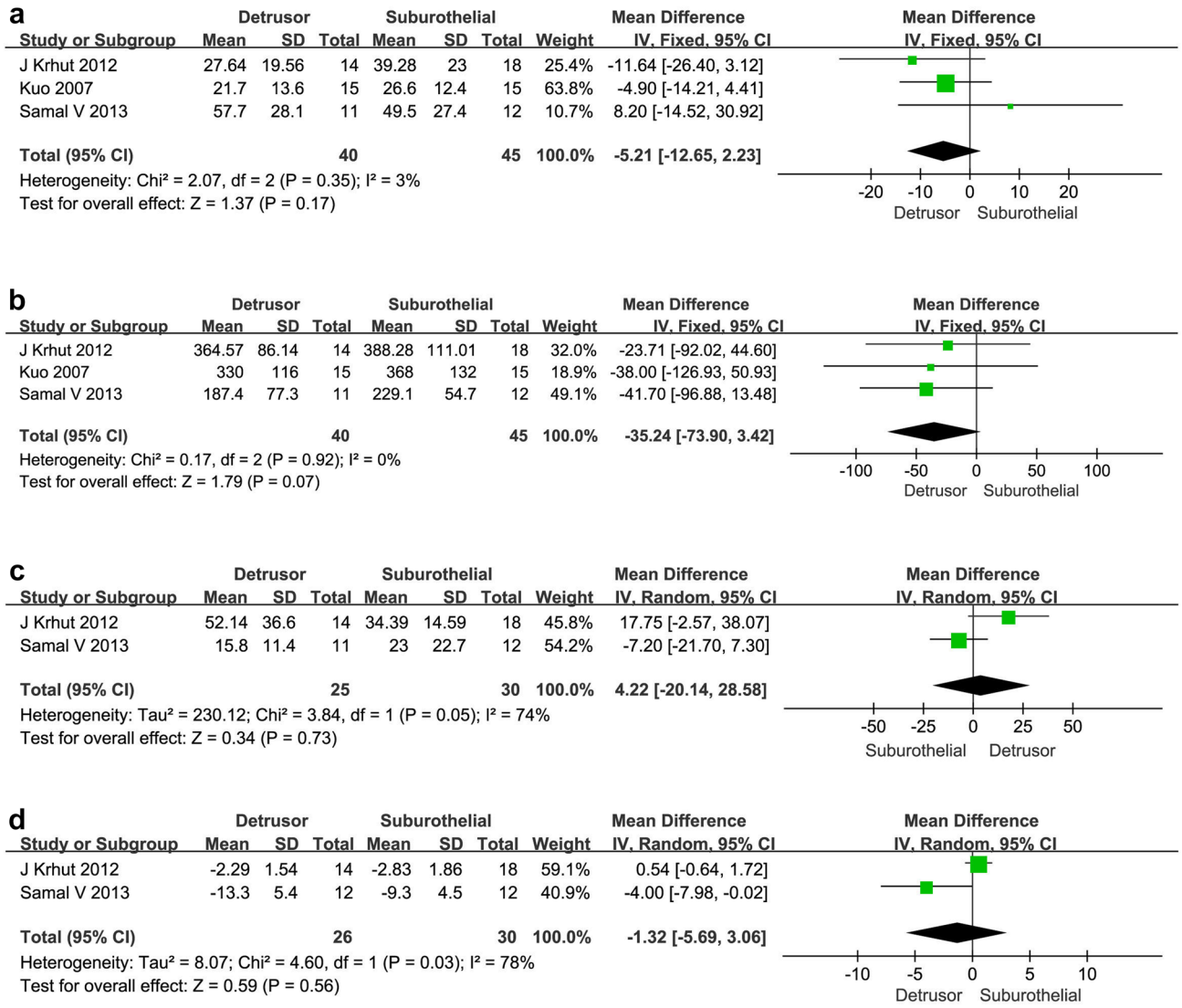


Fig. 6 Effects of intradetrusor and suburothelial injection. **a** Impact on detrusor pressure at the maximum flow rate (mmHg); **b** impact on maximum cystometric capacity (ml); **c** impact on detrusor compliance (ml/cmH_2O); **d** impact on change in number of incontinence episodes (number per day)

Adverse reactions can be observed according to injection or injected materials. Complications due to injection such as hematuria and UTI were observed with similar rates between trigone-including intradetrusor injection and trigone-sparing injection. There was no difference in injected material-related reactions between the two groups. Functional complications such as bladder discomfort or incidence of large post-void residual were not different between the two groups.

Because of variability in bladder wall thickness due to systematic administration according to the vessels of the musculature, depth of injection is a considerable variable in the treatment of OAB. Although BoNT/A was injected under direct visual cystoscopic guidance, depth of injection can only be determined by the surgeon. In this situation, Mehnert et al. assessed the distribution of BoNT/A in the detrusor of the bladder [29]. Using magnetic resonance imaging (MRI), the authors found that about 20% of administrated BoNT/A injections were localized to outside the detrusor. Because submucosal BoNT/A injection does not require deep injection of the needle, it has some advantages, including visible control to target distribution and reduction of the risk of unintended administration to blood vessels in the detrusor. Our findings demonstrate the effects and side effects of submucosal BoNT/A injection. Comparison of submucosal versus detrusor injection indicates that, among the samples herein, the depth of injection had no significant impact on efficacy and safety. Because submucosal injection was

Table 2 GRADE summary of findings. Risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effects of intervention (and its 95% CI)

Outcomes	Studies (*n*)	Patients (*n*)		Anticipated absolute effects* (95% CI)		Relative effects (95% CI)	Quality of evidence (GRADE)
		Trigone-including	Trigone-sparing	Risk with trigone-sparing	Risk with trigone-including		
Symptom score	5 RCTs	185	149	–	–	–	⨁◯◯◯ very low[a,b,c]
Complete dryness rate	4 RCTs	174/312 (55.8%)	138/312 (44.2%)	442 per 1000	635 per 1000 (511–742)	OR 2.19 (1.32–3.63)	⨁⨁◯◯ low[a,c]
Number of incontinence episodes	4 RCTs	174	138	The mean the number of incontinence episodes was 0	The mean the number of incontinence episodes in the intervention group was 0.85 lower (1.55 lower to 0.16 lower)	–	⨁◯◯◯ very low[a,b,c]
Detrusor pressure at the maximum flow rate	4 RCTs	144	110	The mean detrusor pressure at maximum flow rate was 0	The mean detrusor pressure at maximum flow rate in the intervention group was 2.55 lower (4.16 lower to 0.95 lower)	–	⨁⨁⨁◯ moderate[c]
Volume at the first desire to void	3 RCTs	76	73	The mean volume at the first desire to void was 0	The mean volume at the first desire to void in the intervention group was 17.54 higher (1 higher to 34.07 higher)	–	⨁⨁◯◯ low[d]
Incidence of hematuria	5 RCTs	185/334 (55.4%)	149/334 (44.6%)	446 per 1000	494 per 1000 (322 to 668)	OR 1.21 (0.59–2.50)	⨁⨁◯◯ low[a,c]
Incidence of large post-void residual	2 RCTs	79/127 (62.2%)	48/127 (37.8%)	378 per 1000	373 per 1000 (218 to 559)	OR 0.98 (0.46–2.09)	⨁⨁◯◯ low[d]

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: the true effect might be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Downgraded by 1 level due to risk of bias

[b] Downgraded by 1 level due to inconsistency

[c] Downgraded by 1 level due to imprecision

[d] Downgraded by 2 levels due to imprecision

CI confidence interval; *RR* risk ratio; *RCTs* randomized controlled studies

equally effective and safe and was more easily administered; submucosal injection stands to be the recommended method of BoNT/A injection for the treatment of OAB.

Our meta-analysis has some limitations. First, a relatively small number of patients were enrolled in this analysis. Intervention effects can be significantly overstated in small trials where there is incomplete double blinding, allocation sequence generation, and allocation concealment [30]. Second, there was a significant heterogeneity among studies. Clinical heterogeneity was identified in terms of BoNT/A dosage, causes of OAB, and age ranges of patients, and various bladder symptom scores and measurements precluded further synthesis of the data. Finally, we did not separately analyze idiopathic overactive bladder (iOAB) or neurogenic detrusor overactivity (NDO). We also recognized the possible confounding effect due to cause of overactivity. These specific types of OAB differ according to cause and pathologic course. However, OAB is considered as a symptom complex including neurogenic components and myogenic components. Although the causes of NDO and iOAB were different, they are overlapped symptoms and treatments. In other words, they have similar patterns of symptoms in part, and both involve overactivity of the detrusor in bladder; thus, BoNT/A is also used for the control of detrusor overactivity.

Despite the limitations, this study is the first meta-analysis to clarify the effects of site of injection and depth of injection of BoNT/A in patients with OAB. Our results demonstrate the importance of controlling the trigonal area and indicate that depth of injection is not a matter of concern.

Conclusion

Our meta-analysis indicates that the use of different BoNT/A injection sites to treat OAB leads to different outcomes. Trigone-including injection has greater efficacy in terms of improvement in patient symptom score, higher complete dryness rate, and lower frequency of incontinence episodes. Trigone-including injection also provides patients with lower detrusor pressure and higher volume at the first desire to void following treatment, without an increase in adverse effects. In contrast, our findings show no difference in efficacy or safety according to depth of injection.

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Authors' contribution JKJ: study design, data acquisition, analysis and interpretation of data, and writing of the article; KNK: study design, data acquisition, analysis and interpretation of data, and writing of the article; DWK: data acquisition and interpretation of data; YTK: data acquisition; JYK: organizing data; JYK: organizing data and preparing manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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