Article

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Intradetrusor Versus Suburothelial Onabotulinum Toxin A in Adults with Neurogenic and Non-neurogenic Overactive Bladder Syndrome: A Meta-Analysis

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Purpose: This systematic review and meta-analysis aimed to compare the effectiveness and safety of submucosal injection of onabotulinum toxin A (OnabotA) with intradetrusor injection for overactive bladder syndrome (OAB).

Methods: This systematic review is registered with PROSPERO (CRD42021237964). A licensed librarian surveyed Medline, EMBASE, Scopus, and Google Scholar databases to conduct a comprehensive search. Studies comparing suburothelial and intradetrusor techniques of OnabotA injection for OAB were included, along with clinical and urodynamic variables and complications. The studies were assessed for quality on the basis of Cochrane Collaboration guidelines and evaluated using statistical analysis via a random-effect model and I^2 statistic. Data extraction and analysis were conducted using Covidence systematic review platform and Review Manager software.

Results: Six studies with 299 patients were included in the systematic review, with four reporting that suburothelial injection of OnabotA was as effective as intradetrusor injection and two reporting intradetrusor injection to be more effective. The meta-analysis found no significant difference between the suburothelial and intradetrusor groups for mean daily catheter or voiding frequency (mean difference: 2.12 [95% confidence interval (CI): −1.61, 5.84]) and the mean number of urgency/urge incontinence episodes (mean difference: 0.08 [95% CI: −1.42, 1.57]). However, a significant heterogeneity was found among the studies. Only the mean volume at first detrusor contraction showed a significant difference, being higher for suburothelial injection (mean difference: 33.39 [95% CI: 0.16, 66.63]). No significant difference was noted for mean compliance, mean bladder capacity, and mean maximum detrusor pressure. Urinary tract infections (UTIs) ($p = 0.24$) and acute urinary retention ($p = 0.92$) showed no significant difference between the two groups. The risk of bias varied among the studies.

Conclusions: Suburothelial injection of OnabotA is as effective as intradetrusor injection in improving OAB symptoms, and it has similar complication rates. A higher mean volume of the first detrusor contraction was found in a urodynamic study with suburothelial injection.

Keywords: overactive bladder syndrome; onabotulinum toxin A; suburothelial; intradetrusor; meta-analysis

Introduction

The International Continence Society defines overactive bladder syndrome (OAB) as urinary urgency, with or without frequency, nocturia, or urge incontinence [1,2]. It is a common condition that can negatively affect quality of life (QoL). The primary treatment for OAB is behaviour therapy, and in the event of response failure, antimuscarinic agents and beta-3 agonists can be introduced as an additional option [3]. Whilst pharmacological agents may improve symptoms, they are often associated with bothersome side effects, including constipation, dry mouth, and ocular side effects and in more extreme cases, hypertension or behavioural changes. Refractory OAB may be treated with invasive treatments, including neuromodulation of the sacral nerve or tibial nerve and botulinum toxin type A intravesical injections [4]. The US Food and Drug Administration has approved the use of onabotulinum toxin A (OnabotA)

for treating neurogenic OAB and idiopathic refractory OAB in patients who did not respond well to other medications [5].

Botulinum toxin is a neurotoxin produced by the *Clostridium* genus. When injected into the bladder wall, it leads to decreased muscle contractility by preventing the release of acetylcholine in the peripheral nervous system and has an inhibitory effect on neurotransmitters and receptors that mediate sensory neurotransmission. Whilst the anticholinergic properties of OnabotA may have been the initial indication for its use in OAB, OnabotA affects the expression and release of other substances in the bladder. When the bladder is exposed to stressors, OnabotA improves compliance by downregulating the release of Adenosine Triphosphate (ATP) and upregulating the release of nitrous oxide [6]. Additionally, it affects the sensory pathways of the bladder by desensitising unmyelinated C-fibres in the urothelium [7]. Injection of OnabotA superficial to the detrusor muscle (i.e., submucosal injection) is believed to act on receptors and active substances in the urothelium and the submucosal layer of the bladder, thereby decreasing the sensory input. Meanwhile, intradetrusor injection is thought to act via inhibition of presynaptic release of acetylcholine, resulting in chemo-denervation and paralysis [8].

The use of OnabotA has been shown to be effective and well-tolerated in patients with OAB. However, the depth of injection for OnabotA in patients with OAB has no consensus at present. A meta-analysis published in 2018 found three studies that compared submucosal injection of OnabotA with intradetrusor injection and concluded that the two techniques had comparable outcomes. However, the authors compared limited urodynamic and clinical parameters and did not compare the complication rates for these two techniques (although they analysed the complications of trigone sparing and non-sparing injections) [9].

In this systematic review and meta-analysis, the most extensive and updated analysis of all the studies published in literature that compare submucosal injection of OnabotA with intradetrusor injection for OAB with regard to effectiveness and safety is presented.

Methods

Search Methods for Identification of Studies

A systematic review was conducted on the basis of the guidelines of the Cochrane Collaboration [10]. This study protocol is registered with PROSPERO (CRD42021237964), and it followed the PRISMA guidelines [11]. A licensed librarian (JC) surveyed Medline, EMBASE, and Scopus databases to implement a comprehensive search strategy using platform-specific and topic-sensitive medical subject headings. Additionally, a grey literature search and search of additional relevant studies were conducted using the Google Scholar database (JKK, **Supplementary file 1**). The search was performed in August 2022, and all studies published until August 9, 2022, were considered.

Data Collection and Analysis

Studies that compared the suburothelial and intradetrusor techniques of OnabotA injection for OAB were considered for inclusion if the data for both groups could be distinguished even if the studies had more groups. Non-randomised and retrospective studies were included. The outcomes of interest were the clinical and urodynamic variables (mean daily catheter or voiding frequency, number of urgency/urge incontinence episodes, volume at first detrusor contraction, compliance, bladder capacity and maximum detrusor pressure) and complications of the two procedures. Studies were excluded if the outcome could not be linked to the individual techniques.

Data Extraction and Management

The screening, full text review and data extraction were all managed using the Covidence systematic review platform. During the initial screening phase, two authors (PY and DA) independently reviewed the citations and abstracts and then went through the full text of the selected titles. If any disagreements occurred, they were resolved by a fifth author (MEC). One author carried out the data extraction, which was verified by another author to collect the required information from each study.

Assessment of Risk of Bias in Included Studies

The quality of the studies included in the research was assessed by two reviewers on the basis of the study design and implementation. The assessment followed the guidelines provided by the Cochrane Collaboration for evaluating the quality of randomised and nonrandomised studies, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions [12,13]. The studies were graded in accordance with the ROBINS-I tool (https://methods.cochrane.org/robins-i) for nonrandomised studies, whereas the RoB 2 tool (https://methods.cochrane.org/risk-bias-2) was used for randomised controlled studies [13].

Statistical Analysis

A random-effect model was used for the calculation of all effect estimates and 95% confidence intervals (CIs). The Mantel–Haenszel method was used for dichotomous data with odds ratio as effect measure, and the inverse variance method was used for continuous data with mean difference as the effect measure. Two authors (PY and DA) evaluated the clinical heterogeneity, and a meta-analysis was performed after they agreed that no apparent visual heterogeneity was present. Review Manager (RevMan version 5.4; The Cochrane Collaboration, 2020; The Nordic Cochrane Centre, Copenhagen, Denmark) was used for analysing the data and making forest plots for the included studies. I^2

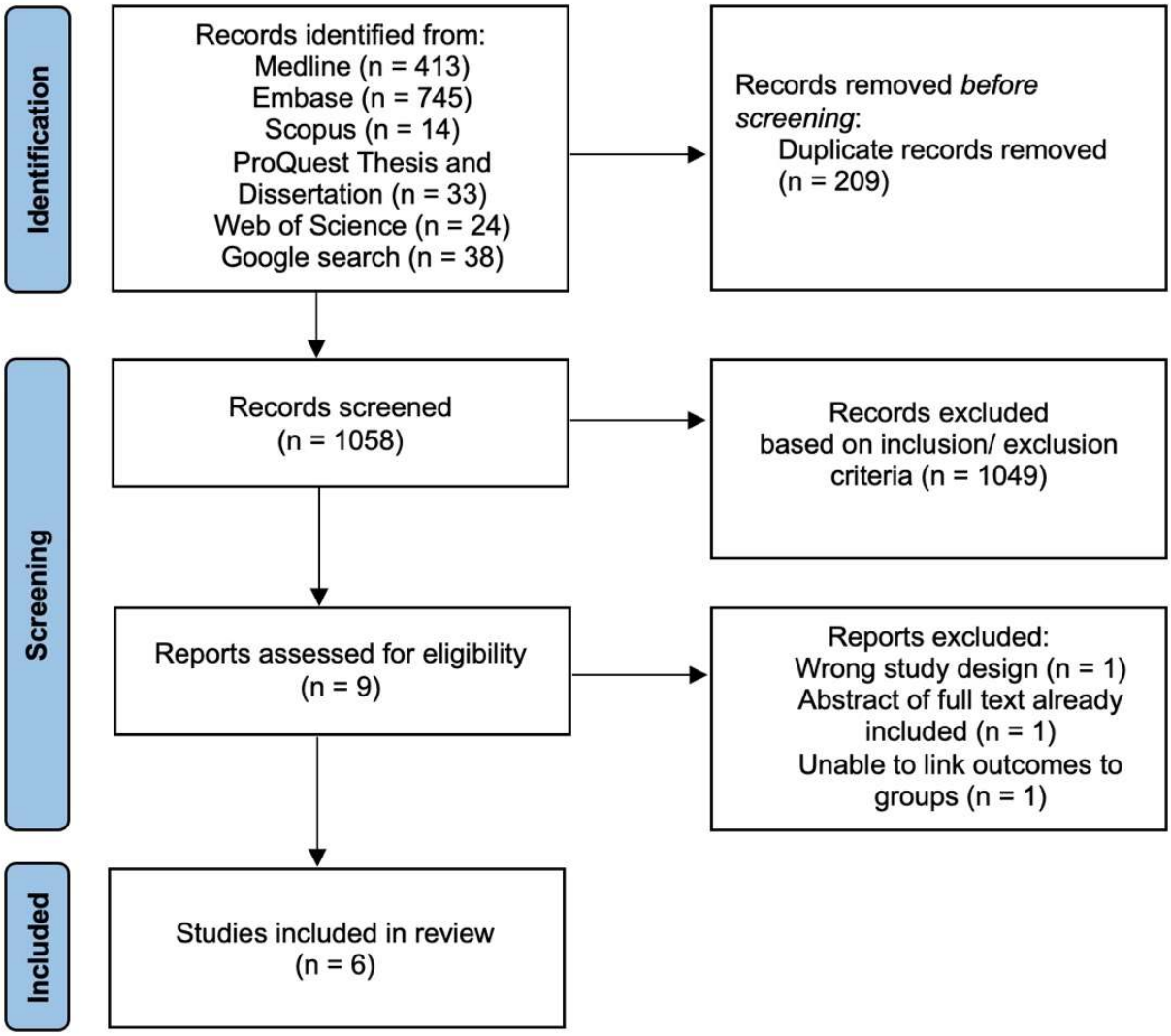

Fig. 1. PRISMA compliant flow diagram of the search strategy and included studies.

statistic was used for statistical assessment of inter-study heterogeneity [14].

Results

Systematic Review

The initial search identified 1267 records, and after the screening process, six studies were included in the qualitative synthesis (Fig. 1). Overall, these six studies had 299 patients (Table 1, Ref. [8,15–19]). These studies consisted of three single-centre prospective randomised studies, one multicentre prospective randomised study, one prospective cohort study and one retrospective cohort study. Three studies included patients with neurogenic detrusor overactivity, two studies had patients with idiopathic detrusor overactivity and one study had overactive bladder patients without detrusor overactivity. The first four studies that were published reported that suburothelial injection of OnabotA was as effective as intradetrusor injection, whereas the two recent ones reported that intradetrusor injection of OnabotA was more effective than suburothelial injection [8,15–19]. Three studies reported the location of injection [15,16,18]. All had at least one group that included trigonal injections; Otherwise, the lateral and posterior walls were used. In the detrusor group of one study, the injections were extratrigonal only [15].

Four studies reported the mean daily catheter/voiding frequency and the number of urgency/urge incontinence episodes amongst the clinical outcomes (Table 2, Ref. [8,15–19]). Whilst Kuo *et al.* [15] and Krivoborodov *et al.* [16] did not report any difference in these parameters before and after OnabotA injection, Krhut *et al.* [17] and Šámal *et al.* [8] found that suburothelial and intradetrusor injections of OnabotA improved these outcomes. Mean

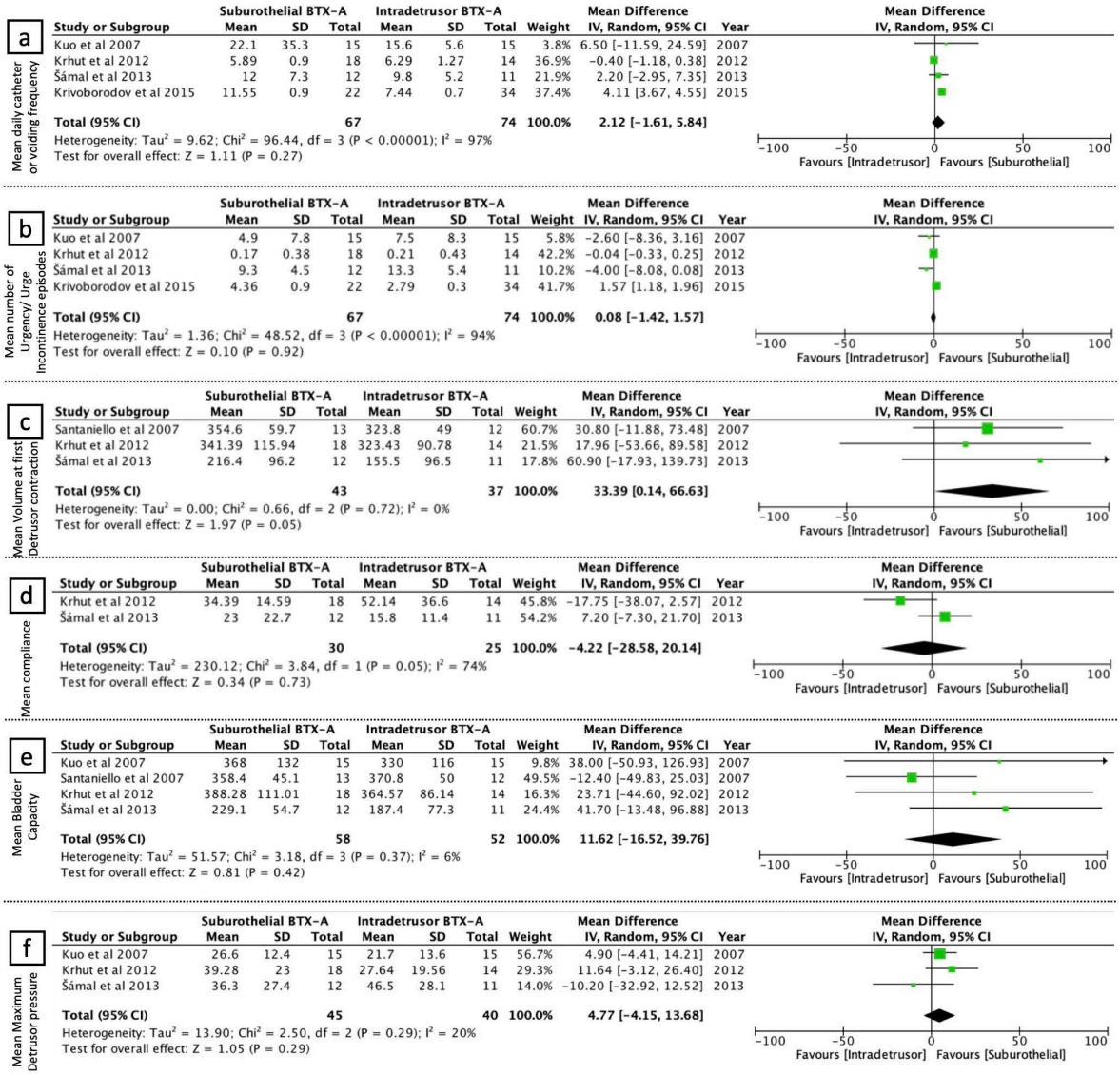

Fig. 2. Forest plots showing overall pooled effect estimates for comparison of mean differences between suburothelial and intradetrusor OnabotA injections. (a) Mean daily catheter or voiding frequency, no difference. (b) Mean number of urgency/urge incontinence episodes, no difference. (c) Mean volume at first detrusor contraction, significant difference. (d) Mean compliance, no difference. (e) Mean bladder capacity, no difference. (f) Mean maximum detrusor pressure, no difference.

bladder capacity was reported by four studies, all of which reported an increase in the capacity after OnabotA injection [8,15,17,18]. Compliance improved after suburothelial and intradetrusor injections of OnabotA although this parameter was reported by two studies only [8,17]. The effect of OnabotA injection was between 6 and 11 months on an average.

Aside from one study that had no complications in either group [18], various complications were reported as outlined in Table 3 (Ref. [8,15–19]). The most common complication after OnabotA injection was urinary tract infection (UTI), followed by acute urinary retention. Two studies reported temporary muscle weakness with intradetrusor OnabotA injection only [16,17].

Meta-Analysis

The overall pooled effect estimates showed no difference between suburothelial and intradetrusor groups for mean daily catheter or voiding frequency (mean difference 2.12 [95% confidence interval (CI): −1.61, 5.84]) and the mean number of urgency/urge incontinence episodes (mean difference 0.08 [95% CI: −1.42, 1.57], Fig. 2a,b).

Table 1. Overview of studies included in the systematic review.

Study no.	Author group	Year	Type of study	Pathology	Patient groups	Number of patients	Male: Female	Mean age (years)	Dose of onabotulinum A	Location of injections	Number of sites injected	Definition of success	Successful treatment at 3 months	Conclusion
1	Kuo *et al.* [15]	2007	Single-centre randomised study	Idiopathic detrusor overactivity	(i) Suburothelial, (ii) detrusor, (iii) bladder base	(i) 15, (ii) 15, (iii) 15	(i) 10:5, (ii) 8:7, (iii) 10:5	(i) 72.1, (ii) 71.6, (iii) 67.9	100 IU (0.5 mL per puncture)	(i) N/A, (ii) extratrigonal (lateral wall, posterior wall, dome of the bladder), (iii) trigonal	(i) 40, (ii) 40, (iii) 10	>50% improvement in symptoms	(i) 93%, (ii) 80%, (iii) 67%	Suburothelial = detrusor
2	Santaniello *et al.* [18]	2007	Single-centre randomised study	Neurogenic detrusor overactivity due to spinal cord injury	(i) Suburothelial, (ii) detrusor	(i) 13, (ii) 12	-	-	300 IU (1 mL per puncture)	Trigonal, lateral wall, posterior wall	(i) 30, (ii) 30	-	-	Suburothelial = detrusor
3	Krhut *et al.* [17]	2012	Multicentre randomised study	Neurogenic detrusor overactivity due to spinal cord injury	(i) Detrusor, (ii) suburothelial	(i) 14, (ii) 18	(i) 9:5, (ii) 17:1	(i) 31.8, (ii) 32.4	300 IU (1 mL per puncture)	N/A	(i) 30, (ii) 30	Willingness to undergo repeat procedure once all benefits of first treatment have diminished	(i) 64.3%, (ii) 88.8%	Suburothelial = detrusor
4	Šámal *et al.* [8]	2013	Single-centre randomised study	Neurogenic detrusor overactivity due to spinal cord injury	(i) Suburothelial, (ii) detrusor	(i) 12, (ii) 11	21:2	Range: 20–58	300 IU (1 mL per puncture)	N/A	(i) 30, (ii) 30	-	-	Suburothelial = detrusor
5	Krivoborodov *et al.* [16]	2015	Prospective cohort study	Overactive bladder without detrusor overactivity	(i) Suburothelial, (ii) detrusor	(i) 22, (ii) 34	13:31	-	100 IU (0.5 mL per puncture)	Trigonal, lateral wall, posterior wall	(i) 20, (ii) 20	>50% improvement in symptoms	(i) 14%, (ii) 65%	Suburothelial < detrusor
6	Hoover *et al.* [19]	2022	Retrospective cohort study	Idiopathic detrusor overactivity	(i) Suburothelial, (ii) detrusor	(i) 83, (ii) 50	0:133	(i) 69.5, (ii) 65.6	100 IU (1 mL per puncture)	N/A	(i) 20, (ii) 20	>50% improvement in symptoms	(i) 65%, (ii) 82%	Suburothelial < detrusor

Table 2. Clinical and urodynamic outcomes of studies included in the systematic review.

Sr no.	Author group	Year	Patient groups	Mean (SD) daily catheter or voiding frequency		Mean (SD) number of urgency/urge incontinence episodes		Mean (SD) volume at first detrusor contraction		Mean (SD) compliance		Mean (SD) bladder capacity in mL		Mean (SD) maximum detrusor pressure		Mean (SD) duration of effect of treatment in months
				Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	
1	Kuo *et al.* [15]	2007	(i) Suburothelial, (ii) detrusor, (iii) bladder base	(i) 17.8 (7.2), (ii) 29.8 (40), (iii) 23.4 (34.1)	(i) 22.1 (35.3), (ii) 15.6 (5.6), (iii) 14.1 (6.2)	(i) 6.8 (6.2), (ii) 11.3 (7.7), (iii) 11.1 (8.7)	(i) 4.9 (7.8), (ii) 7.5 (8.3), (iii) 5.6 (5.4)	-	-	-	-	(i) 243 (133), (ii) 260 (105), (iii) 283 (167)	(i) 368 (132), (ii) 330 (116), (iii) 318 (138)	(i) 24.3 (11.7), (ii) 27.2 (18.8), (iii) 25.9 (22.4)	(i) 26.6 (12.4), (ii) 21.7 (13.6), (iii) 28.3 (25.7)	-
2	Santaniello *et al.* [18]	2007	(i) Suburothelial, (ii) detrusor	-	-	-	-	(i) 242.4 (98.7), (ii) 214.6 (55)	(i) 354.6 (59.7), (ii) 323.8 (49)	-	-	(i) 279.8 (69), (ii) 290.4 (72)	(i) 358.4 (45.1), (ii) 370.8 (50)	-	-	-
3	Krhut *et al.* [17]	2012	(i) Detrusor, (ii) suburothelial	(i) 8.7 (4.25), (ii) 7.11 (1.28)	(i) 6.29 (1.27), (ii) 5.89 (0.90)	(i) 2.5 (1.56), (ii) 3.0 (1.88)	(i) 0.21 (0.43), (ii) 0.17 (0.38)	(i) 148.93 (60.73), (ii) 141.11 (62.85)	(i) 323.43 (90.78), (ii) 341.39 (115.94)	(i) 21.57 (9.86), (ii) 17.94 (6.33)	(i) 52.14 (36.60), (ii) 34.39 (14.59)	(i) 192.43 (71.62), (ii) 198.33 (84.16)	(i) 364.57 (86.14), (ii) 388.28 (111.01)	(i) 75.29 (27.19), (ii) 80.28 (22.09)	(i) 27.64 (19.56), (ii) 39.28 (23.00)	(i) 7.29 (1.27), (ii) 7.11 (1.31)
4	Šámal *et al.* [8]	2013	(i) Suburothelial, (ii) detrusor	(i) 40.7 (6.0), (ii) 41.3 (8.3)	(i) 12.0 (7.3), (ii) 9.8 (5.2)	(i) 12.6 (4.7), (ii) 16.9 (5.7)	(i) 9.3 (4.5), (ii) 13.3 (5.4)	(i) 159.0 (44.2), (ii) 144.0 (57.4)	(i) 216.4 (96.2), (ii) 155.5 (96.5)	(i) 17.0 (8.2), (ii) 20.4 (4.5)	(i) 23.0 (22.7), (ii) 15.8 (11.4)	(i) 230.0 (66.3), (ii) 207.6 (96.5)	(i) 229.1 (54.7), (ii) 187.4 (77.3)	(i) 85.8 (24.8), (ii) 104.2 (43.2)	(i) 36.3 (27.4), (ii) 46.5 (28.1)	(i) 7.3, (ii) 6
5	Krivoborodov *et al.* [16]	2015	(i) Suburothelial, (ii) detrusor	(i) 13.95 (1.7), (ii) 12.26 (0.5)	(i) 11.55 (0.9), (ii) 7.44 (0.7)	(i) 4.95 (0.9), (ii) 6.29 (0.7)	(i) 4.36 (0.9), (ii) 2.79 (0.3)	-	-	-	-	-	-	-	-	-
6	Hoover *et al.* [19]	2022	(i) Suburothelial, (ii) detrusor	-	-	-	-	-	-	-	-	-	-	-	-	(i) 9.5, (ii) 10.9

Table 3. Complications reported by studies included in the systematic review.

Study no.	Author group	Year	No. of patients in suburothelial group	Complications in suburothelial group (no. of patients)	No. of patients in detrusor group	Complications in detrusor group (no. of patients)
1	Kuo *et al.* [15]	2007	15	Dysuria (7) Acute urinary retention (2) Urinary tract infection (2) Gross haematuria (1) Bladder/urethral pain (1)	15	Dysuria (5) Acute urinary retention (2) Urinary tract infection (1) Bladder/urethral pain (1)
2	Santaniello *et al.* [18]	2007	13	None	12	None
3	Krhut *et al.* [17]	2012	18	None	14	Temporary muscle weakness (1)
4	Šámal *et al.* [8]	2013	12	Urinary tract infection (3)	11	Urinary tract infection (2) Temporary muscle weakness (1)
5	Krivoborodov *et al.* [16]	2015	22	None	34	Acute urinary retention (3)
6	Hoover *et al.* [19]	2022	83	Urinary tract infection (21) Acute urinary retention (8)	50	Urinary tract infection (9) Acute urinary retention (4)

Heterogeneity or inter-study variation was detected amongst these studies (97% for mean daily catheter or voiding frequency and 94% for mean number of urgency/urge incontinence episodes, $p < 0.001$).

Amongst the urodynamic parameters, the pooled effect estimates showed significant differences for mean volume at first detrusor contraction only, which was higher for suburothelial injection than for intradetrusor injection (mean difference 33.39 [95% CI: 0.16, 66.63]). Meanwhile, no significant difference was noted between the two groups for mean compliance, mean bladder capacity and mean maximum detrusor pressure (Fig. 2c–f). Analysis of the urodynamic parameters showed that except for mean compliance, where heterogeneity was significant (74%, $p = 0.05$), the remaining parameters did not have significant inter-study variation ($p > 0.05$).

Comparison of the common complications between the two groups revealed that the pooled effect estimates did not show any significant difference between the suburothelial and intradetrusor groups for UTIs ($p = 0.24$, Fig. 3a) and acute urinary retention ($p = 0.92$, Fig. 3b).

Risk-of-Bias Analysis

The assessment of the risk of bias showed that two out of three randomised studies had a low risk of bias, whereas one had some concern (**Supplementary file 2**). One study, which was only published as an abstract, had insufficient information to accurately assess its risk of bias [18]. Of the two nonrandomised studies, one had a serious risk of bias [19], and the other had a critical risk of bias [16].

Discussion

Intravesical OnabotA injection is an alternative treatment option for refractory OAB that does not respond to pharmacological interventions. Some authors have preferred suburothelial injection over intradetrusor injection in the past because the former has a lower reported complication rate [9]. Whilst some authors reported similar efficacy for both methods of injection [8,15,17], recent studies suggest that intradetrusor injection is superior [16,19]. Suburothelial injection may be easier to control visually because of the mucosal bulking or "bleb" and has no risk of accidental administration of the drug into the minor blood vessels. Meanwhile, intradetrusor injection may be associated with extravasation of OnabotA into the perivesical fat, leading to a mean loss of about 1.96–19.20 U when a total amount of as much as 400 U is used [20]. However, this loss is rarely significant clinically.

OAB manifests as frequency and urgency with or without urinary incontinence. Some authors believe that excessive release of adenosine triphosphate in the suburothelial region may lead to the sensation of urgency, and therefore, treating these symptoms could be more effective through suburothelial administration of OnabotA [17,21]. The injection of OnabotA into the bladder modulates the

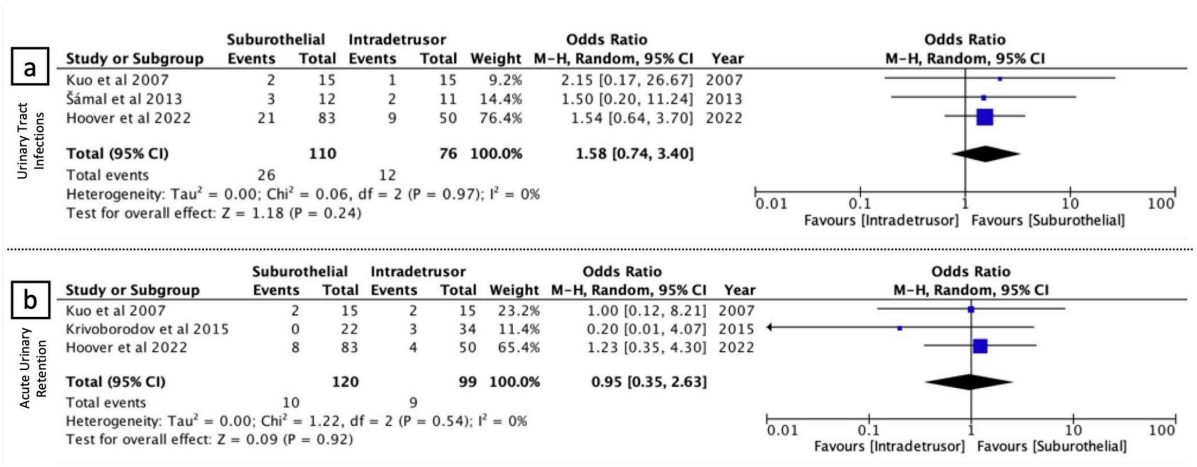

Fig. 3. Forest plots showing overall pooled effect estimates for comparison of odds ratios between suburothelial and intradetrusor OnabotA injections. (a) Urinary tract infections, no difference. (b) Acute urinary retention, no difference.

sensitivity of sensory pathways by decreasing it through the desensitisation of unmyelinated C-fibres in the urothelium. This decrease is achieved through the reduction in sensory receptors, such as purinergic receptor P2X ligand-gated ion channel 3 (P2X3) and transient receptor potential vanilloid 1 (TRPV1), which have been linked to decrease in urgency episodes [22]. The highest concentration of sensory nerves that express TRPV1, P2X3, substance P and calcitonin gene-related peptide are found in the suburothelial plexus and urothelium [23]. Intradetrusor injection of OnabotA blocks the presynaptic release of acetylcholine causing paralysis. However, the release of acetylcholine in the urothelium is not affected by the injection of OnabotA because it is primarily controlled by the cystic fibrosis transmembrane conductance regulator channels, which remain unchanged by the injection [6]. The long-term effects of OnabotA injection are thought to be related to reduction in nerve growth factor release, which affects the unmyelinated C-fibres [22]. The present meta-analysis failed to identify any difference between suburothelial and intradetrusor use in terms of mean daily catheter or voiding frequency or the mean number of urgence/urge incontinence episodes. The effect of OnabotA on symptoms of OAB may not be related to the depth of injection. However, urodynamic detrusor overactivity may still have a relationship with the depth of injection. In this meta-analysis, the mean volume at first detrusor contraction was the only urodynamic parameter that was significantly different between the two groups, and it was higher for the suburothelial group. This finding may indicate that the effects of OnabotA on the afferent signals in the suburothelial region prevent detrusor overactivity. The pooled effect estimates did not show any significant difference between the two groups for mean compliance, bladder capacity and maximum detrusor pressure.

Some authors prefer suburothelial injection of OnabotA over intradetrusor injection because of visual feedback and a lower incidence of complications [15,17]. The most common complication reported in the studies was UTI, and it did not differ between the two groups. One study noted a high incidence of asymptomatic bacteriuria colonisation of the urinary tract (66% for suburothelial and 81% for intradetrusor) [8]. Similarly, the incidence of acute urinary retention was not different between the two groups. Temporary muscle weakness was reported in two patients only, both of whom underwent intradetrusor injection, whereas none of the patients undergoing suburothelial injection had this complication. Normally, such a weakness resolves within 24 h and does not require any treatment [8]. Based on the meta-analysis, the evidence indicating that suburothelial injection of OnabotA is associated with a lower incidence of complications is insufficient.

This review has some important limitations. Firstly, only six studies that met the inclusion criteria were identified in the literature, and they mostly consisted of small sample sizes. This limitation may result in overestimation of treatment effects. Secondly, the definition of OAB was not consistent among included studies, thus contributing to heterogeneity. No subgroup investigations were performed to address the heterogeneity. A notable detail is that one study included patients with OAB symptoms without urodynamic evidence of detrusor overactivity. The findings of this study may not be readily generalisable to all cases of OAB without urodynamic studies or any documented evidence of detrusor overactivity. Studies with diverse definitions were included because this meta-analysis focused on the role of OnabotA in alleviating symptoms of OAB, as traditional management focuses on symptomatic relief and not aetiology. Moreover, studies differed in the manner that OnabotA was applied (volume-dose and number of sites) and the location of injection. Only half of studies identified whether the injection location was trigonal or extratrigonal, which can play a substantial role in the clinical course of

treatment. Next, this study did not analyse how differences in injection volume, which determines diffusion and action parameters, can affect outcomes. The definition of success was not consistent amongst the studies. Whilst three papers defined success as >50% improvement in symptoms, one defined it as willingness to undergo repeat procedure once all benefits of first treatment diminished. The remaining two studies did not provide definition of successful treatment. Finally, most outcomes were measured at 3 months, which is inadequate for estimation of the true treatment effect because OnabotA injection lasts 6–8 months and reinjections are usually required. Despite these limitations, the present systematic review and meta-analysis is the most extensive and updated research on the effect of depth of OnabotA injection on treatment outcomes and complications for OAB. Future cohort analyses should be planned with larger patient groups to discover subtle differences in the outcomes of the two techniques of injection.

Conclusions

The results of this systematic review and meta-analysis showed that suburothelial injection of OnabotA was as effective as intradetrusor injection in improving the symptoms of OAB. Although the urodynamic parameters were not significantly different between the two injection methods, suburothelial injection resulted in a higher mean volume of the first detrusor contraction. Both techniques had similar rates and types of complications. Future studies with larger sample sizes are needed to confirm and clarify these findings.

Availability of Data and Materials

The datasets used and/or analysed during the current study were available from the corresponding author on reasonable request.

Author Contributions

PY and MEC—conceptualized the study; JKK, PY, DA and JC—contributed to study design and methodology including literature search; DA, IA, MC, JDS, MR and JC—contributed to data collection, analysis, and interpretation; MEC and AL—provided supervision throughout the study; PY, DA and IA—participated in drafting the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content. All authors gave final approval of the version to be published. All authors participated fully in the work, took public responsibility for appropriate portions of the content, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or completeness of any part of the work were appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Our study is based on open source data and relevant published studies, so there are no ethical or informed consent issues.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

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