

## Efficacy and Safety of Noninvasive Intravesical Instillation of Onabotulinum Toxin-A for Overactive Bladder and Interstitial Cystitis/Bladder Pain Syndrome: Systematic Review and Meta-analysis



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<b>OBJECTIVE</b>	To investigate the efficacy and safety of noninvasive intravesical instillation of onabotulinum toxin-A (OBTX-A) through systematic review and meta-analysis. Recently, several studies of noninvasive intravesical instillation of OBTX-A have been published. However, its efficacy is not well validated yet compared to well-known efficacy of minimally invasive intravesical injection of OBTX-A.
<b>METHOD</b>	Systematic review and meta-analysis were performed to evaluate the efficacy of noninvasive intravesical instillation of OBTX-A in patients with overactive bladder and interstitial cystitis/bladder pain syndrome by measuring outcomes such as urgency episode per 72 hours, frequency per 72 hours, urgency urinary incontinence, voided volume (VV), postvoided residual volume, maximum flow rate, and patient perception of bladder condition.
<b>RESULT</b>	Six trials in 4 studies that compared instillation of OBTX-A and placebo involving 248 patients (121 experimental and 127 controls) were included for final data extraction. Instillation of OBTX-A significantly increased VV, with a mean difference of 38.48 (95% confidence interval: 76.05, 0.92) compared to the placebo group. However, other outcomes showed statistically insignificant changes. Major adverse events were not reported in the group receiving intravesical instillation of OBTX-A.
<b>CONCLUSION</b>	Intravesical instillation of OBTX-A showed limited efficacy with improvement of VV for treatment of overactive bladder or interstitial cystitis/bladder pain syndrome. More studies are needed to overcome the efficacy of current noninvasive bladder instillation of OBTX-A regarding effective drug transport. UROLOGY 125: 50–57, 2019. © 2018 Elsevier Inc.

Overactive bladder (OAB) is often accompanied by urinary frequency and nocturia, which is defined as urinary urgency regardless of incontinence.<sup>1</sup> Treatment of OAB is important individually and

socially considering high social and economic burden.<sup>2</sup> Moreover, it decreases quality of life of patients and their family.<sup>3</sup>

According to the American Urological Association/Society of Urodynamics and Female Pelvic Medicine & Urogenital Reconstruction Guideline, conservative care through lifestyle modification, vesical training, and pelvic floor muscle training is the first-line therapy to manage OAB. Pharmacologic therapy with anticholinergics such as oral antimuscarinics and oral  $\beta$ 3-adrenoreceptor agonist can be used as a second-line therapy or a combination therapy with conservative care.<sup>4</sup> However, almost half of OAB patients are not treated after second-line therapy or conservative care. For such refractory OAB patients,

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alternative treatments including minimally invasive intravesical injection of onabotulinum toxin-A (OBTX-A) are needed.<sup>5</sup>

Intravesical injection of OBTX-A is a third-line therapy which is a standard option for an OAB patient who is refractory to pharmacologic treatment. Several meta-analyses have reported that intravesical injection of OBTX-A can improve micturition, urgency, urinary incontinence (UI), urgency urinary incontinence (UUI), and cystometric capacity.<sup>6,7</sup> After intravesical injection, OBTX-A can diffuse the entire bladder's smooth muscle through urothelium and reduce the release of neurotransmitters into synapse through a process involving cytosolic translocation protein 25 (SNAP-25).<sup>8,9</sup> Moreover, several studies have proven that OBTX-A has efficacy in relieving the frequency and subjective pain for patients with interstitial cystitis/bladder pain syndrome (IC/BPS).<sup>10</sup> However, intravesical injection of OBTX-A has side effects such as urinary tract infection (UTI), bacteriuria, dysuria, urinary retention, and increasing postvoided residual volume (PVR).<sup>6</sup> It also requires cystoscopic intervention with local or general anesthesia which can cause surgical complications. To reduce side effects while maintaining efficacy, a few studies have investigated intravesical instillation of OBTX-A recently.<sup>8,11-13</sup> However, the effectiveness of intravesical instillation remains controversial.

It has been reported that OBTX-A can diffuse into the bladder's smooth muscle after intravesical instillation when a catalyst such as dimethyl sulfoxide is used.<sup>14</sup> To clarify the effectiveness of bladder instillation of OBTX-A, we performed a systematic review and meta-analysis. Our primary goal was to investigate the clinical efficacy of noninvasive intravesical instillation of OBTX-A in patients with OAB or IC/BPS.

## MATERIALS AND METHODS

A meta-analysis and a systematic review were conducted according to predefined guidelines provided by the Cochrane Collaboration.

### Search Methods for Identification of Studies

Literature search was performed to evaluate the efficacy and safety of intravesical instillation of OBTX-A for OAB and IC/BPS patients. Primary outcomes for efficacy were set as cure or improvement of urgency episodes per 72 hours, frequency per 72 hours, UUI, voided volume (VV), PVR, maximum flow rate (Qmax), and patient perception of bladder condition (PPBC). Outcomes were evaluated after a follow-up period of 4 weeks.

MEDLINE search from 1996 to July 28, 2017 incorporated an optimally sensitive Cochrane Collaboration search strategy with certain MeSH headings, including botulinum toxin, botulinum toxin type A, OAB, and overactive urinary bladder with all sub-headings. The efficiency of intravesical instillation of OBTX-A for OAB patients was searched using both supplementary concept and documentation in the title and abstract. Searching using the Cochrane Collaboration and EMBASE was also performed using the same method as done for MEDLINE. Inclusion

criteria for quality assessment and data extraction were outcome assessments including at least 1 outcome among urgency event, frequency event, UUI, VV, PVR, Qmax, and PPBC.

### Data Extraction and Synthesis

Initial screening of electronic databases for study selection was based on information provided by the title and abstract. Two authors (HYL and JHK) independently performed screening. Any disagreement about the inclusion of studies was discussed among all authors. Authors extracted data such as study year, study design, and inclusion criteria of each study from eligible studies.

### Assessment for Risk of Bias in Included Studies and Reporting Bias

All included studies were assessed for the risk of bias by managing reviewers according to the Cochrane guidelines. Each item was judged as having low risk, unclear risk, or high risk. Any disagreement regarding eligibility during the extraction was discussed and resolved. The following 6 items were assessed: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting.

### Meta-analysis Assessment

We collected 7 outcomes, including urgency episode per 72 hours, frequency per 72 hours, UUI per 72 hours, VV, PVR, Qmax, and PPBC from 6 trials. We compared between before procedure and 4 weeks after the procedure using mean difference (MD) and connected among studies through DerSimonian and Laird random-effects model. We used 95% confidence interval (CI). If the result of the analysis showed  $P > .05$ , we regarded it as homogeneous and the fixed-effect model was taken for meta-analysis. If the result showed  $P < .05$ , we regarded it as heterogeneous and a random-effect model was taken. We measured inconsistency using heterogeneity ( $I^2$ ) statistic.  $I^2 < 25\%$  indicated small or no level of inconsistency while  $I^2 > 50\%$  indicated significant inconsistency. Meta-regression analysis was conducted for urgency episode per 72 hours, frequency per 72 hours, UUI per 72 hours, VV, PVR, Qmax, and PPBC to determine any improvement after bladder instillation.

## RESULTS

### Inclusion of Studies

The initial search identified 465 articles from electronic databases (27 from the Cochrane database, 260 from EMBASE, and 178 from PUBMED). A total of 47 studies were excluded due to duplicated studies or overlapping data. A total of 335 studies were excluded after screening title and abstracts due to nonrelevant topics. Eighty-three studies were eligible for full text analysis. Of these, 24 studies were excluded due to OBTX-A injection in neurogenic detrusor overactivity, 38 studies were excluded due to OBTX-A injection in OAB, and 13 studies were excluded due to OBTX-A injection for other diseases. Only 8 studies were eligible for full-text analysis. Of these, 1 was excluded because it was a review article, 2 were excluded because they were supplementary studies and 1 was excluded because it was a study on other functions of OBTX-A. A detailed flow chart showing the selection process is given in Supplementary Figure 1. Finally, a total of 6 trials in 4 studies were included for final data

extraction. These 4 studies comprised of 248 subjects (121 in the experimental group and 127 in the control group; Table 1).

### Quality Assessment

Supplementary Figure 2 shows risk of bias summary. Overall, the risk of bias was considerably low. One study consisted of a selection and detection bias.

### Meta-analysis Between Intravesical Instillation of OBTX-A and Placebo Group

Detailed findings of meta-analysis are presented in Table 2. The overall MD of urgency episode per 72 hours from the baseline for the OBTX-A intravesical instillation group (experimental group) compared to the placebo group (control group) was  $-3.91$  (95% CI:  $-7.84, 0.03$ ) with  $I^2$  of 0%. Overall MD of frequency per 72 hours from baseline for the OBTX-A intravesical instillation group compared to the placebo group was  $-2.24$  (95% CI:  $-5.10, 0.62$ ) with  $I^2$  of 60.5%. Overall MD of UUI per 72 hours from baseline for the OBTX-A intravesical instillation group compared to the placebo group was  $-2.87$  (95% CI:  $-11.61, 5.86$ ) with  $I^2$  of 82.0%. Overall MD of VV from baseline for the OBTX-A intravesical instillation group compared to the placebo group was  $-38.48$  (95% CI:  $-76.05, -0.92$ ) with  $I^2$  of 0%. Overall MD of PVR from baseline for the OBTX-A intravesical instillation group compared to the placebo group was  $-4.31$  (95% CI:  $-9.34, 0.71$ ) with  $I^2$  of 0%. Overall MD of Qmax from baseline for the OBTX-A intravesical instillation group compared to the placebo group was  $0.21$  (95% CI:  $-2.44, 2.85$ ) with  $I^2$  of 0%. Overall MD of PPBC from baseline for the OBTX-A intravesical instillation group compared to the placebo group was  $-0.06$  (95% CI:  $-0.59, 0.48$ ) with  $I^2$  of 0% (Table 2; Fig. 1 and 2).

### Adverse Events

There was no life-threatening or severe adverse events after intravesical instillation of OBTX-A. Minor adverse events included UTI, dysuria, and hematuria.

### Publication Bias

Total IPSS, voiding IPSS, storage IPSS, quality of life, Qmax, or PVR showed no evidence of publication bias.

## DISCUSSION

Intravesical injection of OBTX-A is a third-line treatment for patients who are refractory to conservative care or medication therapy.<sup>13</sup> Noninvasive intravesical instillation of OBTX-A has been studied recently to substitute minimally invasive intravesical injection for maintaining efficacy while reducing side effects. Intravesical injection of OBTX-A needs anesthesia and has complications such as UTI, urinary retention, and hematuria.<sup>11</sup>

Up to date, several studies have reported the efficacy of intravesical instillation of OBTX-A for OAB or IC/BPS patients. Among the total of 6 trials in 4 studies, 2 studies showed that intravesical instillation of OBTX-A improved micturition frequency and urgency episode per 3 days.<sup>8,11</sup> The other 2 studies showed that none of their measurements was improved after intravesical instillation of OBTX-A.<sup>12,13</sup> All studies compared symptoms before the procedure and at 4 weeks after the procedure. Three

studies selected subjects with OAB symptoms who were over their 20s and refractory to medical treatment in both sexes.<sup>8,11,13</sup> One study selected female OAB patients.<sup>12</sup> In our study, intravesical instillation of OBTX-A showed limited efficacy to improve OAB symptoms. Although this study analyzed 7 measurement outcomes for efficacy, most of these outcomes were not improved after instillation except VV (MD:  $-38.48$ , 95% CI:  $-76.05, -0.92$ ,  $P = .045$ ). Although it was not statistically significant, urgency episode per 72 hours showed marginal efficacy of intravesical instillation of OBTX-A (MD:  $-3.91$ , 95% CI:  $-7.84$  to  $-0.03$ ,  $P = 0.052$ ).

OBTX-A acts on presynaptic neurons in cholinergic nerve terminals and blocks neurotransmitter by disrupting synaptosome-associated protein 25 (SNAP-25).<sup>15</sup> Physiological theory of intravesical instillation with OBTX-A is that it can affect bladder's smooth muscle through urothelium after pretreating the urothelium with protamine sulfate which can improve permeability of the urothelium in a rat model.<sup>16</sup> Others have also reported that dimethyl sulfoxide as a transfer agent could effectively alter the permeability and secondary delivery of intravesical agents.<sup>14</sup> However, our study proved that instillation of OBTX-A had no effect on OAB patients. OBTX-A might have failed to reach the detrusor muscle through the urothelium. This might be also due to the possibility that OBTX-A could not affect the presynaptic neuron after passing the urothelium and reaching the detrusor muscles even if a mediator exists. After OBTX-A goes in the presynaptic neuron of the bladder's smooth muscle, it will interrupt acetylcholine and cause malfunction in the pathologic contraction of the bladder's smooth.<sup>17</sup>

There were 3 meta-analyses studies about the efficacy of minimally invasive intravesical injection of OBTX-A<sup>18-20</sup> (Supplementary Table 1). One study compared the efficacy between OBTX-A injection and mirabegron (25 and 50 mg in that study).<sup>19</sup> Another study compared between OBTX-A injections and other oral therapies including anticholinergics and mirabegron.<sup>20</sup> Only 1 study compared outcomes between OBTX-A injection and the placebo.<sup>18</sup> All studies in the 3 meta-analyses measured outcomes before the procedure and at 12 weeks after the procedure. Cui et al<sup>18</sup> have included 8 articles and compared incontinence-free outcomes, mean number of UI per day, mean number of micturitions per day, maximum cystometric capacity, mean VV, PVR, UTI, and clean intermittent catheterization (CIC). Although there were clinical improvements in incontinence-free outcomes, mean UI per day, the mean number of micturitions per day, maximum cystometric capacity, and mean VV after OBTX-A injection, PVR and UTI were worsened and the frequency of CIC was increased. According to their results, it seems that OBTX-A works as an effective blocker of pathologic detrusor muscle movement which causes storage symptoms of OAB and IC/BPS. Intravesical injection of OBTX-A showed MD of VV was 33.05 (95%

**Table 1.** Characteristics of all studies included in the meta-analysis

Publication		Country	No. of Patients		Age (y)		Male/ Female		Subject Description	Type of Symptom	Experimental Description		
Author / Year	Journal		Tx	Pb	Tx	Pb	Tx	Pb			Treatment	Placebo	F/U Duration (week)
Chuang, et al (2014)	<i>The Journal of Urology</i>	Taiwan, USA	31	31	64	66	13/18	16/15	OAB >8/d, urgency or urge incontinence episode >1/d urgency severity score $\geq 2$ (based on a 3-day voiding diary)	OAB	OBTX-A 200 U/ 10 mL	N/S	4
Kuo, et al (2014)	<i>European Association of Urology</i>	Taiwan, USA	12	12	67	67	10/14 in total		Urgency frequency and/or UUI, and USS of at least 2 confirmed by a 3- day voiding diary	OAB	OBTX-A 200 U	N/S	4
Krhut, et al (2016)a	<i>Scandinavian Journal of Urology</i>	Czech Republic	9	11	52.3	52.2	0/9	0/11	OAB patients	OAB	TC-3 gel + 200 U OBTX-A	N/S	4
Krhut, et al (2016)b	<i>Scandinavian Journal of Urology</i>	Czech Republic	10	11	55.3	52.2	0/10	0/11	OAB patients	OAB	TC-3 gel + 200 U OBTX-A + DMSO	N/S	4
Chuang, et al (2017)a	<i>The Journal of Urology</i>	Taiwan	31	31	53.9	55.9	4/27	4/27	IC/BPS in whom at least 6 months of conventional treatments had failed	IC/BPS	Lipotoxin (OBTX-A 200 U with 80 mg sphingomyelin)	N/S	4
Chuang, et al (2017)b	<i>The Journal of Urology</i>	Taiwan	28	31	47.8	55.9	2/26	4/27	IC/BPS in whom at least 6 months of conventional treatments had failed	IC/BPS	OBTX-A + normal saline	N/S	4

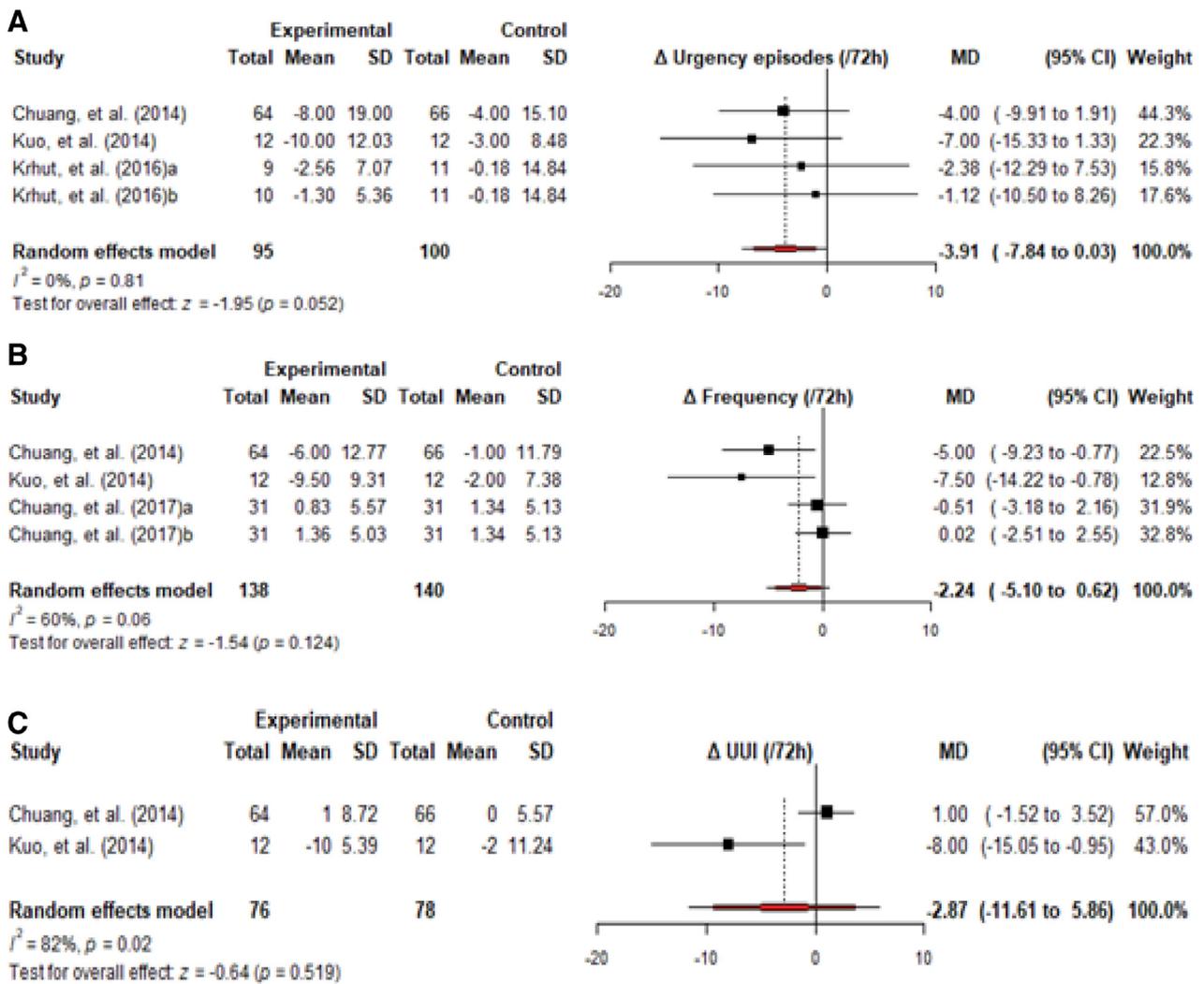
DMSO, dimethyl sulfoxide; IC/BPS, interstitial cystitis/bladder pain syndrome; N/S, normal saline; OAB, overactive bladder; OBTX-A, onabotulinum toxin-A; Pb, placebo; Tx., treatment; UUI, urgency urinary incontinence; USS, urgency severity scale.

**Table 2.** The overall effect size for each outcome

Author (Year)	No. of Patients		Weighted Mean Difference (95% CI)*						
	Tx	Pb	Δ Urgency Episodes (/72h)	Δ Frequency (/72h)	Δ UUI (/72h)	Δ VV (mL)	Δ PVR (mL)	Δ Qmax (mL/s)	PPBC
Chuang, et al (2014)	31	31	-4.00 (-9.91, 1.91)	-5.00 (-9.23, -0.77)	1.00 (-1.52, 3.52)	-	-	-	-
Kuo, et al (2014)	12	12	-7.00 (-15.33, 1.33)	-7.50 (-14.22, -0.78)	-8.00 (-15.05, -0.95)	-43.00 (-127.94, 41.94)	4.00 (-29.77, 37.77)	2.40 (-4.16, 8.96)	-
Krhut, et al (2016)a	9	11	-2.38 (-12.29, 7.53)	-	-	-33.17 (-167.11, 100.77)	-3.89 (-10.63, 2.85)	-2.11 (-11.55, 7.33)	-0.22 (-0.94, 0.50)
Krhut, et al (2016)b	10	11	-1.12 (-10.5, 8.26)	-	-	-27.90 (-127.48, 71.68)	-5.00 (-13.01, 3.01)	0.20 (-7.52, 7.92)	0.15 (-0.66, 0.96)
Chuang, et al (2017)a	31	31	-	-0.51 (-3.18, 2.16)	-	-18.96 (-85.24, 47.32)	0.45 (-41.81, 42.71)	2.23 (-2.39, 6.85)	-
Chuang, et al (2017)b	28	31	-	0.02 (-2.51, 2.55)	-	-66.38 (-139.75, 6.99)	-18.17 (-58.31, 21.97)	-2.46 (-7.18, 2.26)	-
Overall effect	121	127	-3.91 (-7.84, 0.03)	-2.24 (-5.10, 0.62)	-2.87 (-11.61, 5.86)	-38.48 (-76.05, -0.92)	-4.31 (-9.34, 0.71)	0.21 (-2.44, 2.85)	-0.06 (-0.59, 0.48)
<i>P</i> value			0.052	0.124	0.519	0.045	0.092	0.879	0.838
Heterogeneity — <i>I</i> <sup>2</sup> (%)			0.0 (0.0, 52.2)	60.5 (0.0, 86.8)	82.0 (23.8, 95.7)	0.0 (0.0, 12.3)	0.0 (0.0, 0.0)	0.0 (0.0, 68.3)	0 (0.0, NA)
<i>P</i> value			0.811	0.055	0.019	0.917	0.941	0.623	0.502

CI, confidence interval; NA, not available; PPBC, patient perception of bladder condition; PVR, postvoid volume; Qmax, maximum flow rate; VV, voided volume.

\* The process of meta-analysis with paired difference data: estimates using the Hedge's corrected standardized mean difference assuming the random-effect model.



**Figure 1.** Forest pilots of urgency episode per 72 hours, frequency per 72 hours, and urinary urge incontinence (UUI) per 72 hours. The black square signifies weighted mean of each estimate. All data pertain to continuous outcomes. (Color version available online.)

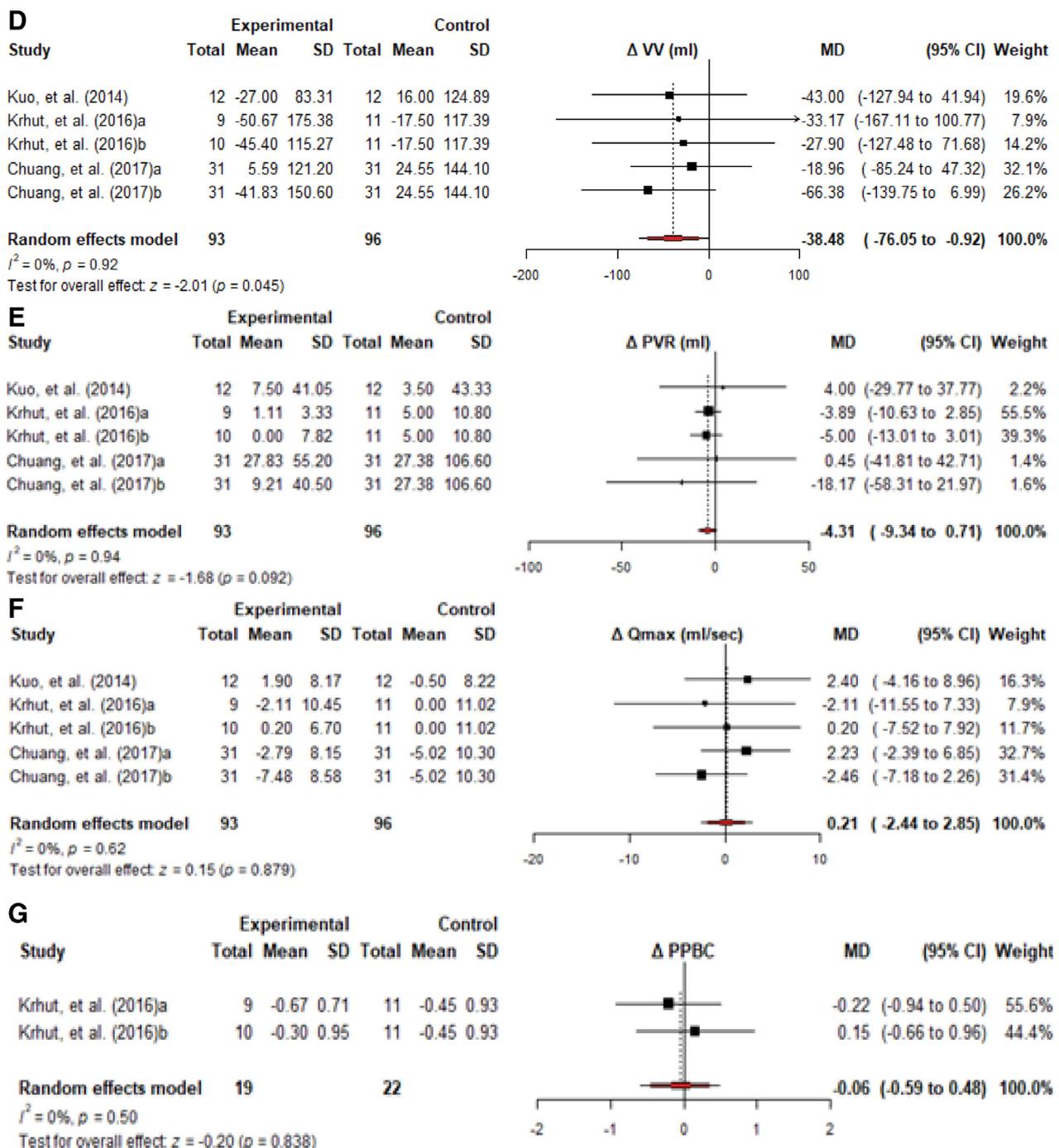
CI: 22.45-43.66),<sup>18</sup> and in our study, MD of VV was  $-38.48$  (95% CI:  $-76.05, -0.92$ ) in the intravesical instillation study, which was similar to that of intravesical injection. Moreover, there were no severe adverse events including performance of CIC.

This study clearly showed that there is a limitation in efficacy of noninvasive intravesical instillation of OBTX-A in those patients. To overcome the limitation, there has to be innovative drug transport method.

Several studies have investigated whether intravesical instillation of OBTX-A using liposome would be an alternative method for intravesical injection form. Fraser et al.<sup>21</sup> have reported that instillation of liposome can affect IC/BPS symptoms by improving the barrier function of urothelium and bladder contraction. One pathogenesis theory of IC/BPS is that urothelial malfunctioning permits transition of an irritant which affects the nerve in bladder smooth muscle and causes bladder pain or urinary frequency. Intravesical

instillation liposome links into malfunctioning urothelium and functions as a barrier that blocks irritants. In 2 studies,<sup>8,11</sup> liposome was used drug intravesical instillation of OBTX-A to deliver OBTX-A to the detrusor muscle, which studies showed clinical efficacy in VV using liposome transport method.

This study has several limitations. First, because there are few studies about intravesical instillation of OBTX-A, the number of subjects was relatively smaller than that of other meta-analysis. Second, there are no long-term follow-up studies, which was shorter than postoperative 3 months. Finally, there exists a quite heterogeneity in patient group including age, disease, and so on. For heterogeneity issue, There was inconsistent strategy during combination of mixture for saline and OBTX. Krhut et al used combination OBTX-A 2 cc added saline 48 cc and others used combination OBTX-A 10 cc added saline or other media 40 cc. Moreover, there was different target disease including interstitial cystitis/bladder



**Figure 2.** Forest plot of voided volume (VV), postvoid residual volume (PVR), maximum flow rate (Qmax), and patient perception of bladder condition (PPBC). The black square signifies weighted mean of each estimate. All data pertain to continuous outcomes. (Color version available online.)

pain syndrome and OAB. However, all the studies have urgency episode per 72 hours, frequency per 72 hours, VV and post-VV as main outcomes. These outcomes are appropriate variables to analyze the efficacy and safety of OBTX.

In conclusion, intravesical instillation of OBTX-A remains controversial showing limited efficacy to treat OAB or IC/BPS. More studies are needed regarding intravesical instillation of OBTX-A in OAB or IC/BPS

refractory to medication therapy or regarding investigating alternative transport method to overcome current intravesical instillation form.

## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.urology.2018.11.037>.

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