ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑ

ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

"Research Methodology in Biomedicine, Biostatistics and Clinical Bioinformatics "

"Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Κλινική Βιοπληροφορική"

ΜΕΤΑΠΤΥΧΙΑΚΗ ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

ΘΕΜΑ:

"Evaluation and meta-analysis of RCTs for the treatment and management of neurogenic bladder"

"Εκτίμηση και μετα-ανάλυση τυχαιοποιημένων κλινικών δοκιμών για τη θεραπεία και τη διαχείριση της νευρογενούς κύστης"

Υπό:

Κωνσταντίνο Τασούδη του Βασιλείου

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Στην οικογένειά μου, το θεμέλιο της ζωής μου, ευχαριστώ για την απέραντη αγάπη και στήριξη που μου προσφέρετε καθημερινά. Η κάθε στιγμή μαζί σας είναι ανεκτίμητη, και η παρουσία σας μου δίνει δύναμη και φως σε κάθε βήμα. Είστε οι άνθρωποί μου, το στήριγμά μου, η πηγή της χαράς μου, και σας ευχαριστώ με όλη μου την καρδιά που είστε δίπλα μου. Χωρίς εσάς τίποτα δεν θα ήταν το ίδιο ούτε θα είχε την ίδια αξία. Σας αγαπώ και σας τιμώ για όλα όσα είστε και κάνετε για μένα.

Abstract

Background: Lower Urinary Tract (LUT) dysfunctions affect millions of patients globally. LUT dysfunctions are really common in patients with neurological diseases. Worldwide, subtype A of Botulinum Toxin A (BTXA) is used regularly in order to treat these disorders.

Introduction: LUT dysfunctions have various patterns of expression. The most prevalent of these is Neurogenic Detrusor Overactivity (NDO), which is strongly associated with neurological diseases and can significantly impact a patient's life.

Objective: Onabotulinumtoxin A is a widely used drug for the treatment of neurogenic bladder. The purpose of this study is to evaluate its efficacy and safety across different dosages in patients with neurogenic bladder.

Data sources: Pubmed, Scopus, Web of Science

Review Methods: Systematic literature review was performed to identify randomized, double-blind, placebo-controlled trials of onabotulinumtoxin A for NDO. Seven randomized controlled trials were incorporated in this meta-analysis. The primary outcome concerned urodynamic parameters including Maximum Cystometric Capacity (MCC) and Maximum Detrusor Pressure (MDP); the mean number of Urinary Incontinence (UI) episodes per week was also assessed. Safety was evaluated by the incidence of various Adverse Events (AE). Data was extracted by one author and statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS v.29).

Results: Seven RCTs involving 1592 patients in total were included in the study, following screening of 1602 potentially relevant articles. The Onabotulinumtoxin A- treated groups showed a significant increase in MCC (Mean Difference (MD): 128.866, 95% Confidence Interval (CI): 98.836, 158.896, $p<0.001$, in the group that received 200 Units of Onabotulinumtoxin A; MD: 151.389, CI: 106.006, 196.773, $p<0.005$, in the group that received 300Units of Onabotulinumtoxin A). There was also a significant decrease in MDP in the Onabotulinumtoxin A-treated groups (MD: -29.051, CI: -39.557, -18.545, $p<0.002$, 200U group; MD: -31.751, CI: -45.226, -18.276, $p<0.01$, 300U group). Additionally, no effect was noticed in the mean number of UI episodes per week (MD: -10.69, 95% CI: -33.86, 12.49, $p=0.11$; MD: -10.55, 95% CI: -59.06,

37.97, p= 0.22, 200U and 300U respectively). Taking AEs into consideration, Onabotulinumtoxin A-treated groups were often associated with more complications , including urinary tract infections (UTI) (LogOR: 0.341, CI: 0.011, 0.67, p=0.045, 200U group; LogOR: 0.424, CI: 0.075, 0.773, p=0.028, 300U group) and urinary retention (UR) (LogOR: 1.746, CI: 0.869, 2.623, p=0.008, 200U group; LogOR: 1.879, CI: 0.679, 3.078, p=0.021, 300U group).

Conclusions: Our meta-analyses found that Onabotulinumtoxin A can be beneficial in improving the urodynamic parameters (MCC and MDP). As far as safety is concerned, the drug-treated groups had a slightly higher likelihood for developing UTI or UR.

Περίληψη

Εισαγωγή: Οι επιπλοκές της κατώτερης ουροποιητικής οδού μπορούν να προκύψουν με διαφορετικά μοτίβα. Το πιο συχνό μοτίβο, που σχετίζεται άμεσα με τα νευρολογικά νοσήματα, αφορά την υπερδραστηριότητα του εξωστήρα μυ της κύστης που έχει σαν αποτέλεσμα την αυξημένη πίεση μέσα στην κύστη.

Στόχοι: Ο σκοπός αυτής της μελέτης είναι να εκτιμήσει την αποτελεσματικότητα και την ασφάλεια του φαρμάκου OnabotulinumtoxinA στη θεραπεία της νευρογενούς κύστης.

Μέθοδοι: Πραγματοποιήθηκε βιβλιογραφική ανασκόπηση σε τρεις βάσεις δεδομένων (Pubmed, Scopus, Web of science) με σκοπό την εύρεση τυχαιοποιημένων, διπλών τυφλών ,κλινικών μελετών που συγκρίνουν την OnabotulinumtoxinA με ένα control group για τη θεραπεία της νευρογενούς κύστης. Η ανασκόπηση ανέδειξε 7 μελέτες που ήταν κατάλληλες για να εισαχθούν στην παρούσα μετα-ανάλυση. Το πρωταρχικό αποτέλεσμα που θέλαμε να αναδείξουμε είναι ότι το φάρμακο αυτό βελτιώνει τις ουροδυναμικές παραμέτρους των ασθενών και κατ΄επέκταση την επιτακτική τους ανάγκη για ούρηση. Επιπλέον ελέγξαμε την ασφάλεια του φαρμάκου συγκρίνοντας την συχνότητα των πιο συχνών επιπλοκών που προέκυψαν μεταξύ των ατόμων που έλαβαν το φάρμακο και αυτών που δεν το έλαβαν. Η εξαγωγή των δεδομένων έγινε από έναν συγγραφέα και η στατιστική ανάλυση των δεδομένων πραγματοποιήθηκε απ΄το πρόγραμμα SPSS.

Αποτελέσματα: Εφτά μελέτες , με σύνολο ασθενών 1.592 άτομα, συμπεριλήφθηκαν στην μελέτη αφού πραγματοποιήθηκε έλεγχος 1.602 άρθρων που μπορεί να ήταν σχετικά με το θέμα μας. Οι ασθενείς που έλαβαν το φάρμακο, είτε στα 200U είτε στα 300U, παρουσίασαν σημαντική βελτίωση στις ουροδυναμικές παραμέτρους τους όχι όμως και στην ανάγκη για επιτακτική ούρηση, σε σύγκριση με αυτούς που δεν το έλαβαν. Επιπροσθέτως, τα άτομα που έλαβαν το φάρμακο παρουσίασαν τις πιο συχνές επιπλοκές σε στατιστικά μεγαλύτερη συχνότητα σε σχέση με αυτούς που δεν το έλαβαν.

Συμπεράσματα: Η μελέτη μας υποστηρίζει πως η OnabotulinumtoxinA αποτελεί ένα πολύ καλό φάρμακο για τη θεραπεία της υπερδραστηριότητας του εξωστήρα μυ της κύστης σε ασθενείς με νευρολογικά προβλήματα. Το όφελος του φαρμάκου μπορεί να υπερκεράσει τις επιπλοκές που προκαλεί.

Introduction

The neurological system regulates the lower urinary tract's two primary processes: effective emptying and low-pressure storage. Any damage or injury to this system may lead to a dysfunction, a condition known as neurogenic bladder (NGB) [1]. NGB can be expressed through various patterns, but the most prevalent of them is NDO, which is strongly associated with neurological diseases such as Multiple Sclerosis (MS), Parkinson's disease (PD) cerebrovascular accident/stroke, Spinal Cord injury (SCI) and spina bifida [2,3]. The urodynamic profile of NDO patients involves elevated bladder pressures, low bladder capacity and consequently urge UI symptoms [4]. These symptoms are preceded by a strong urge to urinate and contain increased urinary frequency, urgency and leakage [5]. Patients experience intense stress and suffering, which has a significant repercussion on their social lives and mental well-being. Thus, they tend to isolate, experience low self-esteem and subsequently limit their participation in social activities[6,7].

Non-surgical management options for NGB include anticholinergic drug as first-line treatment. Nonetheless, lower tolerance of the drugs has been reported because of the bothersome side effects of the drugs, which include muscle weakness, depression, dry mouth, UTI etc [8]. Botulinum toxin (BTX) was first described by van Ermengem in 1897 and is considered to be the second-line drug therapy for NGB. It controls the release of Ach at the presynaptic cholinergic junction and prevents the muscle from contracting[9]. Results have shown that BTXA has a great efficacy in NDO when given in a single dose of 100-300U, though the optimal dose is yet to be defined. Side effects are very uncommon and even when they do occur, they are not dangerous. Most commonly, hematuria and pain have been reported shortly after BTXA injection. Further studies and research is required, but we can say with reasonably high certainty that BTXA is a proven, secure and efficient treatment[10]. In our study, we evaluated the efficacy and safety of OnabotulinumtoxinA across various dosages for treating patients with NDO. We hope that the results will contribute to the establishment of this drug as a safe and effective treatment in the management of patients with NGB.

Materials and Methods

Search strategy

This review was reported and developed using the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines[11]. The review was not registered. Three electronic databases, including PubMed, Web of Science and Scopus were searched from database inception to 30 September 2024. Search terms for the review were divided into three themes, incorporating NGB, treatment and study design. The Boolean operator "OR" was utilized to connect the specified search phrases within each distinct theme, while "AND" was used to combine the three themes together. Search terms were as follows: {"neurogenic detrusor overactivity OR neurogenic bladder OR lower tract dysfunction OR urge urinary incontinence OR overactive bladder" AND "botulinumtoxin A OR onabotulinumtoxin A OR abobotulinumtoxin A" AND "RCT OR randomized controlled trial"}. The selection of the studies for this review was based on the PICOS (population, intervention, outcome, study design) agenda [12].

Inclusion criteria and study selection

Studies were enrolled in this review if the following criteria were met: 1) studies were double blind placebo-controlled randomized trials, 2) included adults of both sexes with NGB due to neurological diseases such as Multiple Sclerosis, Parkinson's disease, Spinal Cord Injury, ischemic stroke, 3) involved intervention with Onabotulinumtoxin A at 200U or 300U, 4) outcome measure were urodynamic parameters as well as the UI episodes, 5) accurate data were available for analysis. Studies were excluded if they: 1) were published as non-English studies, 2) were study protocols, 3) were not completed for various reasons. We carefully reviewed tittles, abstracts and full texts of the articles. Data collection was carried out by one author. If the articles selected did not report all the data, we attempted to communicate with the authors and ask for the research details and digital data. Duplicate references were deleted. The full texts of the selected articles were retrieved in order to extract relevant information and determine whether the paper was eligible for inclusion. A PRISMA flow diagram shows the process that was followed to select the studies.

Data extraction

Data extraction was carried out by one author. From each study we utilized we gathered the following information: first author, year of publication of the study, number of participants, neurogenic disorders, study design, intervention-control, participant characteristics (mean age and standard deviation (SD)) and sample size of each group.

Quality assessment

One author assessed the methodological quality of the included studies using the PEDro scale. Reports indicate that PEDro is a solid and trustworthy tool for assessing the methodological quality[13] involving an 11-question checklist: the first question evaluates external validity, questions 2-9 evaluate internal validity and questions 10-11 evaluate internal interpretability [14]. The PEDro score for the included studies is shown in Table 1. Publication bias was measured using funnel plot and Egger's test was conducted. Where statistical significance is discovered through Egger's test, it is reported. Studies that presented high risk of bias were not excluded.

First author	Eligibility	Random allocation	Conceal allocation	Baseline similar	Subject blinding	Therapist blinding	Assessor blinding	Adequate follow up	Intention-to-treat analysis	Between-group comparison	Points estimate	PEDro score
Schurch B., et al.[15]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Cruz F., et al.[16]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	10
Herschorn S., et al[17]	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	9
Ginsberg D., et al.[18]	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	8
Rovner E., et al.[19]	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	9
Apostolidis A., et al.[20]	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	9
Honda M., et al.[21]	Y	Y	N	Y	Y	Y	N	Y	N	Y	Y	8

Table 1. PEDro score of the included studies

Data analysis

Meta-analysis of the involved studies was conducted using SPSS v.29. Similar interventions and outcome measures from each study were pooled together. Mean Difference (effect size) and 95% CI were used to evaluate the intervention effect of continuous outcomes. Moreover, in consideration of the heterogeneity among the studies the Random-effects model was used regardless of the I square statistic, Q statistic, H or Tau squared. In order to evaluate the incidence of the various AE we used the LogOR[†] (effect size) and Random-effects model. Random-effects model was preferred because it allows us to take into account of the study-to-study variance, to assess the dispersion in effect size across studies and to generalize from the studies in the analysis to the universe of comparable studies, which is what we intend to do.

Results

Study selection

In total, 1602 articles in electronic databases were located as being possibly relevant (1315 PubMed, 162 Scopus, 125 Web of Science). One author carefully retrieved 33 articles from the electronic database search, based on titles and abstract. After the removal of 13 duplicates, we assessed 20 papers. Thirteen of the twenty were excluded for the following reasons: five because they used higher dosages of BTXA, four because they assessed Quality of Life, and four because they were either protocols or could not be completed due to the Covid pandemic. The remaining seven papers utilized in our meta-analysis were double blind, randomized, placebo-controlled trials which used Onabotulinumtoxin A across various dosages (200U and 300U) and enrolled 1592 patients in total. The selection process for the RCTs included and their characteristics are shown in Figure 1 and Table 2 respectively.

[†]LogOR (Logarithm of Odds Ratio): Because we are interested in the incidence of AEs a positive LogOR indicates that the risk of AE is higher in the numerator (treatment group) in our case.

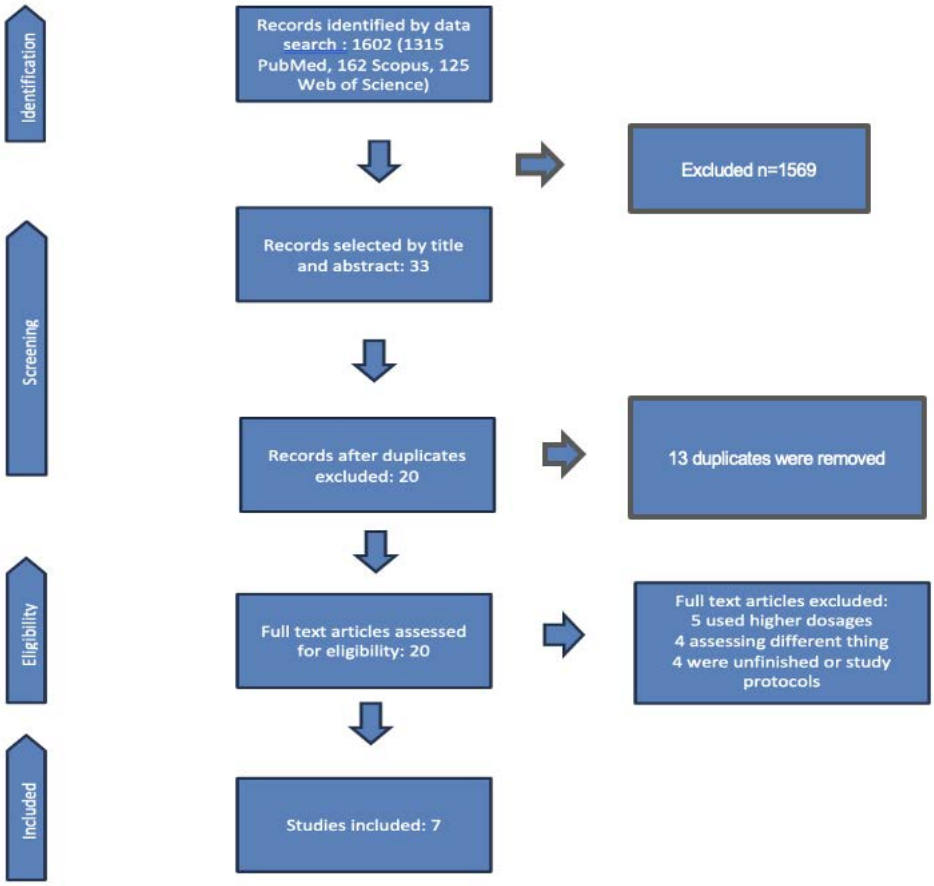


Figure 1. Flowchart of screened studies

First author	Year	Country	Study design	No. of patients	Mean age	Gender (Male%)	Intervention	Control	Drop out (patients)	Follow up (weeks)
Schurch B., et al.[15]	2005	Belgium, France, Switzerland	Double blind, randomized, placebo control	59 (53 SCI, 6 MS)	41 yrs (range 20-72)	39%	200 U: n=19, 300 U: n=19	Placebo: n=21	2	2-6-12-18-24
Cruz F., et al.[16]	2011	Europe, North America, Latin America, South Africa	Double blind, randomized, placebo control	275 (121 SCI, 154 MS)	46 yrs (range 18-80)	46,70%	200 U: n=92, 300 U: n=91	Placebo: n=92	45	2-6-12-52
Herschorn S., et al.[17]	2011	Canada	Double blind, randomized, placebo control	57 (19 SCI, 38 MS)	43 yrs (range 32-50)	60%	300 U: n=28	Placebo: n=29	9	6-24-36-48-60
Ginsberg D., et al.[18]	2012	Europe, USA	Double blind, randomized, placebo control	416 (189 SCI, 227 MS)	46 yrs (range 18-80)	41%	200 U: n=135, 300 U: n=132	Placebo: n=149	87	2-6-12-52
Rovner E., et al.[19]	2013	USA	Double blind, randomized, placebo control	691 (310 SCI, 381 MS)	46 yrs (range 18-80)	42%	200 U: n=241, 300 U: n= 227	Placebo: n=223	14	2-6-12-52
Apostolidis A., et al.[20]	2012	Turkey, Greece, Serbia, Lebanon, Egypt, India	Double blind, randomized, placebo control	73 (73 SCI)	34 yrs (range 18-75)	85%	200 U: n= 17, 100 U: n= 21, 50 U: n= 19	Placebo: n=16	11	2-6-12-54
Honda M., et al.[21]	2021	Japan	Double blind, randomized, placebo control	21 (21 SCI)	49 yrs (range 20-80)	81%	200 U: n= 11	Placebo: n=10	0	2-6-12-48

Table 2. Characteristics of the included studies

Efficacy

Change from baseline at week 6 for the urodynamic parameters was the primary efficacy measurement. Additionally, change of the mean number of UI weekly episodes was measured as a secondary efficacy point. Efficacy analyses were conducted on the intent-to-treat population (all randomized patients).

Urodynamic parameters

Regarding MCC we included five studies[16,18–21] at 200U group vs placebo in pooled analysis and three studies[16,18,19] at 300U group vs placebo in pooled analysis. From these studies we analysed the reported data for MCC at week 6. The infusion parameters that were used in the incorporated trials involved 30 intradetrusor injections via cystoscopy that spared the trigone. Urodynamic parameters in this meta-analysis displayed great improvement for the BTXA groups compared to the placebo group. There was a significant increase in MCC (MD: 128.866, 95% CI: 98.836, 158.896, p<0.001; MD: 151.389, 95% CI: 106.006, 196.773, p=0.005, 200U and 300U group respectively). It is worth noting that Egger's test was found to be statistically significant p=0.013 at 200U group vs placebo, and therefore significant publication bias was displayed. Forest and funnel plots for both groups are presented below. Furthermore, MDP at week 6 was assessed in the pooled analysis. For this analysis five trials[16,18–21]were utilized at 200U group vs placebo and three trials[16,18,19] at 300U group vs placebo. Results suggest that there was a significant decrease in MDP for both BTXA groups compared to placebo (MD: -29.051, 95% CI: -39.557, -18.545, p=0.002; MD: -31.751, 95% CI: -45.226, -18.276, p=0.01, 200U group and 300U group respectively). Forest and funnel plots for both groups are presented below. One more time we had publication bias at 200U group vs placebo because Egger's test was found to be statistically significant p=0.029. Findings above suggest that even at varying dosages BTXA significantly improves urodynamic parameters in patients.

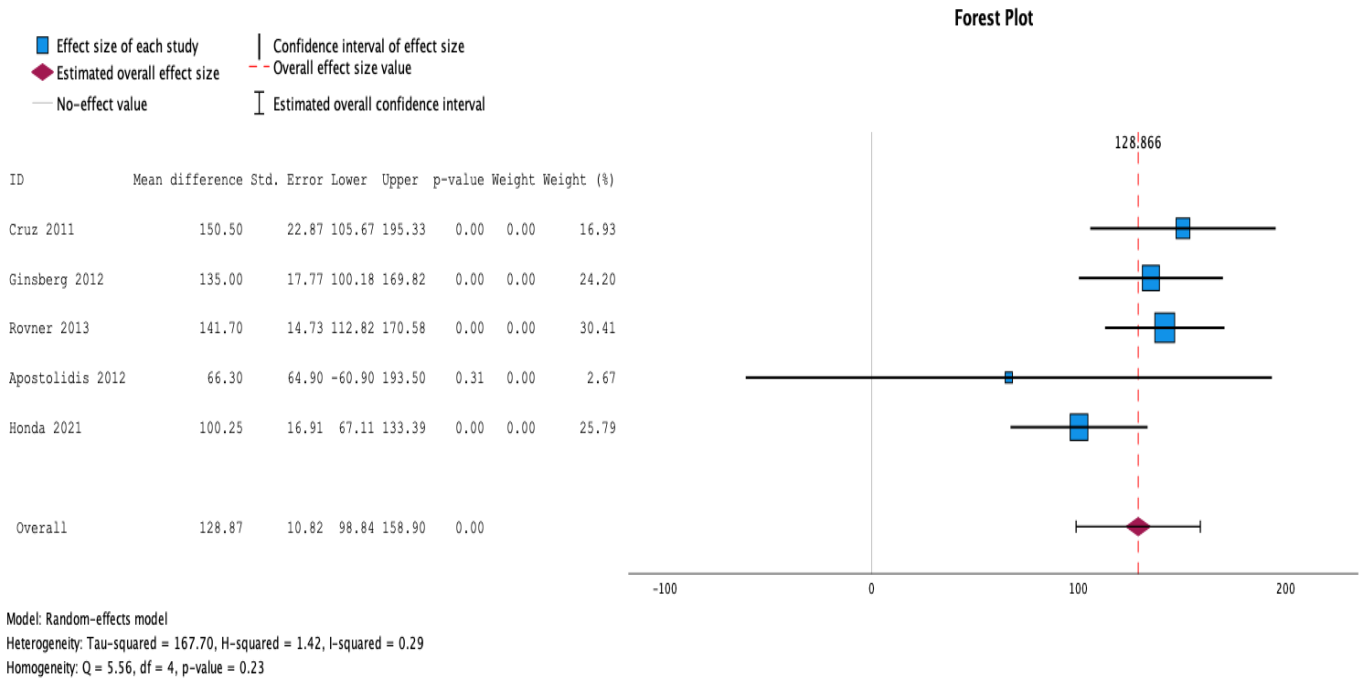


Figure 2. Forest Plot MCC urodynamic parameter of 200U group vs placebo. Pooled analysis revealed significant increase in MCC for the intervention group compared with the control group.

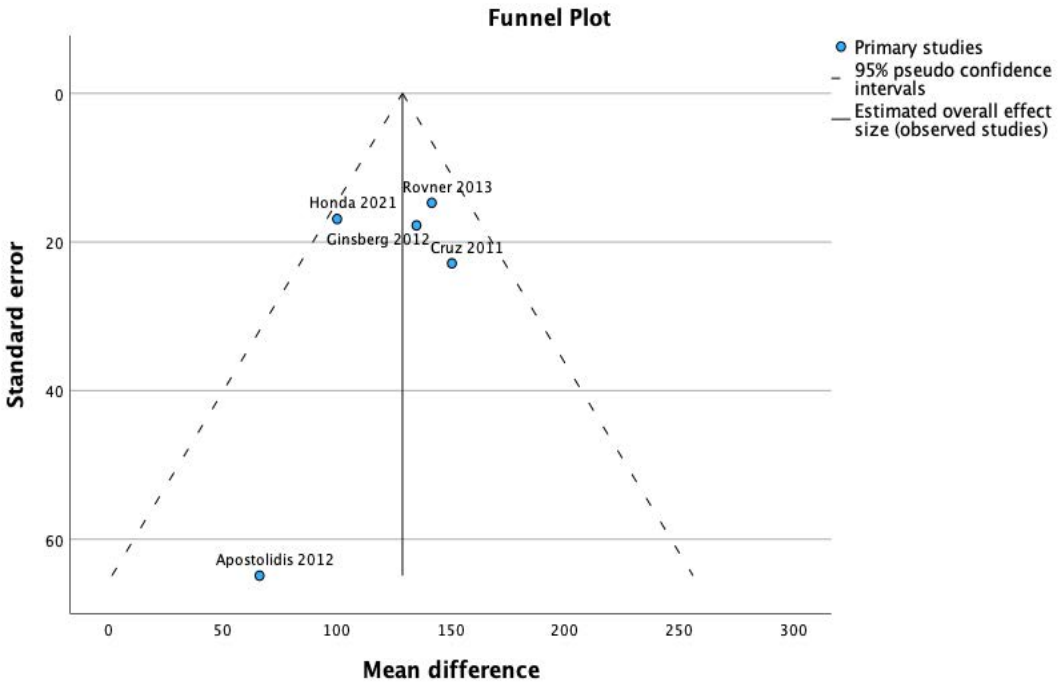


Figure 3. Funnel Plot MCC 200U group vs placebo. Studies are not evenly spread on both sides of the average or plotted near the average, hence publication bias is indicated.

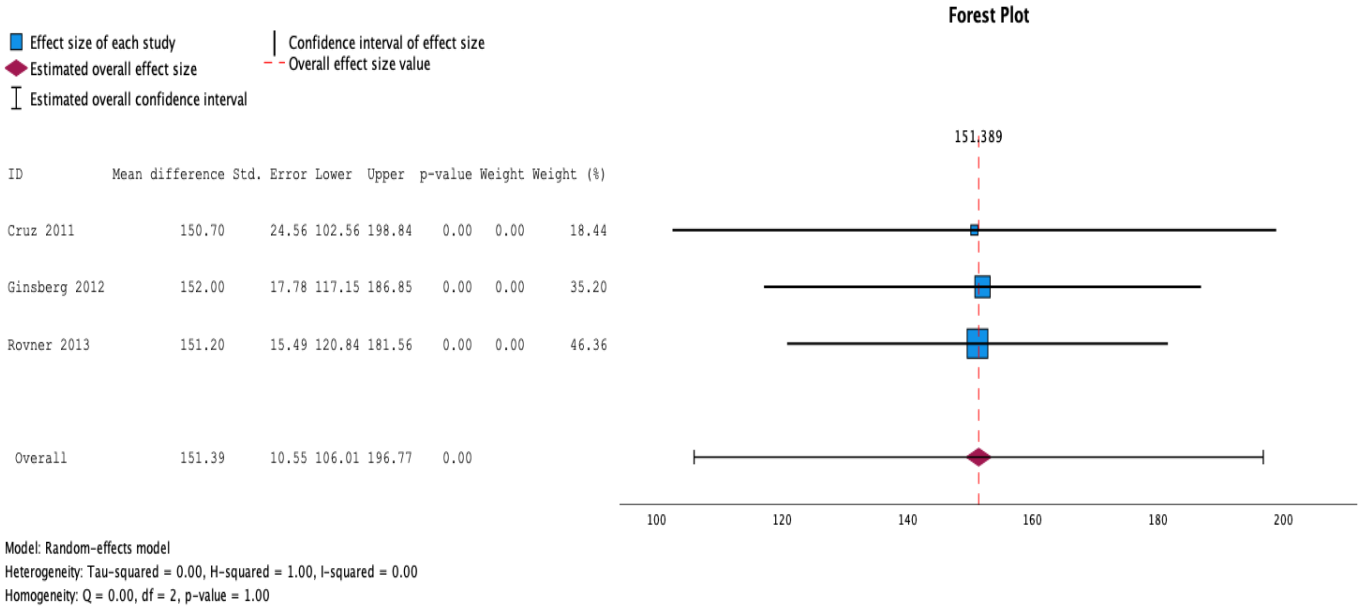


Figure 4. Forest Plot MCC; 300U group vs placebo also indicates that there was a significant increase in MCC for the intervention group compared to placebo.

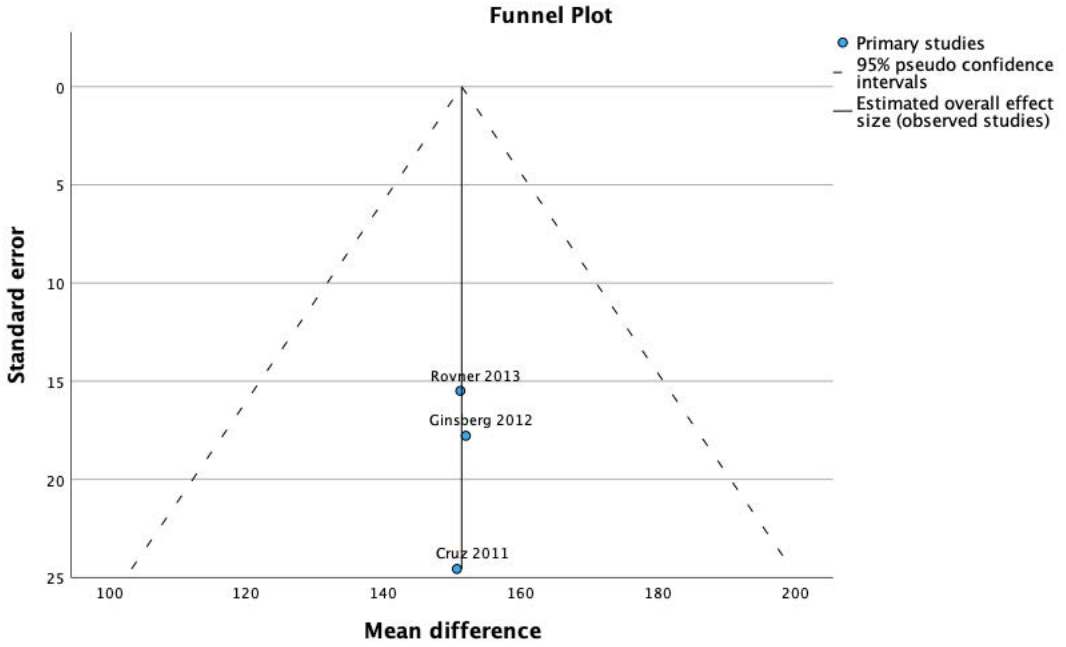
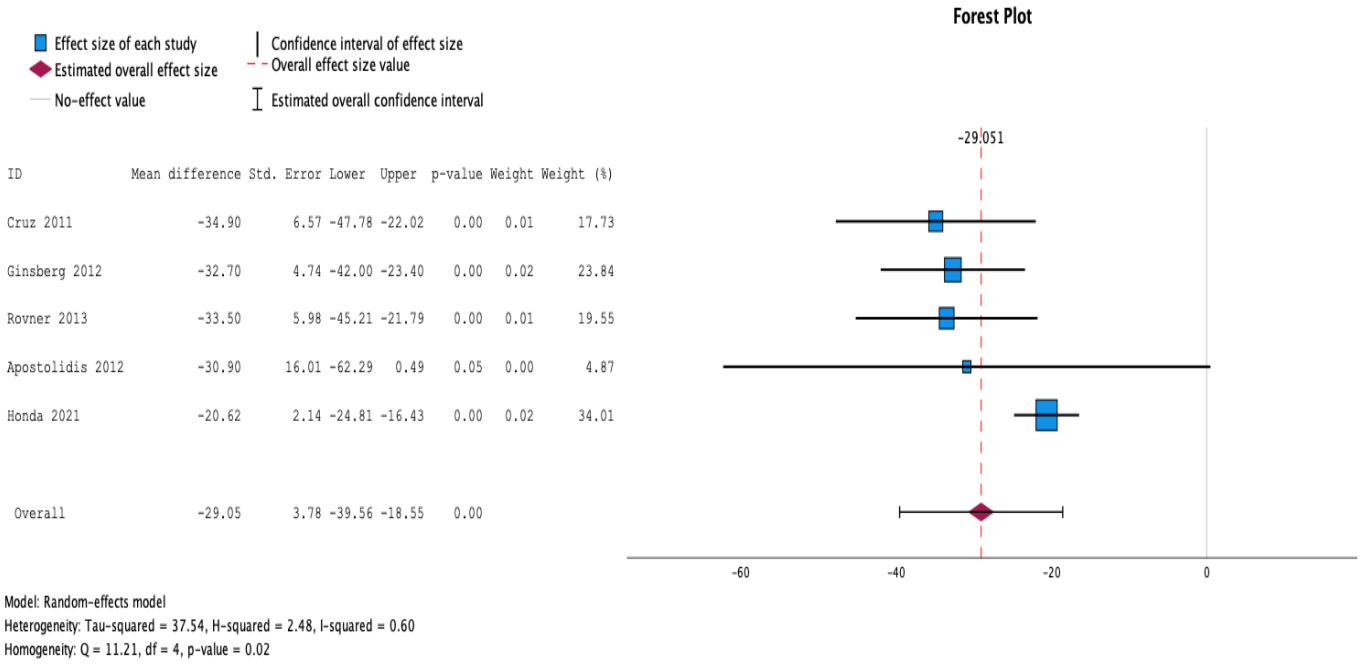


Figure 5. Funnel Plot MCC 300U group vs placebo. Studies are plotted on the average.



ID	Mean difference	Std. Error	Lower	Upper	p-value	Weight	Weight (%)
Cruz 2011	-34.90	6.57	-47.78	-22.02	0.00	0.01	17.73
Ginsberg 2012	-32.70	4.74	-42.00	-23.40	0.00	0.02	23.84
Rovner 2013	-33.50	5.98	-45.21	-21.79	0.00	0.01	19.55
Apostolidis 2012	-30.90	16.01	-62.29	0.49	0.05	0.00	4.87
Honda 2021	-20.62	2.14	-24.81	-16.43	0.00	0.02	34.01
Overall	-29.05	3.78	-39.56	-18.55	0.00		

Figure 6. Forest Plot MDP urodynamic parameter 200U group vs placebo. Pooled analysis revealed significant decrease in MDP for the intervention group compared with the placebo.

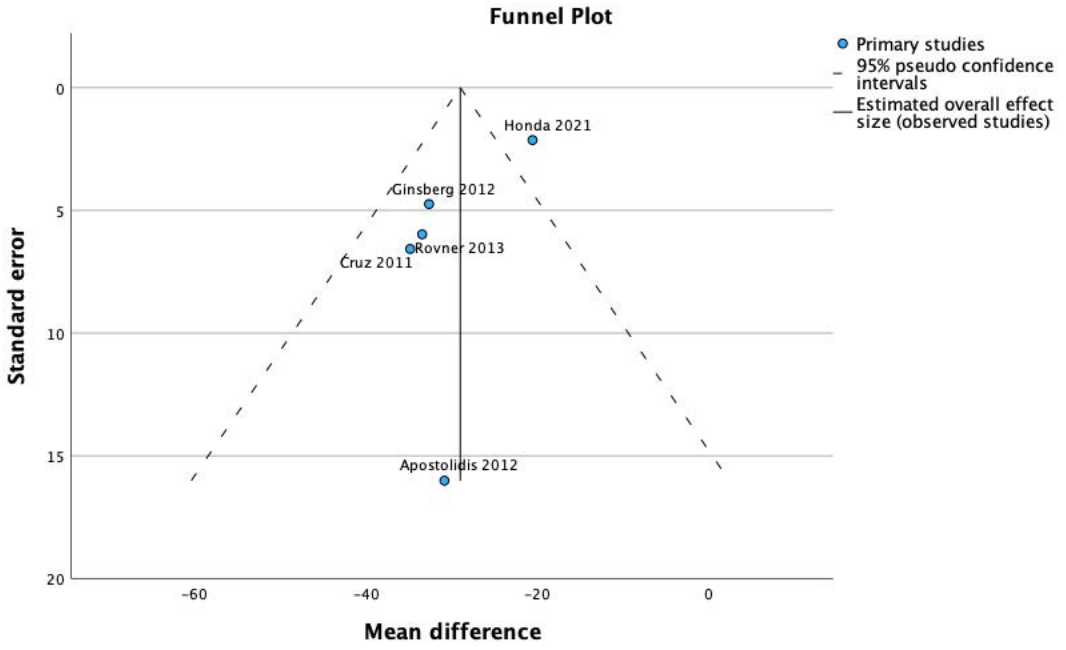


Figure 7. Funnel Plot 200U group vs placebo. Studies are not evenly spread on both sides of the average or plotted near the average, hence publication bias is indicated.

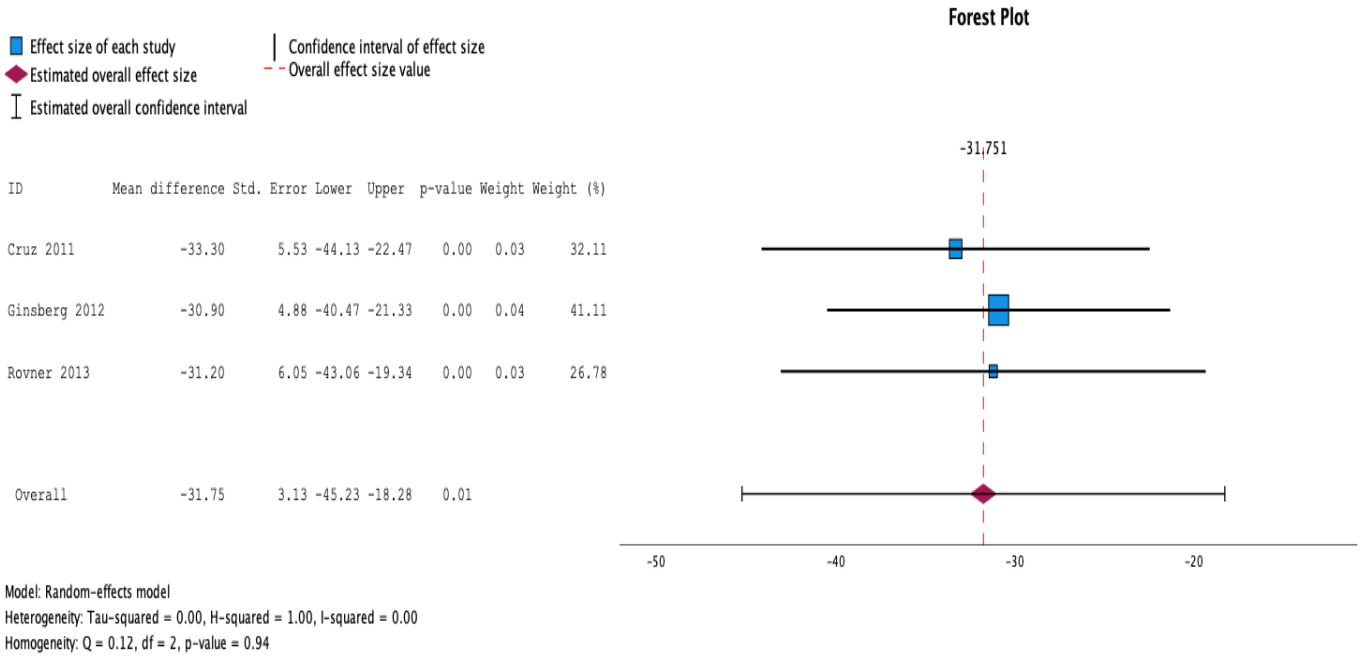


Figure 8. Forest Plot MDP urodynamic parameter 300U group vs placebo. Pooled analysis revealed significant decrease in MDP for the intervention group compared with the placebo.

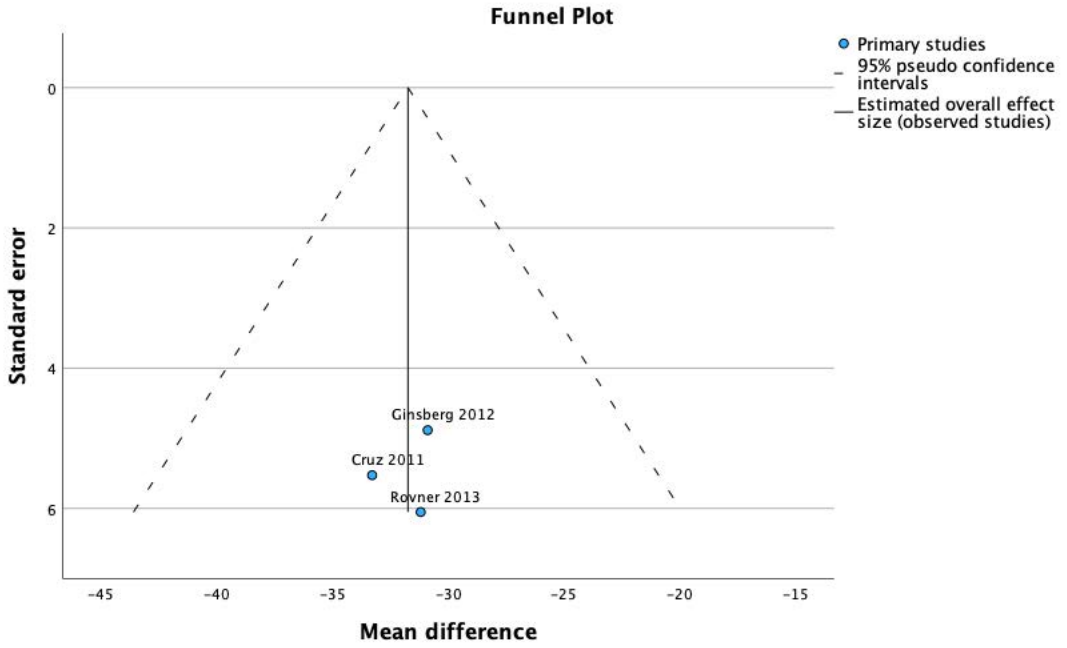


Figure 9. Funnel Plot MDP 300U group vs placebo. Studies are plotted near the average.

UI episodes per week

Only a small number of studies recorded weekly UI episodes, and among those, even fewer provided complete data such as Standard Deviation (SD). Unfortunately, as far as we are concerned, we only managed to gather only two studies[16,18] for meta-analysis. Despite the limited number of studies, we have analyzed them and obtained the results below. There was no statistically significant change in the mean number of UI episodes per week in either the 200U vs placebo or the 300U vs placebo groups (MD: -10.69, 95% CI: -33.86, 12.49, p=0.11; MD: -10.55, 95% CI: -59.06, 37.97, p= 0.22, 200U and 300U respectively). Although urodynamic parameters displayed great change, it is highly possible that UI episodes per week did not exhibit a significant change in BTXA versus placebo groups because of the limited studies included in the pooled analysis. Publication bias could not be measured through Egger's test. Forest and funnel plots for both groups are presented below.

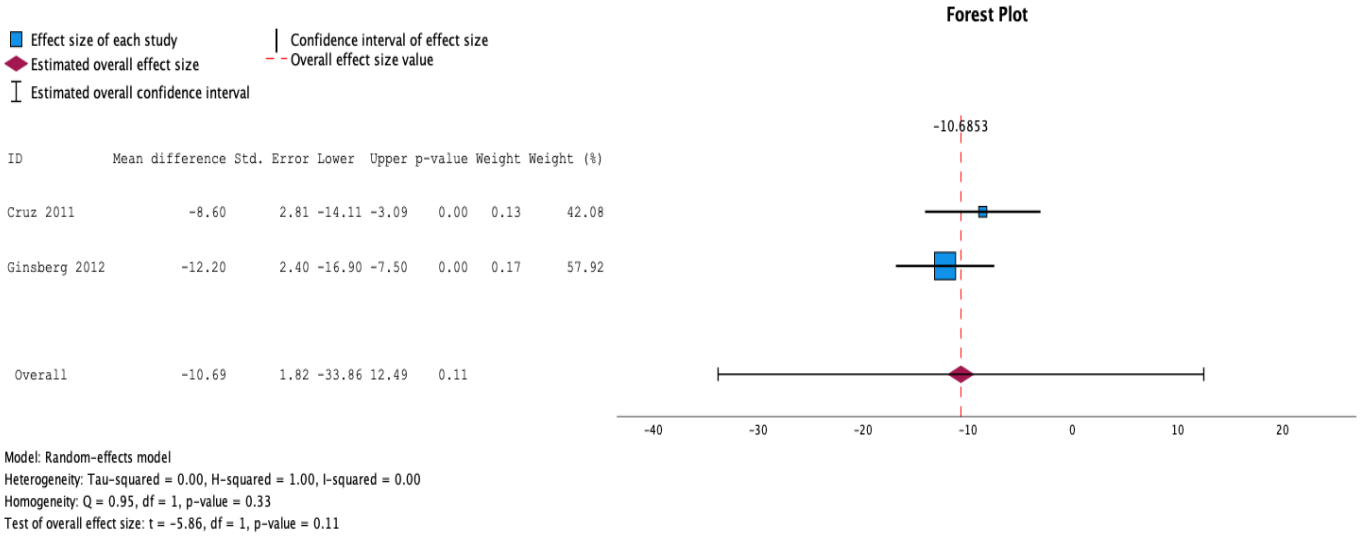


Figure 10. Forest Plot UI episodes per week 200U group vs placebo. Meta-analysis did not reveal any significant change in UI episodes per week probably due to the small number of the studies that were analyzed.

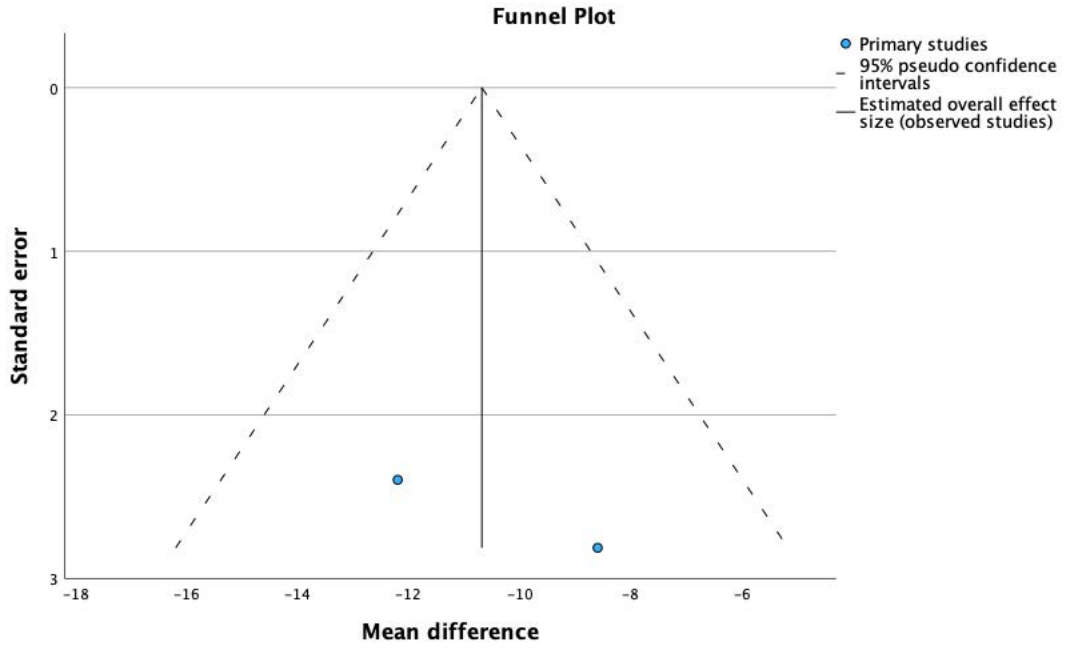


Figure 11. Funnel Plot UI episodes per week 200U group vs placebo. Publication bias could not be assessed due to the small number of the included studies.

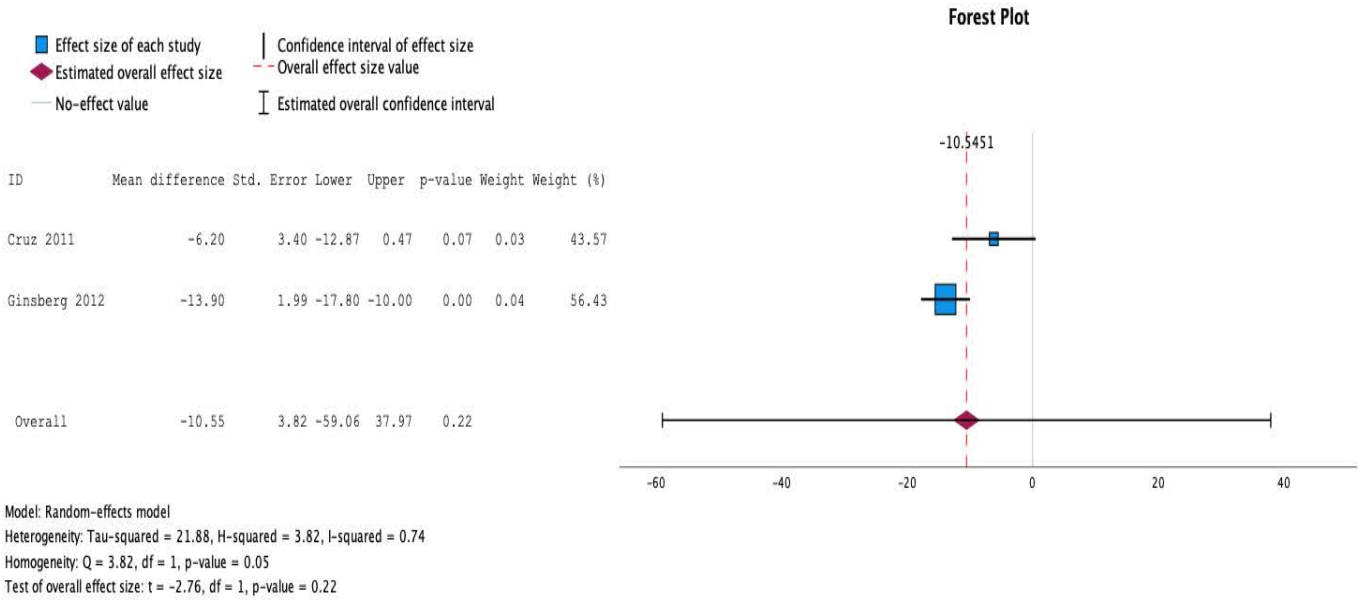


Figure 12. Forest Plot UI episodes per week 300U group vs placebo. Meta-analysis did not reveal any significant change in UI episodes per week probably due to the small number of the studies that were analyzed.

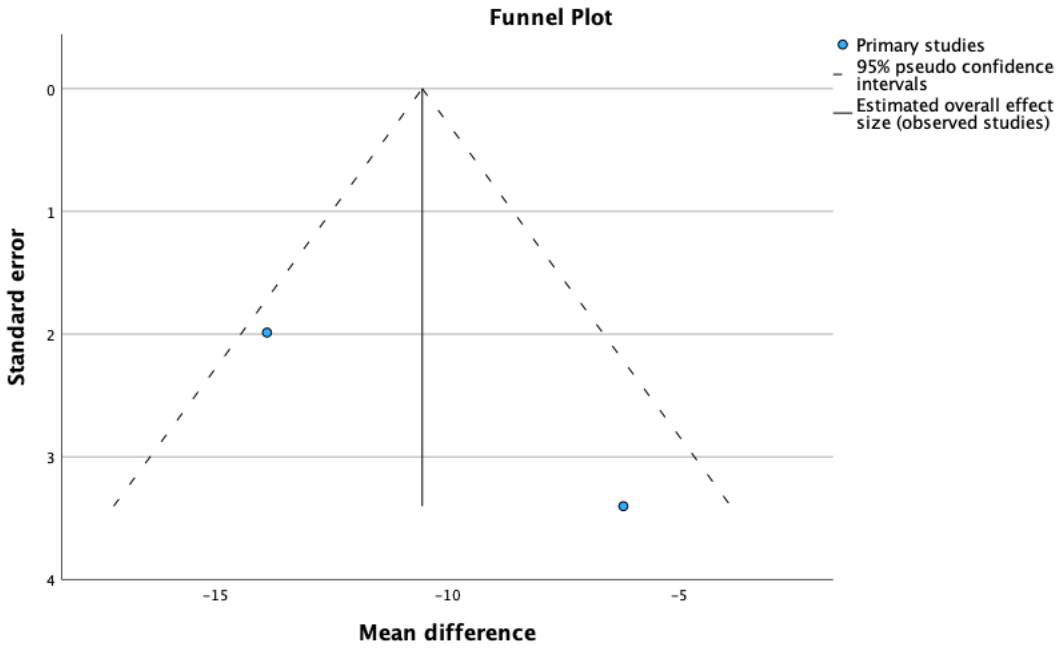


Figure 13. Funnel Plot UI episodes per week 300U group vs placebo. Publication bias could not be assessed due to the small number of the included studies.

Safety

We attempted to assess the safety of the drug by examining the incidence of the most reported AEs. Pooled analysis was independently performed for the AE of Urinary Tract Infection, Urinary Retention and Hematuria. All the included trials reporting AEs, highlighted that they were either temporary or easily handled. Injection site pain was not considered as an AE. For the safety analysis, seven trials[15–21]were used in total. Based on our meta-analyses, UTIs were found to be barely statistically significant in the 200U group compared to placebo, and statistically significant in the 300U group vs placebo (LogOR: 0.34, 95% CI: 0.01, 0.67, p=0.05; LogOR: 0.42, 95% CI: 0.08, 0.77, p=0.03, 200U and 300U group respectively). Forest and funnel plots are following. In addition, UR was also found to be statistically significant in both BTXA groups compared to placebo (LogOR: 1.75, 95% CI: 0.87, 2.62, p=0.01; LogOR: 1.88, 95% CI: 0.68, 3.08, p=0.02, 200U and 300U group respectively). Forest and funnel plots are presented below. Last but not least, hematuria was not found to be statistically significant in either of the BTXA groups compared to placebo (LogOR: 0.44, 95% CI: -0.37, 1.25, p=0.22; LogOR: 0.66, 95% CI: -0.19, 1.51, p=0.1, 200U and 300U group respectively). Forest and funnel plots are shown below. Data suggests that patients who took the drug were relatively more exposed to complications than those who took the placebo.

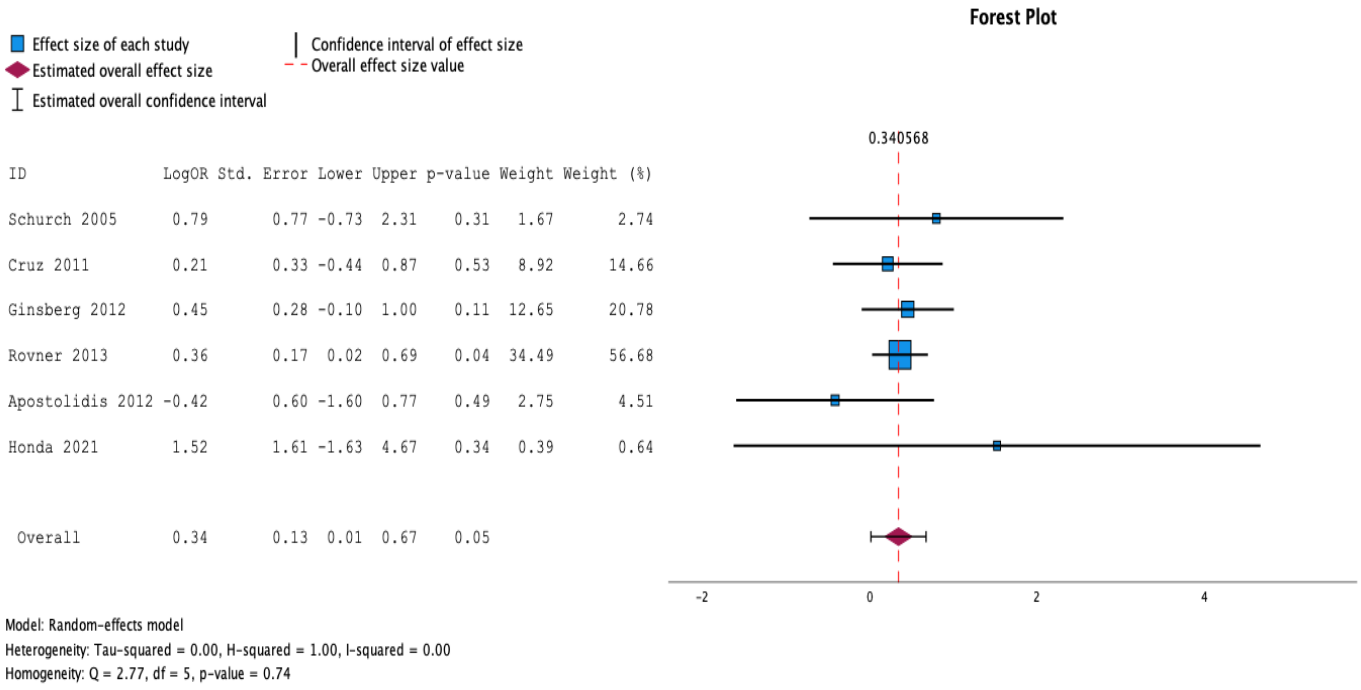


Figure 14. Forest Plot UTI 200U group vs placebo. Positive LogOR implies that the risk of the specific AE was found to be higher at the treatment group.

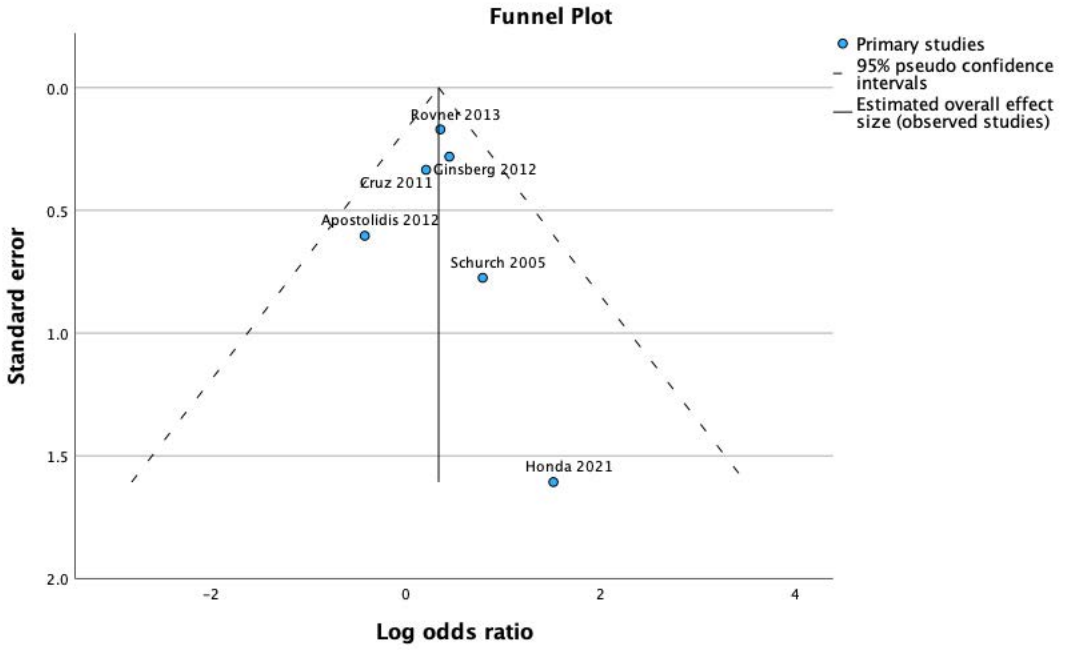


Figure 15. Funnel Plot UTI 200U group vs placebo. Studies are plotted near the average.

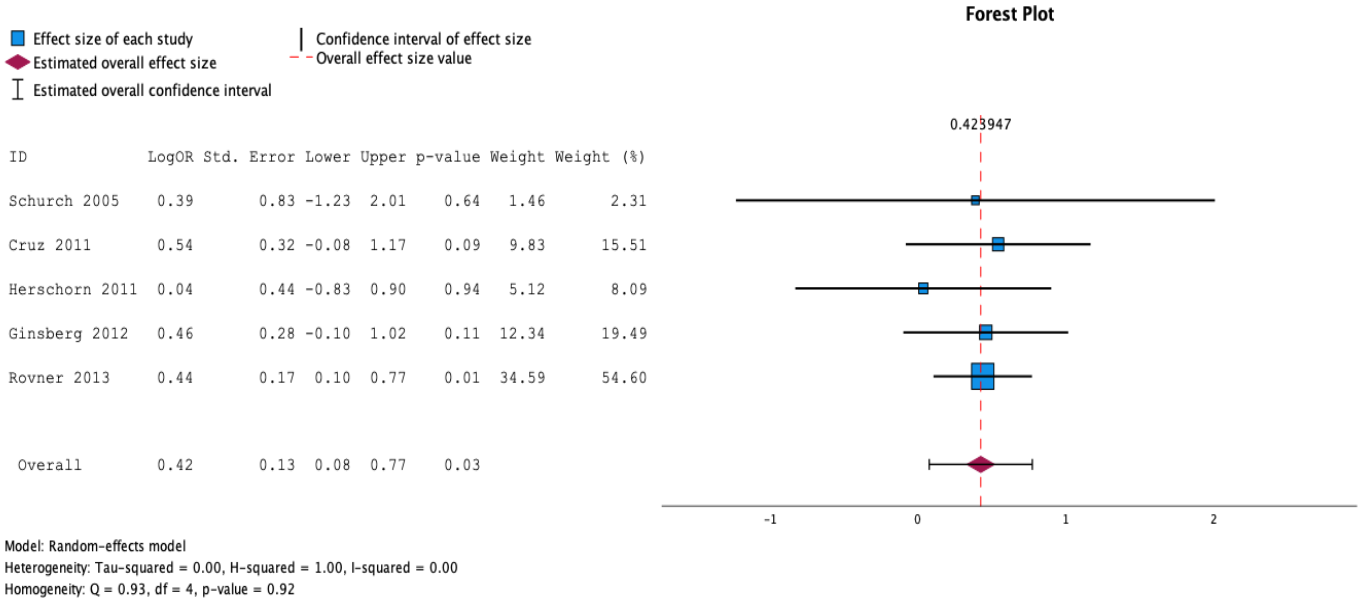


Figure 16. Forest Plot UTI 300U group vs placebo. Positive LogOR implies that the risk of the specific AE was found to be higher at the treatment group.

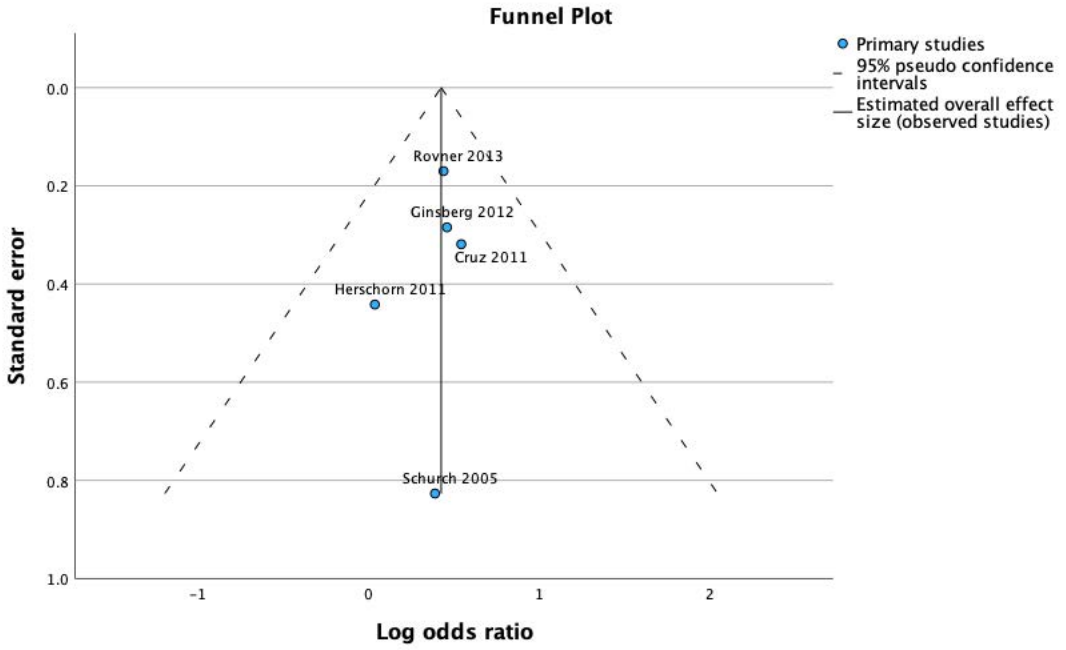


Figure 17. Funnel Plot UTI 300U group vs placebo. Studies are plotted near the average.

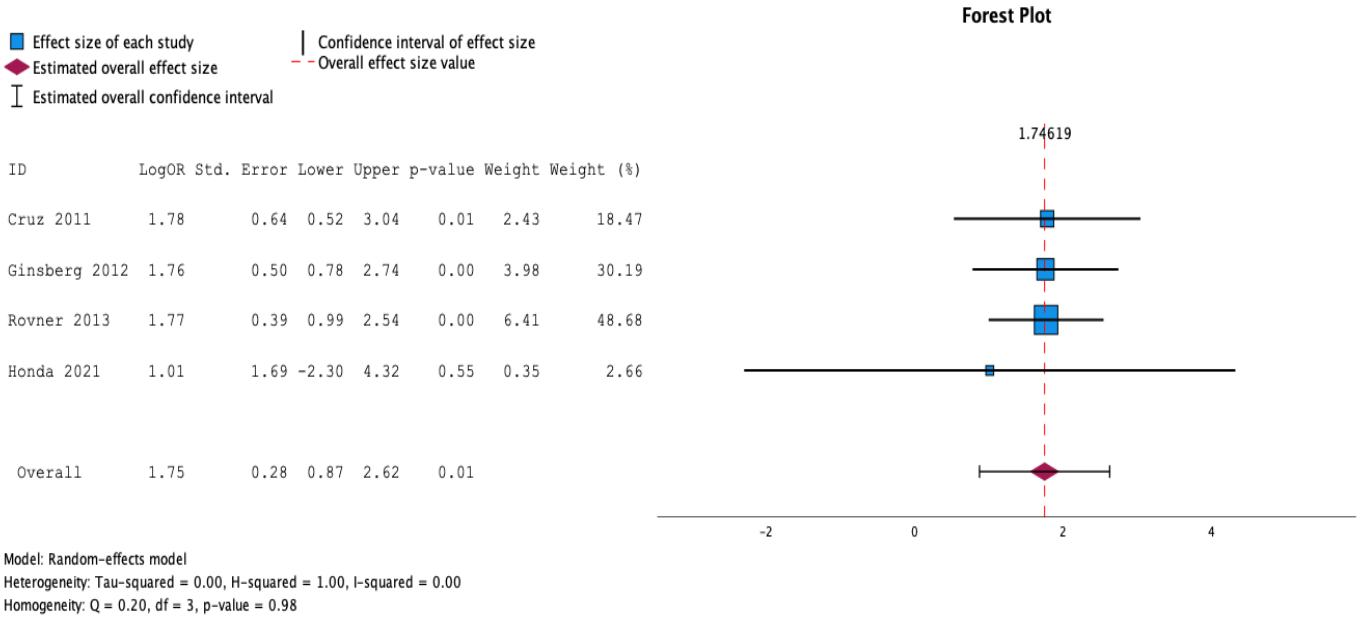


Figure 18. Forest Plot UR 200U group vs placebo. Positive LogOR implies that the risk of the specific AE was found to be higher at the treatment group.

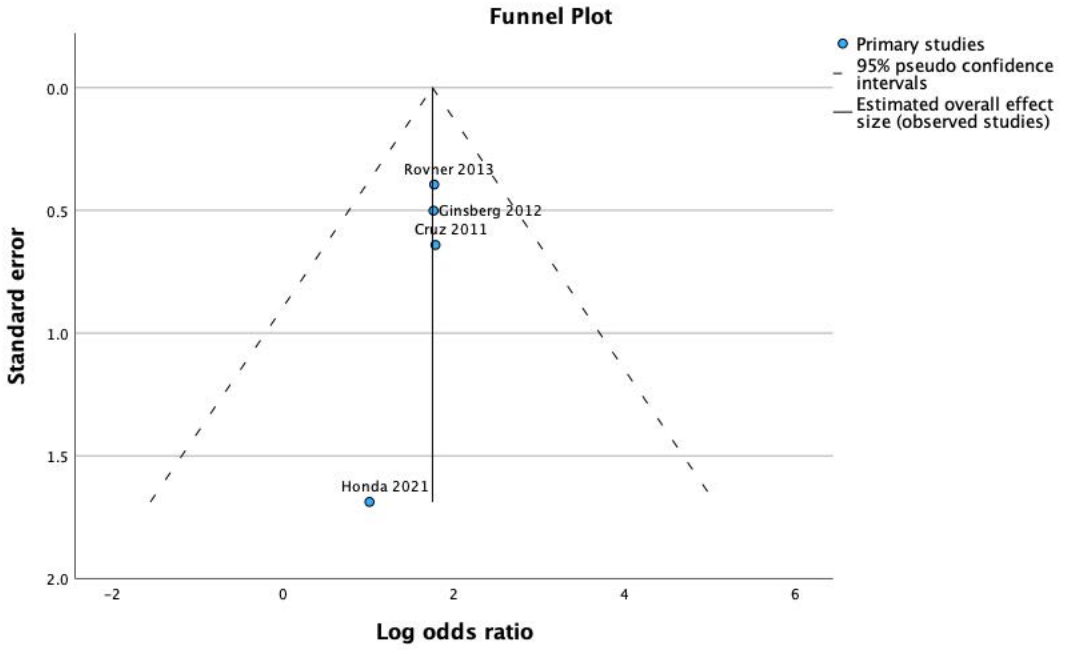


Figure 19. Funnel Plot UR 200U group vs placebo. Studies are plotted near the average.

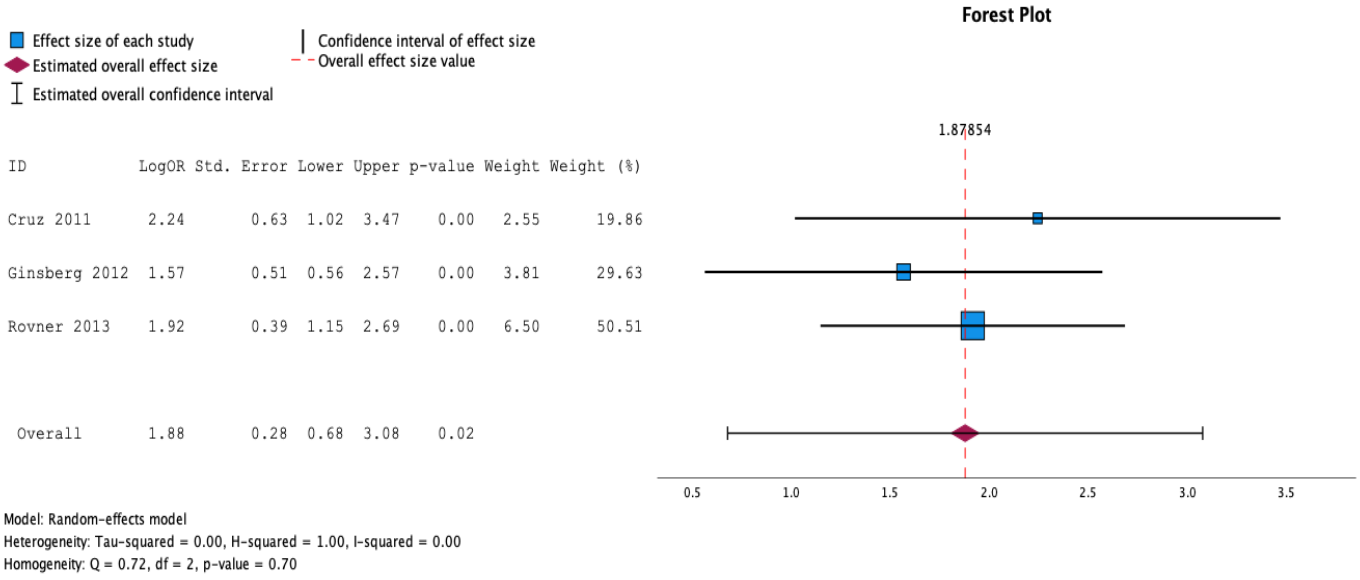


Figure 20. Forest Plot UR 300U group vs placebo. Positive LogOR implies that the risk of the specific AE was found to be higher at the treatment group.

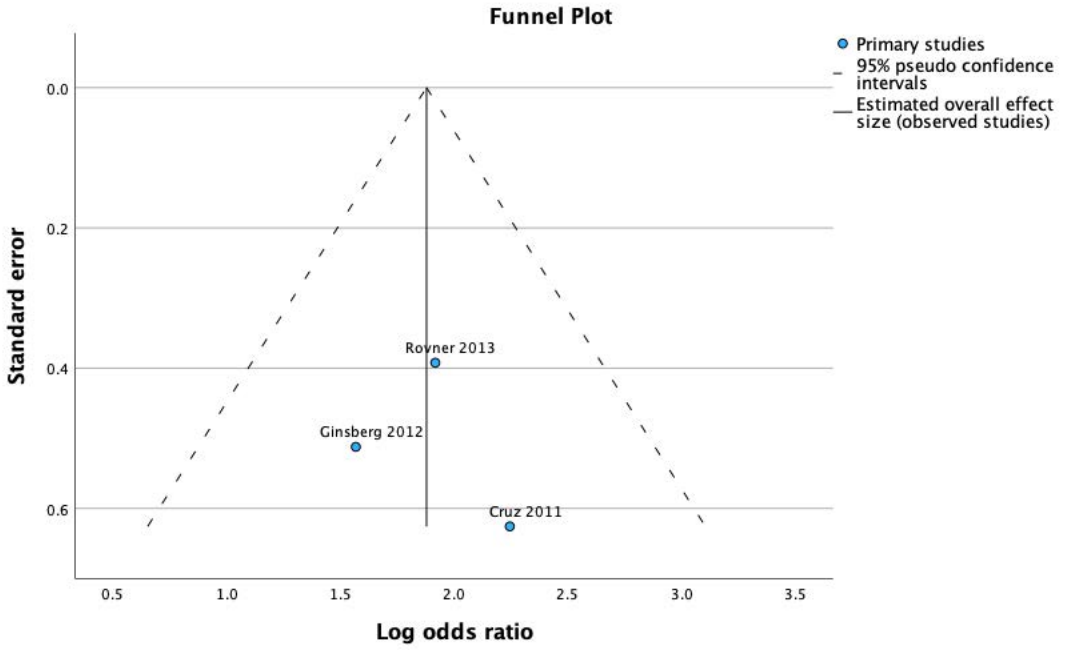


Figure 21. Funnel Plot UR 200U group vs placebo. Studies are plotted near the average.

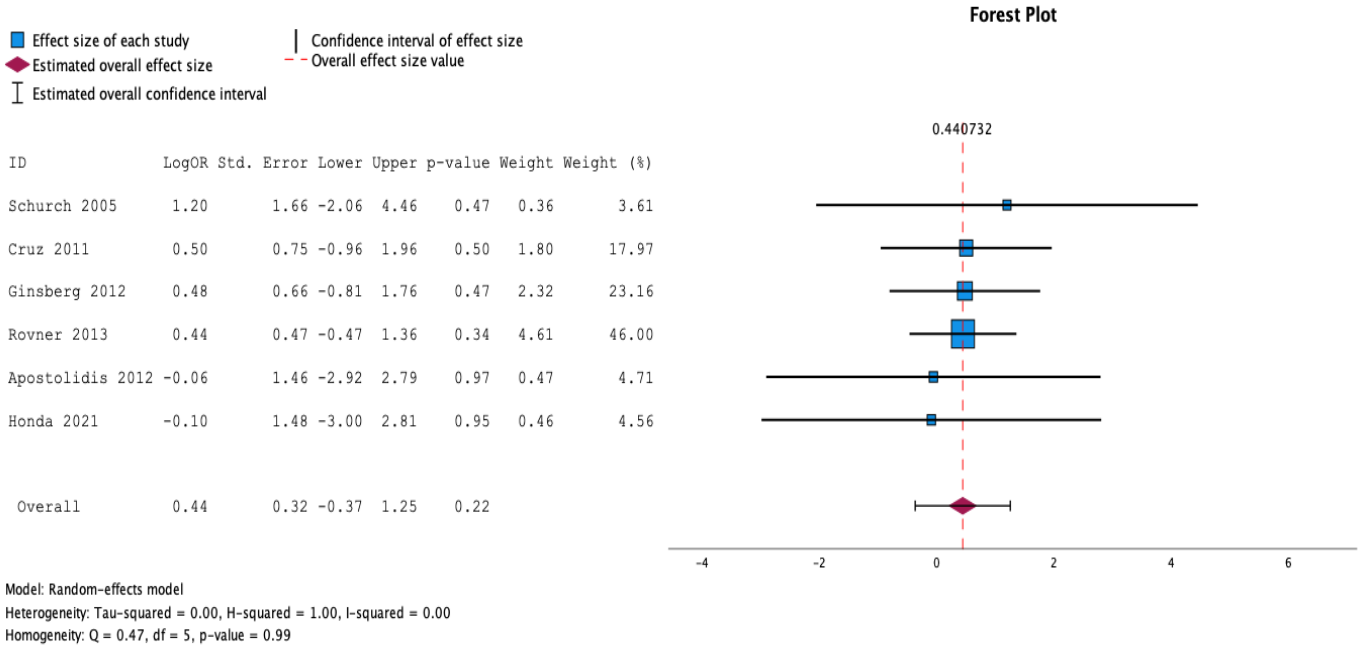


Figure 22. Forest Plot Hematuria 200U group vs placebo. There was no statistically significant difference between treatment group and placebo.

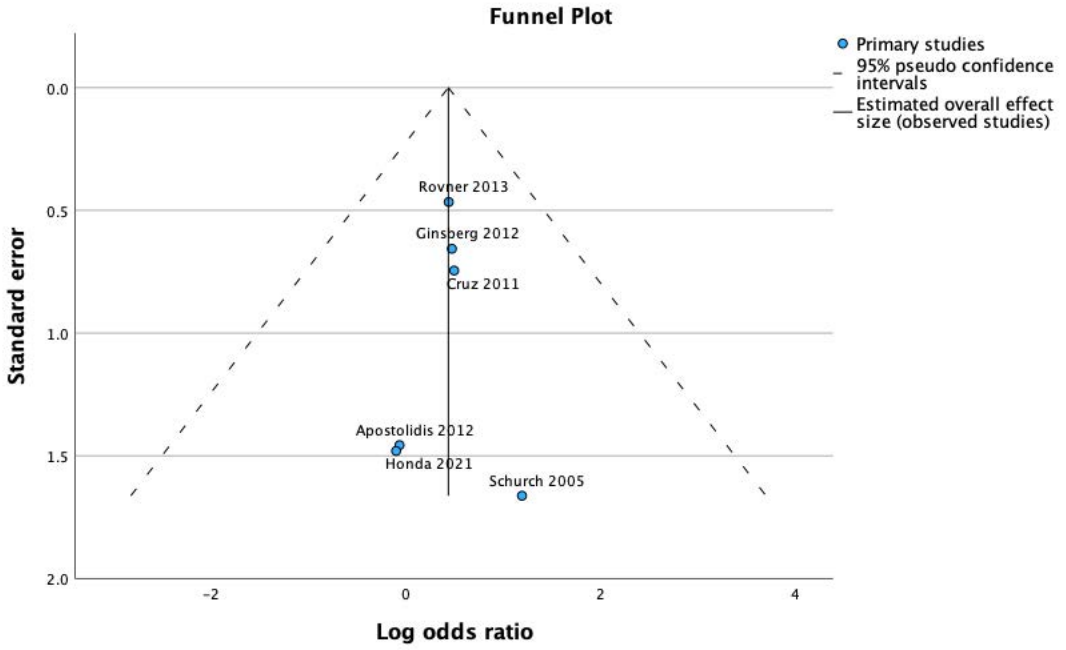


Figure 23. Funnel Plot Hematuria 200U group vs placebo. Studies are plotted near the average.

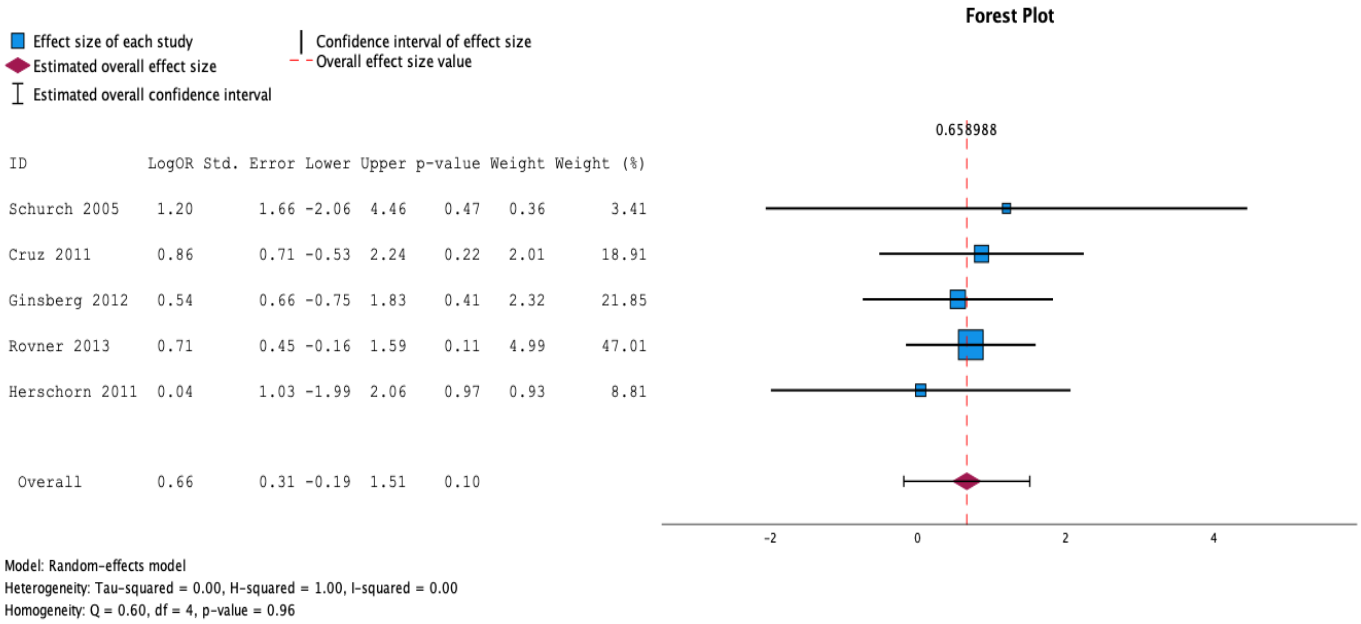


Figure 24. Forest Plot Hematuria 300U group vs placebo. There was no statistically significant difference between treatment group and placebo.

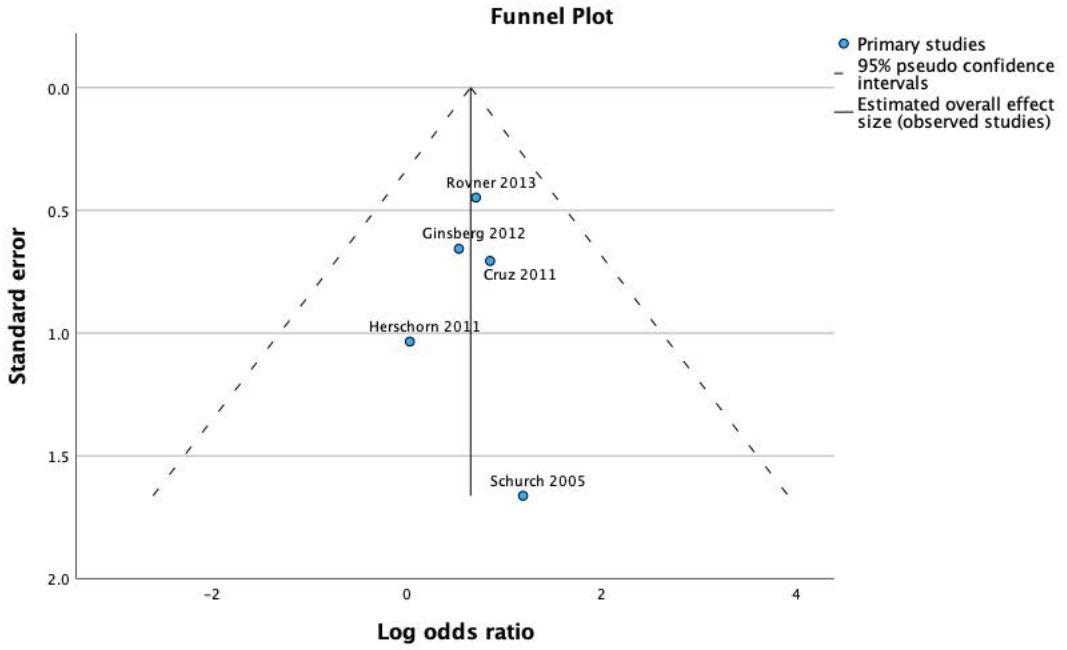


Figure 25. Funnel Plot Hematuria 300U group vs placebo. Studies are plotted near the average.

Study limitations

We acknowledge that our meta-analysis has limitations. First of all, it is limited by the number of the included trials, especially as regards UI episodes per week. Although the authors of several studies were contacted, we did not succeed in acquiring sufficient additional data to include a larger number of studies in our analysis. Additionally, although RCTs are thought to offer the highest quality of clinical evidence, it is possible that we have limited the scope of our study by excluding studies due to design. Furthermore, because extracting and screening of the articles was performed by one author, selection bias cannot be ruled out. Moreover, as previously mentioned, a significant publication bias was detected through Egger's test. Last but not least, our study was restricted to papers published in the English language, meaning that valuable knowledge is probably omitted.

Discussion

Neurogenic lower urinary tract dysfunction is a widespread chronic illness that affects millions of people globally. The crucial goal in the treatment of NDO is to protect the upper urinary tract by lowering intradetrusor pressure and enhancing bladder capacity. These methods also help to reduce the mean number of UI episodes, thereby improving quality of life[22,23]. Regarding MDP, Apostolidis et al stated that the mean decrease in MDP was 44%, in patients treated with BTXA, ranging from 5% to 83%[24]. When interpreting MDP, we should be extremely cautious and take into consideration that MDP is used to describe voiding pressures, despite the fact that many NDO patients are incapable of voiding. Hence it should be interpreted in correlation to some other urodynamic variables such as bladder compliance[25]. Lowering MDP is followed by an up-rise in MCC. This is vital for the NDO patients, as they obtain the capacity to store more urine in their

bladder without needing to void all the time. To the best of our knowledge, published data demonstrate that there is a mean increase in MCC of 85% [24]. Improvement of urodynamic parameters protects the upper urinary tract in NDO patients who would otherwise be at higher risk than the general adult population of developing vesicourenteric reflux, hydronephrosis renal impairment and/or end-stage renal disease[26]. Consequently, when managing and choosing the appropriate treatment for NDO patients, it is important to bear in mind that the upper urinary tract and renal condition of each individual patient should be taken into consideration, and in conjunction with their clinical presentation.

Furthermore, studies confirm the long-term efficacy of the drug. Due to neurotoxin effects, a substantial and long-lasting decrease in local contractility is accomplished by chemical denervation[27]. Recent experimental and clinical results also imply that BTXA may affect the activity of the bladder's afferent C-fibers by prohibiting the release of various neurotransmitters implicated in neurogenic inflammation [28,29]. Through this synergy of actions, BTXA appears to accomplish a profound and long-lasting effect. Studies affirm that the mean interval between two consecutive injections is reasonably long; in particular, Reitz et al reported that it was 200 days, whilst Karsenty et al gave a figure of 260 days[30,31]. Additionally, we should highlight that the patients included in trials are mostly diagnosed with MS or SCI. Although the major number of studies carried out using BTXA are focused on patients having MS or SCI, evidence supports that regardless of the underlying condition, use of the drug benefits patients with NDO. However, because there is still some debate on the topic, further research should be done in order to clarify both the duration of the effect that the drug has on patients, and whether it should be offered to treat NGB irrespective of a patient's underlying condition.

All the RCTs we included in this meta-analysis and the published literature demonstrated that the incidence of the AEs is slightly higher in the BTXA-treated group. However, AEs are mostly related to site pain, procedure-related UTI and hematuria, which can be easily managed. It is also possible that postvoid residual may increase, thus resulting in UR, but such patients already have a difficulty emptying their bladder, and therefore clean intermittent catheterization is required. Finally, muscle weakness and systemic AEs are only stated in a limited number of patients in several papers[32]. When they do occur, they are self-limiting or effortlessly manageable.

Conclusion

To sum up our analysis is in agreement with previously published papers showing that the use of BTXA is undoubtedly beneficial for clinical and urodynamic variables. The evidence that exists is both overwhelming and in favor of BTXA. Nonetheless, further research should be carried out in order to clarify the optimal dose that provides the longest-lasting efficacy, with the lowest number of intolerable effects, the schedule and requirements for follow up injections and which patients are more likely to benefit the most.

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