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The Efficacy and Safety of OnabotulinumtoxinA with Different Dosages for the Treatment of Overactive Bladder Syndrome: A Systematic Review and Meta-analysis

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Abstract: OnabotulinumtoxinA therapy has become widely used in overactive bladder syndrome (OAB), and many relevant articles have been published, however, there is no consensus regarding the clinical effect of onabotulinumtoxinA with the different dosages. Therefore, we conducted this meta-analysis to assess the efficacy and safety of 100 U, 200 U and 300 U onabotulinumtoxinA for the treatment of (OAB). In this project, We performed a comprehensive literature search, which was performed using EMBASE, PubMed, Cochrane database, and Google Scholar for randomized controlled trials (from inception to February 2017). As a result, fourteen studies with 1999 participants were selected. For the efficacy, 200 U of OnabotulinumtoxinA was significantly superior to 100 U, especially in the maximum cystometric capacity (MCC) and maximum detrusor pressure (MDP). Also, its subjective cure rate showed the same tendency. There were no statistical differences between 200 U and 300 U in MCC, MDP and subjective cure rate. For the adverse events, there were no statistical differences among 100 U, 200 U and 300 U OnabotulinumtoxinA in urinary tract infection (UTI) and urinary retention. Therefore, in our study. Compared to 100 U OnabotulinumtoxinA, 200 U OnabotulinumtoxinA has better efficacy while maintaining safety. Although 200 U OnabotulinumtoxinA is comparable to 300 U OnabotulinumtoxinA in terms of safety and efficacy, 200 U OnabotulinumtoxinA is a cost-effective intervention and may appear to be the optimal dosage for OAB populations.

Keywords: OnabotulinumtoxinA, Overactive Bladder, Dosages

1. Introduction

Overactive bladder syndrome (OAB) is a symptom complex including urgency, with or without urge incontinence, but usually with frequency and nocturia [1]. Treatment for OAB includes nonpharmacologic methods such as lifestyle modification (fluid restriction, avoidance of caffeine), bladder retraining, and pelvic floor muscle (PFM) exercise. And the treatment has mainly relied on anticholinergic medication in an attempt to block the parasympathetic innervation of the bladder [1]. However, long-term anticholinergic treatment is unsatisfactory because of insufficient effectiveness and annoying side effects [1].

OnabotulinumtoxinA was first reported by van Ermengem in 1897 and is considered the most potent and

useful biological toxin for humans [3]. It is a neurotoxin produced by the bacterium Clostridium botulinum that prevents acetylcholine release at the neuromuscular junction, resulting in flaccid muscle paralysis [4]. Previous studies have reported on the efficacy and safety of onabotulinumtoxinA compared with placebos. The treatment groups were significantly better in the quality of life (QoL) scores and urodynamic parameters than the control groups, and also showed less adverse effects than the control groups [1, 4-16]. The use of onabotulinumtoxinA to treat overactive bladder (OAB) symptoms is now commonplace and featured in the majority of continence guideline recommendations in patients refractory to conservative treatment and antimuscarinics [5].

OnabotulinumtoxinA therapy has become widely used, and many relevant articles have been published, however, there is no consensus regarding the clinical effect of onabotulinumtoxinA with the different dosages. Recent studies demonstrated significant dose-dependent improvements in urinary symptoms and urodynamic parameters in patients with OAB [6]. Therefore, we performed this systematic review and meta-analysis to evaluate current evidence in support of the optimal dosage of onabotulinumtoxinA for patients with OAB. It may provide clinicians with the selection of the best dosage in the OAB therapy.

2. Methods

2.1. Search Strategy

wE performed a comprehensive literature search using EMBASE, PubMed, Cochrane database, and Google Scholar from inception to February 2017. The search was performed using the MeSH words combined with free words "overactive bladder", "OAB", "Botulinum toxin" and "onabotulinumtoxinA". Each term was associated with multiple synonyms. The research were restricted to humans and English language. Additionally, we manually searched the references and citation lists of all relevant reviews, the conference proceedings and abstracts from ICS, the American Urological Association (AUA), and the European Association of Urology (EAU) [17]. A literature search was performed independently by two review authors. Finally, all available randomized controlled trials (RCTs) were included in this study. Where reported data were incomplete, The authors were contacted.

2.2. Eligibility and Exclusion Criteria

The following inclusion criteria were used to select relevant articles for inclusion in our meta-analysis: (1). A randomized controlled design was used. (2). Patients with symptoms of OAB with or without urge urinary incontinence (UUI), regardless of gender, race, course of disease and the origin of studies. (3). At least 12 weeks of follow-up. the exclusion criteria include: (1). The patients are pregnancy, or age≤18 years. (2). 100 U vs. 200 U or 200 U vs. 300 U of onabotulinumtoxinA was not contained.

2.3. Interventions

Patients were randomly assigned into 3 groups, including 100 U, 200 U, 300 U onabotulinumtoxinA separately. The efficiency and safety of onabotulinumtoxinA compared with placebo had been discussed in other studies, so we only focus on the dosage part of these studies.

2.4. Types of Outcome Measures

Subjective cure rate: Keywords as "satisfied", "somewhat satisfied", "complete achievement", "significant progress" and "symptom improvement" were deemed to subjective cured. We took the satisfied number or the percentage of the treated people to analyze.

Objective cure rate: Two key urodynamic parameters such as the increase of maximum cystometric capacity (MCC) and the decrease of maximum detrusor pressure (MDP) were used.

Adverse events: We took the most common adverse events: urinary tract infection (UTI) and urinary retention as the representative complications.

2.5. Quality Assessment of Studies

The quality of studies was assessed by two authors according to the Cochrane Collaboration Reviewers' Handbook. They were judged by following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Differences were resolved by discussion among the authors.

2.6. Statistical Analysis

Meta-analysis was performed using Review Manager version 5.2 (The Cochrane Collaboration, Oxford, United Kingdom). Dichotomous data were expressed as relative risk (RR), and continuous outcomes were expressed as weighted mean difference with 95% confidence intervals (CIs). Meta-analysis was performed using the fixed effect model or the random effect model, The fixed effect model was used for calculations in the absence of evidence of heterogeneity, and the random effect model was used if heterogeneity was obvious. Statistical heterogeneity was assessed by the I^2 test with significance set at $P<0.05$ and I^2 <50% [3]. We evaluated whether publication bias through visual inspection of funnel plots for asymmetry. in addition, Sensitivity analysis were limited to studies of higher quality so as reconfirming a similar result. A probability of $P<0.05$ was considered to be statistically significant.

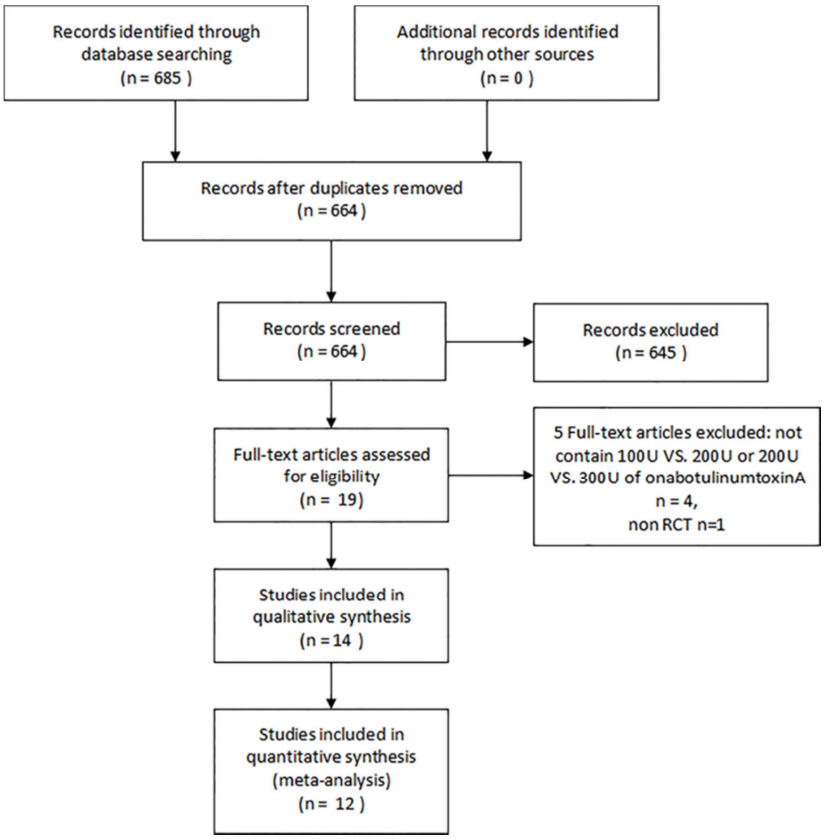

Figure 1. *Flow diagram.*

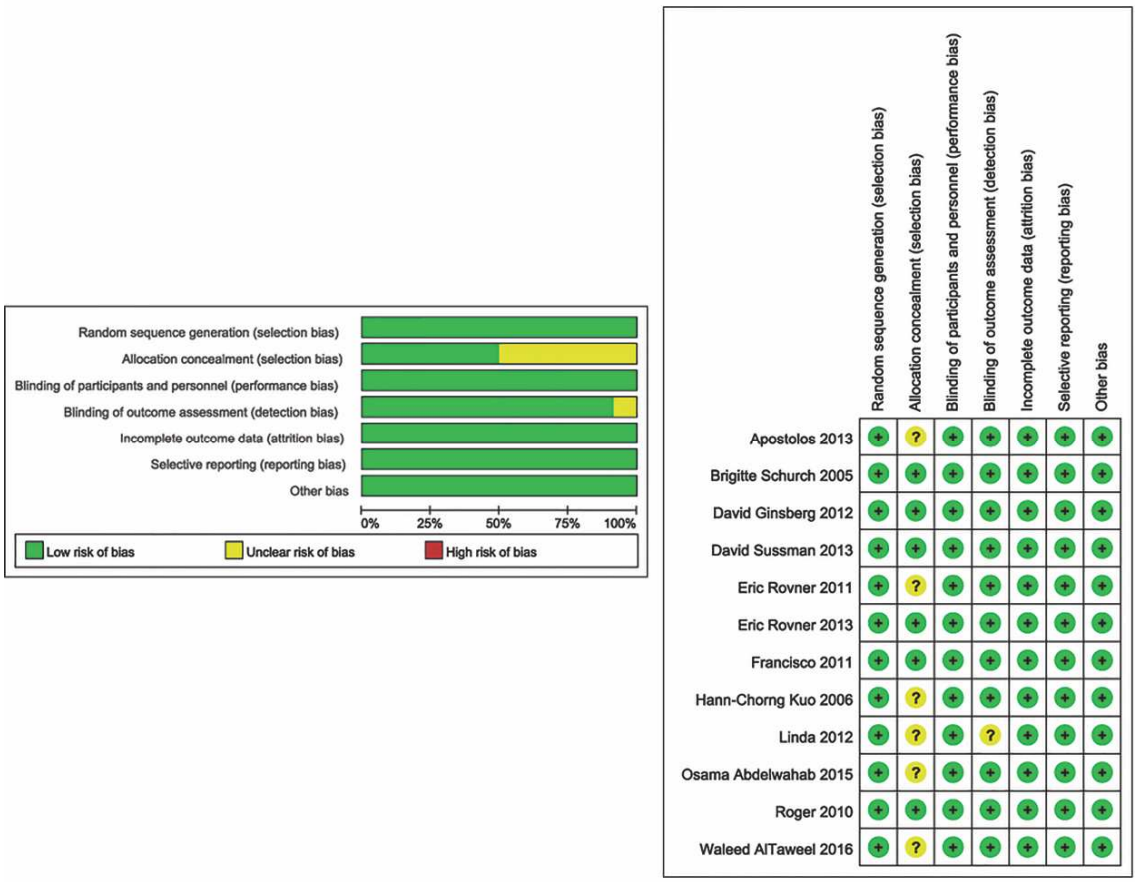

Figure 2. *The results for the assessment of bias risk.*

3. Results

3.1. Description of Studies

Figure 1 presents the process of literature screening. 685 records were identified as being relevant to the present study by the electronic searches of the 3 databases. After excluding 671 records that did not meet eligibility criteria, leaving 14 studies were included in the qualitative synthesis. The reported data were insufficient for 2 of the 14 records, thereby, a total of 12 studies were included for meta-analysis. The results for the assessment of bias risk in the 12 studies included in the quantitative synthesis (meta-analysis) are shown in Figure 2. Overall, every trial was double-blind and had a randomized controlled design. Specifically, 7 trials compared 100 U with 200 U, and 9 trials compared 200 U with 300 U. The baseline characteristics of the studies included in our meta-analysis are showed in Table 1. Eleven of the 14 studies had received support from Allergan Inc..[1, 4, 6-10, 13-16] Most of the research (78.6%) were carried out in the US and Europe.

Table 1. *The baseline Table characteristics of the studies.*

Study	Treatment group	No. of patient	Gender (M/F)	Age, mean (SD), years	Injection method	follow-up
Apostolos Apostolidis et al. 2013 (1)	100U	21	-	-	30 sites, avoiding the trigone	54weeks
	200U	17				
Brigitte Schurch et al. 2005 (2)	200U	19	-	-	30 sites, avoiding the base and trigone	24weeks
	300U	19				
Osama Abdelwahab et al. 2015 (3)	100U	40	-	30.22±8.37	20 sites	36weeks
	200U	40		31.35±7.61		
Linda Brubaker et al. 2012 (4)	100U	48	-	58.8	20 sites, avoiding the trigone	36weeks
	200U	47				
	300U	50				
Clare J. Fowler et al. 2012 (5)	100U	54	4/50	60.8±12.1	20 sites, avoiding the trigone and dome	36weeks
	200U	53	7/46	59.6±14.9		
	300U	56	4/52	58.7±13.0		
David Sussman et al. 2013 (6)	200U	92	38/54	46.0±13.1	30 sites, avoiding the trigone	12weeks
	300U	91	39/52	44.4±13.9		
Eric Rovner et al. 2011 (7)	100U	54	4/50	60.8±12.1	20 sites, avoiding the trigone and dome	36weeks
	200U	53	7/46	59.6±14.9		
	300U	56	4/52	58.7±13.0		
Eric Rovner et al. 2013 (8)	200U	227	93/134	45.9±13.3	30 sites, avoiding the trigone	12weeks
	300U	223	82/141	45.6±13.0		
David Ginsberg et al. 2012 (9)	200U	135	55/80	46±14	30 sites, avoiding the trigone	12weeks
	300U	132	43/89	46±12		
Brigitte Schurch et al. 2007 (10)	200U	56	33/23	41.6±12.8	30 sites, avoiding the trigone	24weeks
	300U					
Roger Dmochowski et al. 2010 (11)	100U	55	-	-	20 sites, avoiding the trigone and dome	36weeks
	200U	52				
	300U	55				
Francisco Cruz et al. 2011 (12)	200U	92	38/54	46.0±13.1	30 sites, avoiding the trigone	12weeks
	300U	91	39/52	44.4±13.9		
Waleed AlTaweel et al. 2016 (13)	100U	11	-	-	-	36weeks
	200U	11				
Hann-Chorng Kuo et al. 2006 (14)	100U	23	43/32	63.4±10.7	40 sites in the posterior and lateral walls of the urinary bladder	12weeks
	200U	27				

3.2. Efficacy in Different Dosages

In order to find out the differences between different dosages of the onabotulinumtoxinA, the analyses were divided into two subgroups: Group onabotulinumtoxinA 100 U vs. 200 U, and group onabotulinumtoxinA 200 U vs. 300 U. Three studies [6, 9, 16] were evaluated about the subjective cure rate of onabotulinumtoxinA 100 U vs 200 U, and four [6, 8, 9, 11] about onabotulinumtoxinA 200 U vs. 300 U with the longest follow-up times respectively. The analysis showed that the subjective cure rate of 200 U was higher than 100 U (P<0.05, RR: 0.78, 95% CI: 0.63~0.96). On the contrary, there was no statistical differences between 200 U and 300 U (P=0.93, RR: 1.01, 95%CI: 0.86~1.17) (Figure 3). One study observed the QoL scores of 200 U and 300 U, and there were no statistical differences between them [14]. Urodynamic parameters Comparison of urodynamic parameters include MCC and MDP at the longest fellow-up times after treatment to baseline data.

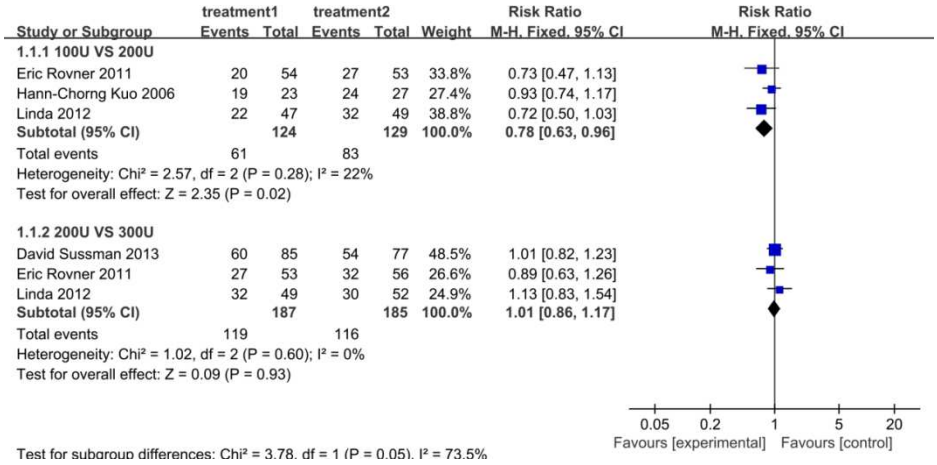

Figure 3. *The results of subjective cure rate.*

There are four studies [5, 9, 15, 16] analyzing MCC of 100 U vs. 200 U, and showed the significant statistical differences (P<0.00001, MD: -63.97, CI 95%: -82.04~-45.91). Thus, the results indicated that 200 U of onabotulinumtoxinA was superior to 100 U in increasing MCC. Five studies [4, 9-11, 14] analyzed MCC of 200 U VS. 300 U, and no statistical differences between them were found. (P=0.14, MD: -15.40, 95% CI: -35.63~-4.84) (Figure 4).

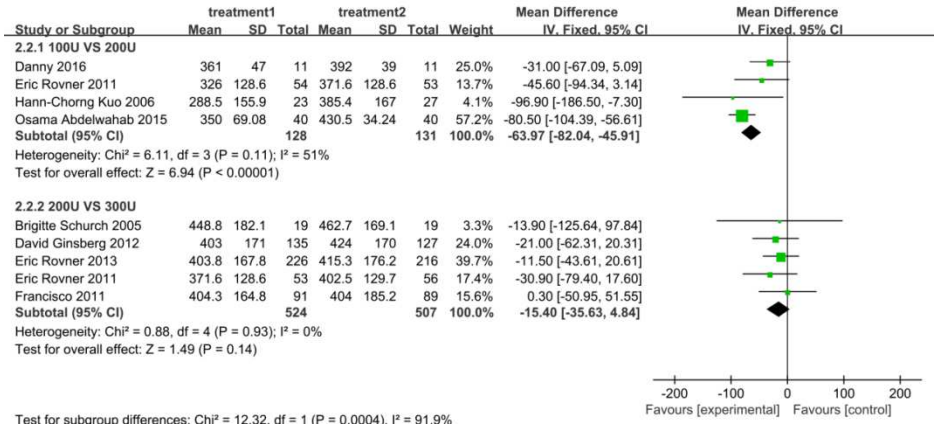

Figure 4. *The result of MCC.*

Likewise, there are four studies [5, 9, 15, 16] about 100 U vs. 200 U and five [4, 9-11, 14] about 200 U vs. 300 U. 200 U onabotulinumtoxinA showed a robust improvement in the mean change from the baseline than 100 U in decreasing MDP (P<0.00001, MD: 7.42, 95% CI: 5.15~9.69). The studies about 200 U vs. 300 U showed no statistical differences (P=0.06, MD: 4.29, 95% CI: -0.20~8.78) (Figure 5).

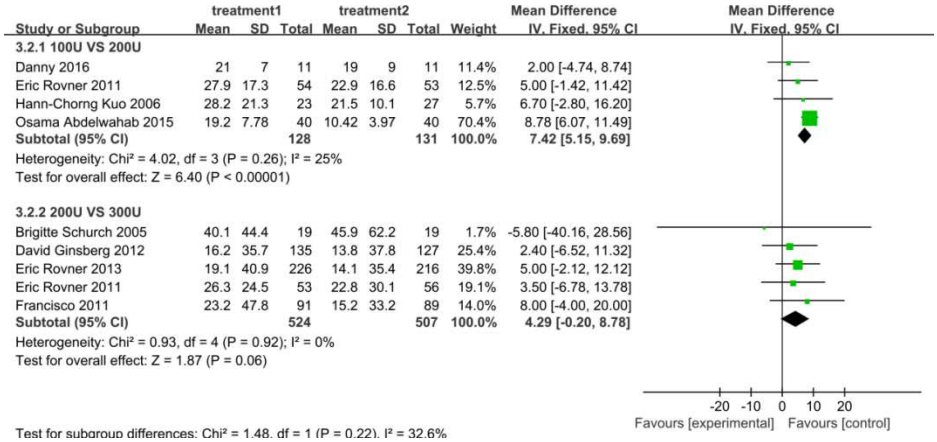

Figure 5. *The result of MDP.*

3.3. Urinary Tract Infection

Five studies [1, 5, 13, 15, 16] included the UTI data of 100 U vs. 200 U, representing 247 participants (127 in the 100 U group, 120 in the 200 U group), and according to our analysis, there were no statistical differences between them (*P*=0.23, RR: 0.80, 95% CI: 0.56~1.15). Moreover, five [4, 10, 11, 13, 14] studies contained UTI data of 200 U vs. 300 U, representing 1029 participants (523 in the 200 U group, 506 in the 300 U group), showing no statistical differences between them, either (*P*=0.62, RR: 0.97, 95% CI: 0.85~1.10) (Figure 6).

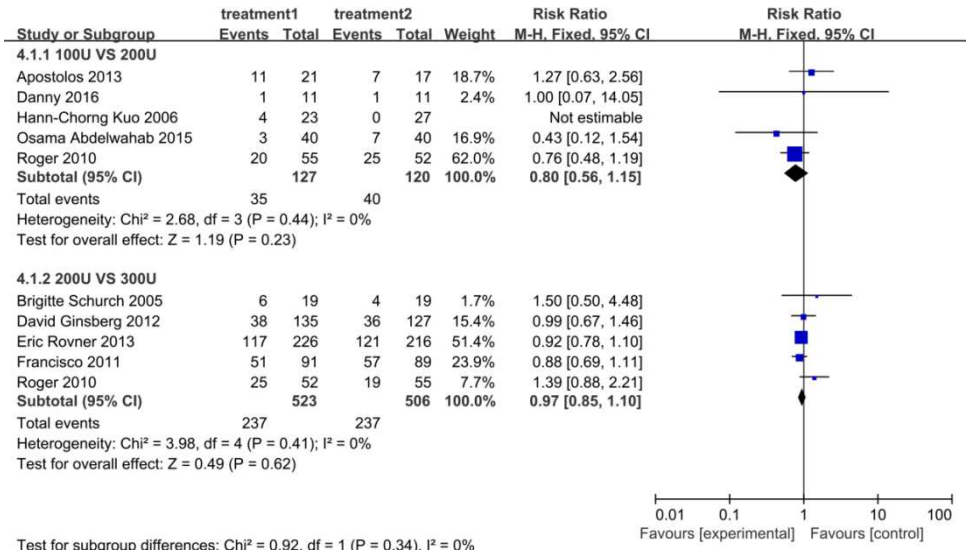

Figure 6. *The result of UTI.*

3.4. Urinary Retention

Four studies [9, 13, 15, 16] included the urinary retention data of 100 U vs. 200 U, representing 286 participants (143 in the 100 U group, 143 in the 200 U group), the pooled estimate of RR=1.11, 95%CI was 0.69-1.77 (P=0.67), and it showed no statistical differences. Five of the studies [9-11, 13, 14] included urinary retention data of 200 U vs. 300 U, representing 1100 participants (557 in the 200 U group, 543 in the 300U group), there were no statistical differences between them (P=0.25, RR: 0.88, 95% CI: 0.70~1.10) (Figure 7).

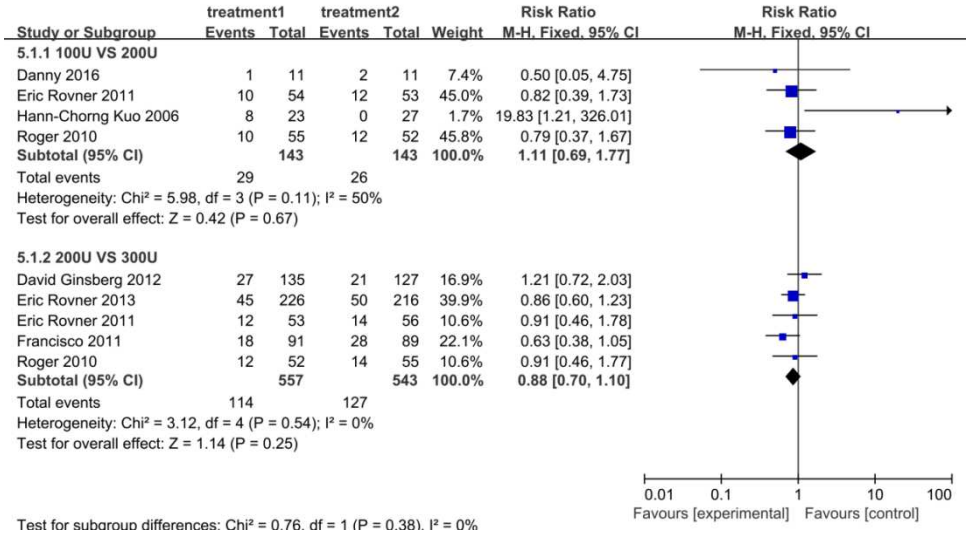

Figure 7. *The result of urinary retention.*

4. Discussion

OnabotulinumtoxinA is currently licensed in certain parts of the world, including China. It is an effective treatment that uses of OnabotulinumtoxinA has already become a second-line treatment in those OAB patients with failed antimuscarinics and conservative measures, but the optimal dosage has not reached a consensus yet. The majority of published studies have utilized a 300 U dose in adults, but

some studies reported using dosage from 100 to 400 U OnabotulinumtoxinA [18-21]. YiSun [22] and Yuanshan Cui [23] suggest that OnabotA improves OAB symptoms with manageable side effects. But they did not discuss the dosages of OnabotulinumtoxinA in depth. Tao Cheng [3] only compared 200 U and 300 U of OnabotulinumtoxinA in their study, their result indicated that the use of onabotulinumtoxinA is a well-established treatment method and any significant differences in efficacy between the 300 U dose and the 200 U dose were not observed that consistent with our study. Xin Zhou [24] compared 200 U and 300 U of OnabotulinumtoxinA with limited studies and less participants. Interestingly, we have come to a different conclusion from their study.

The treatment with botulinum toxin is still lacking the standardization, allowing for a great variety in dosing, frequency and injection sites [25].

This analysis suggests a superior dosage of injecting Onabotulinumtoxin A, which acquire a great potential clinical and also economic value. First, from the aspect of efficacy, 200 U of OnabotulinumtoxinA is significantly superior to 100 U through the longest follow-up time respectively, especially in urodynamic parameters MCC and MDP. The subjective cure rate showed the same tendency but less obvious. Nevertheless, 200 U and 300 U of OnabotulinumtoxinA do not show conspicuous differences. Second, for adverse events, 100 U vs. 200 U, 200 U vs. 300 U were not found differences according to our study, indicating that these three dosages of OnabotulinumtoxinA might cause adverse events in equal measure. But the price of the treatment is still a matter of debate, in whichever clinical center, the price of 200 U might be equal or even significantly lower comparing to 300 U, indicating that the drug could be more affordable and more patients could be treated.

The effect of BoNT/A on inhibiting parasympathetic presynaptic release of acetylcholine (ACh) at the neuromuscular junction is well-known. BoNT/A neurotoxin binds to peripheral cholinergic terminals and inhibits ACh release at the neuromuscular junction [26]. Therefore, there may be a dose-response relationship according to its mechanism. It may also explain the discrepancy of treatment effects between 100 U and 200 U, and why 200 U and 300 U are undifferentiated.

Although the efficacy and safety of this dosage is well-proven, the correct conditions for each particular patient remain still a question, so there are also several potential limitations should be considered in our meta-analysis. Primarily, the causes of overactive bladder syndrome are various, and we do not limit the causes by reason of scanting studies. In addition, because of lacking studies and samples, we can not compare the same parameters within the same follow-up time. However, the study [26] has found that the mean duration of benefit was approximately nine months (36 weeks), thus the longest follow-up times are available to compare. Beyond that, the vast majority of the studies included in our meta-analysis were performed in the Americas and Europe, three of them [7, 9, 11, 27] listed races or ethnicities of participants, and almost all of them were Caucasians or whites. There was one study [16] carried in Taiwan China, but no research has carried out in mainland China yet. The regional discrepancy and the different living habits may also affect treatment outcome.

5. Conclusion

In our study, This meta-analysis compares three dosages of OnabotulinumtoxinA for the treatment of OAB, Compared to 100U OnabotulinumtoxinA, 200U OnabotulinumtoxinA has better efficacy while maintaining safety. Although 200 U OnabotulinumtoxinA is comparable to 300 U OnabotulinumtoxinA in terms of safety and efficacy, 200 U OnabotulinumtoxinA is a cost-effective intervention and may appear to be the optimal dosage for OAB populations.

Conflict of Interest Statement

The authors do not have any possible conflicts of interest.

Acknowledgements

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