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A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS WITH BOTULINUM TOXIN A FOR NEUROGENIC DETRUSOR OVERACTIVITY

Hypothesis / aims of study

To assess the efficacy and safety of botulinum toxin A (BTX-A) in the treatment of neurogenic detrusor overactivity (NDO)

Study design, materials and methods

Pubmed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for collecting the randomized controlled trials (RCTS) from 1979 to September 2013 Eligible studies were included if the following conditions were met: (1) all the published RCTs and the language is limited to English; (2) patients were clinically diagnosed as NDO; (3) BTX-A compared with placebo or different doses of the same BTX-A or repeated injections of BTX-A or different injection sites of the same BTX-A. Studies were excluded if (1) non-RCTs; (2) children; (3) patients with idiopathic detrusor overactivity; (4) animal experiment; (5) full text study is not available; and (6) relevant data was not complete. Meta-analyses were performed by Review Manager 5.2. Each measurement indicator was calculated with standardized mean difference (SMD) or risk ratio (RR). Effective sizes were divided into: insignificant, less than 0.2; small, 0.2-0.5; moderate, 0.5-0.8; and large, more than 0.8.

Results

A total of 8 RCTs involving 1924 patients were included. Six RCTs compared BTX-A with placebo. One RCT compared combined detrusor-trigone BTX-A injections with detrusor injections. One RCT compared BTX-A （Dysport®）500u with BTX-A（Dysport®）750u. The average age ranged from 39 to 50 years. The follow-up ranged from 18 weeks to 60 weeks. Most patients used clean intermittent catheterization at baseline. The amount of BTX-A injected in most studies was 200u and 300u, usually as 30 sites (each 1ml) into the detrusor (sparing the trigone) by cystoscope and under different types of anaesthesia. BTX-A statistically significantly reduced urinary incontinence (UI) episodes (SMD -0.53, 95% CI -0.62 to -0.45, p<0.01), maximum detrusor pressure (MDP) (SMD -0.81, 95% CI -0.91 to -0.70, p<0.01) and increased maximum cystometric capacity (MCC) (SMD 1.01, 95% CI 0.93-1.10, p<0.01) and incontinence quality of life (I-QOL) (SMD 0.87, 95% CI 0.54-1.20, p<0.01) compared with placebo. However, there was a higher incidence of adverse events such as urinary tract infection (UTI) (RR 1.46, 95% CI 1.31-1.64, p<0.01), hematuria (RR 1.79, 95% CI 1.16-2.77, p<0.01), urinary retention (RR 6.11, 95% CI 4.12-9.05, p<0.01). Combined detrusor-trigone BTX-A injections was associated with reduction in UI episodes (SMD -2.12, 95% CI -2.71 to -1.53, p<0.01) and improvement in reflex volume (RV) (SMD 0.70, 95% CI 0.03-1.38, p<0.05) and complete dryness (RR 2.00, 95% CI 1.19-3.35, p<0.01) compared with detrusor injections. There was no statistically significant difference in MCC, bladder compliance (BC), and reflex detrusor volume (RDV) between BTX-A (Dysport®) 500u and 750u.

Interpretation of results

This systematic review and meta-analysis shows statistically significantly improvement in urodynamic outcomes and I-QOL and reduced UI episodes in those injecting BTX-A compared to placebo. UTI and urinary retention were the most common adverse events among patients during treatment. Of the 1393 Patients who received BTX-A,691(49.6%) were reported to have UTI compared with placebo (34.2%). The incidence of hematuria, urinary retention, muscular weakness, and bladder pain is 6% (83 of 1393), 21.4% (291 of 1355), 5.3% (72 of 1355), and 3% (22 of 704) respectively. There was no significant difference in the withdrawals because of any cause (RR 1.39, 95% CI 0.64 to 3.01, p>0.05) and the dropout rate is 2% (22 of 959). There was no statistically significant difference in QOL score (SMD 0, 95% CI -0.46 to 0.46, p>0.05), MCC (SMD -0.41, 95% CI -1.07 to 0.25, p>0.05), and MDP (SMD -0.42; 95% CI -1.08 to 0.24, p>0.05) compared combined detrusor-trigone BTX-A injections with detrusor injections. However, Combined detrusor-trigone BTX-A injections was associated with reduction in UI episodes (SMD -2.12, 95% CI -2.71 to -1.53, p<0.01) and improvement in RV (SMD 0.70, 95% CI 0.03-1.38, p<0.05) and Complete Dryness (RR 2.00, 95% CI 1.19-3.35, p<0.01) compared with detrusor injections. Meta-analysis showed no statistically significant difference in MCC (SMD 0.53, 95% CI -0.03 to 1.09, p>0.05), BC (SMD -0.44, 95% CI -1.00 to 0.12, p>0.05), and RDV (SMD 0.03, 95% CI -0.52 to 0.58, p>0.05) BTX-A（Dysport®）500u and BTX-A（Dysport®）750u. Our systematic review has limitations. Methodological heterogeneity could be found because of different time point (week 2, 6, 12, 24, and 36), types, doses, and injection sites of BTX-A compared with placebo and BTX-A. There are only one RCT compared combined detrusor-trigone BTX-A injections with detrusor injections and one RCT compared BTX-A（Dysport®）500u with BTX-A（Dysport®）750u separately, so the evidence is limited. Some studies design required patients who took anticholinergics at start to continue taking the same dose, so the potential benefits of anticholinergics couldn't be evaluated in patients who received BTX-A. Drug tolerance of repeated injection in patients receiving BTX-A during the treatment remains to be investigated.

Concluding message

This systematic review and meta-analysis has shown that BTX-A is associated with improvement in urodynamic outcomes and I-QOL and reduced UI episodes in patients with NDO. It seems to be well tolerated. However, it is necessary to perform more randomized controlled trials to clarify the optimal dose, duration of effect, number and location of injections, time interval of reinjection, risk factor, and acceptable level of adverse events.

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