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Collaborative Review – Voiding Dysfunction

An Updated Systematic Review and Statistical Comparison of Standardised Mean Outcomes for the Use of Botulinum Toxin in the Management of Lower Urinary Tract Disorders

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Abstract

Context: Botulinum toxin A (BoNTA) has received regulatory approval for use in neurogenic detrusor overactivity (NDO) and overactive bladder (OAB), but it remains unlicensed in other lower urinary tract symptoms (LUTS) indications such as nonneurogenic LUTS in men with benign prostatic enlargement (LUTS/BPE), bladder pain syndrome (BPS), and detrusor sphincter dyssynergia (DSD).
Objective: To compare statistically the outcomes of high level of evidence (LE) studies with placebo using BoNTA for LUTS indications; NDO, OAB, LUTS/BPE, BPS and DSD.
Evidence acquisition: We conducted a systematic review of the published literature on PubMed, Scopus, and Embase reporting on BoNTA use in LUTS dysfunction. Statistical comparison was made between high LE studies with placebo and low LE studies.
Evidence synthesis: In adult NDO, there are significantly greater improvements with BoNTA in daily incontinence and catheterisation episodes (−63% and −18%, respectively; $p < 0.01$), and the urodynamic parameters of maximum cystometric capacity (MCC), reflex volume, and maximum detrusor pressure (MDP) (68%, 61%, and −42%, respectively; all $p < 0.01$). In OAB, BoNTA leads to significant improvements in bladder diary parameters such as daily frequency (−29%), daily urgency (−38%), and daily incontinence (−59%) (all $p < 0.02$). The urodynamic parameters of MCC and MDP improved by 58% ($p = 0.04$) and −29% ($p = 0.002$), respectively. The risk of urinary tract infection was significantly increased from placebo at 21% versus 7% ($p < 0.001$), respectively; the risk of intermittent self-catherisation increased from 0% to 12% ($p < 0.001$). Men with LUTS/BPE showed no significant improvements in International Prostate Symptom Score, maximum flow rate, or prostate volume. There were insufficient data for statistical analysis in DSD, BPS, and paediatric studies. Low LE studies were found to overestimate the effects of BoNTA in all indications, but differences from high LE studies were significant in only a few parameters.
Conclusions: BoNTA significantly improves all symptoms and urodynamic parameters in NDO and OAB. The effect of BoNTA in treating LUTS dysfunction appears to be overestimated in lower as opposed to higher LE studies.

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1. Introduction

Evidence regarding the use of botulinum toxin A (BoNTA) for urologic applications has been rapidly growing over the past 5 yr, leading to its licensing in the management of patients with neurogenic detrusor overactivity (NDO) and overactive bladder (OAB). A previous systematic review of data up to December 2010 showed sufficient evidence for the efficacy and safety of BoNTA for these two indications [1]. The previous systematic review also compared the two different formulations of BoNTA for which there is an established evidence base and reported high level of evidence (LE) data for the use of onabotulinumtoxinA (Botox) in the treatment of NDO and OAB and abobotulinumtoxinA (Dysport) for NDO only. The systematic review confirmed that different formulations of BoNTA cannot be considered generic equivalents due to different isolation, manufacturing, and stabilisation processes. To reflect this, the US Food and Drug Administration has approved new terminology for the various BoNTA preparations available to avoid drug errors and prevent interchange ability.

The data for BoNTA use in nonneurogenic LUTS in men with benign prostatic enlargement (BPE) has some high LE, but for detrusor sphincter dyssynergia (DSD) and bladder pain syndrome/interstitial cystitis (BPS/IC), there was no high LE data. The primary purpose of the current review was to update the data regarding the use of BoNTA since the previous systematic review and compare high-level data against placebo statistically where possible.

Evidence-based medicine forms the cornerstone of medical decision making. There is often concern that high-level studies do not represent real-life practice because patients tend to be highly selected with multiple inclusion and exclusion criteria to fulfil [2]. Conversely, a concern with retrospective cohort studies is that they may not capture complete data. Therefore our secondary aim was to test statistically if there was any difference between the outcomes and safety reported for BoNTA in the management of NDO, OAB, DSD, LUTS due to BPE (LUTS/BPE), and BPS/ IC in LE 1 and 2 studies (high level) versus LE 3 (low level) studies.

2. Evidence acquisition

2.1. Literature search

A systematic review protocol was prepared and registered a priori (PROSPERO 2013: CRD42013003724) based on the previous systematic review [1]. In keeping with the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines [3], we searched the PubMed, Scopus, and Embase databases between December 2010 and April 2013 using the Medical Subject Headings *botulinum toxin A* or search terms *botulinum toxin, botulinum neurotoxin, Botox, onabotulinumtoxinA, Dysport, abobotulinumtoxinA, Xeomin, incobotulinumtoxinA, Prosigne, PurTox*, and *BTX*, and combined with the search terms *neurogenic detrusor overactivity, idiopathic detrusor overactivity, overactive bladder, urge(ncy), urge(ncy) incontinence, sensory bladder, interstitial cystitis, painful bladder, bladder pain, bladder outflow obstruction, detrusor sphincter dyssynergia, benign prostatic hyperplasia/enlargement, adverse events*, and *LUTS*. Where possible, language and article type limits were applied to exclude non–English-language articles, review articles, and editorials/letters. References of articles were screened to identify any missed articles.

2.2. Inclusion and exclusion criteria

Two independent reviewers (AM and AA) performed abstract followed by full-text screening independently, excluding nonrelevant articles that included reviews, letters, editorials, nonhuman, nonclinical, and non–English-language studies. Discrepancies in exclusion were resolved by a third author. Articles were further separated according to indication (Fig. 1). All articles were reviewed for primary and secondary outcomes and adverse events by one author (AM) on a Microsoft Excel spreadsheet. When outcomes of a BoNTA injection were reported at more than one time point, the first injection and outcomes reported closest to 4 wk of follow-up were used.

2.3. Assessment of results and statistical analysis

Data were compiled into high-level data (LE 1 and 2) and lower level data (LE 3). The LEs chosen were those applied by the European Association of Urology [4]. Paediatric studies were evaluated separately.

Individual study data were converted into a "percentage change" format so that they were comparable between studies. This was done by subtracting the pretreatment value from the post-treatment value and dividing by the pretreatment value times 100. The mean and its standard error were calculated for each parameter for the level 1 and 2 studies compared with the level 3 studies. Because it was shown previously that the different formulations differ significantly [1], where possible data were reported separately. A two-tailed t test was used to assess for significant differences ($p < 0.05$) in reported outcomes between placebo and high-level studies and also between high- and low-level data. Individual patient data were obtained for postinjection urinary tract infections (UTIs) and intermittent self-catherisation (ISC) rates because this cannot be standardised by baseline. The Fisher exact test was used to assess significant differences ($p < 0.05$).

All level 1 studies were assessed for risk of bias using the Cochrane Collaboration tool [5]. Each study was marked by two authors and scored for risk of bias as high (<1 mark), moderate (2–3 marks), and low (>4).

3. Evidence synthesis

3.1. Available evidence for the use of botulinum toxin A

Since the last review, the number of high-level studies has at least doubled in NDO, OAB, and LUTS/BPE. There have been similar increases in level 3 reports for all indications. Table 1 shows the up-to-date number of studies and