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MANAGEMENT OF OVERACTIVE BLADDER WITH ONABOTULINUMTOXINA: SYSTEMATIC REVIEW AND META-ANALYSIS.

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ABSTRACT

Objective:

To evaluate the efficacy and safety of OnabotulinumtoxinA treatment in the management of overactive bladder syndrome.

Materials and Methods:

A systematic review of the literature and meta-analysis was performed including randomized controlled clinical trials that compared the use of OnabotulinumtoxinA with placebo, antimuscarinic medication, or different doses of OnabotulinumtoxinA. Eleven studies met inclusion criteria and did not have any exclusion criteria. **Primary outcome:** Improvement of urge incontinence, urinary frequency and/or urinary urgency. **Secondary outcomes:** adverse events (urinary tract infection, urinary retention) and quality of life. Outcomes were evaluated after a 12-week follow-up period. **Analysis:** independent evaluation of the study´s quality using the CONSORT Tool was made. Analysis was performed in Review Manager 5.2™.

Results:

Compared with placebo, OnabotulinumtoxinA significantly decreased the number of episodes of urge incontinence. Urinary tract infection was more frequent in patients treated with OnabotulinumtoxinA compared with placebo. Frequency of urinary retention was not significantly different between patients treated with 100 IU OnabotulinumtoxinA dose versus higher doses. Quality of life was assessed with different instruments in three of the studies, this implied a limitation because it was not possible to compare these data.

Conclusions:

Intravesical injections of OnabotulinumtoxinA showed a statistically significant improvement in the treatment of OAB compared with placebo. Adverse events were more frequent among patients treated with OnabotulinumtoxinA. This meta-analysis takes into account only randomized placebo controlled trials.

Key Words:

OnabotulinumtoxinA; Overactive bladder; Meta-analysis; Urge incontinence; Urinary frequency; Urinary urgency; Urinary tract infection; Urinary retention; Quality of life

Disclosures:

We certify that there are no conflicts of interest, including specific financial interests and relationships, affiliations relevant to the subject matter or materials discussed in the manuscript.

INTRODUCTION

Overactive bladder syndrome is characterized by urinary urgency with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia if there is no proven infection or other obvious pathology[1], with a prevalence of 17% in the general population[2]. The treatment includes changes in lifestyle, improving urination pattern, therapy for strengthening muscles of the pelvic floor, and pharmacologic

agents[3]. Along with lifestyle changes, behavioral modifications and pelvic floor muscle training, antimuscarinic medication and B3 adrenoreceptor agonists are the first and second line treatment for OAB respectively, nevertheless, these drugs have a high rate of adverse effects[4], including dry mouth, constipation, blurred vision and decrease in cognitive function[5] leading to treatment discontinuation in some cases[6].

According to the American Urology Association and European Urology Association guidelines recommendations, OnabotulinumtoxinA intravesical injection is considered one of the third-line treatments for patients without response to second line therapy, as well as neuromodulation[7],[8]. This is a neurotoxin derived from the anaerobic bacteria *Clostridium botulinum*, which has several types, being type A the one with the best results regarding duration [9] . The mechanism of action is based on inhibiting acetylcholine release from presynaptic neurons, as well as adenosine triphosphate (ATP) and P substance liberation in urothelium[9]. The decrease in acetylcholine availability in the neuromuscular junction can cause detrusor paralysis and hence a decrease in symptoms[9]. OnabotulinumtoxinA is applied by cystoscopy and direct injection in multiple sites within the bladder wall[9]. The most frequent adverse effects following the administration of the toxin are urinary retention and urinary tract infection[9].

Several studies have been developed to evaluate the efficacy of OnabotulinumtoxinA in the treatment of overactive bladder, and these have demonstrated its superiority over placebo[10]. The present study aims to evaluate the outcomes, efficacy and safety of OnabotulinumtoxinA application in patients with overactive bladder, given the best evidence available.

MATERIALS AND METHODS

Objective:

To evaluate the efficacy and safety of OnabotulinumtoxinA treatment in the management of overactive bladder syndrome

Primary outcomes for efficacy: cure/improvement of urge incontinence, urinary frequency and/or urinary urgency. **Primary outcomes for safety:** adverse events (urinary tract infection, urinary retention) **Secondary Outcomes**: quality of life.

Outcomes were evaluated after a 12-week follow-up period.

Search strategy:

A search of the medical literature was performed since June 2012 in the following databases: MEDLINE, EMBASE, LILACS, Cochrane, GreyNet and OpenGrey. The search strategy for MEDLINE used the following combination of Medical Subject Headings (MeSH) terms: ("botulinum toxin" OR "botulinum toxins" OR "botox" OR "clostridium botulinum toxins" OR "botulinum toxins type A" OR "onabotulinumtoxinA" OR "botulinum neurotoxin A" OR "oculinum") AND ("idiopathic overactive bladder" OR "overactive bladder" OR "overactive detrusor function" OR "overactive detrusor") NOT ("neurogenic"). This search was subsequently limited to include only studies in humans, with subjects 18 years or older, published in English or Spanish, and including the article types of interest (randomized clinical trials, phase I-IV clinical trials and multicenter studies) with no publication date limits.

The EMBASE search combined the terms “Botulinum toxin A and Overactive bladder” in the Emtree. The search limits were: medication (botulinum toxin A, botulinum toxin, placebo, muscle relaxant agent), pathology (overactive bladder, urine incontinence, incontinence, urinary tract infection, urine retention, urge incontinence, side effect, nocturia, urinary urgency, lower urinary tract symptom, unspecified side effect), type of study (human, controlled study, clinical article, clinical trial, prospective study, randomized controlled trial, controlled clinical trial, double blind procedure, multicenter study, randomized controlled trial [topic], drug dose comparison). There were no limits applied on publication date, journal title or type of publication.

The Spanish search strategy for the LILACS database used the terms “vejiga hiperactiva” AND “toxina botulínica tipo A”. We applied filters according to subject descriptors (vejiga urinaria hiperactiva, toxina botulínica tipo A, incontinencia urinaria, fármaco neuromusculares y calidad de vida), publication type (ensayo clínico controlado), clinical aspect (terapia), limit (humanos), and language (inglés, español). There were no limits on publication date, country or population.

In the Cochrane Library, the search used the terms “botulinum toxin and overactive bladder”. A limit was applied on type of study (trial), and the search did not look for word variations. There was no limit on publication date.

Finally, the grey literature search in GreyNet and OpenGrey used botulinum toxin and overactive bladder as the only terms.

The inclusion criteria included that the selected articles were randomized clinical trials that compared (1) different doses of Onabotulinum toxin A, (2) the use of

OnabotulinumtoxinA versus placebo or (3) the use of OnabotulinumtoxinA versus antimuscarinics. Exclusion criteria included trials conducted in animals, with non-urological indication, written in other languages tan english or spanish, editorial comments, case reports or review papers.

To be included the studies had to assess the efficacy and/ or the safety of the aforementioned techniques and/or predictors of success.

Data organization and extraction:

Data from the studies that met the inclusion criteria, were independently extracted by the five authors using a specially designed format. Any discrepancy encountered was resolved between the first two authors and if there was no consensus, the discussion was sent to the third author.

Data extraction included:

- Bibliographic reference
- Country, city, institutions and date of the study
- Study design
- Verified inclusion and exclusion criteria
- Information on basal features of patients
- Intervention description: presentation, dosage, route of administration
- Description of outcome measurement

- Quality evaluation of the studies
    - Risk of bias
        - Method to generate random assignment
        - Method to maintain assignment concealed
        - Use of masking methods for subjects or investigators for the intervention or in the outcome evaluation
        - Outcomes mentioned in methodology versus outcomes reported (report bias)
        - Lost to follow up
        - Other possible sources of bias
- Validation process for adverse effects
- Use of the intention to treat analysis
- Calculation of study power or sample size estimation
- Informed financing source
- Ethical aspects such as informed consent and ethical approval
- Results
- Number of recruited patients, assigned patients, excluded patients after random assignment, and analyzed subjects

- Outcomes

Treatment effect measurement

The measurement of the intervention effect was completed using risk difference (RD) for dichotomous outcomes, hazard ratio (HR) if density of the frequency was available (time to the event), and with weighted mean difference (WMD) for quantitative variables.

If we had at least two studies with the same outcome, the heterogeneity of the studies was evaluated, first according to the clinical approach, and then with a statistical one:

1. Visual exploration of the forest plot using a random effect method
2. Calculation of statistical I^2, which measures percentage of heterogeneity
3. Calculation of Cochran statistic, whose null hypothesis assumes homogeneity between the studies

If heterogeneity was found, and was greater than 50%, its source was investigated (population, differences in the intervention, differences in outcome measurement).

Statistical analysis was performed through Review Manager 5.2. Treatment primary outcomes to evaluate efficacy were defined as reduction in episodes of urge incontinence, urinary urgency or urinary frequency. Primary outcomes for therapy safety were episodes of urinary retention or urinary tract infection. Quality of Life changes was the secondary outcome.

RESULTS

Studies identified by the literature search

This search strategy retrieved 119 titles in MEDLINE, 139 titles in EMBASE, 114 titles in LILACS and 46 titles in Cochrane, with no results in the grey literature search (Figure 1). Two authors (López HE, Torres L) reviewed the titles and abstracts of this search result in order to select eligible studies for qualitative analysis. The selection was done according to the level of evidence, including only randomized clinical trials (evidence level 1b). Eligible studies were reviewed by the authors using the CONSORT Tool,[11] to include only studies meeting the design of a randomized clinical trial.

Study characteristics

The present review focused exclusively on randomized clinical trials. The quality of randomized clinical trials was evaluated with the Cochrane tool for assessing bias risk[12]. Included studies had an intervention group with OnabotulinumtoxinA injection in the detrusor muscle; the control group could include placebo, anti-cholinergic medications or comparisons of different doses of OnabotulinumtoxinA. Similarly, these studies included reported data on efficacy, safety and patients' quality of life after the intervention (Supplementary Table 1). The adverse effects reported in each study are summarized in Supplementary Table 2. The administration protocol of OnabotulinumtoxinA in each study is described in Supplementary Table 3.

Risk evaluation and bias in the included studies

For each study included, a complete bias risk evaluation was developed (Supplementary Figure 1). Five risk domains were taken into account to define if risk bias was high, low, or not clear[13].

Selection bias: Generation of the assignment sequence and concealment of the assignment. Performance bias: No masking of the subjects, the personnel who makes the intervention, or the evaluators of the outcomes. Detection bias due to lack in masking of the subjects, personnel who makes the intervention, or the evaluators of the outcomes. Other possible sources of bias are wear bias, incomplete data results or report bias defined as not reporting the most important results.

Quality of reporting

Out of the 418 articles retrieved by the search strategy, 16 studies met the inclusion criteria. Six of these articles met at least one of the exclusion criteria, and the remaining 10 articles were included in this systematic review.

For the analysis of the primary outcomes for efficacy 6 studies were comparable for meta-analysis amongst the different outcomes. For the analysis of the primary outcomes for Safety all the 10 studies were included, as they were all comparable for meta-analysis amongst the different outcomes.

Urinary urge incontinence episodes

For this outcome we compared the following studies: Nitti 2013[14], Chapple 2013[15], Dawson 2011[16] and Sahai 2007[17] (Figure 2). There was a statistically significant difference between the injection of OnabotulinumtoxinA and placebo (WMD: -0.8; 95% CI -3.28 to 1.68); this means that patients receiving OnabotulinumtoxinA had 0.8 less episodes of urge incontinence than patients receiving placebo.

At evaluation of the Denys (2012)[18] study, at a reduction greater than 50% of urge and urge incontinence episodes in (Supplementary Figure 2), there was no statistically significant difference between OnabotulinumtoxinA and placebo; the same occurs at evaluation of a reduction greater than 75% of urge and urge incontinence episodes (Supplementary Figure 3).

Urinary urge episodes

For this outcome we compared the following studies: Nitti 2013, Chapple 2013 and Dawson 2011 (Figure 3). There was a statistically significant difference between the injection of OnabotulinumtoxinA and placebo (WMD: -1.26; 95% CI -2.40 to -0.13); this means that patients that receiving OnabotulinumtoxinA had 1.26 less episodes of urge episodes than patients that receiving placebo.

Urinary frequency

We compared the following studies: Nitti 2013, Chapple 2013, Dawson 2011 and Cohen 2009[19] (Supplementary Figure 4). There was a statistically significant difference between the injection of OnabotulinumtoxinA and placebo (WMD: -0.56; 95% CI -1.77 to

0.65); this means that patients that receiving OnabotulinumtoxinA had 0.56 less episodes of micturition than patients that receiving placebo.

Adverse events

Urinary tract infection and urinary retention were the most common adverse events reported after injection of OnabotulinumtoxinA.

Urinary retention

Urinary retention was defined as a post void residue of 200mL.[20] For this outcome, the following studies were compared: Cohen 2009, Dmochowski 2010[21], Dowson 2011, Altaweel 2011[22], Denys 2011, Nitti 2013 and Chapple 2013. There was statistically significant difference between administrations of 100 U of OnabotulinumtoxinA versus placebo (RR: 11.49; 95% CI: 4.6 to 28.70; p= 0.00001) (Figure 4).

Evaluating the studies Sahai 2007, Flynn 2008[23], Tincello 2011[24] and Dmochowski 2010; a similar outcome is seen in dosages of 200U of OnabotulinumtoxinA versus placebo (RR: 5.52; 95% CI: 2.54 to 12.01; p= 0.0001) (Supplementary Figure 5).

For different dosages of Onabotulinum toxin A, using the studies Altaweel 2011 and Dmcochowski 2010, there was no statistically significant difference between doses (RR: 0.70; 95% CI: 0.38 to 1.27; p= 0.24) (Supplementary Figure 6).

Urinary tract infection

Comparison was made between the following studies: Flynn 2008, Dmochowski 2010, Denys 2011, Dowson 2011, Chapple 2013 and Nitti 2013. There was statistically significant difference in the episodes of urinary tract infection between doses of 100U

OnabotulinumtoxinA versus placebo (RR: 02.73; 95% CI: 1.98 to 3.78; p= <0.00001) (Supplementary Figure 7). When we compared 100U of OnabotulinumtoxinA injection versus higher doses in the studies Altaweel 2011, Denys 2011 and Dmochowski 2010 (Supplementary Figure 8), there was no statistically significant difference in the episodes of urinary tract infection when different doses of Onabotulinum toxin A were administered (RR: 0.86; 95% CI: 0.58 to 1.26; p= 0.43).

DISCUSSION

Lack of results and poor adherence to first and second line treatments, have been the reasons to search for new strategies in the management of OAB, an illness that greatly compromises the quality of life of the patients.

OnabotulinumtoxinA intravesical injection is now recommended as a third-line treatment for OAB. In this systematic review we included randomized clinical trials that compare OnabotulinumtoxinA with placebo. A total of eleven studies met the inclusion criteria and risk bias analysis, including a number of 2149 patients.

Compared with placebo, OnabotulinumtoxinA 100U significantly decreased the number of episodes of urge incontinence at 12 weeks post-injection. Frequency of urinary retention and urinary tract infection was more frequent in patients treated with OnabotulinumtoxinA compared with placebo; there were no statistically significant differences in infection rates between patients treated with the 100 IU OnabotulinumtoxinA regimen and those receiving higher doses. There were no differences between outcomes and adverse events related to the injection site. Only one clinical trial compared OnabotulinumtoxinA with anti-cholinergic medications,

showing significant differences in complete improvement of urge incontinence and any type of incontinence[22] (27% vs. 13%, P=0.003). We found that 100U of OnabotulinumtoxinA is an effective treatment for symptoms of OAB.

Study limitations were given by heterogeneity in the reporting of primary and secondary outcomes, different measures of central tendency were used, which make difficult meta-analysis of the data. We also found that the measurement of quality of life was accomplished through different scales so quantitative analysis could not be performed. Not all of the studies included urodynamic data, for this reason this outcome was not mentioned in our analysis.

Despite the limitations described above the results given were meta-analyzed according to the significance of the I squared test for heterogeneity, and the results showed to be statistically significant in favor of the OnabotulinumtoxinA.

CONCLUSIONS

Intravesical injections of 100U of OnabotulinumtoxinA showed a statistically significant improvement in the treatment of OAB compared with placebo at 12 week of injection. Adverse events were more frequent among patients treated with OnabotulinumtoxinA, primarily episodes of urinary tract infection and urinary retention. This meta-analysis takes into account only randomized placebo controlled trials. Standardization in the measurement of quality of life is recommended, so that formal comparisons and analysis are possible in the future.

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Figure 1. Study evaluation and selection

Figure 2. Change in urinary urge incontinence episodes after dose of OnabotulinumtoxinA and placebo

Figure 3. Change in urinary urge episodes after dose of OnabotulinumtoxinA 100 U versus placebo

Figure 4. Frequency of urinary retention among patients who received 100 U of OnabotulinumtoxinA versus placebo

Supplementary Figure 1. Risk of Bias

Supplementary Figure 2. Greater than 50% reduction incontinence

Supplementary Figure 3. Greater than 75% reduction incontinence

Supplementary Figure 4. Change in urinary frequency

Supplementary Figure 5. Frequency of urinary retention (200 U)

Supplementary Figure 6. Frequency of urinary retention (100 U)

Supplementary Figure 7. Urinary tract infection (Toxin vs placebo)

Supplementary Figure 8. Urinary tract infection (Toxin Vs Higher dosis)