Treatment of Non-neurogenic Overactive Bladder with OnabotulinumtoxinA: Systematic Review and Meta-analysis of Prospective, Randomized, Placebo-controlled Clinical Trials*

*Tratamento da bexiga hiperativa não neurogênica com toxina botulínica A: revisão sistemática e metanálise de ensaios clínicos prospectivos, randomizados e placebo-controlados**

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Abstract

We performed a systematic review and meta-analysis of randomized placebo-controlled trials that studied non-neurogenic overactive bladder patients who were treated with 100 units of onabotulinumtoxinA or placebo. The primary purpose of our study was to evaluate the clinical effectiveness with regard to urinary urgency, urinary frequency, nocturia, and incontinence episodes. Our secondary purpose consisted of evaluating the adverse effects. Our initial search yielded 532 entries. Of these, seven studies met all the inclusion criteria (prospective, randomized, placebo-controlled studies, $\geq$ 3 points on the Jadad scale) and were selected for analysis. For all primary endpoints, the toxin was more effective than placebo ($p < 0.0001$; 95% confidence interval [95CI]), namely: urgency (mean difference = -2.07; 95CI = [-2.55–1.58]), voiding frequency (mean difference = -1.64; 95CI = [-2.10–1.18]), nocturia (mean difference = -0.25; 95CI = [-0.39–0.11]) and incontinence episodes (mean difference = -2.06; 95CI= [-2.60–1.52]). The need for intermittent catheterization and the occurrence of urinary tract infection (UTI) were more frequent in patients treated with onabotulinumtoxinA than in patients treated with placebo ($p < 0.0001$). Compared with placebo, onabotulinumtoxinA had significantly and clinically relevant reductions in overactive bladder symptoms and is associated with higher incidence of intermittent catheterization and UTI.

Keywords

- overactive bladder
- systematic review
- botulinum toxin
- randomized controlled trials

Resumo

Realizou-se revisão sistemática e metanálise de estudos clínicos prospectivos, randomizados e placebo-controlados que comparavam a toxina botulínica ao placebo no tratamento da

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bexiga hiperativa. O objetivo primário desta metanálise foi avaliar a eficácia da toxina botulínica em relação à urgência urinária, frequência miccional, noctúria e episódios de incontinência. O objetivo secundário foi avaliar os efeitos adversos. Selecionamos estudos que incluíram somente pacientes com bexiga hiperativa não-neurogênica tratada com 100 unidades de onabotulinum toxina A ou placebo (grupo controle). Foram encontrados 532 estudos após as buscas iniciais, dos quais sete apresentaram todos os critérios de inclusão (estudos prospectivos, randomizados, placebo-controlados, ≥ 3 pontos na escala de Jadad) e fizeram parte desta análise. Para todos os objetivos primários a toxina foi mais eficaz do que o placebo, com $p < 0,0001$ e intervalo de confiança (IC) de 95%: urgência (diferença média = -2,07, IC = [-2,55; -1,58]), freqüência miccional (diferença média = -1,64, IC = [-2,10; -1,18]), noctúria (diferença média = -0,25, IC = [-0,39; -0,11]) e episódios de incontinência (diferença média = -2,06, IC= [-2,60; -1,52]). A necessidade de cateterização intermitente e a ocorrência de infecção urinária (ITU) foram mais frequentes no grupo toxina na comparação com o grupo placebo ($p < 0,0001$). A toxina botulínica promoveu melhora significativa dos sintomas de bexiga hiperativa na comparação com o placebo. Entretanto, está associada a uma maior incidência de cateterismo intermitente e infecção do trato urinário.

Palavras-chave
- bexiga hiperativa
- revisão sistemática
- incontinência urinária
- toxina botulínica
- estudos randomizados controlados

Introduction

The International Continence Society defines overactive bladder as a syndrome characterized by urinary urgency, with or without urgency urinary incontinence, usually accompanied by nocturia and an increase in urinary frequency, in the absence of infection, metabolic or local factors.[1]

Different population studies concluded that overactive bladder is highly prevalent both in males and females, with relevant negative impact on the patients' quality of life (social, physical, psychological, sexual, personal relationships, work, and domestic domains); moreover, it has a considerable financial impact on patients themselves and thus on the health care system.[2–5]

Patients who do not satisfactorily respond to behavioral and/or pharmacological treatment are diagnosed with refractory overactive bladder. This group includes patients with contraindications and intolerable side effects to medication.[6]

While both the European Association of Urology (EAU) and the American Urological Association (AUA) recommend intravesical injection of botulinum toxin A in refractory overactive bladder cases, a vast majority of articles discusses only neurogenic cases of this dysfunction.[7,8]

Our systematic review followed by meta-analysis included only non-neurogenic overactive bladder patients who were treated with 100 units of onabotulinumtoxinA.

Methods

Our study was registered in the PROSPERO database in 2016, under the reference number CRD42016035815.

Prospective randomized placebo-controlled studies featuring Jadad scale methodological quality ≥ 3 were selected.[9] The study populations should necessarily include patients aged 18 years or older with a diagnosis of non-neurogenic overactive bladder syndrome treated with 100 units of onabotulinumtoxinA, at least in one of the arms of the study.

Patients with mixed urinary incontinence and a clear prevalence of overactive bladder complaints were also included. Performance of urodynamic study was not considered a prerequisite for inclusion in our analysis, since overactive bladder diagnosis is clinically suspected and detrusor overactivity may or may not be present. The exclusion criteria comprised use of a dose other than 100 units of onabotulinum toxin A, use of botulinum toxin other than onabotulinumtoxinA, neurogenic cases and literature or systematic reviews.

Primary Outcomes

The primary outcome of our study was to evaluate the clinical effectiveness with regard to the following variables: urgency (complaint of a sudden compelling desire to pass urine that is difficult to defer),[1] urinary frequency (complaint by the patient who considers that he/she voids too often by day),[1] nocturia (complaint that the individual has to wake up at night one or more times to void),[1] and incontinence episodes (complaint of any involuntary leakage of urine).[1]

Secondary Outcomes

The secondary outcome was to evaluate all adverse effects reported in the studies included in the meta-analysis.

Study Search and Selection

We performed a search for randomized clinical trials (RCTs) in the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE.

The MEDLINE search included the following terms: "overactive bladder," "detrusor overactivity," "bladder overactivity," "botulinum toxin," "onabotulinumtoxinA" and "botox."

Only studies in English were selected, and the search was done from the inception of the database, given that the use of botulinum toxin in the treatment of non-neurogenic overactive bladder is relatively recent. Two authors (R. M. A. and C. C. T.) independently reviewed all the abstracts and titles to select the papers that were relevant for review, later analyzing the full

text of the selected studies to determine eligibility. The last online search was performed on June 20th, 2015. A spreadsheet for data collection was created to extract the data of interest in each article, which were then retyped in a single database to avoid loss of data or mistyping of any kind. Any disagreements were resolved by consulting a third author (R. A. C.). Outcomes verified in two articles or more were grouped for meta-analysis.

Statistical Analysis

We summarized binary outcomes based on the number of events using Peto odds ratio in situations with zero number of events in one of the groups, or the Mantel-Haenszel method in situations of a very low event rate. Furthermore, we summarized continuous outcomes (incontinence, urgency, frequency and nocturia) using the mean difference (MD), calculated by the inverse variance method. Precision of estimates appear as 95% confidence intervals (95CIs).

Heterogeneity across studies was evaluated using Cochran Q statistic and Higgins I2.[10] We quantified statistical heterogeneity using I2, informing its value together with the estimates. We considered I2 elevated whenever it was higher than 60%. However, a fixed-effect model was considered when a very small number of studies were included.[10]

In addition to the heterogeneity analyses described above, sensitivity analyses excluding one study at a time were performed to evaluate the influence of individual studies on the overall result. We used the RevMan 5.3 statistical package (Nordic Cochrane Center, Copenhagen, Denmark) to perform the analysis.

Quality Assessment

The quality of studies included in the analysis was independently assessed by two authors (R. M. A. and C. C. T.) using the Jadad scale for RCTs classification.[9] Studies scoring ≥ 3 were considered eligible for inclusion. Any disagreements were resolved by consulting a third author (R. A. C.).

The Jadad scale assesses the quality of published clinical trials based on methods relevant to random assignment, double blinding, and patient flow. There are seven items, but points may be deducted in the last two, which means that the range of possible scores is 0 (bad) to 5 (good).[9] The bias risk was assessed by the use of a Cochrane collaboration tool.[1]

Results

Description of Studies

►**Fig. 1** describes the flow chart for this review. Five hundred and thirty-two articles were retrieved after research on the Cochrane and Medline databases, using the keywords "overactive bladder" OR, "detrusor overactivity" OR "bladder overactivity" AND "botulinum toxin" OR "onabotulinumtoxinA" OR "botox."

Out of those, 333 articles were selected after reading the title and abstract, whereas 271 were excluded since they did not meet selection criteria. Therefore, 62 articles were considered eligible and read in full by two authors. After this initial reading, 53 articles were excluded for using onabotulinumtoxinB and/or for including patients with neurogenic overactive bladder. Eventually, 9 studies met all the inclusion criteria and were selected for this meta-analysis (►**Fig. 1** and ►**Table 1**)

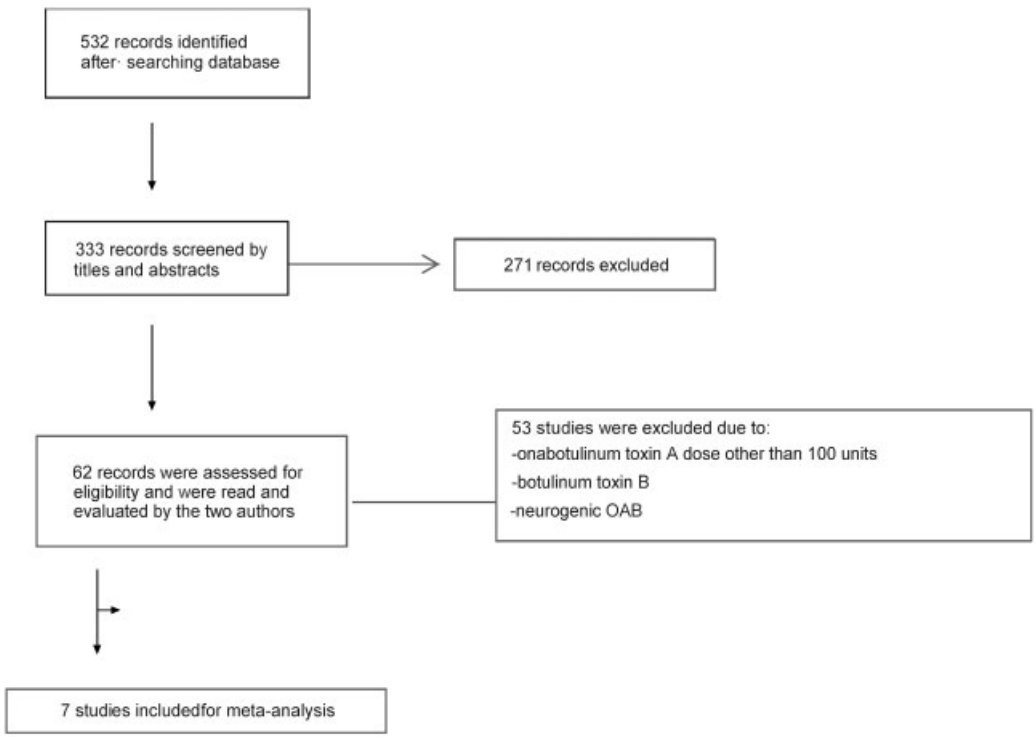

Fig. 1 Flow diagram of article selection.

Table 1 Articles included in the meta-analysis

References	Study design	Jadad scale	N placebo/toxin	Weeks follow-up
Chapple et al.[11]	Multicenter, randomized, double-blind	5	271/277	12
Denys et al.[12]	Multicenter, randomized, double-blind	5	29/70	24
Dmochowski et al.[13]	Multicenter, randomized, double-blind	5	43/268	36
Dowson et al.[14]	Single-center, randomized, double-blind	5	11/10	24
Flynn et al.[15]	Single-center, randomized, double-blind	5	7/15	6
Nitti et al.[16]	Multicenter, randomized, double-blind	5	44/54	36
Rovner et al.[17]	Multicenter, randomized, double-blind	5	44/269	36

Two studies could be included for analysis of urinary urgency, urinary frequency, nocturia, and incontinence episodes. There was no evidence of heterogeneity among the articles, except for urinary incontinence. However, because the number of articles is very small, the fixed-effect model was considered.

It can be observed in ►**Fig. 2** that there was significant reduction in urinary urgency episodes in the toxin group (experimental group) in comparison with the placebo group (control group) (MD = -2.07, 95CI = [-2.55; -1.58]; $p < 0.0001$).

►**Fig. 3** shows that there was significant reduction in urinary frequency in the toxin group (experimental group) when compared with the placebo group (control group) (MD = -1.64, 95CI = [-2.10; -1.18]; $p < 0.0001$).

A similar result was observed in analyzing nocturia episodes (►**Fig. 4**). There was significant reduction in nocturia in the toxin group (experimental group) in relation to the placebo group (control group) (MD = -0.25, 95CI = [-0.39; -0.11]; $p < 0.0001$).

In ►**Fig. 5** we further confirmed that there was significant reduction in the number of urinary incontinence episodes in the toxin group (experimental group) in relation to the placebo group (control group) (MD = -2.06, 95CI = [-2.60; -1.52]; $p < 0.0001$).

Secondary Purposes

Adverse Effects of Catheterization

For analysis of vesical catheterization occurrence, it was possible to include five studies. According to the data (►**Fig. 6**), it is possible to verify that the need for catheterization was significantly higher in the toxin group (experimental

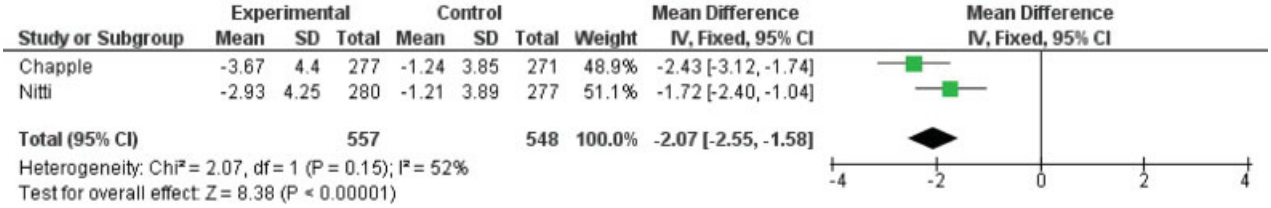

Fig. 2 Forest plot of change in urgency after onabotulinumtoxinA (experimental) and placebo (control) injections.

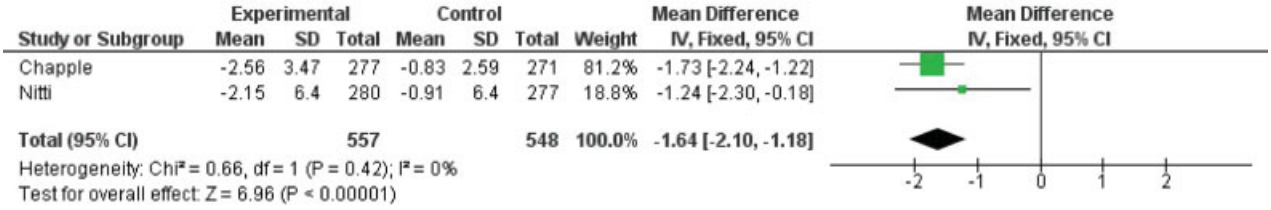

Fig. 3 Forest plot of change in frequency after onabotulinumtoxinA (experimental) and placebo (control) injections.

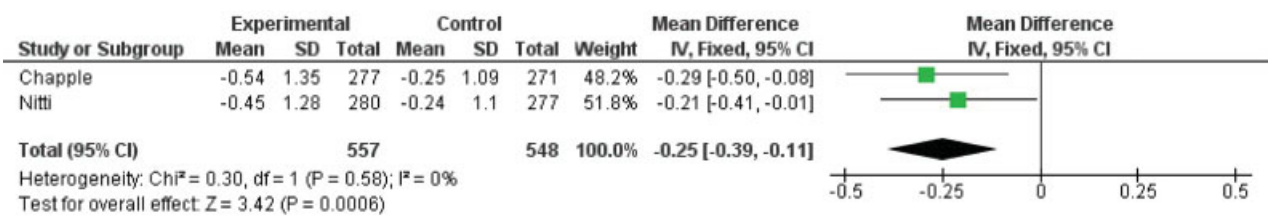

Fig. 4 Forest plot of change in nocturia episodes after onabotulinumtoxinA (experimental) and placebo (control) injections.

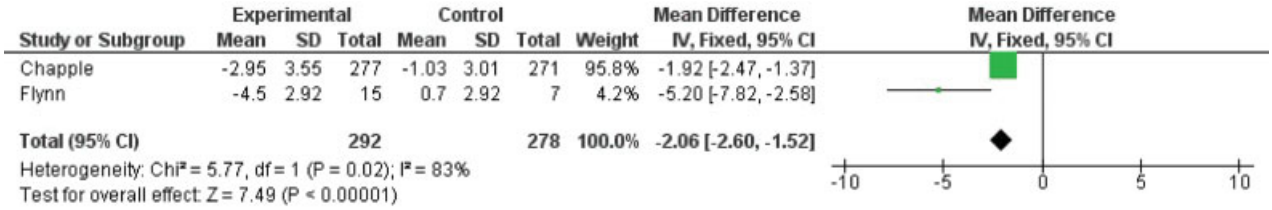

Fig. 5 Forest plot of change in urinary incontinence episodes after onabotulinumtoxinA (experimental) and placebo (control) injections.

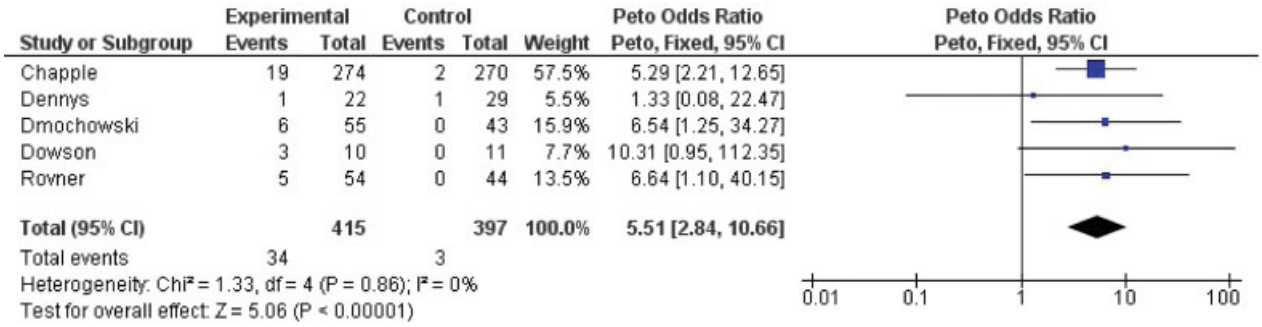

Fig. 6 Forest plot of change of pulmonary vascular resistance-related catheterization after 100 units of onabotulinumtoxinA (experimental) and placebo (control) injections.

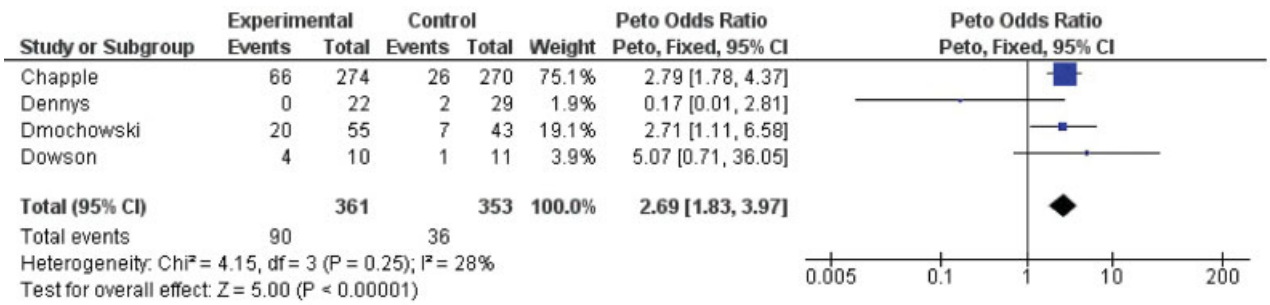

Fig. 7 Forest plot of change of urinary tract infection after 100 units of onabotulinumtoxinA (experimental) and placebo (control) injections.

group) when compared with the placebo group (control group), with no heterogeneity in this analysis.

In ►**Fig. 7** we present the forest plot graph for the data referring to urinary tract infection occurrence. We note in the plot forest graph that the Peto odds ratio meta-analytical value (OR = 2.69, IC (95%) = [1.83; 3.97]; *p* value < 0.0001) is located fully to the right of the vertical line. Such result demonstrates higher probability of urinary infection in the toxin group (experimental) when compared with the placebo group (control). Homogeneity among studies was confirmed by Q (Chi) in the Cochran test (p value = 0.25).

Regarding the quality of life evaluation, it was not possible to perform the meta-analysis, since the authors used different questionnaires, which made it impossible to evaluate this item.

Discussion

Our results demonstrated that the onabotulinumtoxinA had greater efficiency when compared with the placebo in relation to the all the symptoms analyzed (urinary frequency, nocturia, and urinary incontinence episodes). Such results are also in agreement with other systematic reviews and meta-analyses in respect to the subject.[18,19]

There was significant reduction in the number of urinary urgency episodes in the group treated with toxin in comparison with the placebo group. However, none of the studies evaluated urgency intensity, probably because it is a subjective symptom, and it is very difficult to be characterized.

The last Cochrane review (2011)[19] on this topic included 19 studies, mostly with neurogenic patients. In our study, we were interested in demonstrating the efficacy of onabotulinumtoxinA in the treatment of non-neurogenic overactive bladder, which is usually followed by the gynecologist.

We chose to include only articles in which the toxin used was onabotulinumtoxinA because it is the toxin most frequently indicated in Brazil, and it is available to treat overactive bladder in both private and public health services.

Although most studies included analyzed the patients' quality of life, unfortunately it was not possible to perform a systematic review of this variable given that the authors used different tools for this evaluation. Nevertheless, different studies have concluded that botulinum toxin significantly improves patient symptoms and quality of life.[11,20]

In the articles included in our study, the only side effects significantly higher in the toxin group in comparison with the placebo were urinary tract infection and urinary retention. Such

side effects were both more frequent in the 100 units dose. Furthermore, other possible side effects are dry mouth, hematuria, respiratory depression, and general muscular weakness.[21]

Urinary retention was the main complication reported in the studies. According to the literature data, its incidence ranges from 0–72%, depending on the toxin dose used and the definition of urinary retention with or without need for catheterization (which is extremely variable among the authors).[19,20] Most articles included in this meta-analysis considered as urinary retention the presence of post-urination residue $\geq$ 200 mL.[11–13,17]

The need for intermittent catheterization at the 100 units dose, which is the most frequently used dosage in non-neurogenic cases, ranged from 6.9[11]–30%.[14]

It should be noted, however, that the indication of catheterization was varied among the studies. The lowest rate was in Chapple et al,[11] which only indicated it in asymptomatic cases if post-urination residue was $\geq$ 350 mL. In turn, Brubaker et al (2008)[21] indicated intermittent catheterization in cases with post-urination residue $>$ 200 mL after 4 weeks from the injection, regardless of the symptoms. Such differences between the definitions for urinary retention and the need for catheterization render comparison among studies difficult. In addition, possible clinical consequences of asymptomatic urinary retention are not clear. Regardless, such retention is transitory and dose-dependent.[11,20,22]

The primary strength of this systematic review was to only include prospective, randomized, placebo-controlled articles featuring Jadad scale methodological quality $\geq$ than 3.[9] The fact that we have only included patients treated with 100 units of onabotulinumtoxinA and non-neurogenic cases also contributed to facilitate the interpretation of results.

The limitations refer mainly to the differences between injection application techniques, the follow-up time, and the evaluation of quality of life, which undoubtedly renders greater generalization of results.

Conclusion

In comparison with the placebo, onabotulinumtoxinA promotes significant improvement of urinary urgency, urinary frequency, nocturia, and incontinence symptoms. There is higher incidence of urinary retention and urinary tract infection among patients in the toxin group in relation with the placebo group. It was not possible to evaluate the effects on quality of life. This systematic review is endorsed by the Urogynecology Committee of the Federação das Associações Brasileiras de Ginecologia e Obstetrícia (Brazilian Federation of the Societies of Gynecology and Obstetrics, [FEBRASGO, in the Portuguese acronym]) and suggests that the dose of 100 units of onabotulinumtoxinA is effective in the treatment of non-neurogenic refractory overactive bladder.

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