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The role of botulinum toxin in the management of nonneurogenic overactive bladder in children: Highlights for clinical practice. A systematic review

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Abstract

Overactive bladder (OAB) is the most common voiding dysfunction in children; however, nonneurogenic or idiopathic OAB remains poorly studied. First-line treatment includes conservative measures; however, as many patients are refractory, have adverse effects, or are contraindicated for anticholinergics, new options must be explored. This review covers the use of intravesical botulinum toxin (BoNT) for idiopathic OAB treatment in children, emphasizing its efficacy, safety, differences between toxins, doses, and injection techniques. Clinical results were promising, with all 8 studies reporting good results. All authors used BoNT type A (BoNT-A), either onabotulinum or abobotulinum toxin A. Response rates were variable, with full-response percentages of 32%–60%. As proven by the full-response rates of 50%, repeated injections are as safe and effective as first injections. Only a few cases of urinary tract infection, transient urinary retention, and hematuria have been reported, with no major local or systemic adverse effects. Despite these limitations, evidence encourages and supports BoNT-A use as a safe and effective treatment modality for refractory idiopathic OAB in pediatric settings, regardless of dosage and target toxin. To the best of our knowledge, this is the first systematic review of the use of intravesical BoNT-A for idiopathic OAB treatment in children.

Keywords: Botulinum toxin; Idiopathic detrusor overactivity; Idiopathic overactive bladder; Nonneurogenic detrusor overactivity; Nonneurogenic overactive bladder

1. Introduction

Overactive bladder (OAB) constitutes a set of signs and symptoms, such as urinary urgency usually accompanied by urinary frequency and nocturia, with or without urinary incontinence, in the absence of urinary tract infection or other obvious pathology,[1] with estimates of prevalence ranging from 15% to 20% in the pediatric population,[2] decreasing to 12% in the adolescent population.[3]

Overactive bladder is the most common pediatric voiding dysfunction.[4] It is usually associated with disabling signs and symptoms that can negatively impact children's psychological development and quality of life.[5,6] It may have a neurogenic or nonneurogenic etiology. The former is the more widely studied. In contrast, nonneurogenic or idiopathic OAB is less commonly investigated, in terms of its pathophysiological and treatment aspects.[7] Overactive bladder is frequently associated with detrusor overactivity, defined as uncontrolled contractions of the detrusor muscle during the bladder-filling phase of urodynamic testing by the International Continence Society.[8] First-line treatment includes conservative measures, such as education, behavioral therapy, and

pharmacotherapy. The most commonly used drugs are anticholinergics; however, given the high rate of adverse effects (xerostomia, constipation, blurred vision) and contraindications, they are frequently discontinued (approximately 85% after 1 year).[9] Therefore, some new therapeutics, particularly intravesical botulinum toxin type A (BoNT-A) injections, have emerged as possible treatment options.

In urology, BoNT-A was initially used in 1988 in patients with bladder sphincter dyssynergia[4]; however, its first application to the detrusor of paraplegic patients with neurogenic bladder under intermittent catheterization was reported in 2000.[7] Because of experience in treating neurogenic bladder and sphincteric dysfunction, some authors concluded that detrusor overactivity was the most sensitive component susceptible to BoNT-A treatment; therefore, idiopathic OAB patients would also benefit from this treatment.[6]

Recently, some authors have studied this topic, particularly in the pediatric population, and have suggested that BoNT-A is safe and effective for pediatric patients with nonneurogenic OAB that is refractory to conservative treatment. To the best of our knowledge, there are no systematic reviews on the use of BoNT-A in children with nonneurogenic OABs. In this article, we reviewed the literature regarding the use of BoNT-A for pediatric idiopathic OAB, emphasizing its efficacy and safety, differences between different toxins, doses, and application techniques.

2. Materials and methods

2.1. Search strategy

We conducted a systematic literature review on PubMed, Web of Science, and Scopus using the following keywords in different

combinations: non-neurogenic detrusor overactivity, non-neurogenic overactive bladder, idiopathic detrusor overactivity, idiopathic overactive bladder, and botulinum toxin. We restricted articles to those targeting the pediatric population and published in English until June 2021.

2.2. Study selection

Titles and abstracts were screened, followed by a full-text review. We excluded articles that did not characterize symptoms before the intervention or fully describe the procedure with respect to the type of botulinum toxin and doses. In addition, all references in the articles included in the full-text review were screened for further relevant articles. Articles were assessed by 2 independent reviewers, and any differences in article inclusion were discussed and resolved by reaching a consensus.

2.3. Data extraction

The following data were extracted: first author, year of publication, study type, sample size, age of participants, inclusion and exclusion criteria, BoNT type, dilution, doses, whether subsequent injections were performed, injection techniques, follow-up, outcomes, preoperative and postoperative urodynamics, and adverse effects.

2.4. Data analysis

A qualitative analysis was performed to present the results in narrative summary fashion.

3. Results

In total, we included 8 articles reporting the results of intravesical BoNT-A injections on refractory idiopathic OAB in children. Four studies each were retrospective[6,7,10,11] and prospective[5,6,12,13] (Fig. 1; Tables 1 and 2).

The sample size ranged from 8[5] to 46[4] children, for a total of 202 patients in the 8 included studies. Patient ages varied between 4[4] and 19 years.[13]

The studies included children presenting with OAB refractory to conservative treatment (behavioral strategies, rehabilitation, and anticholinergic therapy). Some patients did not improve with conservative treatment, and some had to discontinue anticholinergic therapy because of adverse effects. Conservative treatment varied among studies, as did the period necessary to classify it as refractory (ranging from 6[12] to 20 months of medical and behavioral therapy[5]).

Patients with neurogenic bladder, uropathy, or dysfunctional voiding,[4–6,11,12] children whose constipation was not treated,[6] and patients with previous intravesical BoNT-A injection or bladder surgery were also excluded (Table 1).[4]

3.1. Types and doses of botulinum toxin used for intravesical injection

We observed a substantial heterogeneity in the treatment protocols with respect to the type of toxin, dilution, and dose. In all included studies, the authors used BoNT-A, either onabotulinum toxin A (Botox®)[4,6,11–13] or abobotulinum toxin A (Dysport®).[5,7,10]

With regard to onabotulinum toxin A, dilution and doses varied from 100 U in 10–20 mL[4,6,11] of injectable saline solution and dose ranged from 50[13] to 100 U[4,11–13]; some authors did not report the total doses, but the amount per kilo, 10 U/kg.[6]

Regarding abobotulinum toxin A, dilution varied from 500 U in 20 mL[7] to 25 mL[5] of injectable saline solution, and the injected doses varied from 375 to 500 U[7,10] or 8 U/kg.[5]

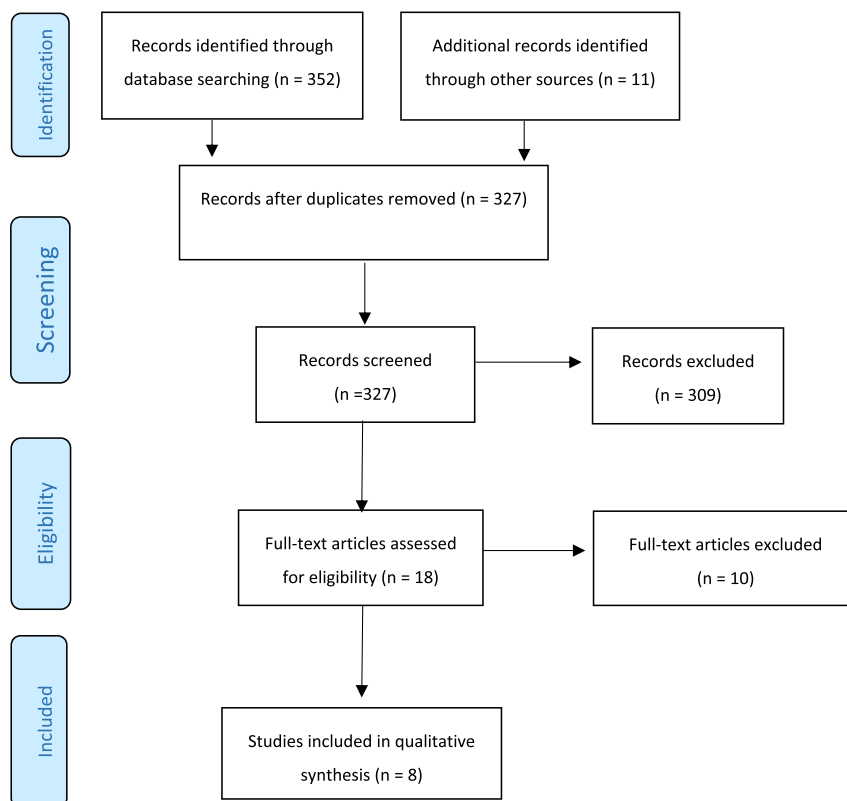**Figure 1.** Flow diagram of articles. Reprinted from Moher et al.[14]

Table 1

Characteristics of the included studies.

Article	Type of study	n	Age, yr	Inclusion criteria	Exclusion criteria
Hoebeke et al.[12] (2006)	Prospective	15	10.8 (8–14)	Refractory idiopathic detrusor overactivity	Neuro or uropathy, voiding dysfunction or pathologic PVRU
Lahdes-Vasama et al.[13] (2011)	Prospective	13	11 (7–19)	Refractory idiopathic urge incontinence	NS
Blackburn et al.[10] (2013)	Retrospective	27	10 (6–16)	Refractory idiopathic urinary incontinence	NS
Léon et al.[5] (2014)	Prospective	8	12.7 (6–11)	Refractory idiopathic lingering and distressing incontinence	Neurological disease, voiding dysfunction
Bayrak et al.[11] (2017)	Retrospective	33	8.75 (5–16)	Refractory idiopathic detrusor overactivity	Neurogenic bladder or bladder outlet obstruction
Uçar et al.[6] (2018)	Retrospective	31	10.2 (7–15)	Refractory persistent urgency and urinary incontinence	Neurogenic bladder, voiding dysfunction, constipation not treated, or incomplete files
Al Edwan et al.[4] (2019)	Prospective	46	8.9 (4–14)	Idiopathic refractory OAB and detrusor overactivity	Previous intravesical BoNT-A, pelvic surgery, bladder dysfunction, PVRU >150 mL
Peeraully et al.[7] (2019)	Retrospective	23	11.8 (9.5–14.4)	Refractory involuntary voiding or urinary incontinence, neurogenic (group 1) and idiopathic (group 2)	NS

BoNT-A = botulinum toxin type A; NS = nonspecified; OAB = overactive bladder; PVRU = postvoid residual urine.

3.2. Protocols of intravesical botulinum toxin injection

Treatment protocols also varied in the injection sites, number of injection points, and need for more than one injection. Before BoNT-A injection, most authors suggested that anticholinergic drugs should be discontinued.[4–7,13] Furthermore, antibiotic prophylaxis was introduced in 6 studies.[4–7,11,13] Intravesical BoNT-A injections were administered under general anesthesia via cystoscopy after filling the bladder with saline solution.[4–7,10–13]

Considering the procedure itself, there was some variability; some authors injected it into the detrusor muscle[5–7,11–13] and some into the suburothelium.[6] In 7 studies, the surgeons spared the trigone,[5–7,10–13] whereas in 1 study, they also preserved the ureteric orifices[6] and the ventral bladder wall,[12] due to their close relationship with the peritoneal cavity. Only 1 study did not spare trigone.[4]

The injection points were also variable in number, ranging from 14[10] to 30,[4,13] but typically from 15 to 20.[6,7,11–13] Second or serial injections have been administered to patients with an incomplete response or symptom relapse after the first injection.[6,7,11–13] Repeated injections may involve increasing doses and punctures, changes in the technique, or any of these.

3.3. Clinical outcomes of intravesical botulinum toxin injection

The preoperative and postoperative symptoms were collected, usually by means of a voiding diary (2–7 days)[4–6,11,12] or simply by recording symptoms such as incontinence episodes[7] or more complete information such as frequency and amount of urgency and incontinence episodes/nocturia/number of pads.[10,13] In only 2 studies, patients' symptoms were assessed using a dysfunctional voiding and incontinence symptoms score[6] and International Consultation

Table 2

Intravesical botulinum toxin injections protocols.

Article	BoNT-A type and dilution	BoNT-A dose first injection	BoNT-A dose reinjections	Procedure
Hoebeke et al.[12] (2006)	Botox® 100 U/15 mL SPS	100 U	100 U, if partial response or relapse (26.7%)	15 pts; detrusor; exclude trigone and ventral wall
Lahdes-Vasama et al.[13] (2011)	Botox® NS	50–100 U	70–200 U (>6–24 mo, 46.2%)	Antibiotic prophylaxis; stop anticholinergics 20–30 pts; detrusor; exclude trigone
Blackburn et al.[10] (2013)	Dysport® NS	400–500 U	-	14 pts; exclude trigone
Léon et al.[5] (2014)	Dysport® 500 U/25 mL SPS	8 U/kg	-	Antibiotic prophylaxis; stop anticholinergics 25 pts; detrusor; exclude trigone
Bayrak et al.[11] (2017)	Botox® 100 U/10 mL SPS	100 U	100 U, if no improvement or relapse (9 mo, 30.3%)	Antibiotic prophylaxis 20 pts; detrusor; exclude trigone
Uçar et al.[6] (2018)	Botox® 100 U/10 mL SPS	10 U/kg (max, 200 U)	10 U/kg (max, 200 U; if no complete response >6 mo)	Antibiotic prophylaxis; stop anticholinergics 20 pts; detrusor or suburothelial (second injection suburothelial); exclude trigone and ureteric orifices
Al Edwan et al.[4] (2019)	Botox® 100 U/20 mL SPS	100 U	-	Antibiotic prophylaxis; stop anticholinergics 30 pts; not exclude trigone
Peeraully et al.[7] (2019)	Dysport® 500 U/20 mL SPS	375 U (<12 yr), 500 U (>12 yr)	375 U (<12 yr), 500 U (>12 yr or only moderate response to initial dose) if no improvement or relapse (48%)	Antibiotic prophylaxis; stop anticholinergics 20 pts; exclude trigone; detrusor

BoNT-A = botulinum toxin type A; Botox® = onabotulinum toxin A; Dysport® = abobotulinum toxin A; NS = not specified; pts = points; SPS = serum physiological solution.

Table 3

Clinical results of intravesical botulinum toxin injections.

Article	Follow-up	Clinical results		Postoperative urodynamics first injection	Adverse effects
		First injection	Reinjections		
Hoebeke et al.[12] (2006)	12 mo	6 mo: full response 60%, partial 20%, no response 20% 12 mo: full response 53.3%	Full response 50% and partial 50%	Most patients refused to perform invasive urodynamics. No differences in uroflowmetry except voided volume; temporary dysfunctional voiding 4.7%	10-d urinary retention (4.7%), presumable temporary vesicoureteral reflux (4.7%), UTI (9.5%)
Lahdes-Vasama et al.[13] (2011)	12 mo	1–3 mo: full/partial response 92% 6 mo: full/partial response 90% 12 mo: full/partial response 55%	1–3 mo: 100% positive response 6–12 mo: 86% positive response	First injection, 6 wk: 67% increase of maximal cystometric capacity and significant decrease of high pressure bladder contractions	UTI (7.7%)
Blackburn et al.[10] (2013)	5 mo	5 mo: full response 44%, 37% improved frequency, 26% improved nocturia, and 26% improved urgency	-	-	2 mo urinary retention (3.7%), UTI (26%), pain (3.7%)
Léon et al.[5] (2014)	18 mo	3 mo: decrease in incontinence episodes and night time incontinence 12 mo: full response 62% 18 mo: 25% reappearance of symptoms	-	2 mo: DO disappeared after 1 injection in 75% and decreased in amplitude in the remaining 25% 12 mo: compliance and bladder's functional capacity improved in 100% 18 mo: reappearance of DO (25%)	Temporary macroscopic hematuria
Bayrak et al.[11] (2017)	9 mo	9 mo: full response 54.5%; decrease in voiding frequency, incontinence episodes, number of pads used; nocturia disappeared 15%	9 mo: no improvement or relapse 100%	First injection, 9 mo: no PVRU volume, mean bladder capacity increased, no significant difference in Qmax. Vesicouretheric reflux decreased in 9%, resolved in 15.2%, and was no change in 6%	Macroscopic hematuria (6%), UTI (18.1%)
Uçar et al.[6] (2018)	12 mo	6 mo: complete response 32.2%, partial 48.4%, and no response 19.4% 12 mo: complete response 61.3%, partial 29%; no response, 9.7%	6 mo: complete response 42.9%, partial 42.5%, and no response, 14.3%	-	Hematuria 1–3 d (11.5%), UTI (5.7%) and transient urinary retention, 3-wk clean intermittent catheterization (1.9%)
Al Edwan et al.[4] (2019)	3 mo	3 mo: improvement in urge incontinence episodes of 57%, in enuresis of 56% and frequency in 38%. Improvement in quality of life. Great improvement in 54% of the patients and improvement, in 30%	-	3 mo: significant improvement in cystometric capacity (increase of 26%). Mean Pdet max decreased by 44% and mean compliance increased by 126%, Complete resolution of DO in 67% of patients	Transient urinary retention (4.4%) < 4 wk, transient hematuria
Peeraully et al.[7] (2019)	25 mo	Group 2: full response 47.8%, moderate 39.1%, no response 13%; median of improvement 6.5 mo	Full response 21.7%, moderate 8.7%, and no response 4.3%; median of improvement 9.5 mo	-	No adverse effects in nonneurogenic group; globally, only 6% (transient difficulties initiating miction, abdominal and penile pain)

DO = detrusor overactivity; Pdet = detrusor pressure; Qmax = maximum urinary flow rate; UTI = urinary tract infection; PVRU = postvoid residual urine.

on Incontinence Questionnaire–Urinary Incontinence Short Form.[4] Noninvasive or invasive urodynamics have also been reported in some studies.

The follow-up period was generally short, varying from 3[4] to 25 months.[7] Therapy response was assessed as follows: "no response" if clinical recovery rate with respect to initial complaints was less than 50%, "partial response" if recovery rate was between 50% and 99%, and "full response" if 100%. Response rates were variable with reported percentages of 32%–60%[6,12] for full responses (Tables 3).

Hoebeke et al.[12] administered 100 U of onaBoNT-A in 15 children and reported 60% full response, 20% partial, and 20% no response at 6 months, as well as 53.3% full response at 12 months. In patients with partial response or relapse (6.7%), a second injection was administered, with a 50% full response. Blackburn et al.[10] administered 400–500 U of aboBoNT-A to 27 children; at 5 months, 44% of the patients achieved full response, 37% im-

proved frequency, 26% improved nocturia, and 26% improved urgency. Uçar et al.[6] included 31 children treated with 10 U/kg (max, 200 U) of onaBoNT-A and reported complete response in 32.2% of the patients, partial response in 48.4%, and no response in 19.4% at 6 months. Patients with absent or partial response at 6 months were administered a second injection, resulting in complete, partial and absent responses of 42.9%, 42.5%, and 14.3%, respectively (n = 21). At 12 months, the response rates were 61.3%, 29%, and 9.7%, respectively.

Peeraully et al.[7] evaluated the efficacy of 375–500 U for incontinence in children with and without neurogenic bladder. In the 23 patients with idiopathic bladder, full response was achieved in 47.8%, moderate response in 39.1%, and no response in 13% of the patients after the first injection and 21.7%, 8.7%, and 4.3%, respectively, after repeated injections. The median interval between the injections was 14 months, and there was no significant difference in the median duration of improvement. No significant

differences in responses were observed between the neurogenic and idiopathic patients. Leon et al.[5] reported an overall decrease in the number of incontinence episodes and night-time incontinence in 8 patients with refractory incontinence who underwent onaBoNT-A intradetrusor injections of 8 U/kg. Detrusor overactivity disappeared after 1 injection in 75% of patients and decreased in amplitude in the remaining 25%. The patient's compliance and bladder functional capacity improved by 100% after 12 months.

Al Edwan et al.[4] found improvements in urge incontinence episodes, enuresis, and frequency among 57%, 56%, and 38% of 46 children (the largest sample) with refractory detrusor overactivity treated with intradetrusor injections of 10 U of onaBoNT-A. Fifty-four percent of the patients reported significant improvement and 30% reported some improvement. They found a significant improvement in cystometric capacity (26% increase); namely, the mean maximum detrusor pressure decreased by 44%, mean compliance increased by 126%, and complete resolution of detrusor uninhibited contractions was reported in 67% of the patients.

Lahdes-Vasama et al.[13] performed intradetrusor onaBoNT-A injections (50–100 U in the first injection and 70–200 U in the second) in 13 children with refractory idiopathic urge incontinence and reported a full or partial response in 92% of the patients at 3 months, 90% at 6 months, and 55% at 12 months after the first injection. At 12 months after the second injection, a full or partial response was observed in 86% of the patients. Bayrak et al.[11] reported full response in 54.5% of 33 children with refractory idiopathic detrusor overactivity treated with 100 U of onaBoNT-A, and a partial response in the others, with a decrease in voiding frequency, incontinence episodes, and number of pads used; nocturia disappeared in 15% of the patients. Uroflowmetry revealed no postvoiding residual urine volume, and the mean bladder capacity increased, with no significant difference in maximum flow rate.

3.4 Adverse effects of intravesical botulinum toxin injection

Neither major local nor systemic adverse effects were observed in the analyzed studies. The most commonly described adverse effects were urinary tract infection,[6,10–13] transient urinary retention (lasting a few days to 8 weeks),[1,4,10,12] and transient hematuria.[4–6,11] Some authors also reported transient vesicoureteral reflux (1 child reported lumbar pain during voiding, but as he refused voiding cystography, the diagnosis was not confirmed),[12] nonspecified pain,[10] abdominal and penile pain,[7] and difficulty initiating micturition.[7]

4. Discussion

As demonstrated previously, BoNT-A seems to be safe and efficacious in treating idiopathic pediatric OAB, regardless of the protocol implemented. There was some heterogeneity in terms of the doses, dilutions, number of injection points, and injection zones. The authors generally used BoNT-A, preferably onabotulinum toxin-A, but there is no consensus regarding the minimum effective dose of BoNT-A injection for idiopathic OAB in pediatric patients. Some authors have stated that the clinically effective dose is less influenced by body weight than by bladder properties (bladder mass and detrusor compliance); therefore, the thicker the bladder wall, the higher the dose of BoNT-A required for a long-lasting effect.[12]

Similarly, there is no agreement on whether to inject the suburothelium or detrusor to preserve the trigone region or not,

as well as on the number of punctures. However, it is worth noting that most injections were administered into the detrusor, sparing the trigone, at 15–20 points.

However, despite the heterogeneity, the clinical results are promising, with most studies reporting good results. For first injections, the full-response rates varied between 32%[6] and 60%.[12] Repeated injections seem to be as safe and effective as first injections, with a full-response rate of 50%.[12] In addition, some authors have found that a full response after the first injection may be a good prognostic factor for further injection therapy.

Thus, we conclude that both ona and aboBoNT-A are effective in treating pediatric idiopathic OAB. Nonetheless, it is essential to determine the minimum dose needed to provide maximum improvement and minimum systemic absorbance to minimize adverse effects and operational costs.

Compared with studies on neurogenic patients, the reviewed studies reported a longer duration of the BoNT-A effect in idiopathic patients. In some studies, there was a 53.3% full-response rate at 12 months. The authors hypothesized that idiopathic OAB may be an expression of a maturation delay in detrusor function rather than a structural anomaly.[7]

The issue of whether trigone should be spared remains unclear. Despite the fact that only 1 study did not spare the trigone, the results were also satisfactory with improvement in urge incontinence episodes in 57% of patients. In fact, a recent randomized study in adults showed greater improvement without increasing adverse effects, such as vesicoureteral reflux, when the trigone was not spared.

Considering vesicoureteral reflux, there are limited data analyzing the role of BoNT-A in its treatment. Bayrak et al.[11] reported a rate of 80% (8 patients) of decrease or disappearance of reflux after BoNT-A injection. The authors suggested that these results might be related to decreased detrusor pressure after injection.

All included patients underwent preoperative urodynamic testing to validate and characterize detrusor overactivity,[5] but only some performed postoperative urodynamics; in 2 studies, patients underwent uroflowmetry or ultrasonographic evaluation of postvoid residual urine volume,[11,12] and in 3 studies, patients underwent invasive urodynamics.[4,5,13] Although urodynamic evaluations are more effective in monitoring therapy response, they are invasive, not performed routinely, and not mandatory for assessing therapeutic responses,[6] particularly in children.

In fact, the role of urodynamics in the follow-up of these patients remains uncertain because there is no solid correlation with clinical findings. Nevertheless, it may be important to evaluate parameters, such as the maximum detrusor pressure and maximum cystometric capacity, compliance, and voiding phase.

Regarding adverse effects, only a few cases of urinary tract infection, transient urinary retention, and transient hematuria have been reported. Blackburn et al.[10] reported a higher urinary tract infection rate (26%), and they did not report having received antibiotic prophylaxis, which may be related. Thus, we conclude that both ona and aboBoNT-A are safe for idiopathic OAB in children, and antibiotic prophylaxis is advisable.

Although rare in the pediatric population, children and their caregivers should be informed of the possibility of urinary retention and the need for temporary intermittent or permanent catheterization. The absence of major adverse effects may be related to the advances in BoNT-A management in neurogenic populations, which were transposed to idiopathic populations, in particular, sparing the trigone and urethral meatus and using lower doses than in neuropathic OAB (inferior to 100 U of onaBoNT-A and 500 U of aboBoNT-A).

However, some authors suggest that recurrent detrusor trauma from repeated injections may result in scarring, ultrastructural and functional changes of the detrusor, and consequent bladder noncompliance[15] and the risk of antibody production; therefore, a longer follow-up would be advisable.[16]

Some limitations of our study include methodological issues, because half of the reviewed studies were retrospective. There was also a lot of heterogeneity concerning BoNT-A injection protocols, particularly the type and doses of the toxin injected and injection technique, the need for repeated injections, and in some studies, the absence of detail about the exact location of the injection sites. Reduced sample sizes and short follow-up periods should also be mentioned.

Another important limitation is the scarcity of studies using validated scores for assessing therapeutic responses based on either the presence of symptoms or overall quality of life, which may prejudice the generalization of the results.

5. Conclusion

Despite the methodological heterogeneity of the studies, small sample sizes, and short follow-up periods, the findings of our review support the use of BoNT-A as a safe and effective treatment modality for refractory idiopathic detrusor overactivity in pediatric patients, regardless of the dose and type of toxin. Although it is still being used as an off-label drug, intravesical BoNT-A may be considered as a second-line therapy option in the management of idiopathic OAB in children.

In the future, it would be desirable to perform robust prospective and placebo-controlled studies, especially to elucidate the minimum doses for maximum effect and minimum adverse effects, ideal number of punctures and injection site, as well as recommendations for multiple injections and intervals between treatments, and to elucidate the role of BoNT-A in vesicoureteral reflux treatment. The use of standardized and validated symptom scores to enable homogeneity and easier assessment of therapy response should be recommended in future studies.

Authors contributions

JBB, MIT: Conceptualization, Investigation, Writing—original draft preparation.
JBB, MIT, GE: Methodology.
JBB, JM: Software.
JBB, MIT, JM, JL, GE: Validation.
JBB, JM, GE: Formal analysis.
JBB, MIT, JM, JL, GE: Writing—review and editing.
All authors have read and agreed to the published version of the manuscript.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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