International Journal of Colorectal Disease (2025) 40:22
https://doi.org/10.1007/s00384-024-04795-5

RESEARCH

Outlet type constipation in adult patients treated with type A botulinum toxin: a cohort study

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Accepted: 21 December 2024

Abstract

Purpose Chronic constipation is a common symptom. Constipation due to pelvic floor disorders remain a therapeutic challenge. Biofeedback therapy is considered as the first-choice treatment for pelvic floor disorders, whenever dedicated expertise is available. Type A botulinum toxin has been used to selectively weaken the external anal sphincter and puborectalis muscle in constipated patients.

Method Eighty-two patients with chronic outlet obstruction constipation were treated with 100 units type A botulinum toxin, injected into the puborectalis muscle and the external anal sphincter.

Results At the 2-month evaluation, a symptomatic improvement was noted in 69 patients. Seven (8.5%) patients had mild flatus incontinence. Stool frequency per week increased from 2.4 ± 0.9 to 5.1 ± 1.0 ($P = 0.0001$). Anorectal manometry demonstrated decreased tone during straining from 91 ± 28 mmHg to 61 ± 27 mmHg ($P = 0.0001$). Defecography after the treatment showed improvement in anorectal angle during straining, which increased from $96 \pm 12°$ to $124 \pm 14°$ ($P = 0.0001$).

Conclusion Type A botulinum toxin relaxes the puborectalis muscle. Pressure values decline after the treatment. Transrectal ultrasonography to guide injections is a safe procedure. Repeated injections were needed to maintain the clinical improvement.

Keywords Botulinum toxin · Chronic constipation · Defecatory disorder · Outlet type constipation

Introduction

Chronic constipation is a common symptom [1, 2]. Recent published criteria for chronic constipation categorize patients as having functional form, constipation-predominant irritable bowel syndrome, or defecatory dysfunction [3–6].

The aetiology of defecatory disorders is characterized by a failure of the puborectalis muscle to relax during efforts to defecate or by its paradoxical contraction [6].

The treatment of this dysfunction is not easy to perform [7, 8]. Surgical treatment has often been unsuccessful [5]. Conceptually, biofeedback appears to be the most appropriate treatment, although several studies using biofeedback techniques have not documented consistent results [9, 10]. This is mainly related to which prevalent form of constipation this treatment is applied to. It is known that biofeedback therapy has little effect on patients with isolated slow transit constipation. On the other hand, about 70% of patients with defecation disorders benefit from biofeedback treatment. Despite this, a recent national evaluation concluded that there is insufficient evidence to conclusively confirm the efficacy of this therapy in patients with chronic idiopathic constipation [9].

Type A botulinum toxin has been used to selectively weaken the external anal sphincter and puborectalis muscle in constipated patients [11–14]. The toxin has also

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Published online: 21 January 2025

been used in constipated patients with associated neurological disorders such as Parkinson's disease [15] or spinal cord injury [16]. It has been demonstrated that the toxin relaxes the puborectalis muscle [17]; consequently, the relaxation of the puborectalis muscle and the external anal sphincter allows the anorectal angle to increase during straining, facilitating evacuation [15, 18]. In this context, however, it must be emphasized that the optimal dose of toxin to be used in constipated adult patients is not well defined. Another aspect that should not be overlooked is the fact that different brands of type A botulinum toxin type show different biological activity [19]. Furthermore, the best method of toxin administration is not well defined. Palpation-guided injection enhanced resting anal pressure compared to endoanal ultrasound injection.

In our previous experiences, we have used type A botulinum toxin in adult constipated patients with promising results [11, 17]. We have used a dose of type A botulinum toxin ranging from 30 to 60 units. In this study, we present the clinical experience on the efficacy of 100 units of type A botulinum toxin injected under transrectal ultrasound guidance in improving rectal emptying in patients with defecatory disorders involving spastic pelvic floor muscles.

Materials and methods

All patients who had symptoms of chronic constipation for the last 3 months, and no organic gastrointestinal pathology, were included in this cohort study performed at Fondazione Policlinico A Gemelli Istituto di Ricerca e Cura a Carattere Scientifico (IRCCS), in a 15-year period (2007–2021). This study follows the STROBE reporting guidelines. The patients have been categorized as functional defecation disorders when they showed abnormal anorectal evaluation pattern with anorectal manometry and impaired rectal evacuation on defecography. The inclusion and exclusion criteria for treatment with type A botulinum toxin are reported in Table 1.

Study design

Each patient provided written informed consent for the study and underwent a baseline evaluation. All patients underwent anorectal manometry and defecography radiography, as described in previous experiences [11]. Two months after treatment, patients underwent the same assessment as performed at baseline.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	1. Incomplete, prolonged and difficult evacuation with constant use of enemas, laxatives and manual maneuvers to facilitate bowel movement
	2. Age > 18 years
	3. Fewer than 3 bowel movement per week
	4. Straining during > 25% of the time
	5. Lumpy or hard stool > 25% of the time
	6. Sensation of anorectal obstruction > 25% of the time
	7. Sensation of incomplete evacuation > 25% of the time
	8. Manual maneuvers required to aid defecation > 25% of the time
	9. Normal colonic transit time study
	10. Failure to relax perineal floor during straining at physical examination
	11. Inability to achieve evacuation of barium paste during defecography, with the lack of a measurable increase in the anorectal angle between rest and attempted evacuation
	12. High pressure levels during straining at anorectal manometry;
	13. Absence of organic causes of constipation documented with colonoscopy and CT-scan
Exclusion criteria	1. Prevalent slow-transit constipation
	2. Constipation due to organic causes
	3. Previous surgical procedures on anal canal and rectum
	4. Previous treatment with type A botulinum toxin
	5. Concomitant oral medications that could interfere with the action of type A botulinum toxin, such as aminoglycosides, baclofen, dantrolene or diazepam
	6. Known hypersensitivity to any of the components of formulation of type A toxin
	7. Pregnant or breast-feeding women
	8. Rectocele at physical examination
	9. Rectocele larger than 3 cm in diameter as measured during defecography

Treatment

Vials containing 100 units of type A botulinum toxin (Botox; Allergan, Inc, Irvine, CA, USA) were used. The vials were stored at − 20 °C and diluted in saline to 50 IU/ml before injections. Two ml were injected perineally with a 23-gauge needle. The two injection sites, on either side of the paradoxically contracting puborectalis muscle, were visualized by transrectal ultrasound. No sedation or local anaesthesia was used during toxin injection.

Aim of the study

The study endpoint was the evaluation of symptom improvement after treatment with botulinum toxin. Secondary objectives are evaluations of the anorectal angle and anal canal pressure during straining.

Follow-up

At the 2-month evaluation, if the symptoms persisted, the examiners could decide to re-treat a patient (rescue treatment) with 200 units of botulinum toxin, as described above. Then, the patients were evaluated with the same protocol 2 months after the rescue treatment. Control was carried out by telephone interviews (once a year). Clinical visit was performed only in patients who complained of specific symptoms.

Statistical analysis

All statistical elaborations were obtained by using StatPlus for Mac (StatPlus, AnalystSoft, Inc., USA). The results were expressed as mean ± standard deviation (± SD) and compared by the Student's *t*-test. All *P*-values were two-tailed. *P*-values of less than 0.05 were considered statistically significant.

Results

During the study period, 82 patients were enrolled. Baseline characteristics are reported in Table 2. Type A botulinum toxin injections were performed easily in all patients. No complications or adverse events were observed during the procedure in any patient.

At the 2-month evaluation, inspection revealed a symptomatic improvement in 69 (84.1%) patients. Stool frequency per week increased from 2.4 ± 0.9 to 5.1 ± 1.0 ($P = 0.0001$). Seven (8.5%) patients had mild flatus incontinence. As compared with baseline values, pressure during straining was reduced by 32% (Table 3). Pressure during straining, at baseline higher than resting pressure (91 ± 28 mmHg vs 79 ± 15 mmHg, $P = 0.001$), decreased at the 2-month evaluation (61 ± 27 mmHg vs 75 ± 22 mmHg, $P = 0.0004$). As compared with baseline values, anorectal angle measured during straining increased by 27% (Table 4).

At the 2-month evaluation, a salvage treatment was proposed to 13 symptomatic patients. This treatment consisted of the injection of 200 units of type A botulinum toxin with the same modalities previously described. Two months after the rescue treatment, symptomatic improvement was observed in all these patients. Stool frequency per week increased from 3.1 ± 0.6 to 4.9 ± 2.2 ($P = 0.008$). Of these patients 3 (23.1%) had flatus incontinence. At the same time, anorectal angle during straining was increased

Table 3 Anal pressures before and after treatment with type A botulinum toxin in 82 patients treated with type A botulinum toxin

Parameters[a]	Baseline	2 months	*P* values[b]
Resting anal pressure	79 ± 15	75 ± 22	0.1
Voluntary contraction	62 ± 19	51 ± 21	0.0005
Pressure during straining	91 ± 28	61 ± 27	0.0001

[a]Values are given as mean ± SD. All patients were included in all evaluations. [b]For the comparison with the baseline values (Student's *t*-test)

Table 2 Characteristics of 82 patients treated with type A botulinum toxin at baseline

Characteristics[a]		
Demographic and clinical data	M/F	37/45
	Age (years)	59.1 ± 13.4
	Duration of symptoms (months)	31.4 ± 13.7
	Stool frequency per week	2.4 ± 0.9
Anorectal manometry (mmHg)	Resting anal pressure	79 ± 15
	Voluntary contraction	62 ± 19
	Pressure during straining	91 ± 28
Defecography (degrees)	Anorectal angle at rest	115 ± 10
	Anorectal angle during straining	96 ± 12

[a]Values are given as mean ± SD. All patients were included in all evaluations

Table 4 Results of defecography before and after treatment with type A botulinum toxin in 82 patients treated with type A botulinum toxin

Parameters[a]	Baseline	2 months	*P* values[b]
Anorectal angle at rest	115 ± 10	114 ± 9	0.5
Anorectal angle during straining	96 ± 12	124 ± 14	0.0001

[a]Values are given as mean ± SD. All patients were included in all evaluations. [b]For the comparison with the baseline values (Student's *t*-test)

in these patients from 88 ± 13° to 126 ± 9° (30% increase, $P = 0.0001$), and the pressure during straining was reduced from 97 ± 29 mmHg to 61 ± 21 mmHg (37% decrease, $P = 0.001$). Pressure during straining decreased with respect to resting anal pressure (83 ± 19 mmHg, $P = 0.01$).

The patients were followed up for an average 30 months. During this time, 21 patients were lost to follow-up. Six patients showed relapse of symptoms 14 months after the treatment. Of these patients, two refused further treatment, while the other 4 were treated with 100 units of toxin. No complications or side effects were reported during follow up period from the remaining 55 patients.

Discussion

Pelvic floor dyssynergia is a common cause of chronic constipation, hallmarked by inappropriate, paradoxical contraction, or a failed relaxation of the puborectalis muscle and external anal sphincter during defecation [14, 18, 20, 21]. Treatment of defecatory dysfunction is not always easy and rapidly effective [22, 23]. Conceptually, biofeedback training is the most logical approach to pelvic floor dyssynergia, although data from controlled studies are lacking [24, 25]. The success rate of biofeedback therapy for pelvic floor dysfunction varies widely between 40 and 90% [5, 26]. Randomized controlled trials have shown biofeedback to be superior to standard therapy (i.e., laxatives) in the treatment of this clinical condition [27, 28]. The limitations of biofeedback for dyssynergic defecation pertain to its availability in selected centres only and the need for multiple clinic visits [19]. A recent randomized controlled trial found home-based biofeedback to improve bowel symptoms and physiology similar to office-based biofeedback; this cost-effective approach may substantially broaden the availability and the use of this treatment [29].

Alternative therapies that produce a reversible reduction of anal canal pressure during straining, inducing an inhibition of the paradoxical puborectalis contraction, may be effective [14, 30]. Among these therapies, the injection of botulinum toxin, both in striated muscles and in smooth sphincters, has proven effective in the treatment of many diseases of the gastrointestinal tract. However, there are a limited number of studies evaluating the use of type A botulinum toxin in the treatment of pelvic floor dyssynergia in adult patients (Table 5) [13, 31, 32]. Among the many published guidelines on the diagnosis and treatment of chronic idiopathic constipation, only the French guidelines report the use of botulinum toxin for the treatment of this disease [26]. The same French guidelines summarize that the toxin induces a reduction in anal resting pressure and improves the relaxation of the puborectalis during straining, emphasizing that adverse events are negligible [33]. Recently, in a review of 189 patients, the median dose of type A botulinum toxin injected per procedure was 100 units, administered in most cases in the lateral area. A symptomatic improvement was documented in 77.4% at the 2-month evaluation and in 46% at 4 months after type A botulinum toxin injection. Complications were observed in a variable percentage, from 0 to 22.6%. The authors therefore emphasize that, although the symptomatic improvement is satisfactory, the clinical benefit worsens 3 months after the injection. The clinical benefit can be maintained with repeated injections, which appear to have no increase in morbidity [13].

The current study provides further evidence of the usefulness of type A botulinum toxin in the management of pelvic floor dysfunction. In our experience, early symptomatic improvement was achieved after treatments, and there were no observable permanent complications. In the present study, we observed 7 cases of mild flatus incontinence after administration of 100 units of toxin. The incidence of mild flatus incontinence increased to 23.1% in the 13 patients treated with 200 units of type A botulinum toxin. High-dose of type A toxin significantly enhanced long-term improvement but also led to a significant higher rate of complications in comparison with low-dose toxin.

Compared with previous trials [11, 17], the better outcomes presented in this study could be a result of injection technique under ultrasonographic guidance. In the present series, also, we have been used higher doses of botulinum toxin than reported in our previous papers [11, 17]. Moreover, we selected patients more carefully and excluded from treatment patients with associated neurological pathologies or patients with anterior rectocele.

Careful patient selection is considered essential by Hompes et al. [34]. The authors treated 56 patients with 100 units of type A botulinum toxin. An initial favourable response was observed in 22 patients (39%). The authors also observed that solitary obstructed defecation symptoms predicted response on logistic regression analysis. In fact, excluding from the analysis non-responders who presented high-grade rectal prolapse, internal anal sphincter myopathy or even chronic anal fissure, the authors observed that the initial response was 96% [34]. With the same dose of toxin, we observed a symptomatic improvement in 84.1% of patients after a single administration.

Table 5 Published results of treatment of pelvic floor dyssynergia with type A botulinum toxin in adult patients

Author	Patients	Drug/dose	Symptomatic Improvement	Other results
Hallan et al.[35]	7	Dysport/Nr	57.1%	Maximum voluntary contraction from 70 to 28 cm H_2O. Anorectal angle from 96 to 124°. Incontinence in 2 patients
Joo et al.[12]	4	Botox/6–15 U	100%	Two patients relapsed. No complications were reported
Shafik et al.[36]	15	Botox/25 U	86.7%	No complications were reported
Maria et al.[17]	4	Botox/30 U	75%	Anal tone during straining from 96.2 to 42.5 mmHg at 4 weeks and to 63.2 mmHg at 8 weeks. Anorectal angle from 94° to 114°. No complications were reported
Ron et al.[37]	25	Botox/20 U	75%	Perianal pain in 3 patients
Maria et al.[11]	24	Botox/60 U	79.2%	Anorectal manometry demonstrated decreased tone during straining from 98 ± 24 mmHg to 56 ± 20 mmHg at 1 month evaluation ($P < 0.01$) and 56 ± 29 mmHg at 2 months follow-up ($P < 0.01$). Defecography after the treatment showed improvement in anorectal angle during straining. No complications were reported
Farid et al.[31]	24	Dysport/100 U	70.8%	Improvement persisted only in 8 (33.3%). No complications were reported
Farid et al.[38]	15	Dysport/100 U	86.7%	Long-term success persisted only in six patients (40%). No complications were reported
Farid et al.[39]	20	Dysport/100 U	75%	Clinical improvement at 1 year 35%. Complications not reported
Hompes et al.[34]	56	Botox/100 U	96%	Isolated obstructed defecation symptoms, but not proctographic or physiological factors, predicted response on logistic regression analysis. In 33 (97%) of 34 non-responders, significant abnormalities were demonstrated: 31 (94%) had a grade 3–5 rectal prolapse, one had internal anal sphincter myopathy, and one had a fissure. Exclusion of these alternative diagnoses revised the initial response rate to 96%
Zhang et al.[32]	31	Xeomin/100 U	77.4%	After treatment, the pressure of the anal canal during rest and defecation was significantly reduced from 93 ± 16.5 mmHg and 105 ± 28.3 mmHg to $63 \pm 8.6.3$ mmHg and 42 ± 8.9 mmHg, respectively. Fecal incontinence in 8 patients

The clinical response to botulinum toxin treatment is influenced by multiple factors. Among these, the dose used, and the method used for injection seem to have a significant importance. In this group of patients, we used a more precise method of injection that helped optimize the diffusion of the toxin. Diffusion of botulinum neurotoxin in tissues is also a dose-dependent phenomenon strongly linked to the dilution volume used. As compared with baseline values, pressure during straining was lower than the pre-treatment value and the resting anal pressure. The reduction of anal canal pressure during straining is directly related to the dose of injected toxin (32% reduction after 100 units of toxin and 37% reduction after 200 units). The increase in the anorectal angle during straining, also, related to the dose of injected toxin (27% after 100 units and 30% after 200 units of toxin), determined an increase in the stool frequency per week. In each case, in absence of any other treatment, these results could be attributed only to the effect of type A botulinum toxin. Furthermore, we have noted that, despite a more precise method of botulinum toxin injection, repeated injections were needed to maintain clinical improvement.

Conclusions

In summary, despite the limitations of this study (single center, no comparison with other therapies), we can consider that type A botulinum toxin is an effective therapy for the treatment of adult patients with defecatory dysfunction. The toxin causes a resolution of the contraction of the puborectalis muscle.

The injection of toxin is easy to perform, and it is performed in an outpatient setting, without the need for hospitalization and/or sedation or anesthesia. The treatment is well tolerated by the patient, who undergoes this therapy more easily than biofeedback training. The injection of toxin does not depend on the patient's willingness to complete the treatment.

Some aspects of this treatment still need to be improved, in particular the duration of the effectiveness of the injections, the standardization of repeated treatments, and the optimal dose of type A botulinum toxin to be administered.

Author contribution Author Contributions: Brisinda G: Conceptualization, Methodology, Data curation, Formal analysis, Writing – Original draft, Writing—Reviewing and Editing. Fico V: Investigation, Formal analysis, Data cu-ration. Tropeano G: Data curation, Formal analysis. Cariati M: Data curation, Formal analysis. Altieri G: Investigation, Formal analysis. Misuriello F: Investigation, Formal analysis, Writing—Reviewing and Ed-iting. Pepe G: Conceptualization, Data curation, Formal analysis. Fransvea P: Methodology, Data curation, Formal analysis. Chiarello MM: Conceptualization, Methodology, Writing—Reviewing and Editing.

Data availability No datasets were generated or analysed during the current study.

Declarations

Institutional review board statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. The research protocol has been notified to the local IRB. Ethical review and approval were waived for this study due to the study which is a retrospective analysis of deidentified data.

Informed consent Informed consent was obtained from all subjects involved in the study.

Competing interests The authors declare no competing interests.

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