Rectal prolapse: enlightenment of the obscure
Wijffels, N.A.T.

Citation for published version (APA):
Excellent response rate of anismus to botulinum toxin if rectal prolapse misdiagnosed as anismus, pseudoanismus, is excluded

Hompes R, Harmston C, Wijffels NAT, Jones OM, Cunningham C, Lindsey I

Colorectal Disease 2012; 14(2):224-30
Abstract

Background: Anismus causes obstructed defaecation as a result of inappropriate contraction of the puborectalis/external sphincter. Proctographic failure to empty after 30 s is used as a simple surrogate for simultaneous electromyography/proctography. Botulinum toxin is theoretically attractive but efficacy is variable. We aimed to evaluate the efficacy of botulinum toxin to treat obstructed defaecation caused by anismus.

Method: Botulinum toxin was administered, under local anaesthetic, into the puborectalis/external sphincter of patients with proctographic anismus. Responders (resolution followed by recurrence of obstructed defaecation over a 1- to 2-month period) underwent repeat injection. Nonresponders underwent rectal examination under anaesthetic (EUA). EUA-diagnosed rectal prolapse was graded using the Oxford Prolapse Grade 1–5.

Results: Fifty-six patients were treated with botulinum toxin. Twenty-two (39%) responded initially and 21/22 (95%) underwent repeat treatment. At a median follow up of 19.2 (range, 7.0–30.4) months, 20/21 (95%) had a sustained response and required no further treatment. Isolated obstructed defaecation symptoms (OR = 7.8, P = 0.008), but not proctographic or physiological factors, predicted response on logistic regression analysis. In 33 (97%) of 34 nonresponders, significant abnormalities were demonstrated at EUA: 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%.

Conclusion: Simple proctographic criteria over diagnose anismus and under diagnose rectal prolapse. This explains the published variable response to botulinum toxin. Failure to respond should prompt EUA seeking undiagnosed rectal prolapse. A response to an initial dose of botulinum toxin might be considered a more reliable diagnosis of anismus than proctography.
Introduction

Inappropriate contraction of the pelvic floor was described in the surgical literature as early as 1964, but it was Preson and Lennard-Jones who coined the phrase ‘anismus’ in 1985. It is best described as a functional disorder of evacuation caused by failed relaxation and/or inappropriate contraction of the striated external anal sphincter muscle during attempted evacuation. It typically results in outlet obstruction-type chronic constipation. It has been variously named spastic pelvic floor syndrome, dyssynergia or puborectalis syndrome. The incidence of anismus in the general population is unknown, but it has been reported, in a chronic constipation series, to range from 20% to 70%. Although the demographics are not completely understood, it is more common in women and in young or middle-aged individuals.

The wide variation in incidence in reported constipation series attests to the difficulty in agreement of firm diagnostic criteria. Initially, diagnosis hinged on the balloon expulsion test and electromyographic demonstration of inappropriate recruitment of striated pelvic floor muscle during attempts at evacuation. More recently, the Rome III criteria have refined the definition and diagnostic criteria for anismus. In practice, the more simple and practical criteria of nonemptying of barium paste on proctography at 30 s, as described by Halligan et al., has come to be used as a surrogate marker for the more complex and impractical gold standard laboratory diagnosis of anismus.

Treatment has generally been in the form of either botulinum toxin injection or biofeedback, the rationale being to relax or retrain the pathophysiological striated puborectalis/external sphincter muscles. Biofeedback has been effective in anismus but is expensive, labour-intensive and time-consuming. Despite its theoretical attractiveness, the success rate of botulinum toxin for the treatment of anismus has been variable and often disappointing, and the reason for this has been unclear. Possible explanations are variable anismus diagnostic criteria across reported botulinum toxin series, inadequate dosing, variable injection sites and a high and variable placebo rate. In this study, the results of treatment of anismus with botulinum toxin injection were reviewed in an attempt to seek an explanation for failures of this treatment.
Method

Since 2005, all patients referred to a tertiary pelvic floor clinic have been prospectively entered into a dedicated database. All patients with a history and examination consistent with outlet obstruction constipation were assessed by defecating proctography and transit studies, anorectal physiology and anal ultrasound.

Anorectal manometry was performed in the left lateral position using a water-perfused nine-lumen vector manometry catheter with a 3.9-mm external diameter (MED 2280; Mediplus, High Wycombe, UK), and data were acquired using an eight-channel transducer (PIP-4-8SS; Mui Scientific, Mississauga, Canada). Pressure was expressed in mmHg, and normal ranges were defined for a maximum resting pressure of 45–85 mmHg and a maximum squeeze increment of > 60 mmHg. Anal ultrasound was performed using a 10-MHz radial transducer (B&K Medical, Naerum, Denmark).

Proctography was performed according to a well-defined local protocol. A 310-ml mixture of 100 ml of barium sulphate paste (Baritop, Barium Sulphate 94.6% w/w; Sanoechemia Ltd, Bristol, UK) and 10 ml of contrast (Gastrograffin; Schering Health Care Ltd, Burgess Hill, UK) was ingested orally 30 min before the procedure to opacify the small bowel. Immediately before the procedure with the patient in the left lateral position, 100 ml of barium paste (Barium Sulphate cream, 60% w/w; E-Z-EM, Anjou, Canada) was injected per anum into the rectum using a 50-ml bladder syringe.

The patient was then seated on a perspex commode. Lateral X-rays were taken with a Siemens Sireskop SD image intensifier (Siemens AG, Forchheim, Germany) at 3 pulses/s, with the patient at rest, during squeeze and during evacuation for 30 s. Proctograms were performed and reported by a radiologist with an interest in pelvic floor imaging. Images were reviewed by a colorectal surgeon. Transit studies were performed using a single X-ray radio-opaque marker technique.

The proctographic diagnostic criterion for anismus was nonemptying of barium after 30s. Proctographic criteria used to compare those responding or not to botulinum toxin included pelvic floor descent (in mm, measured by the furthest caudal travel of the anorectal junction during defaecation attempts), the proportion of patients whose anorectal angle became more acute (narrowing) rather than more obtuse, and the proportion of patients with zero emptying of barium at 30 s.

From January 2008, patients with proctographic evidence of anismus were offered botulinum toxin injection under local anaesthetic using the following protocol. Anal blockade was performed, with the patient in the left lateral position, using a mixture of 20 ml of 0.5% marcaine and 10 ml of 1% lignocaine injected immediately lateral to the outer border of the external sphincter at 3 o’clock and at 9 o’clock. A 21-gauge needle
was directed posteriorly, medially and cranially, and anaesthetic was injected into the ischiorectal space to anaesthetize the perineal branches of the pudendal nerve. Either 100 U of botulinum toxin (Botox; Allergan, Irvine, California, USA) or 500 U (equivalent dose) of Dysport (Ipsen Ltd, Slough, UK) was diluted in 2 ml of normal saline and a 21-gauge needle was passed cranially through the external sphincter to the level of the puborectalis muscle. The needle was then gradually withdrawn, injecting small amounts of the mixture along the length of the puborectalis/external sphincter muscle. One millilitre was given bilaterally at 3 o’clock and at 9 o’clock. Patients were assessed as an outpatient at 6 and 12 weeks. The occurrence of a temporary symptom response (onset of effect 2–3 days, offset 6–8 weeks) was noted. Patients who showed a characteristic positive initial response were offered repeated treatment using the same dose and technique when it was clear that they had developed recurrent obstructive defaecation syndrome.

In patients who failed to have a positive initial response, an examination under anaesthetic (EUA) was performed using a circular anal dilator device (Frankenman International Ltd, Hong Kong, China) to identify any other causes for symptoms. Any demonstrable rectal prolapse was graded using the Oxford Rectal Prolapse Grading system, as previously described. This grades rectal prolapse as low-grade internal rectal prolapse (grade 1 or grade 2; recto–rectal intussusception), high-grade internal rectal prolapse (grade 3 or grade 4; recto–anal intussusception) or external rectal prolapse (grade 5) (figure 2, table 1, page 12,13).

Data analysis was performed using the Statistical Software Package version 15.0 (SPSS Inc., Chicago, Illinois, USA). Categorical variables were compared using the v2 test, while the Student’s t-test was used for continuous data with a normal distribution. Binary logistic regression analysis was used to identify factors predictive for good response. The Cox proportional hazard model was used to examine predictive factors in a multivariate analysis and to exclude possible confounding factors. From a statistical point of view, the limited number of events meant that only a restricted number of possible confounders could be examined; therefore, the preoperative presenting symptom with multiple categories (obstructive defaecation, mixed symptoms, obstructive defaecation + pain, etc.) was recoded into a dichotomous variable by comparing obstructive defaecation with all other presenting symptoms. P ≤ 0.05 was considered statistically significant.
Results

Clinicopathological characteristics
A diagnosis of anismus was made in 56 (19%) of 295 proctograms undertaken for obstructed defaecation and all of these patients completed the treatment protocol. The mean (± SD) age was 47.5 (± 15.1) years and 64% of patients were female (Table 1). Thirty-seven (66%) patients presented with symptoms of obstructed defaecation alone, nine (16%) with perineal pain with (six patients) or without (three patients) obstructed defaecation, seven (13%) with mixed obstructed defaecation and faecal incontinence, two (4%) with solitary rectal ulcer and obstructed defaecation, and one (2%) with slow transit constipation.

Forty-two (75%) patients underwent anorectal physiology. The mean ± SD maximum resting pressure was (±39.7) mmHg and the mean ± SD maximum squeeze increment (MSI) was 69 ± 65.5 mmHg. Thirty-one patients underwent additional anal ultrasounds and all were demonstrated to have an intact internal and external anal sphincter. However, six patients had a thickened internal anal sphincter, four had thickened submucosa and seven were demonstrated to have a thinned internal anal sphincter.

Table 1, Clinicopathologic characteristics of the patients.
Data are given as mean (SD) or n (%), unless stated otherwise. F; female, M; male, MRP, maximum resting pressure; MSI, maximum squeeze increment; OD, obstructed defaecation.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47.5 (±15.1)</td>
</tr>
<tr>
<td>Sex ratio (F:M)</td>
<td>36:20 (64%/36%)</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td></td>
</tr>
<tr>
<td>OD</td>
<td>37 (66%)</td>
</tr>
<tr>
<td>OD + pain</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>OD + FI</td>
<td>7 (13%)</td>
</tr>
<tr>
<td>OD + SRU</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Pain</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>STC</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Anorectal physiology (42/56)</td>
<td></td>
</tr>
<tr>
<td>MRP (mmHg)</td>
<td>58.9 (±39.7)</td>
</tr>
<tr>
<td>MSI (mmHg)</td>
<td>69.0 (±65.5)</td>
</tr>
</tbody>
</table>

Treatment outcome
An initial response to botulinum toxin occurred in 22 (39%) of the 56 patients with a characteristic temporary botulinum toxin dose–response pattern, resulting in resolution of obstructed defaecation symptoms. In these patients a re-response occurred in 21 (95%) of the 22 initial responders after repeat injection, with resolution of symptoms. At a median follow up of 19.2 (range, 7.0–30.4) months, 20 (95%) of 21 patients had a sustained response and required no further treatment. One patient relapsed at 12 months.
Predictive factors | Botulin toxin response | Gender | Presenting symptom | Anorectal physiology
---|---|---|---|---
Positive | Negative | Positive | Negative | Positive | Negative | Positive | Negative
Gender | | | | | | | |
Female | 11/36 (31%) | 11/20 (55%) | 25/36 (70%) | 9/20 (45%) | 0.07
Male | | | 19/37 (51%) | 18/37 (49%) | 0.01
Presenting symptom | | | | | | |
OD | 5/37 (16%) | 60,7 (+/-44,5) | 77,9 (+/-78,2) | 0.8
Not OD alone | 16/19 (84%) | 57,8 (+/-36,9) | 63,5 (+/-56,3) | 0.4

Table 2, Predictive factors of good botox response.
Data are given as mean ± SD or as n positive/total (%). MRP, maximum resting pressure; MSI, maximum squeeze increment; OD, obstructed defaecation. * Chi-square test; § student’s t-test.

Factors predictive of initial response
Logistic regression analysis demonstrated that gender was of borderline significance in predicting a response, with 55% of men responding compared with 31% of women (P = 0.07) (Table 2). A similar difference was also found for patients presenting with obstructed defaecation alone compared with all other presenting symptoms (P = 0.01). Multivariate analysis showed that obstructed defaecation, gender and symptoms were independent prognostic variables (OR = 7.8; 95% CI: 0.028–0.587; P = 0.008). Neither maximum resting pressure nor maximum squeeze pressure was found to have any relationship with response. Proctograms were reviewed retrospectively, in light of which patients had responded to botulinum toxin, to determine the predictability for response of various proctographic criteria, in addition to those of Halligan et al. None was predictive of a response to botulinum.

EUA findings in non-responders
Thirty-three (97%) of 34 initial nonresponders had a treatable other condition, including 31 (94%) with advanced (grade 3–5) rectal prolapse, one with biopsy proven internal anal sphincter myopathy and one with a fissure. Patients with advanced rectal prolapse included one with an external rectal prolapse and 30 with a high-grade internal rectal prolapse (11 were Oxford Prolapse Grade 3 and 19 were Oxford Prolapse Grade 4). EUA was normal in one patient. Excluding the 33 patients with other pathology, the success rate of botulinum was 23 (96%) of 24 patients.

Botulinum toxin side effects
Transient (1 or 2 weeks) minor faecal incontinence, usually to flatus, or minor soiling, occurred in four of 16 patients who ultimately had the alternative diagnosis of prolapse. No patient with either an initial or a subsequent response to botulinum toxin, with resolution of obstructed defaecation symptoms, experienced a continence disturbance.
Discussion

The results show that in patients with anismus diagnosed on simple proctographic criteria, the response rate for botulinum toxin injection is modest, in keeping with the published literature. The wide published variation in response has been puzzling because although variable doses have been used, the technique is simple and standardisable. Possible reasons for the variation include immunoresistance to botulinum toxin, variability in the amount of active drug present in a single vial, the susceptibility of cholinergic cells and the ability of these cells to bind and internalize the toxin and the presence of an appropriate intracellular target. However, no previous report on the efficacy of botulinum toxin injection has questioned the actual accuracy of the diagnoses of anismus.

We found that of the patients who failed to respond to treatment with botulinum toxin, almost all had an alternative diagnosis (usually advanced rectal prolapse) not shown on proctography but seen during EUA. If these patients are excluded, which seems reasonable as prolapse would not normally be treated by botulinum toxin, the response rate rises to over 90%. These findings could explain the variable response published in the literature. There was no obvious difference in the response rates according to findings on dynamic proctography or anorectal physiology. However, the response rate was significantly higher in patients with obstructed defaecation as a sole presentation, and tended also to be higher in the male population.

Anismus is probably a specific disorder of striated muscle function. It has a urological equivalent – Fowler’s syndrome – where demonstrable striated external urethral sphincter muscle dysfunction results in obstructed micturition. Therefore, it is unlikely that prolapse and true anismus commonly co-exist because the pathophysiology of each is likely to be completely different. This observation has major ramifications because about 20% of proctograms undertaken for obstructed defaecation show anismus. If this indicates an over diagnosis of anismus, it also means an under diagnosis of prolapse. This may lead to inappropriate caution in treating prolapse in patients with an initial proctogram showing anismus for fear of exacerbating the functional disorder by anti-prolapse surgery.

The diagnosis of anismus has been reported to require simultaneous electromyography and defaecating proctography, with measurement of intra-rectal pressure to rule out inadequate defaecatory propulsion. However, in practice these tests are rarely available. In 1995, Halligan et al. produced simple proctographic diagnostic criteria for anismus that could replace and act as a surrogate for simultaneous electromyography and defaecating proctography. These criteria have been widely adopted by many units. Interestingly, however, 15% of the patients with anismus in the publication of Halligan et al. also had a high-grade internal rectal prolapse compared with none of the controls. It
should also be noted that incomplete evacuation on proctography was not entirely sensitive or specific for anismus\textsuperscript{10}.

There has been difficulty in defining a gold standard for the diagnosis of anismus. Although electromyography of the puborectalis and external sphincter is thought to be sensitive and specific, it has been suggested that this is, in fact, artifactual, as ambulatory measurements do not reflect those found in the laboratory\textsuperscript{18}. Anal pressures on straining and defecography have been used, alone or in combination with electromyography, but there is poor correlation between these tests, and widely heterogeneous groups have been used in studies to date\textsuperscript{19,20}. It is not surprising therefore that certain commentators have even doubted the existence of anismus as a clinical entity.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Response</th>
<th>Dose*</th>
<th>Repeated</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallan et al\textsuperscript{5}</td>
<td>7</td>
<td>57% improved</td>
<td>3 ng</td>
<td>no</td>
<td>12</td>
</tr>
<tr>
<td>Joo et al\textsuperscript{11}</td>
<td>4</td>
<td>50% improved</td>
<td>12 U</td>
<td>no</td>
<td>12</td>
</tr>
<tr>
<td>Maria et al\textsuperscript{12}</td>
<td>4</td>
<td>100% improved ST</td>
<td>30 U</td>
<td>yes</td>
<td>24</td>
</tr>
<tr>
<td>Ron et al\textsuperscript{14}</td>
<td>25</td>
<td>38% improved</td>
<td>30 U</td>
<td>yes</td>
<td>6</td>
</tr>
<tr>
<td>Maria et al\textsuperscript{13}</td>
<td>24</td>
<td>71% improved</td>
<td>60 U</td>
<td>yes</td>
<td>39</td>
</tr>
<tr>
<td>This study</td>
<td>56</td>
<td>39% improved ST</td>
<td>500 U** yes</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>96% improved ST***</td>
<td>95% improved LT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shafik et al\textsuperscript{15}</td>
<td>15</td>
<td>86% improved ST</td>
<td>25 U</td>
<td>yes</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>86% improved LT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farid et al\textsuperscript{16}</td>
<td>24</td>
<td>71% improved ST</td>
<td>100 U</td>
<td>no</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33% improved LT</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Table 3, Published results of botulinum toxin in anismus.
LT, long term; ST, short term.
*Botox (Allergan) unless otherwise stated.
**Dysport (Ipsen).
***Revised initial response rate.

It is clear, however, is that a therapeutic response to treatment with botulinum toxin, especially in a typical time course (onset in 2-3 days end in 6-8 weeks), confirms the diagnosis of anismus\textsuperscript{8,11-16,21-34}. Since 1998 when it was first used for anismus, several studies have reported on the efficacy of botulinum toxin injection with success rates varying from 33% to 86% (Table 3).

There are several limitations to this study. It is purely observational and the patient numbers are quite small. However to date, this is the largest series of patients treated with botulinum for suspected anismus. It could be argued that as a tertiary referral centre the population of patients with outlet obstruction does not reflect general colorectal practice. Furthermore EUA has never been undertaken in patients responding to botulinum and it is possible that it would also reveal prolapse in some of these
patients. As there was no placebo control in this observational study, it is possible that the responses to botulinum toxin represent a placebo effect, although the pattern of response and re-response would argue against this.

We propose the following management algorithm for anismus. A diagnostic dose is given initially and its effects wear off after 6–8 weeks. Nonresponders do not have true anismus and almost certainly have another underlying condition, which EUA of the rectum should reveal. A positive initial response establishes a firm diagnosis of anismus and will lead to a longer-term clinical benefit with a repeat or therapeutic treatment using the same dose.

**Conclusion**

We suggest that simple surrogate proctographic criteria results in the over diagnosis of anismus. There are other reasons for failure to empty in 30 s, chiefly advanced rectal prolapse. The proctographic over diagnosis of anismus explains the variable published response to botulinum toxin (as a result of failure in prolapse) and leads to the under diagnosis of prolapse, which is best disclosed at EUA with a circular anal dilator device. We suggest that a response to an initial diagnostic dose of botulinum toxin should be regarded as a more reliable diagnosis of anismus than proctography and can be used as a screening tool rather than as a diagnostic tool for anismus.
References

15. Wijffels NA, Collinson R, Cunningham C, Lindsay I. What is the Natural History of Internal Rectal Prolapse Colorectal Dis (in press).