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Intrarectal injections of botulinum toxin versus placebo for the treatment of urge faecal incontinence in adults (FI-Toxin): a double-blind, multicentre, randomised, controlled phase 3 study

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Summary

Background

Non-randomised studies assessing intrarectal botulinum toxin type A (BoNTA) injections for faecal incontinence are promising. We aimed to evaluate the efficacy of BoNTA for the treatment of faecal incontinence in a randomised study.

Methods

In this randomised, double-blind, placebo-controlled study, we included adult patients who had at least one urgency or faecal incontinence episode per week for at least 3 months and who had experienced a failure of

conservative or surgical treatment from eight French specialist hospital units with the skills to manage patients with faecal incontinence. Patients were randomly assigned (1:1) by a central web form to receive intrarectal submucosal injections of either 200 units of BoNTA (Botox; Allergan, Irvine, CA, USA; BoNTA group) or an equivalent volume of saline (placebo group), stratified by Cleveland Clinic Severity scores (CCS score; ≥12 or <12). Patients, investigators, study site staff, and sponsor personnel were masked to treatment allocation up to the 6-month visit. The primary endpoint was the number of episodes of faecal incontinence and urgency per day assessed using 21-day patient bowel diaries 3 months after the treatment. The primary analysis was performed using a modified intention-to-treat (mITT) approach (ie, in all the randomised patients who had received a treatment) with adjustment for baseline faecal incontinence and urgency episodes. After the final data collection at 6 months after injections, patients were unmasked and offered the BoNTA treatment if they were in the placebo group (rescue therapy) without masking, with an additional 6 months of safety follow-up. This trial is registered with ClinicalTrials.gov, number NCT02414425.

Findings

Between Nov 25, 2015, and Nov 25, 2020, we randomly assigned 200 patients to receive either BoNTA (n=100) or placebo (n=100) injections. Due to withdrawals before the injections, 96 patients were included in the BoNTA group and 95 patients were included in the placebo group (mITT analysis). The mean number of faecal incontinence and urgency episodes per day in the BoNTA group decreased from 1·9 (SD 2·2) at baseline to 0·8 (1·8) at 3 months after the injections, and from 1·4 (1·1) to 1·0 (1·0) in the placebo group, with a baseline-adjusted mean group difference at 3 months estimated at −0·51 (95% CI −0·80 to −0·21, p=0·0008). No serious treatment-related adverse events were reported in the trial. The most frequently reported non-serious adverse event (treatment related or not) following the BoNTA or placebo injections was constipation (reported in 68 [40%] of 169 patients who received the BoNTA injections and 38 [40%] of 95 patients who received placebo injections).

Interpretation

BoNTA injections are an efficacious treatment for urge faecal incontinence. Further research will define the optimum selection criteria, dose, site of injection, re-injection frequency, and long-term results.

Funding

General Direction of Healthcare (French Ministry of Health).

Introduction

Faecal incontinence, defined as the recurrent uncontrolled passage of faecal material,[1] is a common condition, with an estimated prevalence of 8·3% in the general adult population in the USA.[2] Faecal incontinence severely affects quality of life by causing psychological disability, stigmatisation, and social exclusion.[3] It also has a substantial economic impact on patients and health-care systems.[4]

Three recognised categories of faecal incontinence have been described. First, passive incontinence involves involuntary leakage without warning, suggesting anal hypotonia or hyposensitive rectum.[5] Second, urge incontinence is characterised by the inability to withstand an urge to defecate and is often attributed to anal hypocontractility or to a hypersensitive or hypercontractile rectum.[6] Third, mixed incontinence is a combination of passive and urge incontinence.[5] Treatment of faecal incontinence depends on the presumed cause and severity of the problem.[7] Many patients can be managed using conservative treatments such as lifestyle changes, dietary improvement, anti-diarrhoeal medications, laxatives, colonic irrigation, or

behavioural techniques such as biofeedback perineal training.[7] However, if symptoms persist, approved therapeutic options remain limited. They include sacral neuromodulation, perianal biomaterial injections to reinforce the anal barrier, or anal sphincter repair in patients with an external anal sphincter defect.[7] All these treatments have drawbacks, including a substantial risk of complications and re-interventions, unreliable availability in some countries, and a reduced response over time.[7] In the event of treatment failure, a colostomy might be the only alternative.[7] There is thus a need for safe and effective treatment options for faecal incontinence refractory to first-line medical treatments.

Research in context

Evidence before this study

We searched PubMed and the Cochrane library with the search terms “faecal/fecal incontinence” and “botulinum toxin” and identified only two series and one case report. The first series included six patients with faecal incontinence and hypercontractile rectum or reservoir. The second series was conducted by the same researchers and included the patients in the first series plus 20 new patients, nine of whom had a neo-reservoir following a proctectomy for rectal cancer. The case report concerned one patient who had faecal incontinence following an ileo-anal anastomosis. The two case series reported a short-term benefit from intrarectal botulinum toxin injections (500 units of Dysport; Ipsen, France) with less than 12 months of follow-up. They showed that rectal or reservoir injections of botulinum toxin for faecal incontinence are feasible, with minor and reversible adverse events. No previous study has shown that botulinum toxin injections are superior to placebo injections.

Added value of this study

To our knowledge, the present study is the first randomised controlled study of intrarectal botulinum toxin type A (BoNTA) injections in patients with urge faecal incontinence or urgency episodes, or both. Intrarectal injections of BoNTA (200 units of Botox; Allergan, Irvine, CA, USA) resulted in improvements in the primary endpoint, which was a decrease in faecal incontinence and urgency episodes per day compared with the placebo (saline), and they were well tolerated by the patients. Key secondary endpoints, including quality of life, delay to postpone defecation, and a positive general impression of the treatment, were better in patients treated with BoNTA injections than in patients treated with placebo injections.

Implications of all the available evidence

The results of the present study showed that intrarectal BoNTA injections as a therapeutic option are a promising approach for treating patients with urgency episodes and urge faecal incontinence refractory to first-line medical treatments. Further studies will be required to optimise the administration of the treatment (doses, injection sites), identify the best candidates, assess the duration of the effectiveness of the treatment, and continue to evaluate adverse effects.

For many years, injections of intra-detrusor botulinum toxin type A (BoNTA) have been used to treat detrusor overactivity resulting in urge urinary incontinence, with good results and few side-effects.[8] BoNTA increases compliance and bladder capacity and delays the appearance of detrusor disinhibited contractions.[9] Based on the experience of urologists treating detrusor overactivity, we hypothesised that intrarectal BoNTA injections might inhibit spontaneous rectal contractions, increase rectal capacity and compliance, and, consequently, markedly relieve urge faecal incontinence in patients.10, 11 Two case series

of BoNTA injections for the treatment of faecal incontinence resulted in improvements in severity symptoms and quality-of-life scores compared with baseline, with no serious adverse events.10, 11 However, to our knowledge, the outcome of intrarectal injections of BoNTA versus placebo has not been compared in a large, adequately powered, multicentre, randomised study.

The overall purpose of the present study was to evaluate the efficacy and safety of intrarectal BoNTA injections in adults with urge faecal incontinence in a randomised placebo-controlled study.

Section snippets

Study design and patients

We designed a randomised, double-blind, placebo-controlled, parallel group study and enrolled patients between Nov 25, 2015, and Nov 25, 2020, from eight French specialist hospital units with the skills to manage patients with faecal incontinence. A central approval for all centres was obtained from the local institutional review board (Haute-Normandie, Oct 17, 2014, number CPP 01/015/2014). The protocol was conducted in compliance with good clinical practice guidelines and the Declaration of…

Results

Between Nov 25, 2015, and Nov 25, 2020, of the 203 patients who consented to participate and were screened, 200 were randomly assigned to receive either intrarectal BoNTA (n=100) or placebo injections (n=100; figure 2). Nine patients withdrew from the trial before the injections, four in the BoNTA group and five in the placebo group (mainly because of consent withdrawal). 191 patients (96 in the BoNTA group and 95 in the placebo group) received the injections and were included in the mITT group …

Discussion

In the present randomised study, a single series of intrarectal injections of 200 units of BoNTA provided a significant improvement in incontinence symptoms compared with placebo at the M3 visit (primary outcome) as well as at the M1 and M6 visits (secondary outcomes). These results were consistent with the two preliminary case series that studied the use of BoNTA to treat faecal incontinence.10, 11

As there is no consensual endpoint for evaluating the treatment efficacy of faecal incontinence,…

Data sharing

Data collected for the study, including individual participant data and a data dictionary defining each field in the set, will not be made available to others. The study protocol can be found in the appendix (pp 7–52). No other data are available.…

Declaration of interests

A-ML is a consultant for Medtronic. FZ is a consultant for Coloplast. LS has received grants from Takeda, Janssen, and AbbVie, is a consultant for Takeda, and has received grants for educational support from Takeda, Janssen, and AbbVie. GA receives support for learning sessions from Wellspect, honoraria for presentations from Laborie, Coloplast, and Convatec, and support for meetings with Coloplast and IPSEN, and sits on the advisory boards of Coloplast, Convatec, and IBSA. FM lectures for…

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