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ORIGINAL CONTRIBUTIONS

EUS-Guided Intragastric Injection of Botulinum Toxin A in the Preoperative Treatment of Super-Obese Patients: a Randomized Clinical Trial

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Abstract

Background Obesity is a disease that is highly prevalent in Brazil, and the associated comorbidities represent a major global public health challenge. Botulinum toxin type A (BTX-A) is a potent neurotoxin and inhibitor of gastric smooth muscle activity. In theory, BTX-A administration should promote early satiety and weight loss because it delays gastric emptying by inhibiting acetylcholine-mediated peristalsis, which is primarily responsible for gastric motility. Because results in the literature are discrepant, the efficacy of intragastric injections of BTX-A as a primary treatment for obesity remains unknown. The objective of this prospective, double-blind, single-center randomized study was to evaluate the effects of endoscopic ultrasound-guided intragastric BTX-A injections, as a bridge to bariatric surgery, in super-obese patients.

Methods Thirty-two super-obese patients were randomized to one of two groups: BTX-A, in which 200 units of BTX-A were injected into the gastric antrum and body; and control, in which the same injections were performed with 0.9% saline. Weight, body mass index (BMI), and loss of excess weight were measured monthly over a 6-month period. Gastric emptying scintigraphy was performed before and after the procedure.

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Results The patients in both groups showed significant weight loss over the course of the study ($p < 0.001$). There were no statistically significant differences between the groups regarding weight loss, excess weight, total loss of excess weight, total weight loss, or change in BMI.

Conclusions Intragastric injection of BTX-A does not appear to be an effective method of achieving preoperative weight loss in super-obese patients.

Keywords Obesity · Botulinum toxins · US endoscopy · Gastric emptying

Introduction

Obesity has traditionally been treated through programs involving dietary changes, physical exercise, behavioral modification, psychological guidance, and the use of appetite-suppressant drugs. However, that approach has limited potential for achieving sustained weight loss, being effective in less than 5% of cases [1].

The evolution of weight gain becomes catastrophic when the body mass index (BMI) of an individual surpasses 50 kg/m^2, at which point the individual is classified as being super-obese. For such individuals, bariatric surgery is the best option [2]. However, even effective surgical treatments for weight loss are invasive and can promote serious adverse events [3, 4].

Endoscopic procedures to control obesity could provide some of the benefits obtained with surgery, having the additional advantages of being potentially reversible and presenting lower risk profiles, as well as being a viable option for patients who are not candidates for surgery or are at high risk for intraoperative and postoperative adverse events [5]. Such procedures can also help promote preoperative weight reduction and control comorbidities such as type 2 diabetes, dyslipidemia, and hepatic steatosis, thus reducing surgical risk [6–9].

It has been suggested that using medications or performing procedures to inhibit gastric motility would reduce gastric emptying, which could induce a prolonged feeling of satiety [10–13]. However, medications for doing that are not yet available [14]. Innovative methods such as left gastric artery ablation are still in pilot study and will likely be a new option for appetite control [15]. Gastric motility has its myoelectric activity, dependent on the interstitial cells of *Cajal*, which are known as the gut pacemakers [11, 12]. Attempts to control the pacemakers with gastric electrical stimulation have already been tried, but the evidence is low of success [16]. Acetylcholine is considered the most important stimulant of intrinsic (myenteric) and extrinsic (vagal) innervation [17–19]. Botulinum toxin type A (BTX-A), produced by the gram-positive anaerobic bacteria *Clostridium botulinum*, binds with high affinity to cholinergic nerve endings [20–23], selectively inhibiting their activity, which makes it a powerful inhibitor of muscle contractions [19, 24–26]. Because vagal stimulation is required for propulsion, it has been hypothesized that BTX-A administration would delay gastric emptying [10, 12, 27]. The use of BTX-A has already been tested in animals [13, 28] and in a few other randomized trials studies [29–32] for weight loss, but its results were controversial. The objective of this study was to evaluate the use of BTX-A and dietary changes to achieve preoperative 10% of total weight loss, as a bridge to bariatric surgery, in super-obese patients. This is the first randomized controlled trial in this patient setting.

Materials and Methods

The inclusion criteria were being super-obese (i.e., having a BMI > 50 kg/m^2), being a candidate for bariatric surgery, and being between 18 and 65 years of age. We excluded patients who met any of the following criteria: having severe coagulopathy or requiring anticoagulant therapy, having a hematological disease, having a disease of the gastrointestinal tract (including ulcers, esophageal or gastric varices, hypertensive gastropathy, and Los Angeles grade C or D esophagitis), having a severe cardiovascular disease, and having a congenital or acquired anomaly of the gastrointestinal tract, such as atresia or stenosis. In addition, patients who were pregnant, lactating, or intending to become pregnant within the next 12 months were excluded, as were those who had a psychiatric illness, those who had previously been treated with botulinum toxin, those who had hypersensitivity to any of the components of BTX-A, those who had a history of neoplasia, those who had tested positive for HIV infection, those who had previously undergone gastrointestinal surgery, those who were using corticosteroids chronically, those who were using weight-loss medication, those who had been treated for obesity in the last 3 months, and those who had thyroid dysfunction.

Study Design

This was a prospective, double-blind, single-center randomized study involving patients recruited from the Bariatric Surgery Department of the *Hospital das Clínicas*.

Randomization

A computer-based randomization list was generated with the online software Research Randomizer with 1:1 ratio (www.randomizer.org). An independent researcher not involved in this trial created the randomization list and sealed sequential opaque envelopes containing the random allocation sequence. The complete list generation occurred before the first enrollment.

Randomization Was Performed with Computer Software

During procedures of eligible patients, an independent researcher (IBR) opened the sealed envelope in the exam room immediately after the operator obtained an optimal position for puncture. Patient was blinded to the allocation.

The sample size calculation showed that the minimum number of patients required was 32. Patients were randomized and allocated to one of the two groups (Fig. 1): control, in which the patients received endoscopic ultrasound-guided injections of 0.9% saline into the gastric antrum and gastric body; and BTX-A, in which the patients were injected with a total of 200 units of BTX-A (Botox; Allergan, Irvine, CA, USA), in five separate injections (40 units per injection). In the BTX-A group, the injection sites were as follows: the proximal portion of the greater curvature of the stomach, 2 cm above the previous injection, 2 cm below the greater curvature of the stomach, the anterior wall of the stomach, and the posterior wall of the stomach. All targets are guided and confirmed by endoscopic ultrasound. During a 6-month period prior to undergoing bariatric surgery, the patients in both groups followed a diet divided in phases: in phases 1–3 (the first 14 days), the patients were on a restricted (clear) liquid diet of up to 700 kcal/day, gradually evolving depending on the symptomatology; in phases 4–6 (from day 15 to day 25), the diet further evolved, depending on patient tolerance, up to 800 kcal/day; and in phases 7 and 8 (from day 26 through the end of the 6-month period), the patients were allowed to have up to 1000 kcal/day of solid food and the diet was adapted on an individual basis. The diets were composed of 30% proteins, 20% fats, and 50% carbohydrates.

The patients were evaluated by a team of endoscopists, endocrinologists, psychologists, and nutritionists—on a weekly basis in the first month and every 2 weeks from the second to the sixth month. Patients who missed scheduled appointments were contacted by telephone and encouraged to return to treatment. At each visit, anthropometric measurements, including weight and BMI, were taken and the amount of excess weight lost was determined. Gastric emptying scintigraphy was performed before the procedure, to determine the basal gastric emptying rate, and after the procedure, to identify the presence or absence of gastroparesis and determine the true efficacy of the drug injected into the gastric wall.

In the BTX-A group, four microinjections (each of 10 units of BTX-A diluted in 0.5 mL of 0.9% saline) were performed with standard 5-mm injection needle, at the respective cardinal points 3 cm from the pyloric sphincter and repeated twice in the direction of the gastric angle, at 2-cm intervals, for a total of 12 microinjections. Four injections were performed around the gastric cardia, and four injections were performed in the region of the greater curvature of the gastric body. The injections were guided by endoscopic ultrasound, with the objective of adequately identifying the gastric muscle layer. The same procedures were applied in the control group, although the injections contained 0.9% saline rather than BTX-A.

Statistical Analysis

To detect a difference of more than 10% of total weight loss between BTX-A and sham, with a two-sided 5% significance level, a power of 80%, a 95% confidence interval and comparing with the previous randomized studies [30–32], the sample size of 32 patients in each arm was determined to a binary outcome equivalence trial. We performed descriptive analyses of all of the study variables. Quantitative variables are expressed as medians, with minimum and maximum values, or as means with standard deviations as appropriate. Qualitative variables are expressed as absolute and relative frequencies. For the comparison of means between the two groups, Student's *t* tests were used. For the comparison of the groups over the course of the study period, we used repeated-measures analysis of variance. The data were processed with

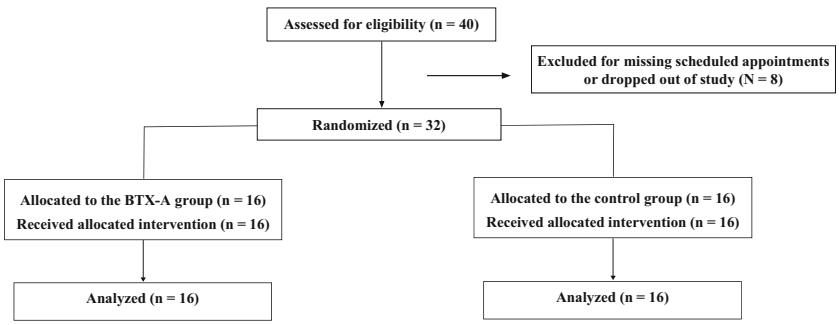

Fig. 1 Flowchart of participants through the study

the Statistical Package for the Social Sciences, version 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

Considering a 20% dropout rate, a total of a total of 40 eligible patients, 8 missed multiple scheduled appointments and decided to drop out of the study. Those patients were excluded from the analyses. Therefore, 32 patients were evaluated: 16 in the control group and 16 in the BTX-A group.

Results

The mean age of the patients in the sample was 43.75 ± 10.49 years, with a median of 44.50 years (range, 25–63 years). Of the 32 patients, 18 (56.3%) were female. There were no adverse events related to the use of BTX-A or resulting from the endoscopic procedure in either group (Table 1).

Weight Loss

Over the course of the study, the mean weight loss among the patients in the BTX-A and control groups was 24.3 kg (range, 4.8–63.7 kg) and 20.2 kg (range, 0.9–49.6 kg), respectively (Tables 1 and 2). All the weight characteristics are shown in Table 3. There was no statistically significant difference between the groups in terms of the total weight lost over the course of the evaluations ($p = 0.152$) or in terms of the mean weight loss recorded at any of the evaluations ($p = 0.304$). In both groups, the difference between the mean body weight measured before the procedure and that measured after the procedure was significant ($p < 0.001$) (Table 4).

BMI

At baseline, the mean BMI was 58.7 kg/m^2 (range, 50.6–72.0 kg/m^2) in the BTX-A group and 58.8 kg/m^2 (range, 50.0–72.1 kg/m^2) in the control group (Table 4). There was no statistically significant difference between the groups in terms of the overall change in BMI over the course of the evaluations ($p = 0.143$) or in terms of the mean BMI recorded at any of the evaluations ($p = 0.423$).

Table 1 Baseline characteristics of the 32 super-obese patients evaluated

Characteristic	Mean	SD	Median	Minimum	Maximum
Height[a]	1.67	0.11	1.65	1.48	1.91
Weight[b]	165.13	29.93	165.50	112.30	236.00
BMI[c]	58.69	5.56	57.67	49.96	72.13
Ideal BMI	24.90	0.00	24.90	24.90	24.90
Ideal weight	69.89	9.51	67.79	54.54	90.84
Excess weight	95.25	22.25	95.20	57.02	147.99

SD standard deviation

[a] Height expressed in meters

[b] Weight expressed in kilograms

[c] BMI expressed in kilograms per square meter

Table 2 Body weight, over the course of the study, by group, among the super-obese patients evaluated

Group	Time point	Number	Mean	SD	Minimum	Maximum
Control	Baseline	16	156.88	21.51	126.00	204.80
	1 month	16	145.31	21.31	99.00	190.00
	2 months	16	141.15	19.50	96.60	180.10
	3 months	16	140.92	20.56	96.20	188.00
	4 months	16	139.26	21.69	93.50	193.00
	5 months	16	138.63	22.04	92.40	193.00
	6 months	16	139.80	23.18	90.00	200.00
BTX-A	Baseline	16	173.39	35.26	112.30	236.00
	1 month	16	158.43	33.95	99.30	219.20
	2 months	16	152.91	33.51	97.20	215.00
	3 months	16	149.18	33.50	95.60	213.60
	4 months	16	147.56	33.73	94.00	213.00
	5 months	16	146.84	33.97	94.00	213.00
	6 months	16	145.83	34.26	97.80	209.00

SD standard deviation

Body weight expressed in kilograms

Total Weight Loss, Excess Weight at Baseline, and Loss of Excess Weight

There was no statistically significant difference between the two groups in relation to total weight loss (TWL), excess weight at baseline, proportional loss of excess weight (EWL), weight loss, proportional weight loss, or change in BMI (Tables 3 and 4).

Scintigraphy

Of the 32 patients evaluated, 15 were excluded from the scintigraphy analysis, because they underwent the examination only once—either before or after the procedure. Therefore, only 17 patients (10 in the control group and 7 in the BTX-A group) underwent scintigraphy twice—once before the procedure and once after the procedure. By analyzing this group specifically in this setting, there was no statistically significant difference between the groups in terms of the mean gastric emptying rate recorded at any of the evaluations over the course of the study ($p = 0.362$) or in terms of the difference between the pre- and postprocedure mean gastric emptying rates ($p = 0.283$) (Table 5).

Table 3 Characteristics of each individual group with initial weight, excess weight, weight loss, total weight lost, and excess weight lost

(a) Control group

	Group control - patient	Initial weighta	Excess weight	Weight loss	%TWL[b]	%EWL[c]
	1	169	96.19	15	8.88%	15.59%
	2	140	79.40	18.3	13.07%	23.05%
	3	180	109.72	7.7	4.28%	7.02%
	4	162	94.21	33	20.37%	35.03%
	5	145.6	77.81	22.5	15.45%	28.92%
	6	158	103.46	0.9	0.57%	0.87%
	7	141	70.72	12	8.51%	16.97%
	8	173	102.72	49.6	28.67%	48.29%
	9	132.6	75.83	9.6	7.24%	12.66%
	10	145	83.62	31	21.38%	37.07%
	11	207.2	124.72	20.2	9.75%	16.20%
	12	167	91.61	33	19.76%	36.02%
	13	133	67.65	3	2.26%	4.43%
	14	185	103.43	40.5	21.89%	39.16%
	15	150	82.21	1	0.67%	1.22%
	16	236	147.99	27	11.44%	18.24%
Minimum		132.60	67.65	0.90	0.57%	0.87%
Maximum		236.00	147.99	49.60	28.67%	48.29%
Mean		164.03	94.46	20.27	12.14%	21.30%
Median		160.00	92.91	19.25	10.59%	17.61%

(b) BTX-A group

	Group BTX-A - patient	Initial weight	Excess weight	Weight loss	% TWL[b]	% EWL[c]
	1	204.8	113.96	4.8	2.34%	4.21%
	2	126	65.40	36	28.57%	55.04%
	3	165	97.21	25.4	15.39%	26.13%
	4	139	75.26	30	21.58%	39.86%
	5	220	142.87	23.6	10.73%	16.52%
	6	170	89.32	27.6	16.24%	30.90%
	7	135	75.18	10.6	7.85%	14.10%
	8	166	98.21	26.4	15.90%	26.88%
	9	112.3	57.02	14.5	12.91%	25.43%
	10	204.8	125.91	63.7	31.10%	50.59%
	11	153	85.21	13.3	8.69%	15.61%
	12	175	108.03	18	10.29%	16.66%
	13	126	70.72	19.1	15.16%	27.01%
	14	206	125.32	31.9	15.49%	25.45%
	15	178	100.87	18	10.11%	17.84%
	16	179	106.19	27	15.08%	25.43%
Minimum		112.30	57.02	4.80	2.34%	4.21%
Maximum		220.00	142.87	63.70	31.10%	55.04%
Mean		166.24	96.04	24.37	14.84%	26.10%
Median		168.00	97.71	24.50	15.12%	25.44%

[a] Weight expressed in kilograms

[b] Total weight loss expressed in percentage = %TWL = [(initial weight) − (post-op weight)]/[(initial weight)] 100

[c] Excess weight loss expressed in percentage = %EWL = [(initial weight) − (post-op weight)]/[(initial weight) − (ideal weight)] (in which ideal weight is defined by the weight corresponding to a BMI of 24.9 kg/m^2

Table 4 Excess weight at baseline, as well as weight loss and change in BMI over the course of the study, by group, among the super-obese patients evaluated

Variable	Group	Number	Mean	SD	Minimum	Maximum	*p**
Excess weight[a]	Control	16	87.80	15.05	65.40	113.96	0.056
	BTX-A	16	102.80	25.98	57.02	147.99	
% of excess weight lost (EWL)	Control	16	21.30	14.68	0.87	48.29	0.339
	BTX-A	16	26.10	13.25	4.21	55.04	
Weight lost	Control	16	20.27	14.55	0.90	49.60	0.414
	BTX-A	16	24.37	13.40	4.80	63.70	
% of weight lost (TWL)	Control	16	12.14	8.75	0.57	28.67	0.342
	BTX-A	16	14.84	7.34	2.34	31.10	
Change in BMI[b]	Control	16	− 5.88	4.90	− 14.07	0.85	0.097
	BTX-A	16	− 8.69	4.40	− 20.10	− 1.32	

SD standard deviation

*Student's *t* test

[a] Weight expressed in kilograms

[b] BMI expressed in kilograms per square meter

Discussion

Endoscopic techniques can induce weight loss in many different ways, including changing dietary intake and the gastric emptying rate. What such endoscopy modalities have in common is the goal of reducing appetite, increasing the perception of satiety, and promoting weight loss [5, 33–36]. Techniques such as left gastric artery ablation as gastric electrical stimulation have already been tried for appetite control and are part of yet another range of treatment options for obesity that are under study and development [15, 16, 37].

Intragastric injection of BTX-A was first used as a means of inducing weight loss in humans by Rollnik et al. in 2003 [38]. But the use of BTX-A has already been established for decades as the use in esthetic and therapeutic procedures as anal fissure with promising results [21, 39–42]. A double-blind, randomized study with intragastric injection of BTX-A demonstrated that was associated with delayed gastric emptying, increased satiety, and weight loss [30]. The advantages of using intragastric injection of BTX-A as a treatment for obesity would be the absence of serious adverse events related to the procedure, regardless of the technique, dose, or injection site [43–45]. Its mechanism of action is the inhibition of acetylcholine-mediated motility of the gastric antrum and gastric body. The rationale of this method is that inhibition of the gut pacemakers (the interstitial cells of *Cajal*) would delay gastric emptying and increase satiety [11, 12, 17, 37]. For this reason, we decided to make injections of BTX-A in these targets. The efficacy of the method has not been widely discussed in the medical literature, and there have been calls for additional randomized studies in order to determine whether or not it is an effective therapeutic modality [43, 44]. The findings of the present study suggest that the practice should be abandoned.

Table 5 Gastric emptying before and after intragastric injection of BTX-A, by group, among the super-obese patients evaluated

Group	Timing		Number	Mean (%)	SD (%)	Minimum (%)	Maximum (%)
Control	Preprocedure	1 h	10	55.90	19.97	37.00	89.00
		2 h	10	28.80	14.23	13.00	53.00
		4 h	10	2.40	1.65	1.00	6.00
	Postprocedure	1 h	10	59.20	24.10	16.00	98.00
		2 h	10	27.00	23.69	1.00	74.00
		4 h	10	6.90	12.73	0.00	41.00
BTX-A	Preprocedure	1 h	7	55.86	18.38	38.00	83.00
		2 h	7	33.57	19.52	14.00	68.00
		4 h	7	5.43	7.25	1.00	21.00
	Postprocedure	1 h	7	66.00	17.65	38.00	92.00
		2 h	7	32.14	30.59	6.00	79.00
		4 h	7	10.71	13.41	2.00	36.00

Log-transformed variable

SD standard deviation

Previous studies evaluating intragastric injection of BTX-A as a treatment for obesity have produced conflicting results. For example, in the largest randomized study to date, conducted by Foschi et al. [30] in 2008, which included 24 patients receiving BTX-A (200 units) or placebo (saline), the weight loss observed after intragastric injection of BTX-A was significantly different from that observed in the placebo group. However, we found no such difference. That discrepancy is likely due to the effects of gastric motility, given that the gastric emptying rate was similar in our patients. There are also methodological differences between the two studies. The patients in both of the groups presented significant weight changes throughout the study period ($p < 0.001$), which can be attributed to changes in lifestyle and diet, since we did not find a statistically significant difference in mean gastric emptying rate recorded at any of the evaluations ($p = 0.362$) or in terms of the difference between the pre- and postprocedure mean gastric emptying rates ($p = 0.283$). Although inhibiting gut pacemakers to increase satiety is theoretically the main mechanism of action of botulinum toxin [20, 31, 32, 37], we found no difference between our BTX-A and control groups in terms of the gastric emptying rate in groups exclusively analyzed.

The US Food and Drug Administration has established efficacy targets for obesity devices/therapies according to a benefit-risk paradigm [46]. Greater risk equals greater benefit. The risk of intragastric injection of BTX-A is categorized as class I (the lowest). To be considered effective, an obesity treatment should result in the overall weight loss being 5% greater in individuals receiving the treatment than in controls following the same program of diet and physical exercise. In our study, the mean overall weight loss in the BTX-A group was 24.3 kg, which corresponds to a loss of 14.8% of the initial weight at 6 months of follow-up, compared with 20.2 kg (21.3%), with no statistically significant difference between the groups.

This study has some limitations. First, because this is the first study of its kind, there are few studies of the topic in the current medical literature. The literature on the use of BTX-A as a primary treatment for obesity comprises only randomized studies [29–32] and systematic reviews [43–45, 47]. Another limitation is that not all of our patients adhered to the treatment protocol, which resulted in some data being missing, such as those for the scintigraphy examinations. However, our findings are in keeping with those of a systematic review [43], as well as with those of three independent, high-quality, homogeneous randomized trials [29, 31, 32], in which BTX-A administration was also found to have no advantages over placebo.

Conclusion

Intragastric injection of BTX-A does not appear to be an effective endoscopic treatment for preoperative weight loss in super-obese patients.

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Author Contributions IBR wrote the manuscript; MSVF, LHMM, DTHdM, ETHdM, FACB, and SEM performed the procedures; VOB, MdPGN, WMB, and EGHdM critically reviewed the article for important intellectual content; MAS followed the patients at the bariatric surgery outpatient clinic; GCN monitored the nutritional status of the patients; CMRDB carried out the statistical analysis; and EGHdM, IBR, MSVF, LHMM, DTHdM, CMRDB, VOB, ETHdM, GCN, FACB, MdPGN, SEM, WMB, and MAS approved the final draft of the article.

Compliance with Ethical Standards

Conflict of Interest One author reports receiving personal fees from Apollo Endo Surgery, Fractyl Labs, GI Windows, GI Dynamics, Ethicom Endosurgery, and Alacer Biomedica, all unrelated to the submitted work. All other authors declare that they have no conflict of interest.

Ethical Statement The study was approved by the Research Ethics Committee of the University of São Paulo School of Medicine *Hospital das Clínicas*.

Consent Statement Informed written consent was obtained from all participants.

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