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Intragastric injection of botulinum toxin in the treatment of obesity: a single-center study

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Hasan Tankut Köseoğlu, Kerem Kenarli, Ahmet Akbay, Çağdaş Erdoğan, Alper Macif, Meryem Didem Göktaş, Mevlüt Hamamci, Çağdaş Kalkan, Firathan Sarialtin and Mahmut Yüksel

Abstract

Background: In recent years, various novel surgical and non-surgical therapeutic options have been developed for treating obesity. Due to its disputed success, intragastric botulinum toxin A (BTX-A) injection is still being debated.

Objectives: We aim to contribute to this controversial issue in the literature by sharing our center's findings regarding intragastric BTX-A injections in the treatment of obesity.

Design: Patients with a body mass index (BMI) of greater than 25 kg/m^2 and at least one obesity-related complication, or a BMI of greater than 30 kg/m^2 without complications, were eligible for the study if they were between the ages of 18 and 65.

Methods: Following the same procedure, two endoscopists administered BTX-A to all patients. All patients were evaluated for obesity by measuring their lipid profile, hormone profile, and insulin resistance level before treatment.

Results: In our study on 82 patients, we saw a significant mean weight loss (–9.2 kg, $p < 0.001$) in the second month, and there was no additional mean weight loss in the sixth month of follow-up. In addition, this result seems to be independent of the patient's insulin resistance. We did not see any serious side effects in any of the patients.

Conclusion: Although the use of intragastric injection of BTX-A in the treatment of obesity is a controversial issue, we showed in our study that it causes significant weight loss. Further studies are needed on this subject, as it can be a safe method when the ideal dose and application site are combined with appropriate patient selection.

Keywords: body mass index, botulinum, endoscopic treatment, obesity, weight loss

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Correspondence to:
Hasan Tankut Köseoğlu
Department of Gastroenterology, Ankara Bilkent City Hospital, Üniversiteler Mah. 1604. Cd. No: 9, Çankaya, Ankara 06800, Turkey
tankutkoseoglu@gmail.com

Kerem Kenarli
Ahmet Akbay
Çağdaş Erdoğan
Alper Macif
Mevlüt Hamamci
Çağdaş Kalkan
Mahmut Yüksel
Department of Gastroenterology, Ankara Bilkent City Hospital, Çankaya, Turkey

Meryem Didem Göktaş
Department of Internal Medicine, Ankara Bilkent City Hospital, Çankaya, Turkey

Firathan Sarialtin
Department of Radiology, Ankara Bilkent City Hospital, Çankaya, Turkey

Introduction

The rising prevalence of obesity is a major public health concern, as it is associated with a number of chronic diseases that can lead to premature death.[1] In 2016, 13% of the world's adult population, or about 650 million people, were obese. The prevalence of obesity is projected to continue to grow, reaching 19.7% of the world's population (1.12 billion individuals) by 2030, according to a study by Kelly *et al.*[2] It is a complex condition that requires a variety of treatment approaches, including lifestyle changes, medication, and surgery. For these reasons, especially in the last 20 years, many new surgical and non-surgical treatment methods have come to the fore in the treatment of obesity. While reduced-calorie diets and increased physical activity are essential for obesity management, most patients find it difficult to make permanent changes to their lifestyle habits. Studies have shown that weight loss interventions, such as diet, exercise, and behavioral therapy, are not always effective in the long term for people with obesity.[3] Bariatric surgery is a more effective treatment for weight loss than

other therapies but it is also more invasive and can cause serious side effects.[4] It is also not available to patients with a body mass index (BMI) $<35\,kg/m^2$, even if they have other health conditions that are related to obesity.[5] Therefore, the ideal method in the treatment of obesity should be both successful weight loss and a procedure with low side effects. This shows the importance of endoscopic treatment methods.[6]

Bariatric endoscopy procedures performed through the gastrointestinal tract using flexible endoscopy are less invasive, more cost-effective, and reversible than traditional weight-loss surgery while still effectively replicating some of the anatomical features and physiological effects of the latter.[7,8] Among these procedures, methods that act by affecting gastric function regulation include intragastric injections of BTX-A, gastric electrical stimulation, and vagal nerve blocking.[9] BTX-A injections into the stomach wall inhibit the release of acetylcholine, which paralyzes the injected muscle and slows down gastric emptying. BTX-A also blocks the secretion of ghrelin, a hormone that stimulates appetite. A meta-analysis and meta-regression by Bang *et al.*[10] found that intragastric BTX-A injections are a safe and effective treatment for obesity.

The effectiveness of gastric injections of BTX-A as a primary treatment for obesity is not well established, as the results of studies in the literature are inconsistent. The inconsistent results of studies on the efficacy of intragastric BTX-A injections for obesity may be due to the small sample sizes of the studies, the differences in the location of the injections, the doses of BTX-A used, and the skill of the operators who performed the injections.[11] This study aims to contribute to the literature by sharing our center's experience in recent years when the effectiveness of intragastric BTX-A injection in the treatment of obesity has been discussed. Our secondary aim is to reveal other factors that may be effective in the success of intragastric BTX-A injection.

Design and methods

The study was conducted at the Ankara Bilkent City Hospital from January 2022 to April 2023. All morbidly obese patients who required treatment to reduce their body weight were evaluated according to the admission criteria. The protocol for the study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki. All patients provided informed consent for the diagnostic and therapeutic procedures.

The following were considered exclusion criteria: a history of cancer, pregnancy (even potential), stomach surgery, or gastrointestinal diseases. None of the patients included in the study were receiving any other weight loss treatment. All patients had a preliminary interview with a dietitian to assess their eating habits and rule out binge eating. During the first week, they kept a food diary to evaluate the amount of calories consumed and the proportion of fat, protein, and carbohydrates.

In total, 82 obese patients between the ages of 18 and 65, with a BMI of $>25\,kg/m^2$ and at least one obesity-related complication (such as osteoarthritis, etc.), or a BMI of $>30\,kg/m^2$ without complications, were enrolled in the study. Body weight and height were measured, and BMI was calculated immediately before the endoscopic injection. All patients were evaluated for obesity by measuring their lipid profile, hormone profile, glycated hemoglobin (HbA1c), fasting and postprandial blood sugar tests, and HOMA-IR level before treatment. The two endoscopists who performed the practice were experts with at least 20 years of experience. Weight and BMI were measured 2 and 6 months after treatment, respectively. All measurements were performed by a dietitian. On these visits, symptoms and the occurrence of adverse effects (minor side effects such as nausea, vomiting, and abdominal pain) were recorded. The patients were allowed to eat as usual.

Two vials of BTX-A (Botox®, Allergan Incorporated, or Dysport®, abobotulinumtoxinA; Ipsen) were reconstituted with a 0.9% sodium chloride solution. Since only these two brands are licensed in our country, one of these two brands was used. Each vial contained 100 U of botulinum toxin A (BTX-A), for a total of 200 U of BTX-A in 20 mL of diluent. The microinjections prepared to contain 25 U of BTX-A were performed at four points around the stomach, starting 3 cm from the pyloric ring, and the microinjections prepared to contain 10 U of BTX-A were performed four times to the proximal of the antrum, four times to the incisura angularis, and two times to the distal of the corpus. The total dose was 200 U. BTX-A was injected into the gastric wall using a standard

5-mm sclerotherapy needle. The needle was inserted deeply into the gastric wall, and the BTX-A solution was injected slowly. The procedure took less than 30 min to complete. No significant acute side effects were recorded. All patients were observed for 1 h.

Statistical analysis

IBM Corp., Armonk, NY, USA, used IBM SPSS Statistics for Windows, version 25.0, to conduct the analyses. In qualitative data, descriptive statistics are displayed as numbers (n) and percentages (%). In quantitative data, the median and minimum–maximum values are provided for non-normally distributed data, whereas the mean and standard deviation are provided for normally distributed data. Since the assumptions of a normal distribution were not given, the Friedman test was utilized to compare repeated measurements. For all statistics, the Type 1 margin of error (alpha) was accepted at 0.05. A two-tailed p value of 0.05 was considered significant.

Results

The median age of the overall study population was 35 (28–41), and 85.4% of the participants ($n=70$) were female. In half of the patients ($n=41$, 50%), Botox was utilized, and in the other half ($n=41$, 50%), Dysport was used. In 84.1% ($n=69$) of the patients, there were no adverse reactions attributable to the procedure. For 61% ($n=50$) of the patients, there were no comorbidities found prior to the procedure. A total of 39% ($n=32$) of patients had comorbid diseases. Among these, HT was seen most frequently in 38% of those with comorbid diseases ($n=12$). While 50% ($n=41$) of the study's patients did not have a history of obesity in the family, 40.2% ($n=33$) did in one of the parents, as did 4.9% ($n=4$) in one of the siblings, 2.4% ($n=2$) in one of the children, and 2.4% ($n=2$) in one of the other family members. In total, 65.8% ($n=54$) of the patients held a bachelor's degree or higher. While 39% ($n=32$) of the patients did not smoke or drink, 51.2% ($n=42$) did smoke, 2.4% ($n=2$) drank, and 7.3% ($n=6$) did smoke and drink alcohol. 63.4% ($n=52$) of the patients had an HbA1c value below 5.7 when the patients' HbA1c levels were assessed. On the other hand, the HbA1c readings of 29.3% ($n=24$) of the patients were prediabetic and ranged from 5.7 to 6.4. A total of 6.3% ($n=6$) of the patients were diabetic and had a HbA1c level above 6.4. HOMA-IR levels of 45.1% ($n=37$) of the patients were discovered to be below 2.7 and normal when the patients were assessed for insulin resistance. On the other hand, insulin resistance was seen in 54.9% of the patients ($n=45$) with HOMA-IR levels equal to or above 2.7. Table 1 provides demographic information, laboratory results, and descriptive statistics for the study group.

The mean patient body weight at the beginning of the study was 98.6 kg, and the mean BMI was found to be 35.78 kg/m^2 when the entire study group was examined. The patients' mean weights and BMIs in the second month following the procedure were 89.38 kg and 32.43 kg/m^2, respectively. According to baseline weight and BMI values, the change in weight and BMI values after 2 months was −9.4% and statistically significant ($p<0.001$). At the end of the sixth month, the patients' mean weight was 88.38 kg (−10.4%), and their mean BMI was 32.01 kg/m^2. No statistically significant difference was discovered when compared to the second month ($p=0.458$), even though there was a statistically significant difference when compared to the baseline mean weight ($p<0.001$). Figure 1 depicts the patients in the study group's shifts in weight from baseline to the second and sixth months.

Table 2 shows changes in the patient's initial weight, second-month weight, and sixth-month weight in relation to HOMA-IR values, HbA1c values, and BTX-A type. According to the beginning weight, the difference between the measurement values at the second and sixth months was found to be statistically significant for all three parameters. The difference between the measurement values for the second and sixth months of weight, however, was not statistically significant. On the other hand, no statistically significant difference was found in the change in weight according to the type of BTX-A used, HbA1c level, or HOMA-IR level.

Conclusion

Levels of the peptides cholecystokinin,[12] ghrelin,[13] and PYY[14] are linked to the fasting-eating cycle and the motor function of the gastrointestinal tract. When lipids like triglycerides or fatty acids are injected into the duodenum, they cause early satiety, relaxation of the stomach, and less emptying of the stomach. This is at least partly because cholecystokinin is released.[15] These connections suggest that the

Table 1. Demographic information, laboratory results, and descriptive statistics for the study group.

	Total ($n=82$)
Age, years	35 (28–41)
Gender (*n*, %)	
Female	70 (85.4)
Male	12 (14.6)
Botulinum toxin type (*n*, %)	
Botox	41 (50)
Dysport	41 (50)
Adverse effect (*n*, %)	
No	69 (84.1)
Yes	13 (15.9)
Comorbidities (*n*, %)	
No	50 (61)
Yes	32 (39)
Obesity in the family (*n*, %)	
No	41 (50)
Parents	33 (40.2)
Siblings	4 (4.9)
Children	2 (2.4)
Other	2 (2.4)
Education (*n*, %)	
Primary school	3 (3.7)
Mid school	1 (1.2)
High school	24 (29.3)
Bachelor's degree	49 (59.7)
Master's degree	5 (6.1)
Habits (*n*, %)	
No	32 (39)
Smoking	42 (51.2)
Alcohol	2 (2.4)
Smoking and alcohol consumption	6 (7.3)
Socioeconomic status (*n*, %)	
Intermediate	64 (78)
Upper	18 (22)
HbA1c (*n*, %)	
<5.7	52 (63.4)
5.7–6.4	24 (29.3)
>6.4	6 (7.3)
HOMA-IR (*n*, %)	
<2.7	37 (45.1)
>2.7	45 (54.9)
Height (cm) mean ± standard deviation	165.58 ± 7.58
Body weight (kg) mean, (min–max)	98.6 (73–150)
BMI (kg/m²) mean, (min–max)	35.78 (28.34–53.78)
Body weight at 2 months (kg) mean, (min–max)	89.38 (69–138)
Body weight at 6 months (kg) mean, (min–max)	88.38 (66–128)
HbA1c (%) mean, (min–max)	5.68 (4.9–9.7)
Fasting glucose (mg/dL) mean, (min–max)	98.07 (75–274)
Post-meal glucose (mg/dL) mean, (min–max)	110.44 (62–405)
AST (U/L) mean, (min–max)	25.47 (13–66)
ALT (U/L) mean, (min–max)	36.37 (14–118)
Albumin (g/L) mean ± standard deviation	45.3 ± 0.21
Creatine (mg/dL) mean, (min–max)	0.73 (0.52–1.13)
Total cholesterol (mg/dL) mean ± standard deviation	191.34 ± 37.59
LDL (mg/dL) mean ± standard deviation	115 ± 31.42
HDL (mg/dL) mean ± standard deviation	47.03 ± 10.54
Triglycerides (mg/dL) mean, (min–max)	146.5 (55–388)
TSH (mU/L) mean, (min–max)	2.22 (0.17–7.51)
Androstenedione (nmol/L) mean, (min–max)	7.91 (1.05–30.10)
DHEA-S (µg/dL) mean, (min–max)	183.40 (43.8–346.66)
HOMA-IR mean, (min–max)	4.75 (0.8–33.5)
Insulin (mU/L) mean, (min–max)	17.78 (3.9–93.6)
C-peptide (µg/L) mean, (min–max)	2.65 (1.29–8.38)
Hgb (g/dL) mean, (min–max)	13.65 (8.5–15.9)
Platelet ($\times 10^9$/L) mean, (min–max)	269.24 (158–477)

ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; DHEA-S, dehydroepiandrosterone sulfate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; Hgb, hemoglobin; LDL, low-density lipoprotein; TSH, thyroid stimulating hormone.

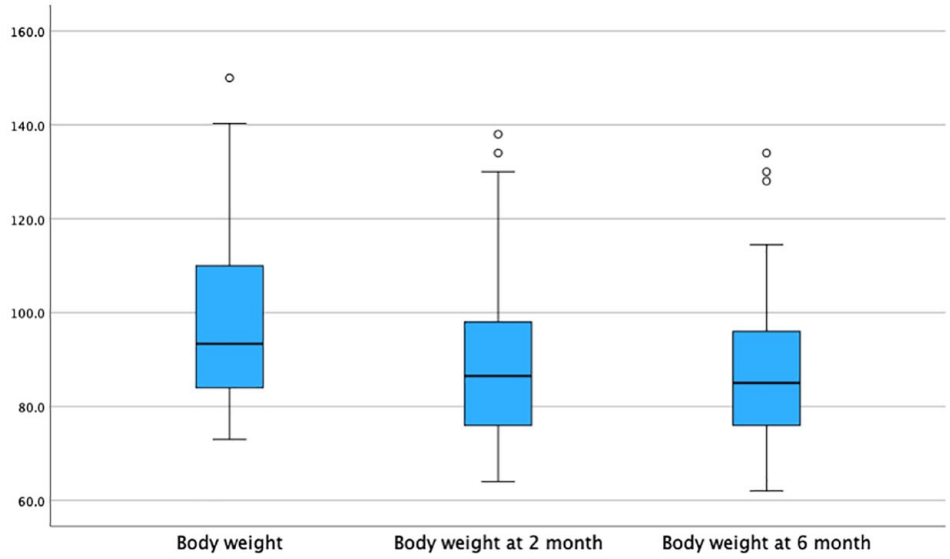

Figure 1. Weight change from baseline.

Table 2. Weight changes according to the type of botulinum toxin used, HOMA-IR, and HbA1c values.

	Body weight median, (min–max)	Body weight at 2 months, median (min–max)	Body weight at 6 months, median (min–max)	*p* Value
HOMA-IR				
<2.7	86.5 (73–139.6)	78.5 (69–114.5)	82 (66–114.5)	<0.001
>2.7	105.5 (71–150)	93.5 (71–138)	91 (71–134)	<0.001
HbA1c				
<5.7	92.5 (71–140)	84 (64–131)	84.5 (62–114.5)	<0.001
5.7–6.4	88.5 (73–150)	81 (71–138)	81.5 (71–128)	<0.001
>6.4	112.5 (93–140.3)	110 (88–134)	112 (86–134)	0.015
Botulinum toxin type				
Botox	93 (71–140.3)	87 (64–134)	86 (62–134)	<0.001
Dysport	93 (73–150)	84 (69–138)	85 (66–128)	<0.001

HbA1c, glycated hemoglobin.

way cholecystokinin and PYY affect satiety is linked to changes in the way the digestive tract moves. Inhibiting the motility of the stomach could be effective in reducing food intake.

The results of studies on the effectiveness of intragastric BTX-A injections for obesity are inconsistent. In 2005, eight patients with a median BMI of 47 were given 500 U of gastric antral BTX-A injections to help them lose weight. This was a small, open-label, prospective trial. At the 1-month follow-up, all patients lost weight, with a median weight loss of 2.6 kg and 3 patients continued to lose weight 4 months after injection.[16] In the same year, a study on endoscopy-guided gastric antral BTX-A injections in 12 obese

patients found no significant change in body weight or gastric emptying time compared to baseline values.[17] Since then, multiple randomized controlled trials (RCTs) have had mixed results. Studies have evaluated the injection of BTX-A in different locations of the stomach (e.g. gastric angulus, antrum, or a combination of antrum and fundus) at different doses (100–500 U) compared to placebo. Many RCTs evaluating injection into the antrum or angulus found that weight loss was comparable between the BTX-A and placebo groups.[16–22] RCTs that have shown statistically significant weight loss have injected BTX-A into both the antrum and fundus of the stomach. A double-blind placebo RCT that showed the most statistically significant weight loss in obese patients injected BTX-A into both the antrum and fundus. The trial included 24 morbidly obese patients who received BTX-A 200 U or placebo injections into the antrum and fundus of the stomach. At 8 weeks, all patients in the BTX-A group had a statistically significant mean weight loss of 11 kg compared to 5.7 kg in the placebo group ($p < 0.0006$). They also had a decrease in mean BMI of 4 compared to 2 in the placebo group ($p < 0.001$).[23] A RCT in 2012 evaluated the injection of BTX-A (200 *versus* 300 U) into the antrum and fundus of 20 obese patients. The trial found statistically significant weight loss, decreased triglyceride levels, and fasting ghrelin levels with longer gastric emptying times in both treatment groups at 12 weeks.[24] In our study, we performed a total of 200 U of botulinum, including the antrum, and we looked at the follow-up of the patients in the second and sixth months. While the mean body weight was 98.6 kg at baseline, it was 89.4 kg at 2 months (−9.4%) ($p < 0.0001$) and 88.4 kg (−10.4%) at 6 months. We observed that the mean body weight decreased by 9.2 kg in the second month of the application and that the decreased body weight was preserved in the sixth month, although there was no additional weight loss.

A meta-analysis of six studies concluded that BTX-A interventions had no benefit in terms of reducing weight or BMI in obese patients. However, the meta-analysis did not consider the injection site as an important variable.[11] Another meta-analysis of four systematic reviews and six studies concluded that intragastric injection with BTX-A is an ineffective procedure for reducing body weight and body mass index when the Knapp–Hartung method is applied.[25] Because the fundus of the stomach is the main source of ghrelin and has a sensory function that regulates the total gastric capacity,[26] we included the fundus as a target area for BTX-A injection. Our results confirm the findings of previous double-blind, placebo-controlled trials that show that inhibition of the cholinomimetic synapses of the stomach in the antrum and fundus can reduce the threshold of satiety in obese patients.[27] Satiety after a standard meal increased significantly after just 1 week and remained high during the follow-up period. As expected, the effect on BMI was also significant. There was no difference in the change in weight according to the type of BTX-A used, HbA1c level, or HOMA-IR level. This result supports that the BTX-A injection is not affected by the patient's diabetic variables due to its mechanism of action.

It is important to emphasize that intragastric administration of BTX-A to reduce body weight in obese patients is very safe. There were no significant side effects, except for minor side effects such as nausea, vomiting, and stomach aches. In the classification by the US Food and Drug Administration, where the methods used in the treatment of obesity are analyzed, intragastric injection of BTX-A is classified as level 1, which means no serious adverse events were reported.[11] According to the report recently published by the World Health Organization, iatrogenic botulism cases have been reported in some countries, including our country.[28] The ideal dose and method of administration of intragastric BTX-A injection in the treatment of obesity have not been defined due to conflicting study results. For this reason, we see very different application doses and applications made by people who do not have sufficient competence. We think that this may cause serious side effects such as iatrogenic botulism. In addition, the reported cases were reported from a private hospital and may contain some conflict of interest.

Finally, we would like to address the main objection to the use of BTX-A to reduce gastric capacity and increase after-meal satiety: the short-lasting effect. In this study, we planned an observation period of 6 months, and the effect of BTX-A was fully evident for 8 weeks and persisted for 6 months. Therefore, the effect of a single administration is limited, but we believe that repeated injections can safely prolong the effect.

In summary, the limited number of studies investigating the effects of BTX-A on weight loss in

obese patients has shown mixed results at best. The variability in the results may be due to small sample sizes, and differences in the location of injection, dose, or operator skill. Many physicians believe that a higher-powered, randomized, double-blind, controlled trial is needed to evaluate the potential of BTX-A injections into the fundus of the stomach for weight loss.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Hasan Tankut Köseoğlu: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Project administration; Resources; Supervision; Writing – review & editing.

Kerem Kenarli: Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Ahmet Akbay: Data curation; Formal analysis; Investigation; Methodology; Resources; Software.

Çağdaş Erdoğan: Conceptualization; Data curation; Formal analysis; Funding acquisition; Visualization; Writing – original draft.

Alper Macif: Data curation; Investigation; Resources; Supervision; Validation; Visualization; Writing – original draft.

Meryem Didem Göktaş: Conceptualization; Data curation; Formal analysis; Resources; Software; Supervision.

Mevlüt Hamamci: Conceptualization; Data curation; Investigation; Methodology; Project administration; Supervision; Writing – original draft.

Çagdas Kalkan: Conceptualization; Data curation; Methodology; Project administration; Resources; Validation; Visualization.

Firathan Sarialtin: Conceptualization; Data curation; Methodology; Project administration; Supervision; Validation.

Mahmut Yüksel: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Writing – original draft; Writing – review & editing.

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ORCID iD
Kerem Kenarli https://orcid.org/0000-0002-5952-2706

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