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ORIGINAL ARTICLE

Is *Helicobacter pylori* positiveness a factor in the success of the intragastric injection of Botulinum toxin in the treatment of obesity?

Mide içi Botulinum toksini enjeksiyonunun obezite tedavisindeki başarısında *Helicobacter pylori* pozitifliği bir faktör müdür?

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Background and Aims: Obesity is becoming more common around the world. Although there have been many developments in the treatment of obesity recently, endoscopic treatment methods have an important place due to their low side effects and higher success rate compared to behavioral treatments. Although studies on intragastric botulinum toxin injection have had confusing results, the reason why the treatment causes these different results has not been clarified. Our aim in this study was to evaluate the presence of *Helicobacter pylori* infection, which may affect the success of intragastric botulinum toxin injection treatment. **Materials and Methods:** Patients with a body mass index of greater than 25 kg/m^2 and at least one obesity-related complication, or a body mass index of greater than 30 kg/m^2 without complications, were eligible for the study if they were between the ages of 18 and 65. In all patients, a biopsy was taken for *Helicobacter pylori* evaluation from the stomach antrum simultaneously with intragastric botulinum toxin administration. **Results:** In our study on 80 patients, compared to their beginning weight, the patients' weights in all groups decreased statistically significantly ($p < 0.001$). However, neither *Helicobacter pylori* density nor *Helicobacter pylori* presence had a statistically significant impact on weight loss in the second or sixth months. **Conlusion:** It has been shown that *Helicobacter pylori* infection, which is one of the conditions that may cause conflicting results of intragastric botulinum toxin administration, has no effect on weight loss.

Key words: Obesity, Botulinum, *Helicobacter pylori*, body mass index, endoscopic treatment, intragastric injection

Giriş ve Amaç: Obezite dünya çapında giderek yaygınlaşmaktadır. Son yıllarda obezite tedavisinde pek çok gelişme yaşansa da endoskopik tedavi yöntemleri, davranışsal tedavilere göre yan etkilerinin düşük olması ve başarı oranının daha yüksek olması nedeniyle önemli bir yere sahiptir. İntragastrik Botulinum toksin enjeksiyonu ile ilgili yapılan çalışmalarda kafa karıştırıcı sonuçlar olmasına rağmen bunun sebebi hala açıklığa kavuşturulamamıştır. Bu çalışmadaki amacımız *Helicobacter pylori* enfeksiyonunun intragastrik Botulinum toksin enjeksiyon tedavisi başarısı üzerindeki etkilerini değerlendirmektir. **Gereç ve Yöntem:** On sekiz ile 65 yaşları arasında, vücut kitle indeksi 25 kg/m^2'nin üzerinde ve en az bir obezite ile ilişkili komplikasyonu olan veya komplikasyon olmadan vücut kitle indeksi 30 kg/m^2'den fazla olan 80 hasta çalışmaya dahil edildi. *Helicobacter pylori* değerlendirmesi için intragastrik Botulinum toksini uygulaması esnasında mide antrumundan biyopsiler alındı ve hastalar *Helicobacter pylori* pozitifliği veya negatifliğine göre iki gruba ayrıldı. **Bulgular:** Çalışmamızda her iki grupta da başlangıç kilolarına göre istatistiksel olarak anlamlı azalma görüldü ($p < 0.001$). Ancak mide mukozasında *Helicobacter pylori* varlığı veya yoğunluğunun kilo kaybı üzerinde istatistiksel olarak anlamlı bir etkisi yoktu. **Sonuç:** İntragastrik Botulinum toksini uygulamasında çelişkili sonuçlara neden olabilecek durumlardan biri olan *Helicobacter pylori* enfeksiyonunun kilo kaybına etkisinin olmadığı gösterilmiştir.

Anahtar kelimeler: Obezite, Botulinum, Helicobacter pylori, vücut kitle indeksi, endoskopik tedavi, intragastrik enjeksiyon

INTRODUCTION

Obesity is a long-lasting, worsening, and recurring condition that is becoming more common worldwide. It is linked to increased illness and death, as well as a decrease in quality of life. Treating obesi-

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ty necessitates a comprehensive medical approach that includes behavioral interventions, medication, endoscopic procedures, and bariatric surgery. The amount of weight loss achieved with any of these methods is highly variable, and long-term weight maintenance is difficult. Obesity is a significant health issue in the contemporary world, according to the World Health Organization. It is estimated that more than half of the world's population will be overweight or obese by the year 2030 (1).

Obesity is a complex condition that is difficult to manage. Traditional methods of weight loss, such as diet and exercise, are often not effective in the long term (2). Bariatric surgery is more effective, but it is also more invasive and can have serious side effects (3). Moreover, only a small percentage of patients who are eligible for bariatric surgery actually receive it (4). Endoscopic treatment methods are a newer approach to weight loss that offer some advantages over traditional methods. They are less invasive, reversible, and have a shorter recovery time. However, they are not as effective as surgery and may not be available for all patients. The ideal method for treating obesity would be a combination of effective weight loss and low-side effects. Endoscopic treatment methods show promise as a new option for people with obesity, but more research is needed to determine their long-term effectiveness and safety (5).

Endoscopic intragastric Botulinum toxin type-A (BTX-A) injection is a minimally invasive procedure that uses an endoscope to inject BTX-A into the stomach. BTX-A is a neurotoxin that blocks the release of acetylcholine, a neurotransmitter that causes muscle contraction. When BTX-A is injected into the stomach wall, it paralyzes the stomach muscles, slowing gastric emptying. This makes the patient feel full sooner and eat less food. BTX-A also blocks the secretion of ghrelin, a hormone that stimulates appetite. This further helps to reduce hunger and promote weight loss (6). Endoscopic intragastric BTX-A injection is not a cure for obesity, but it can be an effective way to help people lose weight and improve their health. The procedure is less invasive than surgery and has fewer side effects. If the patient is not satisfied with the results or the resulting side effects the procedure can be reversed.

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. While some meta-analyses show that it is beneficial for weight loss (6), some have found that it is not beneficial (7). 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, the skill of the operators who performed the injections, and other reasons that are not yet known.

Approximately half of the world's population is infected with *Helicobacter pylori (H. pylori)* (8). Although *H. pylori* infection is the main cause of chronic gastritis and peptic ulcer disease (9), the spectrum of gastroduodenal effects associated with the development of infection is quite wide. *H. pylori* infection can disrupt the secretion of gastrointestinal hormones such as somatostatin and cholecystokinin (10). *H. pylori* infection can affect gastric emptying. This is due to the increased release of leukotrienes, nitric oxide, and other substances, which can lead to gastrointestinal smooth muscle relaxation and delayed gastric emptying. Alternatively, an increase in 5-hydroxytryptamine and other substances can affect gastrointestinal smooth muscle contraction, resulting in gastrointestinal motility disorders (11-13).

Our aim in this study was to evaluate whether *H. pylori* positivity is a possible factor affecting the success of intragastric BTX-A treatment by comparing *H. pylori*-positive and *H. pylori*-negative

patients with intragastric BTX-A injection for the treatment of obesity.

MATERIALS and METHODS

The study was conducted at our centre 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 (Ankara Bilkent City Hospital, Presidency of Clinical Research Ethics Committee, No. E1-23-3989) 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 motility diseases. 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.

Eighty patients with obesity between the ages of 18 and 65, with a body mass index (BMI) of > 25 kg/m^2 and at least one obesity-related complications (such as osteoarthritis, sleep apnea 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, HbA1c, fasting and postprandial blood sugar tests, and homeostatic model assessment of insulin resistance (HOMA-IR) level before treatment. In all patients, a biopsy was taken for *H. pylori* evaluation from the stomach antrum simultaneously with intragastric BTX-A administration. Body weight and BMI were measured two and six months after treatment, respectively. All measurements were performed by a dietitian. On these visits, symptoms and the occurrence of adverse effects 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, for a total of 200 U of BTX-A in 20 mL of diluent. Starting 3 cm from the pyloric ring, microinjections with 25 U of BTX-A were given at four points around the stomach. Microinjections with 10 U of BTX-A were given 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 minutes to complete. No significant acute side effects were recorded. All patients were observed for 1 hour.

Statistical Analysis

Analyses were made by using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA). 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% (n = 68) of the participants were female. In 48.8% of the patients (n = 39), Botox was utilized, and in 51.2% (n = 41), dysport was used. In 91.2% (n = 73) of the patients, there were no adverse reactions attributable to the procedure. For 61.3% (n = 49) of the patients, there were no comorbidities found prior to the procedure. While 48.8% (n = 39) of the study's patients did not have a history of obesity in the family, 41.2% (n = 33) did in one of the parents, as did 5% (n = 4) in one of the siblings, 2.5% (n = 2) in one of the children, and 2.5% (n = 2) in one of the other family members. While 38.7% (n = 31) of the patients did not smoke or drink, 51.3% (n = 41) smoke, 2.5% (n = 2) did drink, and 7.5% (n = 6) did smoke and drink alcohol. The patients who participated in the study had mean HbA1c levels of 5.68 (4.9 - 9.7) and mean HOMA-IR levels of 4.75 (0.8 - 33.5). Gastric biopsy results revealed that *H. pylori* was not found in 50% of the patients (n = 40). On the other hand, while 8.8% (n = 7) of the patients had 2+/3+ *H. pylori* detected, 41.2% (n = 33) of the patients had 3+/3+ *H. pylori* detected. Table 1 and 2 provides demographic information, laboratory results, and descriptive statistics for the study group.

The mean patient body weight at the beginning of the trial was 98.6 kg (73 - 150), and the mean BMI was found to be 35.74 kg/m2 (28.34 - 53.78) when the entire study group was examined. The patients' mean body weights and BMIs in the second month following the procedure were 89.38 (69 - 138) kg and 32.43 kg/m2 (25.34 - 50.71), respectively. According to baseline weight and BMI values, the change in weight and BMI values after two months was statistically significant ($p < 0.001$). At the end of the sixth month, the patients' average weight was 88.38 kg, and their BMI was 32.01 kg/m2. No statistically significant difference was discovered when compared to the second month ($p = 0.458$), even though there

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

	Total (n = 80)
Age, years	35 (28 - 41)
Gender (n, %)	
Female	68 (85)
Male	12 (15)
Botox type (n, %)	
Botox	39 (48.8)
Disport	41 (51.)
Adverse effect (n, %)	
No	73 (91.2)
Yes	7 (8.8)
Comorbidities (n, %)	
No	49 (61.3)
Yes	31 (38.7)
Obesity in family (n, %)	
No	39 (48.8)
Parents	33 (41.2)
Siblings	4 (5)
Children	2 (2.5)
Other	2 (2.5)
Helicobacter pylori (n, %)	
None	40 (50)
+2	7 (8.8)
+3	33 (41.2)
Endoscopic findings (n, %)	
Pangastritis	56 (70)
Antral gastritis	20 (25)
Esophagitis	4 (5)
Habits (n, %)	
No	31 (38.7)
Smoking	41 (51.3)
Alcohol	2 (2.5)
Smoking and alcohol consumption	6 (7.5)
Height (cm) mean ± standart deviation	165.57 ± 7.58
Body weight (kg) mean, (min - max)	98.6 (73 - 150)
BMI (kg/m²) mean,(min-max)	35.74 (28.34 - 53.78)
Body weight at 2 month (kg) mean, (min-max)	89.38 (69 - 138)
Body weight at 6 month (kg) mean, (min-max)	88.38 (66 - 128)

was a statistically significant difference when compared to the baseline weight ($p < 0.001$).

According to the presence and density of *H. pylori*, weight changes at the second and sixth months in patients receiving gastric Botulinum toxin treatment were assessed in Table 3. Compared to their beginning weight, the patients' weights in all groups decreased statistically significantly ($p < 0.001$). However, neither *H. pylori* density nor *H. pylori* presence had a statistically significant impact on weight loss in the second or sixth months. Figures 1-3 compare the participants' initial, second, and sixth-month weights based on the presence and density of *H. pylori*.

Table 2 Laboratory results for the study group

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)	36.36 (14 - 118)
Albumine (g/L) mean ± standart deviation	45.3 ± 0.21
Creatine (mg/dl) mean, (min - max)	0.73 (0.52 - 1.13)
Total cholesterol (mg/dl) mean ± standart deviation	191.34 ± 37.59
LDL (mg/dl) mean ± standart deviation	115 ± 31.41
HDL (mg/dl) mean ± standart 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)
HbA1c mean, (min - max)	5.68 (4.9 - 9.7)
Insuline (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 - 5.9)
Platelet ($x10^9$/L) mean, (min - max)	269.23 (158 - 477)

HbA1c: Glycated hemoglobin; AST: Aspartate aminotransferase; ALT: Alanine transaminase; LDL: Low density lipoprotein; HDL: High density lipoprotein; TSH: Thyroid stimulating hormone; DHEA-S: Dehydroepiandrosterone sulphate; HOMA-IR: Homeostatic model assessment of insulin resistance; Hgb: Haemoglobin.

Table 3 Weight changes according to presence and density of *Helicobacter pylori*

HP	Body Weight Median, (min - max)	Body Weight at 2 Month Median, (min - max)	Body Weight at 6 Month Median, (min - max)	p Value
No *HP*	93 (73 - 111)	86 (64 - 105)	85 (62 - 104)	< 0.001
2+	115 (83 - 150)	104 (73 - 138)	91 (73 - 138)	0.016
3+	93.7 (80 - 140.3)	88 (69 - 134)	86 (66 - 134)	< 0.001

HP: Helicobacter pylori

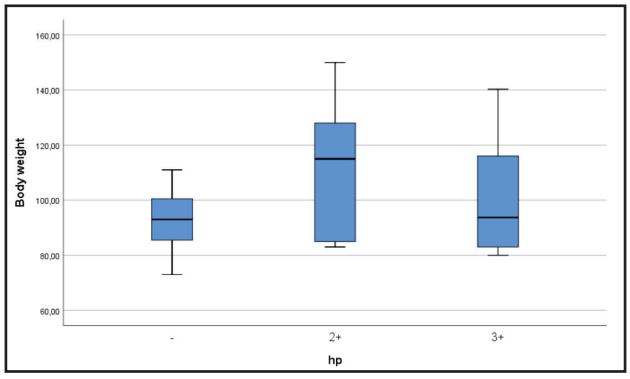

Figure 1 Baseline body weight according to *H. pylori* presence and density.

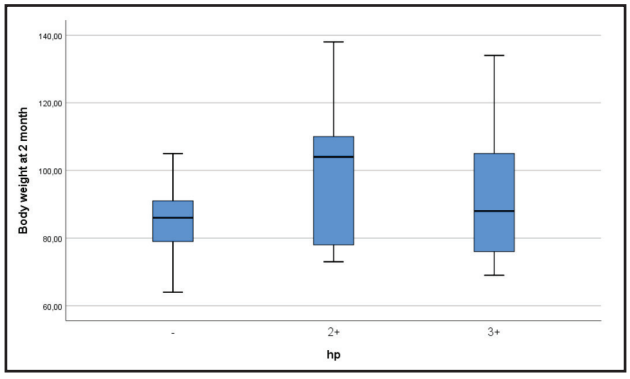

Figure 2 Second month body weight according to *H. pylori* presence and density.

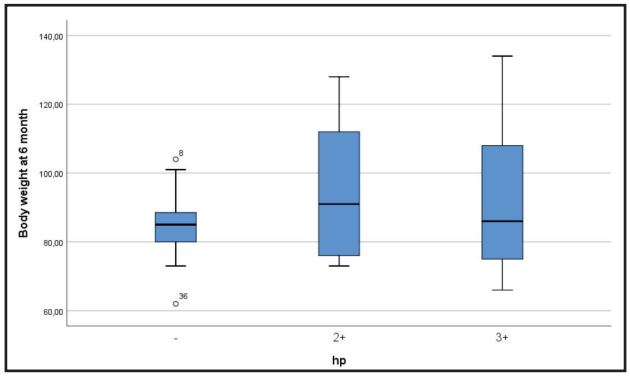

Figure 3 Sixth month body weight according to *H. pylori* presence and density.

DISCUSSION

Non-systematic reviews have been published regularly since 2007 (19), supporting the use of BTX-A as a primary treatment for obesity. This may have led doctors to use this technique in their daily practice. Although intragastric injection of BTX-A has been used clinically for more than ten years, its effectiveness is still being debated. Different results have been obtained in meta-analyses on this subject. Bang et al. found that intragastric injection of BTA was effective for the treatment of obesity (6). A meta-analysis of seven studies involving 115 patients found that the injected dose of BTX-A ranged from 100 to 500 IU. Four studies used the antrum-only injection method, while three studies used the wide-area injection method. The number of injections ranged from 5 to 20. A recent meta-analysis of four randomized controlled trials involving 96 patients found that BTX-A therapy alone is not an effective treatment for obesity (7). The meta-analysis found that BTX-A therapy resulted in a mean weight loss of 4.2% at 6 months, which was not significantly different from the placebo group. The studies included in this meta-analysis, as in other meta-analyses, used a wide variety of BTX-A doses, sites, and number of injections, which has created heterogeneity. Similarly, there are inconsistencies in the results of other recent meta-analyses with heterogeneity problems. Another recent meta-analysis, including five studies, showed significant weight loss in patients with BMI > 40 kg/m^2 (27) and, lastly, a 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 (28). There can be many factors -BTX-A doses in studies, injection stomach areas, patient selection, etc.- affecting all these confusing results. The injection of BTX-A into different parts of the stomach may lead to different results. For example, injecting BTX-A over the pylorus, the circular muscular structure at the end of the stomach, can theoretically lead to temporary paralysis of the pylorus. This can result in a decrease in the pressure

inside the stomach, which can help maintain sufficient gastric emptying (29,30).

Based on previous studies showing that *H. pylori* influences gastric motility (31) and ghrelin secretion (32), we conducted this study to see if it would have an effect on the success of BTX-A injection. There is no previous study on this subject in the literature. Studies investigating the effect of *H. pylori* on ghrelin and therefore gastric motility have shown that as *H. pylori* density increases, its effect on gastric motility changes through multiple mechanisms (33). Therefore, it is more accurate to examine subgroups not only based on *H. pylori* positivity but also based on *H. pylori* density. According to the presence and density of *H. pylori*, weight changes at the second and sixth months in patients receiving gastric Botulinum toxin treatment were assessed and compared to their beginning weight. The patients' weights in all groups decreased statistically significantly ($p < 0.001$). However, neither *H. pylori* density nor *H. pylori* presence had a statistically significant impact on weight loss in the second or sixth months.

H. pylori prevalence is 10 - 50% in developed countries and 80% in developing countries, the annual incidence being 1% and 5 - 10%, respectively. The epidemiology of *H. pylori* varies widely according to age, socioeconomic status and geographic area (34). In descriptive studies on *H. pylori* in our country, the incidence was found to be 82.5% (35), and this situation should definitely be taken into consideration in treatments that may have an effect on the pathophysiological results of *H. pylori*.

The main limitations of our study are its single center, a small number of patients, and a heterogeneous patient population. This limits the ability of the study to draw conclusions regarding long-term outcomes. In addition, since the gastric emptying time of the patients included in the study was not measured objectively, some other factors that may affect gastric motility may have been missed.

There is no previous study on this subject in the literature. In conclusion, a cautious approach is required in interpreting the results of this study, and further studies examining other factors that may be effective, such as the ideal dose, ideal injection sites, and *H. pylori* infection, are needed to support the use of intragastric BTX-A injection as a treatment for obesity.

Ethics: *The protocol for the study was approved by the local ethics committee of Ankara Bilkent City Hospital, with the number E1-23-3989 and date of 12.09.2023.*

Conflicts of Interest: *None of the authors have any potential conflicts of interest associated with this research.*

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