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Weight loss after intragastric botulinum toxin injection in different weight individuals

Farklı ağırlıktaki bireylerde intragastrik botulinum toksin enjeksiyonu sonrası kilo kaybı

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ABSTRACT

Background: Intragastric injection of Botulinum toxin A has been shown to induce weight loss, slowering gastric motility as a result of inhibition of the acetylcholine-mediated gastric contractions. The aim of this study was to observe the effects of endoscopic intragastric injections of intragastric injection of botulinum toxin A in obese patients.

Material and Method: A total dose of 400 U intragastric injection of botulinum toxin A was injected endoscopically into the antrum, corpus and fundus regions of the stomach. The follow-up results of 102 patients sub-grouped according to body mass indices values and evaluated the weight loss status were evaluated. Weight loss data was collected on the monthly follow-up visits for three consecutive months.

Results: At the end of the third month, all subjects lost body weight, with a mean total weight loss ratio ranging between 4.76-19.47%. Mean total body weight loss percentages were significantly higher in Class II and III obese subjects compared to the normal- and over-weight and Class I obese individuals. Gastrointestinal adverse effects were observed in only five (4.9%) of the patients.

Conclusion: Intragastric injection of botulinum toxin A administration with a dose of 400 U is a convenient method for weight loss for the individuals of different body mass indices.

Keywords: Botulinum toxin, botulinum toxin injection, obesity, weight loss

ÖZ

Amaç: İntragastrik Botulinum toksin A enjeksiyonunun, kilo kaybını indüklediği ve asetilkolin aracılı gastrik kasılmaların inhibisyonu sonucu gastrik motiliteyi yavaşlattığı gösterilmiştir. Bu çalışmanın amacı, obez hastalarda intragastrik botulinum toksin A enjeksiyonunun endoskopik intragastrik enjeksiyonlarının kilo kaybı üzerine etkilerini gözlemlemektir.

Gereç ve Yöntem: Toplam 400 U intragastrik botulinum toksin A enjeksiyonu endoskopik olarak midenin antrum, korpus ve fundus bölgelerine enjekte edildi. Vücut kitle indeksi değerlerine göre alt gruplara ayrılan 102 hastanın takip sonuçları ve kilo verme durumları değerlendirildi. Kilo kaybı verileri, birbirini izleyen üç ay boyunca aylık takip vizitlerinde kaydedildi.

Bulgular: Üçüncü ayın sonunda tüm hastaların vücut ağırlığında azalma gözlendi ve toplam ortalama kilo kaybı oranı %4,76-19,47 arasında değişti. Ortalama toplam vücut ağırlığı kaybı yüzdeleri Sınıf II ve III obez bireylerde normal ve aşırı kilolu ve Sınıf I obez bireylere göre anlamlı olarak daha yüksekti. Gastrointestinal yan etkiler hastaların sadece beşinde (%4,9) gözlendi.

Sonuç: 400 U'luk dozla intragastrik botulinum toksini enjeksiyonu uygulaması, farklı vücut kitle indekslerindeki bireylerde kilo kaybı amacıyla kullanımı uygun bir yöntemdir.

Anahtar Kelimeler: Botulinum toksini, botulinum toksin enjeksiyonu, obezite, kilo kaybı

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INTRODUCTION

Obesity is a paramount public health concern worldwide with an increasing prevalence. According to the World Health Organization (WHO), 39% of adult individuals are overweight, and the rates are projected to increase (1). As of the year 2017, The Organization for Economic Co-operation and Development (OECD) reported in their survey results of 36 countries that more than one in two adults are overweight or obese in their area of interest (2).

Obesity is often accompanied by chronic conditions such as diabetes, coronary artery disease, hypertension, sleep apnea, gastroesophageal reflux disease, and bone and joint problems as well as a worsened life quality (3). Due to its burden on the individual and health system, it is essential to find practical solutions for the treatment of obesity for the patients eligible for different types of interventions. Alongside the bariatric and metabolic surgery solutions, minimally invasive endoscopic procedures are gaining among the patients and the physicians. Especially for the patients who do not consider surgery, these applications are demanded in an increasing proportion. Additionally, not only overweight or obese individuals but also normal-weight patients who complain excess weight are in search of a cost-effective and temporary procedure for weight loss.

Botulinum toxin is a neurotoxin produced by the gram-positive anaerobic bacteria Clostridium botulinum, and effects through the blockage of synaptic vesicles that secrete the neurotransmitter acetylcholine, thus inhibiting the contraction of the muscle of interest. The Botulinum toxin isotype A (BtxA) has been employed in different muscle-related applications by different practicing physicians from fields of neurology to plastic surgery (4). The use of BtxA in smooth muscle for the treatment of conditions such as gastrointestinal motility and digestive disorders is relatively novel compared to its wide use on skeletal muscle (5). Being the main stimulatory of the vagal nerve, inhibiting the release of acetylcholine was expected to cause decelerated food passage from stomach to duodenum, associated with reduced food intake and increased satiety (6). Vagus-mediated antral contractions are necessary for food propulsion into the duodenum, and BTxA injections in the antrum are associated with reduced food intake in rats (7,8). Both animal and human studies reporting the injection of BtxA to the gastric antrum is related to increased satiety and weight loss ratio (9,10).

In the present study, we aimed to investigate the effect of intraparietal gastric BtxA injection on our patient groups for weight management and to evaluate the ratio of weight loss. The body mass indices (BMI) of patients in our study group are highly variable, and the obtained results could improve the understanding of BtxA applications in the clinical practice.

MATERIAL AND METHOD

This study was approved by the university /local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.Istanbul University Cerrahpaşa-Cerrahpaşa Medical School Institutional Ethical Board approved the study (2019/83045809-604.01.02) and all stages were conducted following the Declaration of Helsinki between August-March 2019. Informed consent was obtained from all patients.

Individuals with a history of chronic, endocrine or autoimmune disease, pathologies associated with esophagus, stomach or duodenum confirmed by endoscopy, regular use of medications that would affect the outcomes of the study were excluded. The patients younger than 18 years old and older than 65 years old were also excluded.

The patients with a mean age of 38±11.6 years (range, 19-62 years), were divided into four different groups based on body weight as follows: Group 1: normal- and over-weight individuals with a BMI of <30 kg/m^2; Group 2: Class I obese with a BMI of 30-34.9 kg/m^2; Group 3: Class II obese with a BMI of 35-39.9 kg/m^2; Group 4: Class III obese with a BMI of ≥40 kg/m^2. All the four groups of patients were similar for gender, age, and total dose and number of the BTxA injection.

The study was conducted in the Istanbul Cerrahi Hospital. Same surgeon performed the endoscopic procedures and BtxA administration. After overnight fasting, patients underwent esophagogastroduodenoscopy under sedation using an operative gastroscope. The patients with esophagitis and/or stomach ulcer were excluded.

Botulinum Toxin Type-A (Botox, Allergan, USA) was reconstructed in 0.9% sodium chloride, and a total volume of 35 mL solution containing a total dose of 400 U BTxA per patient was given using a sclerotherapy needle. A total of 35 punctures (1 mL injection volume of each) with equal space between were applied on the gastric wall in a circular pattern, being a total of 100 U BtxA for each of the fundus and antrum, and 200 U BtxA on the gastric body. The overall time for the procedure was less than 10 minutes.

After patients were rested for the dissolution of sedation and observed for any acute adverse effects, they were discharged and directed for a visit to the hospital dietician and were given a diet of 1200 kcal/day. The

patients were restricted for the intake of solid food for three consecutive days, then started a diet tailored for their individual needs. The patients were followed for three months after the procedure on every monthly time points. Three postprocedural visits were planned for all patients. Body weight, BMI, and biochemical measures were performed on every visit. The same calibrated scale was used for all weight measurements with the patients wearing light clothing and were without shoes.

The patients were not scheduled for a physical activity programme, and asked for carrying on their daily routine.

Statistical Analysis

The statistical evaluation of this study was performed using the statistical program SPSS v.11.5 (SPSS Inc, Chicago, IL). Results were expressed as mean±standard error of the mean (S.E.M.). Differences between groups were compared using Student's t-test for unpaired data. Differences during the follow-up period in the same group were compared using a two-tailed Student's t-test for paired data. A p-value <0.05 was considered statistically significant.

RESULTS

Of the 102 participants, 83 (81.3%) were women; mean age was 38 years (range, 19-62 years), mean baseline BMI was 31.3 kg/m^2 (range, 22-51.2 kg/m^2), and mean baseline weight was 86.7 kg (range, 57-129 kg).

Table 1 lists baseline BMI, baseline body weight, the percentage of weight loss on the first, second and third months following the treatment, weight, and BMI at the end of the third month for all patients. Compliance with follow-up visits was 91.2%.

At the end of the third month, all subjects lost body weight, with a mean weight loss ratios of 10.24%, 9.81%, 14.27%, 17.48% for the Groups 1, 2, 3, and 4, respectively. The mean BMI and weight were significantly different from the baseline values at the end of the third month for Groups 1, 2, and 4. Mean body weight loss percentages were significantly higher in Group 3 and 4 when compared to that of Groups 1 and 2 at the second and third -month time points. We observed a decreasing trend of body weight until the end of the third month study period for all subjects. Nearly all of the subjects reported a feeling of early satiety in the follow-up visits. Body weight loss change over time was shown in **Figure**.

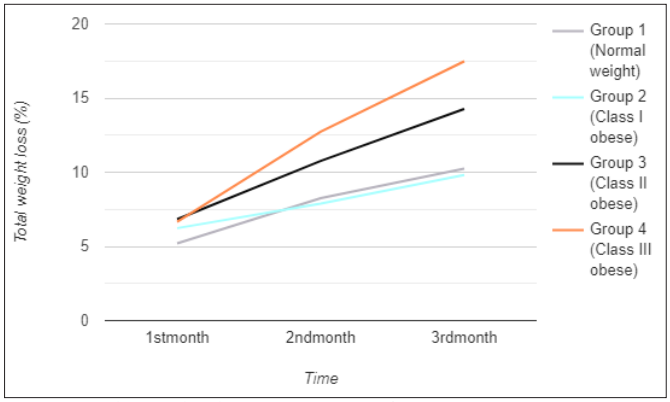

Figure. Body weight change over time after gastric injections. Lines represent mean body weight change over time for each treatment group.

Although the mean weight loss percentage was highest in Group 4 consisted of Class III obese, and this result reached statistical significance when compared to the groups 1 and 2. No acute side effect was observed within a few days following the procedure. Three patients reported transient diarrhea, and two patients reported bloating and abdominal cramps within the follow-up period.

Table. Total weight loss and reduction of BMI data among the subgroups after intragastric botulinum toxin type-A injection.

	Group 1 (n=44)	Group 2 (n=36)	Group 3 (n=16)	Group 4 (n=6)
BMI	**Normal weight <30 kg/m^2**	**Class I obesity 30-34.9 kg/m^2**	**Class II obesity 35-39.9 kg/m^2**	**Class III obesity ≥40 kg/m^2**
Baseline weight	72.9±1.35 (57.0-100.0)	91.3±2.0 (71.7-120.3)	101.5±2.40 (85.0-120.0)	119.9±1.36 (109.4-129.3)
Baseline BMI	26.65±0.29 (22.26-29.86)	32.58±0.22 (30.62-34.97)	36.88±0.32 (35.22-38.75)	43.43±1.62 (40.47-51.27)
3rd month weight	64.90±9.06*** (53.0-82.2)	82.75±5.93** (69.1-100.0)	84.15±9.15** (75.0-93.3)	95.0±5.02** (94.0-102.0)
3rd month BMI	24.23±1.78* (20.63-24.60)	29.48±0.41* (29.51-30.46)	32.20±2.90** (29.29-35.11)	35.99±0.72** (34.07-35.26)
Total weight loss (%)				
1st month	5.20±0.40 (1.88-7.74)	6.23±0.34 (3.83-10.16)	6.83±0.84 (3.33-9.11)	6.66±0.89 (4.87-7.67)
2nd month$^{\phi}$	8.25±0.85 (4.83-12.07)	7.89±0.95 (4.76-11.34)	10.76±1.25 (8.37-12.60)	12.74±1.21 (10.16-14.33)
3rd month$^{\wedge}$	10.24±0.85 (7.56-16.51)	9.81±2.02 (4.76-13.71)	14.27±5.19 (9.07-19.47)	17.48±0.59 (12.88-19.07)

*p<0.05
**p<0.01
***p<0.001
$^{\phi}$: Statistically significant difference between the Groups 1&3; 2&3 (p<0.05); 1&4; 2&4 (p<0.01)
$^{\wedge}$: Statistically significant difference between the Groups 1&3; 1&4; 2&3; 2&4 (p<0.01)

DISCUSSION

The Botulinum toxin isotype A based treatment modalities are widely accepted and used by a variety of disciplines in the field of medicine. The procedure is cost-effective, especially for the individuals who are in need of weight loss within a few months time and with a relatively lower BMI that does not reach to an obesity level. Additional indications include the obese that do not in demand of a bariatric surgery procedure. Although bariatric and metabolic surgery solutions are advocated for the treatment of obesity, surgery has its own disadvantages of being highly invasive, and causing morbidity and even mortality in some cases (11). The onset of the effect starts within a week, and the effect resolves after 3 to 6 months depending on the applied dose, characteristics of the patient and applied location, and sensitivity to the toxin (12).

Our data suggest that the weight loss after injection of 400 U BTxA on antrum, corpus and fundus regions of the gastric mucosa followed a significantly increasing trend during the three-month follow-up period. Furthermore, the ratio of the total weight loss was significantly higher in the patients with Class II and III obesity at the end of the second and third months following the treatment. These findings agree with the results of previous studies.

Several reports are demonstrating that Btx-A injected into the antrum and fundus of the stomach slowers gastric emptying and altered gastric motility, resulting in rapid weight loss. Furthermore, BtXA administration on the gastric wall has shown to reduce food intake and body weight in both animal and human experimental studies (8,9,13).

Gastric emptying was shown to be significantly related to antral contractility and motility, and BTxA is not related to slower peristalsis down to the duodenum due to its ineffectiveness on gastric muscles (14). Despite the presence of reports on the use of BTxA injection for weight loss, controversial reports are claiming that the treatment is ineffective independent of the dose (15). The methodologies set for the studies differ in specific ways, resulting in the current controversion on this treatment modality. Sample size, injection dose, application region, patient characteristics are highly variable among the reports. In a placebo-controlled study by Foschi et al. (13) a total BTxA dose of 200 U given into the submucosa layers of antrum and fundus of 12 Class II and III obese patients provided a mean weight loss of nearly 12 kg at the end of the two months, which is similar to our findings.

There are studies analyzing the effect of different doses of BtXa injection on gastric emptying and did not found a relationship between these two variables for both solid and liquid types of food (16-18). The controversy among different reports might be laying on the varying natures of the studies. For instance, Topazian et al. (16) compared the effects of BtXa injections of different doses on the gastric antral muscularis propria and conclude that BtxA administration was not related to early satiety, altered eating behaviors, and loss of body weight, whereas delayed gastric emptying at a dose of 300 U. There are additional studies reporting that the BtXA injection on only the antrum of the stomach did not result in increased satiety for obese individuals. However, the study size consisted of eight obese individuals, which might be small for a definite conclusion (19).

Gracis JM et al. (20) suggests that the effect of BtXA on stomach might be related to the width of the injected sites on the organ. The positive findings of our study might be a result of relatively higher BTxA dose of 400 U and a broad range of the application area. In our observations, patients mentioned decreased hunger and an increase in satiety; however, we did not file a reporting document or rate a score on their verbal reports.

The reports claiming the inefficiency of BtXA injection on weight loss established a treatment dose of 200-300 U. Therefore, the reason for the promising effects presented in our study might be a consequence of the relatively higher BtxA dose. Although there are small number of studies that administered a dose of BtxA up to 500 U, they did not exclude the diffusion of the toxin from gastric area to the surrounding cavities or nearby locations, reducing the effect of the injection.

The injection depth is also not known by the surgeon whether the injected toxin reached the muscularis propria or subserosa. Thus, it can be concluded that the injected content would be distributed among these layers via various intercellular connections. Higher doses might be considered for individuals who did not experience a positive effect from the treatment; however, the possible side effects might arise, and that should be considered cautiously. Although there are no data on the maximum number of BTxA administration per patient during the time and its effects on gastric tissue, weight loss and eating behaviours, the repetitive use of BtXA for weight loss is not suggested owing to the long-term side effects, low cost-effectiveness, and possible tolerance and resistance in the course of time (21).

It should be noted that eating behavior and sense of satiety is not only related to local and mechanic mediators but also psychological factors. Thus, the randomized trials evaluating the presence of any type of eating disorder may be beneficial for a better understanding of the BTxA effect on weight loss.

Although a wide variety of adverse effects, including fatigue, headache, and gastrointestinal symptoms were reported after BtxA injection, we observed gastrointestinal symptoms in five (4.9%) of the patients.

Since the stomach size and gastric capacity differs for each individual, the BtxA dose might be modified to exclude any possible adverse effects (22). The five patients who reported side effects like diarrhea and bloating were in the groups of normal weight and Class I obesity, therefore smaller doses might be administered to these in order to obtain maximum efficiency.

One limitation of our study was the relatively shorter follow-up period. Given the half-life of BTxA in the organism, a six-months follow-up would yield a more comprehensive evaluation. Additionally, we did not record a diat-diary, and eating patterns might differ between the individuals.

The strength of our study lies in its larger sample size and longer follow-up period. Additionally, we sub-grouped patients according to their initial BMI and evaluated the weight loss ratio between each sub-group. Also, the application regions for BtxA injections consisted of three different regions on the gastric wall (antrum, corpus, fundus) with differing toxin doses. Although the weight loss ratio in our study group might a result of a combined effect of diet and BtxA injection, we observed that the patients who reported that they did not strictly follow the dietary restrictions in the follow-up visits also lost weight.

In conclusion, our study shows that injection of 400 U BtxA onto three different regions of the gastric wall is a safe and efficient method in weight loss for patients of different BMIs. We hope that our promising results may guide further clinical studies with high sample size on the use of BtxA administration.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Istanbul University Cerrahpaşa-Cerrahpaşa Medical School Institutional Ethical Board (Permission granted: 2019, Decision no: 83045809-604.01.02).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. WHO. Obesity and overweight. Key facts. Available at: http://www.who.int/mediacentre/factsheets/fs311/en/ Date accessed: April, 2020.
2. OECD. Obesity Update 2017. Available at: https://www.oecd.org/els/health-systems/Obesity-Update-2017.pdf Date accessed: April, 2020.
3. Nyberg ST, Batty GD, Pentti J, et al. Obesity and loss of disease-free years owing to major non-communicable diseases: a multicohort study. Lancet 2018; 3: 490-7.
4. Hallett, M. One man's poison—clinical applications of botulinum toxin. N Engl J Med 1999; 341: 11-20.
5. Lemiere S, Bruley Des Varannes S. Pharmacologic actions and therapeutic importance of botulinum toxin in digestive diseases. Gastroenterol Clin Biol 1999; 23: 229-37.
6. Avena, NM, Rada PV. Cholinergic modulation of food and drug satiety and withdrawal. Physiol Behav 2012; 3: 333-6.
7. Cullen JJ, Kelly KA. Motility disorders of the gastro-intestinal tract: gastric motor physiology and pathophysiology. Surg Clin N Am 1993: 743: 1145-60.
8. Gui D, De Gaetano A, Spada PL, Viggiano A, Cassetta E, Albanese A. Botulinum toxin injected in the gastric wall reduces body weight and food intake in rats. Aliment Pharmacol Ther 2000; 14: 829-34.
9. Coskun H, Duran Y, Dilege E, Mihmanli M, Seymen H, Demirkol MO. Effect on gastric emptying and weight reduction of botulinum toxin-A injection into the gastric antral layer: an experimental study in the obese rat model. Obes Surg 2005; 15: 1137-43.
10. Bang CS, Baik GH, Shin IS, et al. Effect of intragastric injection of botulinum toxin a for the treatment of obesity: a meta-analysis and meta-regression. Gastrointest Endosc 2015; 81: 1141-9.
11. Plecka Östlund M, Marsk R, Rasmussen F, Lagergren J, Näslund E. Morbidity and mortality before and after bariatric surgery for morbid obesity compared with the general population. Br J Surg 2011; 98: 811-6.
12. Topazian M, Camilleri M, De La Mora-Levy J, et al. Endoscopic ultrasound-guided gastric botulinum toxin injections in obese subjects: a pilot study. Obes Surg 2008; 18: 401-7.
13. Foschi D, Lazzaroni M, Sangaletti O, Corsi F, Trabucchi E, Bianchi Porro G. Effects of intramural administration of botulinum toxin a on gastric emptying and eating capacity in obese patients. Dig Liver Dis 2008; 40: 667-72.
14. Mittermair R, Keller C, Geibel J. Intragastric injection of botulinum toxin a for the treatment of obesity. obes Surg 2007; 17: 732-6.
15. Bustamante F, Brunaldi VO, Bernardo WM, et al. Obesity treatment with botulinum toxin-a is not effective: a systematic review and meta-analysis. Obes Surg 2017; 27: 2716-23.
16. Topazian M, Camilleri M, Enders FT, et al. Gastric antral injections of botulinum toxin delay gastric emptying but do not reduce body weight. Clin Gastroenterol Hepatol 2013; 11: 145-50.
17. Garcia-Compean D, Mendoza-Fuerte E, Martinez JA, Villarreal I, Maldonado H. Endoscopic injection of botulinum toxin in the gastric antrum for the treatment of obesity. results of a pilot study. Gastroenterol Clin Biol 2005; 29: 789-91.
18. Júnior AC, Savassi-Rocha PR, Coelho LG, et al. Botulinum A toxin injected into the gastric wall for the treatment of class III obesity: a pilot study. Obes Surg 2006; 16: 335-43.
19. Gui D, Mingrone G, Valenza V, et al. Effect of botulinum toxin antral injection on gastric emptying and weight reduction in obese patients: a pilot study. Aliment Pharmacol Ther 2006; 23: 675-80.

20. Gracis JM, Simpson DM. Botulinum toxin therapy. The Neurol 2000; 6: 98-100.

21. Brin MF. Botulinum toxin: chemistry, pharmacology, toxicity, and immunology. Muscle Nerve 1997; 6: 146-68.

22. Granstrom L, Backman L. Stomach distension in extremely obese and normal subjects. Acta Chir Scand 1985; 151: 367-70.