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ORIGINAL CONTRIBUTIONS

How Taking into Account the Pyloric Tonus Contributes to Treatment Success While Administering Gastric "Botulinum Toxin A" for Weight Loss

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Abstract

Purpose To analyze how considering the structure of normotonic pylorus (NP) or hypotonic pylorus (HP) contributes to treatment success in patients administered gastric botulinum toxin A for weight loss.

Materials and Methods We measured body mass indexes (BMIs) of the patients who applied for gastric botulinum toxin A (BTA) for weight loss, before and 6 months after the procedure. The patients' pylori were classified as normotonic pylorus (NP) if, during endoscopy, they had a normal peristaltic motion and was closing completely, and as hypotonic pylorus if they were not closing properly or were aperistaltic. We compared the patients' mean pre-operative and 6-month post-operative BMIs. The groups were compared using the chi-square test where a $p < 0.05$ was considered significant.

Results The study included 178 patients administered gastric BTA. In the assessment made without considering the pyloric structure, the mean BMI decreased from 34.76 ± 7.65 to 33.09 ± 7.80 kg/m^2, while the difference was not statistically significant ($p < 0.06$). Conversely, in the analysis performed considering the structure of pylorus, the mean pre-operative BMI of the 45 patients with HP structure was 35.16 ± 7.07 kg/m^2 which decreased to 35.11 ± 7.03 kg/m^2 6 months after the procedure; hence, the difference was not statistically significant ($p < 0.7$). The mean pre-operative BMI of the 133 patients with NP structure, 34.63 ± 7.84 kg/m^2, decreased to 32.40 ± 8.05 kg/m^2 6 months after the procedure and the difference was statistically significant ($p < 0.05$)*.

Conclusion We advise to be selective in BTA administration and to administer BTA to the patients who, endoscopically, have a NP structure.

Keywords Normotonic pylorus · Hypotonic pylorus · Gastric Botox · Obesity

Introduction

Obesity today continues to be a rapidly increasing threat all over the world, especially in the developed industrial societies. Affecting notably the cardiovascular, respiratory, endocrine, and musculoskeletal systems, it has the potential to cause numerous diseases [1]. In essence, obesity is a public health problem [2]. The leading factor of the increase in obesity rates during the last 50 years is the industrial developments and the development of automation systems, which have replaced the labor-intensive work. Although one of its main factors is still the idle lifestyle, eating habits also play an important part in obesity. The role of a high-energy, liquid sugar-based, and carbohydrate-intensive diet in obesity is undeniable [3, 4]. Along with a proper diet, such methods as drug regimens, bariatric and metabolic surgeries, stomach balloon application, and botulinum toxin A (BTA) application are presently being used for obesity control. Various studies on the administration of gastric BTA report a diverse set of results [5, 6]. BTA is administered at doses ranging from 100 to 300 U [7]. Surgical methods stand out as the most effective

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and permanent treatments. However, endoscopic treatments have also become widespread in recent years since they are less invasive and easily performed. One of those methods is the intragastric BTA injection. It produces its effects by inhibiting the motility of the stomach muscles through "acetyl choline." The procedure of administering gastric BTA aims to prolong gastric emptying and thus to extend the duration of feeling full. BTA has a reversible effect since its effects disappear on average 3 to 6 months after its injection [6]. However, there are studies that involve different results and methodologies for the effect of gastric BTA on weight loss. With reference to our clinical observations and the complexity of the results in the literature, we considered that patients who failed to lose weight after gastric BTA application may have problems associated with the pyloric function. Any deterioration in pyloric tone is known to have a potential to affect the gastric emptying time [8]. In such a case, the gastric emptying time would also be affected due to the paralysis of gastric muscles, which is one of the effect mechanisms of BTA. This study aimed to identify the correlation between weight loss and pyloric function after gastric BTA treatment.

Materials and Methods

Among the patients who applied for gastric BTA application for weight loss, those who did not have any obstacles for BTA application were included in the preliminary study. Both the endoscopy and BTA application were performed by the same endoscopist in all the patients. The study excluded those who had an active bleeding during endoscopy and/or had an active ulcer, malign lesion, or any lesion suspected with malignancy as well as those who use drugs affecting gastric contractility and pyrokinesis. The overweight and obese patients who failed to lose weight by dieting and exercising were included in the study. The endocrinology consultation performed did not reveal any pathology. Along with their demographic data, those patients' pre-operative and 6-month post-operative heights, weights, and body mass indexes (BMIs) were recorded. There exists no classification that ensures endoscopic identification of pyloric tone. But patients' pyloric apertures were classified in two categories as regards the endoscopic appearance of the stomach: "normotonic pylorus" and "hypotonic pylorus." The category "hypotonic pylorus" (HP) included the patients whose pylori appeared to be open without any peristaltic activity in the pylori during endoscopy, whose pyloric apertures remained the same despite the stimulants to the peripyloric region with endoscope, or the closing of whose pyloric apertures remained insufficient albeit partially closed, and the category "normotonic pylorus" (NP) included those with normal pyloric activity.

BTA was administered to the patients who had no mass lesion, active bleeding, infection, or suspicious lesion in the esophagogastroduodenoscopy performed. Two BTA bottles, each containing 100 U lyophilized "onabotulinum toxin A" according to their sales form on the market, were diluted with a total of 20 cc saline solution (0.9% NaCl). The BTA solution prepared was injected to the intramuscular distance on the stomach wall at 20 separate points in total—each injection being 1 cc (including 10 proximal and 10 distal points)—circularly at 3- to 4-cm proximal and distal portions in reference to incisura angularis during the endoscopy performed under sedation. After the endoscopy procedure, the patients were kept under surveillance for 4 h, and then those with normal vital signs were discharged after observation. Six months after the operation, we measured the heights, weights, and BMIs of the patients who underwent endoscopic BTA. The patients whose data were complete were included in the study.

The data thus obtained were recorded and analyzed using SPSS statistical software. The differences between groups were analyzed using chi-square test, and a $p < 0.05$ was considered significant.

Results

The study included 178 patients who underwent gastric BTA application, including 114 females and 64 males. Table 1 presents the distribution of age and BMI measurements of the patients by groups.

As reported in the measurements made 6 months after gastric BTA application, the number of patients with a BMI below or equal to 30 kg/m^2 was 35, of which 24 were females and 11 were males. The 120 patients whose BMIs were ranging from 30.01 to 40.00 kg/m^2 included 74 females and 46 males. Also, the 23 patients who had a BMI above or equal to 40.01 kg/m^2 included 16 females and 7 males. Six months after the gastric BTA application, the mean BMI of female patients decreased from 35.38 ± 8.04 to 34.02 ± 8.24 kg/m^2, and the difference was not statistically significant ($p < 0.07$). In the same vein, the mean BMI of male patients decreased from 33.68 ± 6.96 to 31.44 ± 7.02 kg/m^2 6 months after the application, and the difference was statistically significant ($p < 0.05$)*. Six months after the application, the mean BMI of the whole group decreased from 34.76 ± 7.65 to 33.09 ± 7.80 kg/m^2, and the difference was not statistically significant ($p < 0.06$) (Table 2).

Predicated on the endoscopic appearance of pylorus in women, the pylori of 26 of the 114 patients were in HP structure while 88 had a NP structure. Besides, the mean pre-operative BMI of the 26 patients with HP structure was 36.80 ± 7.02 kg/m^2 which decreased to 36.46 ± 6.93 kg/m^2 6 months after the procedure; hence, the difference was not statistically significant ($p < 0.4$). The mean pre-operative BMI of the 88 female patients with NP structure, 34.96 ± 8.34 kg/

Table 1 Patient statistics before administering gastric "botulinum toxin A"

	Female	Male
Total number of patients (*n*)	114	64
Mean age (years)	32.64 ± 14.28	30.22 ± 10.74
Median age (years)	29	27
Minimum age (years)	18	18
Maximum age (years)	63	57
Mean BMI (kg/m^2)	35.38 ± 8.04	33.68 ± 6.96
Minimum BMI (kg/m^2)	27.40	28.92
Maximum BMI (kg/m^2)	46.76	41.07
Number of patients with a BMI below or equal to 30 kg/m^2 (*n*)	17	8
Number of patients with a BMI ranging from 30.01 to 40.00 kg/m^2(*n*)	79	49
Number of patients with a BMI above or equal to 40.01 kg/m^2 (*n*)	18	7

m^2, decreased to 33.29 ± 8.62 kg/m^2 6 months after the procedure and the difference was not statistically significant ($p < 0.06$). Predicated on the endoscopic appearance of pylorus in men, the pylori of 19 of the 64 patients were in HP structure while 45 had a NP structure. Additionally, the mean pre-operative BMI of the 19 patients with HP structure was 33.28 ± 7.18 kg/m^2 which decreased to 32.93 ± 7.14 kg/m^2 6 months after the procedure; hence, the difference was not statistically significant ($p < 0.2$). The mean pre-operative BMI of the 45 male patients with NP structure, 33.99 ± 6.88 kg/m^2, decreased to 30.66 ± 6.95 kg/m^2 6 months after the procedure and the difference was statistically significant ($p < 0.04$)*. Based on the endoscopic appearance of pylorus in the whole study group, the pylori of 45 of the 178 patients were in HP structure while 133 had a NP structure. Also, the mean pre-operative BMI of the 45 patients with HP structure was 35.16 ± 7.07 kg/m^2 which decreased to 35.11 ± 7.03 kg/m^2 6 months after the procedure; hence, the difference was not statistically significant ($p < 0.7$). The mean pre-operative BMI of the 133 patients with NP structure, 34.63 ± 7.84 kg/m^2, decreased to 32.40 ± 8.05 kg/m^2 6 months after the procedure and the difference was statistically significant ($p < 0.05$)* (Table 3).

Discussion

The increased prevalence of obesity, one of the most serious comorbid health problems of our time, has reached to an alarming rate. Obesity should be considered as a public health problem and preventive medicine should be brought into the forefront. In preventive medicine, however, the most essential approach includes limiting energy intake and abandoning sedentary life.

On the other side, numerous modalities are implemented in therapeutic medicine. Those include diet programs, physical activities, invasive surgical procedures (bariatric and metabolic surgeries), and gastric balloon and BTA applications. Being one of the endoscopic treatments of obesity, BTA injection shows its possible effect by slowing down gastric emptying and increasing satiety by creating temporary paralysis at the

Table 2 Comparison of pre-operative and 6-month post-operative patient data in gastric "botulinum toxin A" application

	Female	Male
BMI before Botox application, mean BMI (kg/m^2)	35.38 ± 8.04	33.68 ± 6.96
BMI 6 months after Botox application, mean BMI (kg/m^2)	34.02 ± 8.24 ($p < 0.07$)	31.44 ± 7.02($p < 0.05$)*
BMI before Botox application below or equal to s30 kg/m^2 (*n*)	17	8
BMI 6 months after Botox application below or equal to 30 kg/m^2 (*n*)	24($p < 0.01$)*	11 ($p < 0.04$)*
BMI before Botox application from 30.01 to 40.00 kg/m^2 (*n*)	79	49
BMI 6 months after Botox application from 30.01 to 40.00 kg/m^2 (*n*)	74 ($p < 0.08$)	46 ($p < 0.06$)
BMI before Botox application above or equal to 40.01 kg/m^2 (*n*)	18	7
BMI 6 months after Botox application above or equal to 40.01 kg/m^2 (*n*)	16 ($p < 0.08$)	7 ($p < 0.99$)

Table 3 Evaluation of the results of "botulinum toxin A" application along with the tonus of pylorus

	Female		Male		Female + male
	NP	HP	NP	HP	NP
Number of patients (*n*)	88	26	45	19	133
Total number of patients (*n*)	114		64		178
Pre-operative BMI mean BMI (kg/m^2)	34.96 ± 8.34	36.80 ± 7.02	33.99 ± 6.88	33.28 ± 7.18	34.63 ± 7.84
6-month post-operative BMI mean BMI (kg/m^2)	33.29 ± 8.62 ($p < 0.06$)	36.46 ± 6.93 ($p < 0.4$)	30.66 ± 6.95 ($p < 0.04$)*	32.93 ± 7.14 ($p < 0.2$)	32.40 ± 8.05 ($p < 0.05$)*

injection site [9]. After Foschi et al. [10] reported that BTA treatment was superior to the placebo group in 2017, a vast number of non-systematic reviews have been published, which support the use of BTA as a primary treatment for obesity. As a result, the technique has become widely used in daily practice all over the world, given also that it is minimally invasive. Nevertheless, the efficacy of BTA treatment still remains unknown since the results available in the literature are highly inconsistent and methodologically heterogeneous [11].

In their study, Park et al. reported that gastric BTA application is an effective method to lose weight [12]. Also, Li et al. reported in their study that BTA was successful in weight loss [13]. In their experimental study, Coskun et al. reported that they achieved a significant weight loss when they administered Botox-A to the gastric antrum in obese rats [5]. On another note, Sanchez Torralvo et al. suggest in their meta-analysis that intragastric botulinum toxin injection may be a useful and safe method in the treatment of obesity; however, there is a need for more well-designed, placebo-controlled, and long-term studies conducted on a sufficient sample size [2]. Gui et al. set forth that BTA application in morbidly obese patients produces no statistically significant results in weight loss [6].

Additionally, the site of BTA administration in the stomach (antrum, fundus, or both), the injection points, the total amount of BTA injected, and the post-procedure hypocaloric diet have revealed different results in terms of decline in BMI [6, 7, 10, 14].

In our study, however, a total of 200 units of BTA was injected to the stomach antrum. The patients were prescribed a hypocaloric diet. The BMI decline in all patients was 34.76 ± 7.65 to 33.09 ± 7.80 kg/m^2 at the end of the 6-month period, which was not statistically significant ($p < 0.06$). But our past experiences showed that, among the patients who underwent a gastric BTA procedure, we could not achieve successful results in those who had HP structure. For all patients regardless of the structure of pylorus, when we analyzed this outcome by keeping measurable records, we managed to support with data that we were more successful in patients with NP structure.

However, in our evaluation made taking into account the pylorus structure, the mean pre-operative BMI of the 133 patients with NP structure, 34.63 ± 7.84 kg/m^2, was found to regress to 32.40 ± 8.05 kg/m^2 6 months after the procedure and the difference was statistically significant ($p < 0.05$)*. In 45 patients with HP structure, on the other hand, the difference between the mean BMI before the procedure and the mean BMI 6 months after the procedure was found to be statistically insignificant ($p < 0.7$). As we analyze the patients with NP structure in themselves, the obtained results were found to be statistically insignificant ($p < 0.06$) even though they prove a weight loss in female patients with NP structure. In male patients with NP structure, however, the weight loss was found to be statistically significant ($p < 0.04$)*. However, since we did not find any studies taking into account pyloric structure in the literature, we could not manage to compare the data of patients with NP and HP structures.

Endoscopic and subjective evaluation and classification of pyloric laxity is a limiting factor in our study. It can be thought that midazolam used for anesthesia in patients may have pylori relaxant effect. But there is no study in the literature focusing on the effect of midazolam on pyloric pressure. Besides this, it is reported in a study that the effects of midazolam on the pressure of the sphincter of Oddi could not be clearly revealed and in another study that it may cause an increase in the esophageal distal pressure [15, 16]. Although literature provides no clear information on its effects on the pylorus, the study was also limited by the facts that midazolam used in premedication is likely to loosen the pylorus and there is no reference in the literature on the coexistence of BTA injections for the treatment of pyloric laxity and obesity. Hence, it may be considered as an advantage that our study revealed such a correlation. If the results are supported by other studies which provide an objective motility assessment, this would contribute to the selection of patients who will undergo the procedure.

Conclusions

Gastric BTA application produces successful results for the selected patient group. We do not commend this procedure to patients with HP structure due to the low chance of success in

BTA application. However, we recommend BTA application to all patients with NP structure, especially to male patients with NP structure. Further studies are needed including placebo group and objective assessment of pyloric function in this subject.

Authors' Contributions MK collected the information, reviewed the literature, and wrote the manuscript. UE collected the information. MK and UE critically reviewed the manuscript and approved the final form. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed 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. For this type of study, formal consent is not required.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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