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Effects of Botulinum Toxin (BoNT) and Factors on Weight Loss in Normotonic Pylorus (NP) and Hypotonic Pylorus (HP) Patients at Multivariate Level

İsmail Özsan [a*], Münevver Turanlı [b++], Serdal Gündüz [c†] and Kadir Yılmaz [d#]

[a] Department of General Surgery, Okan University, Istanbul, Turkey.
[b] Istanbul Commerce University, Faculty of Humanities and Social Sciences, Department of Statistics, Sütlüce, Istanbul, Turkey.
[c] Cyprus Health and Social Sciences University, General secretary, Turkish Republic of Northern Cyprus
[d] Istanbul Commerce University, Graduate School of Sciences, Department of Statistics, Istanbul, Turkey.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: In this retrospective research, it was aimed to evaluate effects of botulinum toxin (BoNT) and factors on weight loss in normotonic and hypotonic pylorus patients at multivariate level.

[++] Prof. Dr.;
[#] Postgraduate;
[†] Associate Professor, General Secretary;
**Corresponding author: E-mail: dr_ozsanozsan@yahoo.com;*

Methods: A total of 671 patients attempted to our clinic between 2020 July to 2022 July were subjected to the study divided by two groups as NP (n=581) and HP (n=90).
Results: Most of patients were female in both groups were females, but male rate in NP group was significantly higher ($p<0.05$). BMI, weight, weight difference and BMI difference means were significantly higher in NP group ($p<0.05$). Ursactive rate was significantly higher in HP group ($p<0.05$). Weight difference was significantly correlated with group ($r=-0.267$; $p<0.01$), gender ($r=0.161$; $p<0.01$), BMI ($r=0.303$; $p<0.01$), BMR ($r=0.267$; $p<0.01$), height ($r=0.143$; $p<0.01$), weight ($r=0.328$; $p<0.01$) and medicine usage ($r=-0.082$; 0.05). BMI difference was significantly correlated with group ($r=-0.262$; $p<0.01$), BMI ($r=0.305$; $p<0.01$), BMR ($r=0.158$; $p<0.01$) and weight ($r=0.239$; $p<0.01$). Generalized Linear Model (Logit Model) results showed that NP ($B=3.497$; $p<0.01$), BMI ($B=0.342$; $p<0.01$) and BMR ($B=0.004$; $p<0.01$) had significant contribution on weight difference.
Conclusion: BoNT is more effective in normotonic pylorus patients than hypotonic pylorus for weight loss and BMI reduction.

Keywords: Botulinum toxin; normotonic; hypotonic pylorus.

1. INTRODUCTION

The United States Food and Drug Administration (FDA) originally approved the use of botulinum toxin (BoNT) in 1989 to treat strabismus. Since then, botulinum toxin research has increased dramatically, which has resulted in the development of newer formulations with a wider range of applications [1-3]. Neurotoxigenic strains of anaerobic, spore-forming bacteria of the genus Clostridium produce BoNT, which are protein neurotoxins [4-6]. The gram-positive, anaerobic, rod-shaped bacterium Clostridium botulinum generates the neurotoxic proteins known as botulinum toxins [3]. Long-term usage of BoNT increases the chance that patients will acquire neutralizing antibodies and stop responding to the drug. High protein loads in some formulations, high individual and cumulative doses of BoNT, and brief intervisit intervals, particularly with booster injections, are all factors that raise the likelihood of developing resistance to BoNT [7-9].

The control of gastric emptying is greatly influenced by the tone of the pyloric sphincter. The pylorus receives non-adrenergic, non-cholinergic innervation that is mostly inhibitory and causes sphincter relaxation [10]. The lack of proper techniques for pyloric assessment has prevented researchers from fully understanding pyloric processes and treatments for ailments like gastroparesis [11]. It is known that any decrease in pyloric tone has the potential to impact how quickly the stomach empties. Due to the paralysis of the stomach muscles in such a scenario, one of the effect mechanisms of BoNT, the gastric emptying time could also be impacted [12]. The heart and pyloric rhythms are robust to temperature changes. Throughout a wide range of temperatures, the triphasic pyloric rhythm is preserved [13].

Althought it is difficult to confirm DM and pyloric nature which are important in view of gastroparesis without manometry, its effect on weight loss must be evaluated in order to prevent obesity. In literature, there have been studies comparing BoNT on HP and NP patients, there have not been found any research comparing HP and NP patients at multivariate level. Thus, it was aimed to evaluate effects of botulinum toxin (BoNT) and factors on weight loss in normotonic and hypotonic pylorus patients in this retrospective research.

2. METHODS

Endoscopy and botox procedures were performed by the same surgeon. Before the procedure, the stomach was evaluated with endoscope in terms of benign and malignant diseases. Patients having cancer, ulcer and other chronic diseases which may affect results of the study were excluded in the study. Pyloric tone was evaluated with endoscopy before the procedure. Patients with normal tone were called normotonic pylorus, and those with low tone were considered hypotonic. If the pylorus closed and opened spontaneously, it was called normotonic pylorus, and if it was constantly open and loose, it was called hypotonic pylorus. No manometric measurements were made in the study; it was decided by the visual experience of the endoscopy physician.

Under surgical sedation, clostridium botulinum toxin was applied to 500 units of antrum, 125 units of preploric, 125 units of cardia, and 250

units of fundus. After the procedure, the patient was kept under observation for one hour. The patients were followed up once a week for 6 months by a single dietitian. After the procedure, a liquid diet was applied for the first week, followed by a carbohydrate-restricted and protein-based diet.

A total of 671 patients were subjected to the study divided by two groups as NP (n=581) and HP (n=90). Ethical approval was taken from Cyprus Health and Social Sciences University.

Nominal and ordinal parameters were described with frequencies, and scale parameters were evaluated with means and standard deviations. Kolmogorov Smirnov Test was used for normality of scale parameters. Fischer's Exact test and Chi-Square Likelihood ratio. Kolmogorov Smirnov test was used for normality test of research parameters. Since all scale parameter distributions were non-normally distributed, nonparametric tests were used. Mann whitney U test was used for scale parameter differences. Spearman's rho correlation analysis and Generalized Linear Model (Logit Model) were used for relational analysis. SPSS 25.0 for windows was used for analysis at 95% Confidence Level at 0.05 singificance level.

3. RESULTS

Most of patients were female in both groups were females, but male rate in NP group was significantly higher ($p<0.05$). BMI, weight, weight difference and BMI difference means were significantly higher in NP group ($p<0.05$). Ursactive rate was significantly higher in HP group ($p<0.05$). Age, height, last weight, hormone usage, hunger, medicine, illness and diet history differences were insignificant ($p>0.05$) (Table 1).

Spearman's rho correlation analysis results showed that weight difference was significantly correlated with group ($r=-0.267$; $p<0.01$), gender ($r=0.161$; $p<0.01$), BMI ($r=0.303$; $p<0.01$), BMR ($r=0.267$; $p<0.01$), height ($r=0.143$; $p<0.01$), weight ($r=0.328$; $p<0.01$) and medicine usage ($r=-0.082$; 0.05). BMI difference was significantly correlated with group ($r=-0.262$; $p<0.01$), BMI ($r=0.305$; $p<0.01$), BMR ($r=0.158$; $p<0.01$) and weight ($r=0.239$; $p<0.01$) (Table 2).

Table 1. Baseline characteristics of patient groups and difference analysis results

Group	NP (n=581)	HP (n=90)	Total (n=671)	p value
Gender, n (%)				
Female	486 (83.6)	82 (91.1)	568 (84.6)	0.042[a]
Male	95 (16.4)	8 (8.9)	103 (15.4)	
Age	35.66±9.23	35.43±8.86	35.63±9.18	0.915[b]
BMI	31.15±3.82	29.87±3.79	30.98±3.84	0.002[b]
Height	167.42±8.04	166.33±6.74	167.27±7.88	0.256[b]
Weight	87.60±14.32	82.62±11.39	86.93±14.06	0.002[b]
Last weight	77.73±13.26	76.90±11.79	77.62±13.07	0.782[b]
Weight difference	9.87±6.23	5.72±4.45	9.31±6.18	0.000[b]
Last BMI	27.66±3.77	27.77±3.66	27.67±3.75	0.749[b]
BMI difference	3.49±2.12	2.10±1.66	3.30±2.12	0.000[b]
Ursactive, n (%)	4 (0.7)	22 (24.4)	26 (3.9)	0.000[a]
Hormone, n (%)	16 (2.8)	4 (4.4)	20 (3.0)	0.275[a]
Hunger, n (%)				
Low	6 (1.0)	2 (2.2)	8 (1.2)	
Moderate	195 (33.6)	31 (34.4)	226 (33.7)	0.825[c]
High	308 (53.0)	47 (52.2)	355 (52.9)	
Very high	72 (12.4)	10 (11.1)	82 (12.2)	
Medicine usage, n (%)	195 (33.6)	29 (32.2)	224 (33.4)	0.452[a]
Illness, n (%)	219 (37.7)	31 (34.4)	250 (37.3)	0.319[a]
Diet history, n (%)	436 (75.0)	72 (80.0)	508 (75.7)	0.188[a]

a. Fischer's Exact Test, b. Mann Whitney U Test, c. Chi-Square Likelihood ratio, SD: Standard Deviation, BMI: Body Mass Index, BMR: Basal Metabolic Rate

Table 2. Spearman's rho correlation between research parameters and BMI and weight difference

Weight difference	Weight difference	BMI difference
Group	-0.267**	-0.262**
Gender	0.161**	0.070
Age	-0.032	0.004
BMI	0.303**	0.305**
BMR (Kcal)	0.267**	0.158**
Height	0.143**	-0.004
Weight	0.328**	0.239**
Ursactive	0.064	0.073
Hormone	-0.036	-0.020
Hunger	0.002	0.004
Medicine usage	-0.082*	-0.073
Meal	-0.066	-0.063
Diet	0.067	0.069
Illness	-0.031	-0.031

**p<0.05 **p<0.01*

Table 3. Generalized Linear Model (Logit Model) for significantly correlated factors with weight difference

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test	
			Lower	Upper	Wald Chi-Square	p
(Intercept)	-11.437	2.6564	-16.644	-6.231	18.539	0.000
[Group=NP]	3.497	0.6451	2.233	4.762	29.390	0.000
[Group=HP]	0[a]	.	.	.	.	.
[Gender=Female]	.593	0.9304	-1.231	2.417	0.406	0.524
[Gender=Male]	0[a]	.	.	.	.	.
[Medicines=No]	0.714	0.4655	-0.198	1.627	2.354	0.125
[Medicines=Yes]	0[a]	.	.	.	.	.
BMI	0.342	0.0657	0.214	0.471	27.135	0.000
BMR (Kcal)	0.004	0.0012	0.001	0.006	10.221	0.001
(Scale)	31.946[b]	1.7441	28.704	35.554		

a. Null categories are reference categories

Table 4. Spearman's rho correlation analysis results for relationship between BMI difference and baseline characteristics of patient groups

BMI difference	NP (n=581)		HP (n=90)		Total (n=671)	
	r	p	r	p	r	p
Gender	0.072	0.082	-0.093	0.382	0.070	0.070
Age	-0.009	0.837	0.091	0.393	0.004	0.925
Ursactive	0.030	0.467	0.546**	0.000	0.073	0.060
Hormone	-0.041	0.322	0.133	0.212	-0.020	0.614
Hunger	-0.008	0.850	0.033	0.757	0.004	0.909
Medicines	-0.116**	0.005	0.213*	0.044	-0.073	0.060
Meal	-0.038	0.363	-0.032	0.763	-0.063	0.104
Diet	0.048	0.249	0.358**	0.001	0.069	0.076
Illness	-0.054	0.196	0.119	0.263	-0.031	0.428

**p<0.05 **p<0.01*

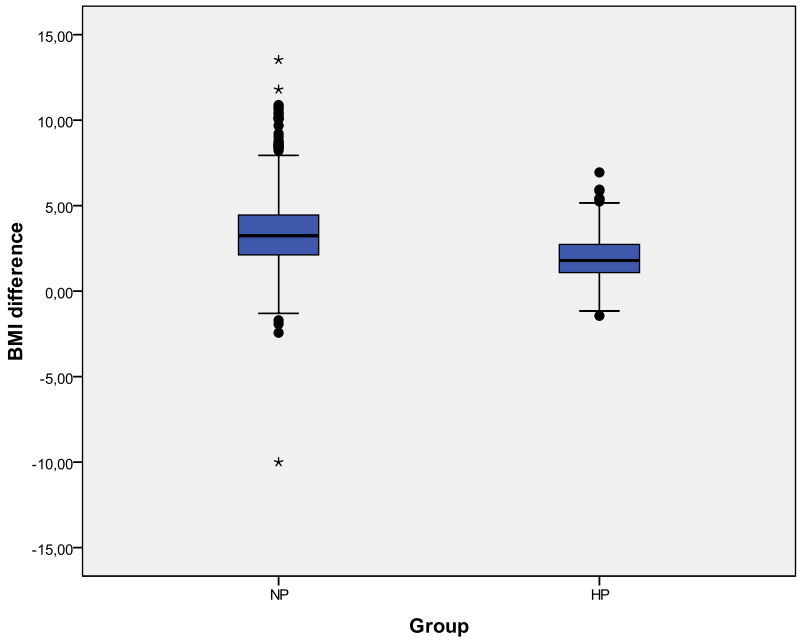

Fig. 1. BMI differences and ranges for patient groups

Since BMI difference was not significantly correlated with height, weight difference was accepted as dependent variable. BMI parameter was accepted as independent variable instead of weight and height. Generalized Linear Model (Logit Model) results showed that NP (B=3.497; p<0.01), BMI (B=0.342; p<0.01) and BMR (B=0.004; p<0.01) had significant contribution on weight difference (Table 3).

BMI difference was negatively correlated with medicine usage in NP group (r=-0.116; p<0.01). In HP group, BMI difference was positively correlated with Ursactive (r=0.546; p<0.01), medicine usage (r=0.213; p<0.05) and diet (0.358; p<0.01). In total group or for all patients, BMI difference was not significantly correlated with research parameters (p>0.05) (Table 4).

4. DISCUSSION

BoNT, which was first approved by the FDA for the treatment of strabismus in 1989, has subsequently been the subject of many clinical studies. BoNT, which is an in vitro strain of Clostridium Botulinum bacteria, is protein-based and has a muscle contraction-reducing effect [14]. Due to this effect, BoNT is used effectively in many areas, especially in aesthetic interventions for wrinkle removal. The basic approach is usually the same application method. In BoNT application, due to this effect on the muscles and the effect on the volume in the area where it is applied, BoNT has been used extensively in the areas of slimming and weight loss in recent years.

The main purpose of the treatments used for weight loss is to provide the balance between the energy taken and the energy spent, and to provide energy intake below the daily energy needed until the weight is lost and the ideal weight is reached. In this way, it is to ensure that the body gets the energy it needs from the fats it contains and stores. The most effective way to limit energy intake is to reduce the volume of the stomach by reducing eating and drinking. Reducing eating and drinking is a process that requires willpower and force the body. Nutrition-oriented weight loss methods, over eating and drinking, generally give slower results in weight loss [15-17]. However, gastric reduction surgery or invasive procedures allow for more effective weight loss in a shorter time. BoNT method is one of these invasive methods.

The control of gastric emptying is greatly influenced by the tone of the pyloric sphincter [18-20,10].

Therefore, there is an important and effective relationship between pyloric tone and stomach empty [21-26]. Pyloric tone differences may cause differences in the behavior of the stomach

and the effect of the strategy applied to lose weight. Therefore, the process of weight loss via BoNT with the pyloric strain needs to be examined. The findings of our study showed that weight loss with the BoNT method was more effective in the NP group. In our study, the differences in gender, BMI, weight, Ursactive, weight change and BMI change between the NP and HP groups were statistically significant. In the analysis, the differences between the two groups were examined on a multivariate basis, taking these differences into account.

Number of clinical researches on BoNT is very limited. In one research, Kanlioz and Ekici [12] reported that BoNT has more effective in NP patients compared to HP patients. In our study, correlation analysis results showed that there was a significant relationship between weight change and pylori type, gender, BMI, BMR, height, weight, and drug use. However, multivariate analysis results showed that weight change and pylori species, BMI and BMR values were in a significant interaction, and BMI and BMR parameters affected the weight lost together with the pylori species. While BMI and BMR were already expected parameters, despite the effect of these two parameters, the pylori strain was effective and the difference in weight given was greater in the NP group.

The most important limitation of the research is that there has not been enough work in this field due to the limitations imposed in some countries regarding BoNT. In fact, this situation provides both the limitation of the study and its being a pioneer in the field. Another limitation of the study is that the clinical parameters are limited in the application of BoNT, since the application is generally partially non-invasive. This situation shows both the limitations of the research and the non-invasive level of weight loss with the BoNT method.

Although studies and clinical data on BoNT reveal that the BoNT method is less invasive than surgical methods and is more effective in losing weight, it has not yet been approved in the field of bariatric surgery worldwide, since there has not been enough clinical studies in this area yet. However, it has been approved by the ministry of health and related organizations in many countries. In this regard, more clinical studies are needed in order to be an effective and less invasive alternative in the fight against obesity which and to benefit the patient. In this respect, the research is important in terms of contributing to the limited studies in the literature and spreading the subject to a larger sample for further meta-analysis. Another important aspect of the study is that it reveals the effect of pylori on weight loss and thus contributes to a more effective literature infrastructure for BoNT applications.

5. CONCLUSION

Although pylori type, gender, BMI and BMR parameters have significant effect on weight loss in BoNT treatment at univariate level, effect of gender is insignificant at multivariate level. Pylori type is an important parameter affecting weight loss after BoNT application. BoNT is more effective in normotonic pylorus patients than hypotonic pylorus for weight loss and BMI reduction.

DATA AVAILABILITY

Data of the research is stored to OSF with following link:

Link and DOI:

https://osf.io/tnkc6/

DOI 10.17605/OSF.IO/TNKC6

CONSENT

It is not applicable.

ETHICAL APPROVAL

Since the research was retrospective, ethical approval was taken, but patient consent was not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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