Original Article

Comparison of safety and efficacy of intragastric botulinum toxin-A versus gastric balloon

Raed M. Tayyem, Haitham G. Qandeel, Hamzeh I. Al-Balas, Farah R. Tayyem[1], Jehad Z. Fataftah[2], Mahmoud I. Al-Balas

Departments of General and Special Surgery, Faculty of Medicine, The Hashemite University, Zarqa, [1]Department of Dental Surgery, Faculty of Dentistry, Jordanian University of Science and Technology, Irbid, [2]Department of Radiology, The Hashemite University, Zarqa, Jordan

Abstract

Background: A prospective case-matched study was conducted to compare the safety and efficacy of endoscopic intragastric botulinum toxin-A (EIBT) versus endoscopically planned gastric balloon (EPGB), as a treatment for obesity.

Methods: A total of 176 patients (matched for age and sex) were equally divided to undergo EIBT ($n = 88$) or EPGB ($n = 88$). Patients who received EIBT were restricted to a body mass index (BMI) of 25 to 35 kg/m^2, whereas a BMI >25 kg/m^2 was allowed in the EPGB group. The main measured outcomes were weight loss, procedure duration, complications, early satiety, and quality of life (QoL).

Results: The patients were followed up for a mean of 6 months. The mean weight loss was greater in the EPGB group than in the EIBT group (15.6 kg vs. 9.3 kg, $P < 0.001$). However, the percentage excess weight loss and the satiety score were greater in the EIBT group (59.1% vs. 42.2%, $P < 0.001$; and 3.5 vs. 2.3, $P < 0.001$) respectively. The procedure duration was shorter for EIBT patients (10 min vs. 15 min, $P < 0.001$). The postoperative complication rate recorded in the EPGB group was significantly higher (30% vs. 9%, $P = 0.001$). Adverse symptoms lasted longer in EPGB (5.2 days vs. 0.7 days, $P < 0.001$). Both groups enjoyed similar improvements in QoL.

Conclusion: EIBT is a safe and effective treatment for mild obesity. Although the weight loss was greater in the EPGB group, the percentage excess weight loss, procedure duration, postoperative complications, and symptom duration were significantly better in the EIBT group. QoL improvement was comparable between the two groups.

Keywords: Botulinum Toxin-A, endoscopy, gastric balloon, intragastric injection, obesity, percent excess weight loss, quality of life, weight loss

Address for correspondence: Dr. Raed M. Tayyem, Department of General Surgery, The Hashemite University, Zarqa, Jordan.
E-mail: rtayyem@yahoo.com

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See accompanying Editorial

INTRODUCTION

The epidemic of obesity has been steadily progressing over the last two decades but has worsened significantly during COVID-19.[1] Several diseases are associated with obesity, such as diabetes mellitus (DM), hyperlipidemia, metabolic syndrome, hypertension (HTN), ischemic heart disease (IHD), and obstructive sleep apnea (OSA).[2-5]

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Modest weight reduction (10 kg) has a positive effect on the cardiovascular system, blood sugar, and plasma lipids.[6] Weight loss maintenance is crucial for attaining the beneficial effects of weight reduction.[4]

Although conservative management of obesity utilizing diet and exercise is tempting, several studies have shown that maintenance of weight loss, in the long run, is questionable.[7,8] Although conservative modalities result in 4 to 8% weight loss, the majority of patients regain weight shortly after.[9,10] Although some patients gain weight following bariatric procedures, bariatric procedures remain more favorable in terms of achieving long-term weight loss, as several studies have shown that bariatric surgery is the only effective intervention that provides enduring weight loss in the severely and morbidly obese.[11-13]

This leaves individuals with mild obesity (class one as per the World Health Organization classification)[14] with the question: What is the ideal method to manage their excess weight? Relentless medical endeavors to improve or discover new modalities for treating mild obesity has led to several approaches and methods for clinicians to perform, such as behavioral (diet and exercise), pharmacological, and psychological interventions, and more recent endoscopic approaches, including endoscopic intragastric botulinum toxin A injection and endoscopically planned gastric balloon (EPGB). A systematic review determined that EPGB is safe and provides additional benefits to weight loss compared to conventional treatment.[15] These results were echoed in a previous meta-analysis that evaluated the efficiency of EPGB in contrast to conventional modalities.[16] A new revolution in obesity treatment involves injecting the stomach wall with botulinum toxin A (BTA). BTA has been used safely in other disciplines for many years, including aesthetic, gynecological, and urological procedures.[17] BTA helps to speed up weight loss by relaxing the gastric muscles, delaying gastric emptying, and keeping patients feeling full for longer, resulting in early satiety and reduced food intake.[18,19]

In this study, we postulate that EIBT is a safe and effective approach for the treatment of mild obesity, which could be utilized in conjunction with conventional methods to maximize weight loss. A prospective case-matched study was conducted to compare the outcomes of EIBT and EPGB.

METHODS

Inclusion and exclusion criteria

Adults aged between 18 and 60 years with a body mass index (BMI) >25 kg/m^2 were included. Inclusion to the EIBT group was restricted to patients with a BMI of 25 to 35 kg/m^2, whereas a BMI >25 kg/m^2 was allowed in the EPGB group.

Patients with comorbidities that could interfere with the endoscopic procedure, such as large hiatus hernia or peptic ulcer, pregnancy and lactation, myopathy or neuromuscular disorders, and hypersensitivity to BTA, were excluded from the study.

Preoperative evaluation

Patients were assessed in a bariatric clinic where a detailed medical history was obtained. Blood pressure, height, weight, and BMI were recorded. Routine blood tests were also performed. In addition, patients received thorough counseling by a specialist dietician.

Endoscopic technique

The endoscopic procedures were performed by experienced bariatric surgeons in the endoscopy suite under conscious sedation after a 10-h fast. A local anesthetic oral spray (lignocaine 10%) was used to reduce discomfort.

Endoscopic Intragastric Botulinum Toxin-A (EIBT) injection

One hundred units of Botox® (Allergan Pharmaceuticals, USA) or 300 units of Dysport® (Galderma Laboratories, USA) were diluted in 50 mL of normal saline. Injections were administered into the gastric antrum, cardia, and fundus under direct endoscopic visualization.

Endoscopically placed gastric balloon (EPGB)

Orbera® (Apollo Endosurgery, USA), Silimed® (Silimed, Brazil), or Silirus® (Silirus, Russia) intragastric balloon systems were used. The balloons were placed in the fundus of the stomach under direct endoscopic vision. They were inflated using 600 mL of saline dyed with 2 mL of methylene blue.

Post-procedure care

The patients were discharged from the endoscopy suite after 30 to 60 min of observation. Patients were given prescriptions consisting of a proton pump inhibitor (PPI), anti-emetics, and analgesia. They were instructed to undergo a liquid diet for 1 week, which was later followed by a reduced-calorie diet that was advised by the dietician (1200–1300 kcal/day). The patients were also encouraged to walk daily for 30 to 45 min. The patients were reviewed in the bariatric outpatient clinic every month to assess their progress, including weight loss and any adverse side effects, for a period of 6 months. Lastly, the balloons were removed via endoscopy after a mean period of 6 months. The authors' rationale to follow up patients for only 6 months was that balloons were removed

at 6 months and BTA effects wore off by 6 months. The primary aim of the study was to compare the safety and efficacy of EIBT versus EPGB. It was not one of the study's aims to evaluate the long-term effects of EPGB and EIBT as earlier studies have thoroughly evaluated the long-term effects of non-bariatric interventions. Several studies have failed to demonstrate maintenance of weight loss in the long term utilizing non-surgical management of obesity.[7,8,20] Conservative modalities result in 4 to 8% weight loss; however, 90% relapse within 5 years.[9,10,21] Maintenance of weight loss is crucial in attaining the beneficial effects of weight reduction including resolution of comorbidities and improve QoL.[4]

Ethics

Ethical approval of the study was granted by the Hashemite University Ethics Committee.

Data collection and statistical analysis

The primary outcome of this study was to assess weight loss and percentage excess weight loss (%EWL = weight loss/excess weight). A BMI of 25 kg/m^2 was used to define the ideal weight for excess weight. The secondary outcomes were procedure duration, early satiety, and treatment complications. The satiety score was created using a Likert scale ranging from 1 to 5 (1 = normal appetite up to 5 = complete loss of appetite).

Minor and major complications were recorded during the perioperative period and during each visit. Minor complications included nausea, vomiting, abdominal pain, and minor upper gastrointestinal (GI) bleeding. Major complications related to endoscopy included mortality, major bleeding, and injury to the upper gastrointestinal organs. Major complications related to the balloon included early balloon removal, balloon rupture, and balloon migration. Major complications related to BTA included muscle weakness, double vision, dysphagia, and allergic reactions to BTA (e.g., dyspnea, chest pain, fever, joint pain, and skin rash).

Data were collected prospectively using Microsoft Excel. Statistical analysis was performed using the SPSS software (version 25, SPSS Inc., USA). Quantitative continuous variables are expressed as means with standard deviations (SD). Categorical data were compared using the Chi-square test, and continuous data were compared using Student's *t*-test with a confidence interval (CI) of 95%. Statistical significance was set at $P < 0.05$. Analysis of covariance (ANCOVA) was used to statistically control for the possible effects of an additional confounding variable (covariate).

RESULTS

Baseline characteristics of patients

Table 1 shows that baseline characteristics in EIBT and EPGB were comparable, including age (36.9 vs. 34.8, $P = 0.20$) and female sex (74% vs. 83%, $P = 0.10$). However, EPGB group was heavier on average with statistically significant differences in the initial weight (111.7 kg vs. 89.7 kg, $P < 0.001$), excess weight (43.0 kg vs. 17.1 kg, $P < 0.001$), and BMI (40.6 kg/m^2 vs. 30.7 kg/m^2, $P < 0.001$). In addition, obesity comorbidities were more prevalent in the EPGB group (23/88 vs. 11/88, $P = 0.04$). The age and sex were closely matched between both groups but the BMI was not closely matched due to difficulties in recruiting more patients in the era of the COVID-19 pandemic. However, ANCOVA was used to statistically control for the possible effects of an additional confounding variable (covariate).

Weight loss

Univariate analysis of variance was applied to explore the differences between the EIBT and EPGB groups, by statistically controlling covariates, including age, sex, baseline weight, and obesity comorbidities. Table 2 illustrates that, at a mean follow-up of 6 months, the weight loss was in favor of EPGB. The difference between EIBT and EPGB was statistically significant, including weight (80.4 kg vs. 96.1 kg, $P < 0.001$), weight loss (9.3 kg vs. 15.6 kg, $P < 0.001$), BMI (27.7 kg/m^2 vs. 34.9 kg/m^2, $P < 0.001$), and BMI loss (3.2 kg/m^2 vs. 5.6 kg/m^2, $P < 0.001$). However, %EWL was better in the EIBT group (59.1% vs. 42.2%, $P < 0.001$).

Satiety score

The EIBT group scored higher on the satiety scale (3.5 vs. 2.3, $P < 0.001$).

Table 1: Baseline clinical and biochemical characteristics*

	EIBT (*n*=88)	EPGB (*n*=88)	*P*
Age-years	36.9 (10.6)	34.8 (10.5)	0.20
Number of females (%)	65 (74%)	73 (83%)	0.10
Initial weight in kgs	89.7 (13.7)	111.7 (22.0)	<0.001
Excess weight in kgs	17.1 (8.6)	43.0 (18.5)	<0.001
BMI kg/m^2	30.7 (2.9)	40.6 (6.3)	<0.001
Number of patients with comorbidity (%)	11 (13%)	23 (26%)	0.04
SF36 score 0-100	48.4 (22.3)	49.6 (21.5)	0.80
Glucose mmol/L	6.8 (2.5)	6.1 (1.1)	0.10
HbA1c %	6.4 (1.7)	6.0 (0.9)	0.39
Total cholesterol mmol/L	5.1 (1.1)	4.8 (0.7)	0.12
Triglyceride mmol/L	2.7 (2.0)	2.4 (1.7)	0.42
CRP mg/L	14.8 (11.1)	18.1 (14.0)	0.18
WBC count	8.2 (2.6)	9.6 (1.4)	0.29

*Values are means (standard deviation) unless otherwise indicated. BMI=body mass index, CRP=C-reactive protein, WBC=white blood cell

Table 2: Weight loss, procedure duration, satiety, complications, and biochemical parameters at 6 months follow-up*

	EIBT	EPGB	*P*
Weight (kg)	80.4 (10.8)	96.1 (19.6)	<0.001†
Weight loss (kg)	9.3 (5.1)	15.6 (8.8)	<0.001†
%EWL	59.1% (22.9)	42.2% (28.3)	<0.001†
BMI (kg/m^2)	27.7 (2.0)	34.9 (5.8)	<0.001†
BMI loss (kg/m^2)	3.2 (1.7)	5.6 (3.1)	<0.001†
Satiety score (1-5)	3.5 (1.2)	2.3 (1.1)	<0.001†
Procedure duration (min)	10.0 (2.8)	15.1 (5.4)	<0.001†
SF36 (score 0-100)	85.1 (14.6)	78.5 (17.9)	0.10†
Complication rate	8/88 (9%)	26/88 (30%)	0.001
Duration of symptoms (days)	0.7 (0.6)	5.2 (1.9)	<0.001
Glucose (mmol/L)	5.3 (0.5)	5.1 (1.1)	0.61
HbA1c (%)	5.4 (0.8)	5.3 (0.7)	0.72
Total cholesterol (mmol/L)	4.0 (0.4)	4.2 (0.7)	0.49
Triglyceride (mmol/L)	1.7 (0.3)	1.5 (0.7)	0.51
CRP (mg/L)	8.9 (5.6)	7.5 (4.1)	0.43
WBC count	8.5 (1.8)	7.8 (2.0)	0.28

*Values are means (standard deviation) unless otherwise indicated. †*P* value corrected after statistically controlling covariate factors of sex, age, baseline weight, and obesity comorbidities. %EWL=percent excess weight loss, BMI=body mass index, CRP=C-reactive protein, WBC=white blood cell

Procedure duration

The average procedure duration was shorter for EIBT patients than for the EPGB group (10.0 min vs. 15.1 min, $P < 0.001$), taking into consideration that endoscopists are required to insert the scope twice to place the balloon.

Quality of life

The SF36 scores were comparable between both the groups (85.1 vs. 78.5, $P = 0.10$)

Complications

No deaths occurred in either group. Only 9% of patients with EIBT complained of nausea, vomiting, and abdominal pain, that settled quickly in less than 1 day. However, 30% of EPGB patients complained of nausea, vomiting, and abdominal pain that required them to proceed to the emergency room (ER) more than once to receive intravenous antiemetics and analgesics. Their symptoms lasted for an average of 5 days. Four patients required removal of the balloon early in the EPGB group due to patient intolerance of gastric upset symptoms despite maximal medical therapy. No major complications were recorded in either group (i.e., no toxicity or allergic reactions to botulinum occurred).

DISCUSSION

Managing mild obesity can be challenging, as the standard traditional treatment alone (diet and exercise) might not be adequate for achieving weight targets. Pharmacological interventions have been attempted with modest success and a large rebound in weight gain.[8] EPGB has also been attempted with promising results on weight loss, particularly if the intervention was coined with thorough follow-up by the dietician.[22]

Previous studies assessing BTA in the treatment of obesity have shown conflicting results.[23,24] Several randomized and non-randomized studies have shown the benefits of EIBT in terms of weight reduction in obese patients.[18,19,25-34] In contrast, other studies concluded that EIBT did not seem to be an effective method for achieving weight loss.[35-38] The disappointing results of some of these initial reports may indicate a flaw in the technique, poor choice of patients, or lack of dietician follow-up.

EPGB has established itself as a valuable tool in obesity management, particularly in cases that are refractory to standard traditional treatments. In addition, EPGB and EIBT are minimally invasive, as they are performed endoscopically. Therefore, it is natural to compare EIBT with EPGB. To the best of our knowledge, this is the first study published in the literature comparing EIBT with EPGB.

The total number of patients included was 176, distributed equally between the EIBT and EPGB groups. The demographic and clinical characteristics were similar in both groups, with no evidence of a significant difference in terms of age or sex. However, there were differences in weight and obesity comorbidities. This reflects the fact that patients with mild obesity were only considered for EIBT, contrary to the EPGB group where a BMI above 25 kg/m^2 could be included (BMI range: 27–56 kg/m^2).

At a mean follow-up of 6 months, both groups experienced considerable and statistically significant weight loss. The EIBT group lost an average of 9.3 kg (which was similar to previous studies) compared to 15.6 kg in the EPGB group.[19] Interestingly, %EWL was better in EIBT, which may indicate that EIBT is a good treatment modality for mild obesity. A possible alternative explanation is that BMI selection to <35 kg/m^2 in the EIBT may have played a role. The substantial weight loss in both groups ensured that they enjoyed improvement in their QoL.

EIBT reduced appetite in 79% of our patients, which is a crucial factor considering that successful weight management depends on appetite control. This is clearly demonstrated in the gastric sleeve, as the gastric fundus is removed, resulting in diminished ghrelin hormone levels, thus reducing appetite. BTA may modify appetite through its action as a neurotoxin that inhibits the release of acetylcholine, thus causing muscle paralysis, which reduces gastric motility and prolongs gastric

emptying.[39] Procedure safety is another important factor to consider. One-third of patients who underwent EPGB complained of severe gastric upset. Five patients suffered from severe relentless symptoms to a degree that necessitated balloon removal. EIBT, in contrast, achieved similar results regarding weight loss with an almost complete absence of adverse effects during or after the procedure.

ANCOVA was used to statistically remove the effect of covariates (weight and BMI difference). However, weight and BMI differences remain a study limitation. Other limitations include a lack of randomization and recruitment of a relatively small sample size, that may have confounded the findings. To obtain more conclusive results, further studies are needed to assess the long-term results of both procedures.

CONCLUSION

In conclusion, this prospective case-matched study is the first to compare the outcomes of EIBT with those of EPGB. After a mean follow-up of 6 months, weight loss and improvement in QoL were comparable between the two groups. EIBT did not cause serious side effects. These results provide further evidence to show that EIBT is a minimally invasive, safe, and effective procedure capable of suppressing appetite and producing weight loss.

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Conflicts of interest

There are no conflicts of interest.

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