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The Clinical and Metabolic Effects of Intragastric Balloon on Morbid Obesity and Its Related Comorbidities

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Obesity is becoming increasingly prevalent worldwide, and its metabolic sequelae lead to a significant burden on healthcare resources. Options for the management of obesity include lifestyle modification, pharmacological treatment, surgery, and endoscopic bariatric therapies (EBTs). Among these, EBTs are more effective than diet and lifestyle modification and are less invasive than bariatric surgery. In recent years, there have been significant advances in technologies pertaining to EBTs. Of all the available EBTs, there is a significant amount of clinical experience and published data regarding intragastric balloons (IGBs) because of their comparatively long development period. Currently, the United States Food and Drug Administration (FDA) has approved three IGBs, including Orbera (Apollo Endosurgery, Austin, TX, USA), ReShape Duo (ReShape Medical, San Clemente, CA, USA), and Obalon (Obalon Therapeutics, Carlsbad, CA, USA). The aim of this review is to summarize the available literature on the efficacy of IGBs in weight loss and their impact on obesity-related metabolic diseases. **Clin Endosc 2021;54:9-16**

Key Words: Bariatrics; Endoscopy; Intragastric balloon; Metabolic; Obesity

INTRODUCTION

Obesity is a highly prevalent chronic condition that represents a public health problem worldwide, and it is likely that this situation will persist in the future.[1] The clinical importance of obesity is not limited to the condition itself, but the related comorbidities associated with obesity, such as diabetes mellitus, hyperlipidemia, non-alcoholic fatty liver disease (NAFLD), hypertension, cardiac disease, cerebrovascular diseases, and metabolic syndrome.[2] Furthermore, obesity is also associated with an increased risk of all-cause mortality.[3,4] However, the management of obesity is complex and requires a multifaceted approach. Majority of patients with obesity fail to achieve sustained weight reduction or maintain optimal weight by dietary and lifestyle modifications and pharmacological therapies alone.

Among the several modalities used in managing obesity, the most successful effective long-term options for weight loss are bariatric surgeries such as sleeve gastrectomy and Roux-en-Y gastric bypass, which report a 55% to 85% excess weight loss (EWL).[5,6] However, these surgical interventions have reported mortality rates ranging from 0.2% to 1.0%, re-intervention rates of 4.3% to 8.3%, and serious adverse events reported in 26% of cases.[7] Therefore, very few patients eventually undergo bariatric surgery to manage their obesity and its associated metabolic conditions. Hence, there has been growing interest in endoscopic bariatric and metabolic therapies (EBMTs) over the past decade. EBMT devices are designed such that they are not only efficacious in weight loss, but also have potential for reversibility and are cost-effective when compared to bariatric surgery.[8] The main mechanisms of EBMT include space occu-

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pation, reducing gastric capacity, modification of gastric motor function, and malabsorption. Among the several EBMTs that have been developed, the intragastric balloons (IGBs) are the most widely used in clinical practice.

Although many methods of bariatric therapies have been developed to date, the ultimate goal of managing obesity is to correct the associated metabolic disease rather than weight loss itself. This review will discuss the various available IGBs, focusing on their effect on weight loss and the improvement in obesity-related complications and metabolic diseases.

INTRAGASTRIC BALLOONS

IGBs are devices that occupy space in the stomach to induce early satiety. Prior studies suggest that an IGB volume of at least 400 mL is required for proper weight reduction.[9] Weight loss after placement of an IGB occurs due to delayed gastric emptying as well as restricted food intake due to the decreased stomach volume. In addition, stretching of the stomach wall stimulates the vagus nerve receptors and brain centers responsible for satiety.[10] Also, changes in the activity of gastrointestinal hormones and neuropeptides that affect appetite control play a crucial role. However, the exact mechanisms remain unclear.

Although this technique was introduced in the 1980s,[11] it was withdrawn from commercial use due to ineffective weight loss, spontaneous balloon deflation, and device-related complications such as gastric ulcers, gastric perforations, and intestinal obstructions that require surgical intervention.[12] Since then, there have been significant advances in technology (e.g., the use of more durable silicone-based materials), and several IGBs have been used in the clinical setting for more than 25 years. To date, the United States Food and Drug Administration (FDA) has approved three types of IGBs,[13-15] while several others are in process for approval.

Of these balloon devices, Orbera™ (Apollo Endosurgery, Austin, TX, USA; Fig. 1A), also formerly known as the Bio-Enterics Intragastric Balloon, is the most widely available worldwide. Since its introduction in 1996, this type of balloon has been utilized in over 250,000 patients and was approved by the United States FDA in 2015.[13] The balloon is placed endoscopically into the gastric lumen and filled with 400–700 mL of sterile saline. An optional 10 mL of methylene blue may also be added to aid in detection of spontaneous balloon perforation and deflation. The balloon is resistant to gastric acid and is indicated for insertion for up to six months. ReShape Duo™ (ReShape Medical, San Clemente, CA, USA; Fig. 1B), a dual balloon system, was approved at the same time.[14] This device contains two balloons that are interconnected by a flexible wire, which minimizes the risk of migration when one balloon deflates. Obalon™ (Obalon Therapeutics, Carlsbad, CA, USA; Fig. 1C), which was approved by the FDA in 2016,[15] is characterized by its gas-filled design and the ability to be inserted via swallowing the deflated balloon in its capsule form under fluoroscopic guidance. A maximum of three balloons can be placed in the stomach due to a smaller balloon capacity of 250 mL. All three FDA-approved IGBs are indicated for patients with a body mass index (BMI) of 30 to 40 kg/m^2 (class I and II obesity) who have failed to respond to lifestyle modifications and nutritional interventions. Additionally, the ReShape Duo is only indicated for patients with an existing obesity-related comorbidity (i.e., diabetes mellitus, hypertension, hyperlipidemia),[16] whereas the Orbera does not have this requirement. Until recently, no other effective bariatric procedure could be applied to patients in this group, since patients with a BMI greater than 40 kg/m^2 or BMI 35–40 kg/m^2 with obesity-related comorbidities are generally considered for bariatric surgery.

In recent years, several other IGBs have been developed for weight reduction, such as Spatz Balloon (Spatz FGIA, Great Neck, NY, USA),[17] Elipse™ Balloon (Allurion Technologies, Wellesley, MA, USA),[18,19] Heliosphere BAG (Helioscopie Medical Implants, Vienne, France),[20] Medsil® (CSC MEDSIL, Moskovskaya oblast, Russia),[21] LexBal (Lexel Medical, Buenos Aires, Argentina),[22] and End-ball (Endalis, Brignais, France),[23] all of which are awaiting FDA approval; further clinical studies with IGBs are expected. Spatz3 (Fig. 1D) is another fluid-filled silicone balloon. This balloon was developed to overcome several limitations of earlier balloons, such as short-term implantation and difficulty in balloon volume adjustment. One of the main advantages of this balloon is its adjustability, making it easier to tailor volumes according to patient tolerance and weight loss. Additionally, Spatz3 is the only IGB that can be left in place for up to 12 months among the currently available IGBs. The Elipse (Fig. 1E) is the first procedureless IGB that does not require endoscopy to place or remove it.[19] It is a swallowable saline-filled balloon, similar to the Obalon, though it self-deflates by natural degradation of the soluble substance inside the balloon and is naturally excreted through the gastrointestinal tract after approximately 16 weeks. The Heliosphere BAG (Fig. 1F) is an air-filled polyurethane balloon covered with a silicone envelope. Fluid-filled balloons have been reported to frequently induce nausea and vomiting after the time of balloon insertion due to excess balloon weight, and they may be associated with a higher rate of intolerance and early removal.[24] Thus, this air-filled device was introduced to avoid these disadvantages. The End-ball (Fig. 1G) is a saline/air-filled polyurethane balloon and is the most commonly used IGB in Korea.[25] Conventional IGBs are filled with either saline or air, each with their respective advantages and disad-

Fig 1. (A) Orbera (http://apolloendo.com), (B) ReShape Duo,[16] (C) Obalon (http://www.obalon.com), (D) Spatz3,[17] (E) Elipse,[25] (F) Heliosphere BAG,[20] (G) End-ball (http://www.endalis.com).

vantages. Air-filled balloons are well tolerated but less effective in terms of weight loss, while saline-filled balloons are more effective with regard to weight loss, but are associated with more adverse events.[24,26] The unique feature of the End-ball is that the endoscopist can select the saline-to-air ratio in the balloon for infusion.

CHARACTERISTICS OF INTRA-GASTRIC BALLOONS WITH FDA APPROVAL OR IN THE PROCESS OF FDA APPROVAL

Orbera (Apollo Endosurgery, Austin, TX, USA); FDA-approved

(1) Silicone, single balloon filled with 400–700 mL of saline
(2) Endoscopic placement / Endoscopic removal after deflation
(3) Implanted for up to a maximum of 6 months

ReShape Duo (ReShape Medical, San Clemente, CA, USA); FDA-approved

(1) Silicone, double balloon filled with 450 mL of saline per balloon
(2) Endoscopic placement / Endoscopic removal after deflation
(3) Implanted for up to a maximum of 6 months

Obalon (Obalon Therapeutics, Carlsbad, CA, USA); FDA-approved

(1) Gelatin capsule, up to 3 balloons filled with 250 mL of gas

(2) Insertion via swallowing in capsule form, verification of gastric location done via fluoroscopy or pressure reading/endoscopic removal with deflation
(3) Implanted for 3–6 months

Spatz (Spatz FGIA, Great Neck, NY, USA); not FDA-approved

(1) Silicone, single adjustable balloon filled with 400–800 mL of saline
(2) Endoscopic placement / Endoscopic adjustment of fill volume / Endoscopic removal
(3) Implanted for up to a maximum of 12 months

Elipse (Allurion Technologies, Wellesley, MA, USA); not FDA-approved

(1) Polymer film, single balloon filled with 450–550 mL of saline
(2) Insertion via swallowing in capsule form, verification of gastric location done via fluoroscopy or pressure reading/degradation and excretion naturally through the GI tract at 4 months with complete deflation

Heliosphere BAG (Helioscopie Medical Implants, Vienne, France); not FDA-approved

(1) Polyurethane and silicone, single balloon filled with 550 mL of air
(2) Endoscopic placement / Endoscopic removal
(3) Implanted for up to a maximum of 6 months

End-ball (Endalis, Brignais, France); not FDA-approved

(1) Polyurethane, single balloon filled with 600 mL of air/saline; endoscopist can select any ratio of air to saline for infusion
(2) Endoscopic placement / Endoscopic removal after deflation
(3) Implanted for up to a maximum of 6 months

WEIGHT LOSS AND METABOLIC EFFECTS OF INTRA-GASTRIC BALLOONS

The goal of an IGB is to induce weight reduction and assist with the management of obesity-related comorbidities, with adequate safety. An IGB is suitable for patients with a BMI of 30–40 kg/m^2 (class I and II obesity).[27] In patients with severe or morbid obesity (BMI >40 kg/m^2 to >50 kg/m^2, class III and IV obesity), IGB placement can help in preparation for bariatric surgery by reducing the surgical risk or facilitate non-bariatric interventions that could not be safely performed due to weight limits (i.e., orthopedic surgery, organ transplantation).[28-36]

Prior to its recent FDA approval, the weight loss effect of IGB was proven through early clinical studies in Europe. A retrospective study of 2,515 cases conducted in Italy, which has been one of the largest until now, demonstrated a mean BMI loss of 4.9±12 kg/m^2 over the 6-month study period.[37] Furthermore, 44.3% of obesity-related complications, including hypertension, diabetes mellitus, dyslipidemia, respiratory disorder, and osteoarthropathy, resolved and another 44.8% of them improved during the study period. In one meta-analysis[38] of 16 studies involving 3,608 patients who underwent IGB placement, there was a reported mean BMI loss of 5.7 kg/m^2 and a %EWL of 32.1% at the time of balloon removal. Additionally, obesity-related complications, including hypertension, diabetes mellitus, and dyslipidemia, also improved. These positive outcomes have also been reported with a %EWL range of 34%–50% in several prospective randomized controlled studies (RCTs) comparing IGB (Orbera) to dietary and lifestyle interventions (Table 1).[39-43] Furthermore, IGBs have also been shown to be superior in weight reduction to pharmacological therapies, and similar to laparoscopic adjustable gastric banding.[44] The other FDA-approved IGBs, Reshape Duo and Obalon, also have similar weight loss effects.[45,46]

More recently, four systematic reviews and meta-analyses on the efficacy of weight loss with IGBs have been published. The first meta-analysis, which included 1,683 patients in 17 studies using the Orbera, demonstrated a mean %EWL of 25.44%, and the results met the American Society for Gastrointestinal Endoscopy (ASGE) PIVI criteria of 25% EWL.[29] In the second meta-analysis, Moura et al.[47] reviewed nine studies involving 669 patients using either the Orbera, Reshape Duo, or air-filled balloons, which compared IGB plus diet to sham plus diet. They found a mean %EWL of 14% favoring the IGB group. The third meta-analysis involving 20 studies with 1195 patients demonstrated a similar %EWL of 14.2% at 3 months after IGB placement.[48] In another meta-analysis, Kotinda et al.[49] reviewed 13 RCTs involving 1,523 patients using either the Orbera, Reshape Duo, Obalon, Spatz, or Heliosphere, which compared IGB with sham or lifestyle intervention, and showed that the difference in mean %EWL and % total weight loss (%TWL) at follow-up was 17.9%, and 4.4%, respectively, and was significantly higher in the IGB group. Singh et al. also conducted a systematic review and meta-analysis comparing the efficacy, safety, and durability of IGB versus endoscopic sleeve gastroplasty (ESG).[50] They found that the mean %TWL at 12-month follow-up with ESG was 17.5% as compared to 10.3% with IGB placement.[50]

Table 1. Prospective, Randomized Controlled Trials of Intragastric Balloons

IGB device	Study	Country	IGB implant time (wk)	Number of subjects		%EWL	%TBWL	BMI loss (kg/m^2)	*p*-value
				n (total)	Study arm				
Orbera	Genco et al. (2006)[39]	Italy	12	32	16 (IGB + diet) 16 (sham + diet)	34.0±4.8 2.1±1.0	NR	5.8±0.5 0.4±0.2	<0.001 (%EWL)
Orbera	Konopko-Zubrzycka et al. (2009)[40]	Poland	24	36	21 (IGB) 15 (diet + exercises)	NR	12.3 2.3	NR	<0.001
Orbera	Peker et al. (2011)[44]	Turkey	24	32	16 (IGB) 16 (laparoscopic band)	39.3 32.3	NR	NR	0.189
Orbera	Farina et al. (2012)[41]	Italy	24	50	30 (IGB + diet + exercise) 20 (sibutramine + diet + exercise)	NR	14.5±1.2 9.1±1.5	NR	<0.05
Orbera	Lee et al. (2012)[42]	Singapore	24	18	8 (IGB + diet + exercise) 10 (sham + diet + exercise)	NR	NR	1.69±0.89 0.54±0.54	<0.001
Orbera	Fuller et al. (2013)[43]	Australia	24	66	31 (IGB + behavioral modification) 35 (behavioral modification alone)	50.3 16.9	14.2 4.8	5.1 1.7	<0.001 (%EWL)
Rehape Duo	Ponce et al. (2015)[45]	USA	24	326	187 (IGB + diet + exercise) 139 (sham + diet + exercise)	25.1±1.6 11.3±1.9	7.6±5.5 3.6±6.3	2.7±1.9 1.3±2.3	0.004 (%EWL)
Obalon	Sullivan et al. (2018)[46]	USA	24	387	198 (IGB + exercise) 189 (sham + exercise)	23.9±19.2 12.4±18.8	6.6±5.1 3.4±5.0	2.3±1.8 1.2±1.8	<0.001 (%EWL)

BMI, body mass index; %EWL, % excess weight loss; IGB, intragastric balloon; NR, not reported; %TBWL, % total body weight loss.

While weight reduction can be achieved significantly by IGB placement, it should be noted that the effect may only be short-term due to regain of weight within one year after removal, as reported in some studies.[51] A long-term outcome after treatment with an IGB and IGB removal (4.8 ± 1.6 years) was evaluated through a prospective study in Switzerland.[52] The study reported that only about 1/4 of the patients were able to maintain clinically significant weight loss after IGB removal, and the other 3/4 required additional measures for weight reduction, such as bariatric surgery, repeat IGB placement, or taking sibutramine for short periods. Thus, the main limitation of IGBs is that their impact on long-term weight loss is still unclear. Therefore, several other methods are currently being evaluated, such as combining IGBs (combination therapy in tandem with IGB or as a sequential therapy following IGB removal) not only with dietary and lifestyle modifications and pharmacotherapy but also with other types of endoscopic bariatric therapy that have different weight loss mechanisms.

In addition to effective weight loss, obesity-related comorbid conditions have also been shown to be considerably improved by IGB placement. Several studies have reported substantial improvements in patient condition secondary to IGB placement, as defined by reduction in the required drug doses or mitigation of treatment methods for diseases such as diabetes mellitus, hypertension, and dyslipidemia.[53,54] NAFLD has also been reported to improve after IGB placement. This has been demonstrated by improvements in liver function tests, steatosis on magnetic resonance imaging scans, and other histologic findings.[42,55,56] In addition, respiratory disorders have also been reported to improve after Orbera placement, with one study reporting an overall improvement in lung function parameters.[57] Another study reported that a weight reduction of approximately 15% of baseline body weight obtained by insertion of an IGB substantially decreased the severity of obstructive sleep apnea in patients with morbid obesity.[58]

Obesity is accompanied by adipose tissue remodeling with adipocyte hypertrophy and alterations in cellular composition that promote a chronic low-grade inflammatory state.[59,60] This pro-inflammatory state, which is mediated by an unbalanced production of various cytokines and adipokines, seems to play an important role in the development of metabolic disorders, such as insulin resistance.[59,61,62] Weight reduction achieved by IGB placement, similar to weight reduction obtained by other methods, could have favorable effects on the inflammatory status and metabolic profile, which can in turn decrease the risk of cardiovascular events. A small prospective observa-

tional study involving 42 patients with obesity using IGB for 6 months found reduced serum levels of leptin and high sensitive C-reactive protein, as well as improved insulin resistance and lipid profile, which may decrease cardiovascular risk, and adiponectin/leptin ratio.[63] In spite of the many trials on weight reduction, information regarding the metabolic benefits of IGBs is relatively limited. A meta-analysis of 40 studies that included at least one metabolic parameter and evaluated the effect of IGB placement on metabolic comorbidities, concluded that IGB placement substantially improved fasting blood glucose, hemoglobin A1c, serum triglyceride levels, and blood pressure. Hemoglobin A1c and fasting blood glucose in patients with diabetes mellitus were shown to be decreased by 17% and 15%, respectively.[64] The odds ratio for diabetes resolution after IGB placement was 1.4 (95% confidence interval, 1.3–1.6). Another meta-analysis showed the beneficial effects of IGB placement on the improvement of liver enzymes and NAFLD in patients with obesity.[65] Thus, IGB can be provided as an additional therapeutic option for obese patients with metabolic syndrome, as part of a multidisciplinary approach to management.

ADVERSE EVENTS

Patients usually complain of accommodative symptoms during the initial weeks post-placement. The most common adverse event after IGB placement is reported to be nausea and vomiting (23.3%) and abdominal pain (19.9%), followed by gastroesophageal reflux (14.3%), diarrhea or constipation (10.4%), gastric stasis (8.3%), and gastric ulceration (0.3%).[30] Early removal of IGB has been reported in 3.5% of cases and is mostly due to nausea, vomiting, and abdominal pain,. However, several of these symptoms can be managed conservatively without the need for IGB removal. Of these symptoms, aggravation of acid reflux can occur after IGB placement, and up to 7% of patients may experience reflux symptoms that are severe enough to require early balloon removal.[56,66,67] This highlights the importance of proton pump inhibitor (PPI) therapy after IGB placement and why patients who are unable to tolerate PPI are not ideal candidates for IGB placement.[68]

Serious adverse events are rare with IGBs. Migration has been reported in 1.4% of cases, small bowel obstruction in 0.3%, and gastric perforation in 0.1% of patients.[29] Few case reports have also demonstrated intestinal obstruction that occurred due to balloon deflation with subsequent distal migration, requiring surgical removal.[69-72] Although most deflated balloons will be spontaneously expelled from the rectum.

CONCLUSIONS

The field of EBMT is evolving, and new devices are being rapidly introduced. IGBs are one of the most mature and widely used EBMTs worldwide. Several IGBs are currently available for use in clinical practice, and more devices are in the development phase. IGB placement provides a minimally invasive, safe, and effective method for managing patients with obesity and related metabolic comorbidities. Currently, the use of IGBs is still infrequent in Korea due to cost and accessibility; however, better insurance coverage and reduced costs through non-endoscopic options in the near future may lead to wider availability.

Conflicts of Interest

Jonah Cohen is a consultant for Boston Scientific. The other authors have no potential conflicts of interest.

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