



Future role for endoluminal procedures in “high-risk” bariatric patients



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ABSTRACT

Bariatric surgery remains the gold standard for therapy of the morbidly obese patient. However, these procedures are not without risk. Risk factors for adverse events and readmission after bariatric surgery are well studied. Included in these risk factors are preoperative weight, liver size, and medical comorbidities that can be improved with modest weight loss before bariatric surgery and other major abdominal procedures. This article reviews intragastric space-occupying devices, endoluminal gastric volume reduction procedures, gastric content aspiration therapy, and endoluminal duodenal exclusion as possible choices to “bridge” the high-risk patient to bariatric surgery and as a possible alternative to bariatric surgery. The current state of the literature is robust for the intragastric balloon, supporting both primary and preoperative indications. The limited literature support for gastric volume reduction, gastric content aspiration, and endoluminal barrier therapy is reviewed.

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1. Introduction

Obesity remains a public health threat and epidemic in the United States. A total of 34.9% of Americans are currently obese [1]. From 2000–2010, the number of people suffering from morbid obesity (body mass index [BMI] > 40 kg/m²) increased 70%, to 6.6% of the total US population, nearly 15.5 million individuals [2]. The “super” morbidly obese population with a BMI of greater than 50 kg/m² grew even faster. Increasing body mass is associated with increasing incidence and severity of medical comorbidity. Bariatric surgery is recognized as the most effective and durable treatment for patients with a BMI > 40 kg/m² [3]. Bariatric surgery has never been safer than it is today with mortality as low as 0.1% and enteric leak rates as low as 0.65% [4]. But, as the degree of obesity and severity of the weight-related medical burden increase, severely ill patients with multiple comorbidities can be considered of high risk to accept or tolerate the inherent risks of bariatric surgery. As has been the case with carotid stents, and coronary stents before that, high-risk patients are often the open door through which innovative therapies arrive.

1.1. Which clinical factors define “high-risk”?

Fernandez et al [5] first systematically reported bariatric surgical perioperative risk and risk factors from Virginia Commonwealth University in 2004. Multivariate logistical regression analysis of retrospectively collected data identified age, preoperative weight, and hypertension as risk factors for mortality within 2011 patients undergoing open and laparoscopic gastric bypass (LGB). In 2007, the Obesity Surgery Mortality Risk Score was developed and validated [6,7]. This scoring system identifies 5 important risk factors for determining which patients may be at high risk for bariatric surgery. The scoring system awards 1 point for each of the following clinical factors; BMI greater than 50 kg/m², presence of hypertension, male sex, age greater than 45 years, and pulmonary embolism risk. Pulmonary embolism risk includes, among other factors, the presence of right heart failure and obstructive sleep apnea. Patients presenting for bariatric surgery with 4 or 5 of the Obesity Surgery Mortality Risk Score clinical risk factors experienced a 7.56% postoperative mortality following gastric bypass.

In 2006, in response to safety concerns with bariatric surgery by the Center for Medicare and Medicaid Services, the American Society of Metabolic and Bariatric Surgery (ASMBS) and the American College of Surgeons (ACS) independently established 2 “Center of Excellence” programs. Each program began prospective data collection from accredited centers.

The Bariatric Outcomes Longitudinal Database was established to collect data from the ASMBS administered center of excellence program. The BOLD collaborators reported a study of prospectively

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collected multicenter data including over 36,000 patients who underwent LGB from 2007–2009 [8]. The resulting risk stratification model of 90-day composite adverse events included age (40–64 years, ≥ 65 years), male sex, BMI (50–59.9 kg/m², ≥ 60 kg/m²), obesity hypoventilation syndrome, back pain, diabetes, pulmonary hypertension, ischemic heart disease, functional status, and American Society of Anesthesiology classes 4 or 5.

Readmissions within the ACS-National Surgical Quality Improvement Program (NSQIP) data registry public use file have been reported in 2 publications for patients having laparoscopic sleeve gastrectomy or LGB from 2012–2013 [9,10]. Khorgami et al reported on a total of 35,655 patients (17,101 laparoscopic sleeve gastrectomy and 18,554 LGB). A total of 1758 patients (4.9%) were readmitted within 30 days of surgery. Significant modifiable and nonmodifiable factors for readmission were discovered on multivariate analysis. The modifiable clinical factors included functional status, preoperative renal function, insulin-dependent diabetes, longer operative time, and procedure choice. Nonmodifiable factors included race, history of cardiac disease with previous intervention, bleeding disorders, and steroid use for a chronic condition. The authors proposed preoperative focus on improving functional status, which when poor nearly doubles the risk for readmission (odds ratio = 1.94, 95% CI: 1.06–3.55). Garg et al reported on 18,296 ACS-NSQIP patients who underwent primary bariatric surgery. The overall readmission rate was 5.22%. Modifiable preoperative characteristics associated with readmission were BMI > 50 kg/m², diabetes, and hypertension.

In 2012, the ASMBS and ACS programs were merged to form the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Project (MBSAQIP). Currently, clinical data on nearly 80% of all bariatric operations performed in the United States, both primary and revision, are collected prospectively within the MBSAQIP data registry. Semiannually, the MBSAQIP quality improvement committee issues a report to all 721 participating centers with risk-adjusted outcomes. In the most recent report, risk adjustment was performed for 33 available predictors, among them were sex, age, diabetes, hypertension, renal insufficiency, obstructive sleep apnea, and preoperative functional status [11].

Although many of the available high-risk predictors, such as sex and age, are unalterable, some risk factors, including cardiac, renal, and pulmonary function, can be improved with relatively modest weight loss. Bariatric surgery has never been safer than it is today, reporting mortality as low as 0.08% [12]. However, as risk stratification becomes more specific and safer endoluminal therapies become a reality, we ask the question, “What is the role for endoluminal therapies in high-risk bariatric patients?”

2. Intra-gastric balloon

Intra-gastric balloons (IGBs) are air or fluid filled, space-occupying devices that decrease the volume of food and calories consumed at mealtime and delay gastric emptying. There are 2 IGB devices approved for use in the United States. The devices are indicated for use in adults over the age of 22 years with a BMI of 30–40 kg/m² who have “failed” more conservative weight reduction alternatives [13]. Currently approved devices are placed with endoscopic guidance under moderate sedation. After a maximum implantation time of 6 months with concomitant nutritional and behavioral therapy, the patient returns to the endoscopy suite where the device fluid is evacuated and the device is removed transorally. Balloon extraction is performed under either moderate sedation or a short general anesthetic. Procedure times are generally under 15 minutes for each step. There are IGB devices under development now that can be placed and inflated without the need for endoscopy and are self-deflating and designed to pass in

the fecal stream without the need for general anesthesia for device extraction [14,15].

Coincident with the Food and Drug Administration (FDA) approval of the IGB in the United States, multiple systematic reviews and meta-analyses of IGB therapy have been published [16–19]. Two series have evaluated the available and qualifying randomized control trials [16,19]. These analyses confirmed a reduction of BMI with IGB therapy as compared with medical therapy alone of 1.1–1.59 kg/m², absolute weight loss of 2–4.6 kg, and percentage of excess weight loss (%EWL) of 11.16%–14.25%. Two additional systematic reviews included case series for analysis [17,18]. The American Society for Gastrointestinal Endoscopy (ASGE) Bariatric Task force sought to evaluate whether IGB therapy met the societies' recommended therapeutic effect for a primary or “bridge” intervention. IGB therapy met both criteria with a primary effect of 12 months, %EWL of 25.44%, and therapeutic difference to control of 26.9% EWL. The ASGE nonprimary (“bridge” therapy) goal (total body weight loss [TBWL] $> 5\%$) was met with a 12.3% TBWL at 6 months.

IGB therapy has generally been well tolerated. There is a well-described postprocedure symptom complex of abdominal pain, nausea, vomiting or regurgitation, and symptoms of gastroesophageal reflux. These symptoms generally last 1–7 days and can be minimized with the use of medical therapy. However, this symptom complex is largely responsible for the 3.3%–7% early extraction rate [17,18,20], and there have been reports of aspiration and even death [21].

The IGB has been available outside the United States for over 12 years. There appears to be a role for the IGB therapy as a “bridge” to bariatric surgery for the high-risk patient. Aside from meeting weight loss expectations, weight loss related to IGB therapy has been shown to affect many of the risk factors associated with bariatric surgical complications. IGB therapy has been shown to improve left ventricular function [22]; decrease visceral fat up to 16.2% [23]; decrease insulin resistance, HbA1C, and fasting blood glucose [24,25]; and improve abnormalities in liver-associated enzymes [26,27]. Weight loss from IGB therapy can also decrease restrictive ventilatory defects [28,29], improve the airway anatomy, and essentially resolve obstructive sleep apnea as measured by Apnea/Hypopnea Index in patients with an average pre-IGB therapy BMI of 55.8 kg/m² [30].

Hepatomegaly and liver disease are particularly meaningful in bariatric surgery. Hepatic steatosis and liver size are associated with intraoperative difficulty, prolonged operative time, bleeding, and conversion to laparotomy during laparoscopic bariatric surgery [31,32]. Short-term presurgical dietary interventions are the standard for liver size reduction before bariatric surgery [33]. IGB therapy is 3 times more effective than preoperative dietary intervention for reduction of liver size (32% vs 14%) [33]. Frutos et al [31] reported a 31.8% reduction in liver size and 22.14% EWL in “super” morbidly obese patients who had IGB therapy for the 6 months before gastric bypass.

The risk of bariatric surgery in the setting of liver disease and cirrhosis has been specifically studied [34]. Patients with uncompensated cirrhosis have been reported to have an absolute risk of postoperative mortality of 16.3% and odds ratio of 21.2 as compared with compensated cirrhosis. Despite this risk, there is an imperative to treat obesity in the setting of cirrhosis. Significant weight loss can improve both liver function and the histologic severity of the liver disease [35]. In patients requiring liver transplant, presurgical weight loss directly increases their candidacy for a donor liver by altering the donor-recipient graft weight ratio, improving comorbidities, and reducing the operative risk [36,37]. In their recent meta-analysis, Popov et al [26] reported that weight loss associated with IGB therapy improved nonalcoholic steatohepatitis histology scoring, improved liver-associated enzymes, and

decreased liver fat fraction by both magnetic resonance imaging and ultrasound. IGB can be used as a “bridge” therapy to both liver transplantation and definitive bariatric surgery.

The use of IGB as a primary or “destination” therapy in high-risk individuals is limited by the short recommended duration of therapy and the propensity for weight gain following extraction of the IGB device [38]. However, the IGB appears to be safe and more effective in consecutive applications than in a single application alone. Genco et al [39] reported on 100 patients who were randomly assigned to a single 6-month balloon treatment vs 2 consecutive 6-month treatments. The consecutive therapy group experienced greater excess BMI loss at 1 year (51.9% vs 25.1%) and lower BMI after 2 years of follow-up (36.8 vs 41.1 kg/m²). Lopez-Nava et al [38] reported on 112 patients with consecutive IGB therapy vs single IGB application controls. The consecutive group experienced additional weight loss, whereas two-thirds of the single IGB therapy group developed weight gain of at least 50% of their lost weight following IGB extraction. Finally, consecutive IGB therapy has been compared to laparoscopic adjustable gastric band placement, with similar weight loss as compared with laparoscopic adjustable gastric band at 6 months, greater %EWL at 12 months, and similar weight loss at 18 months [40]. The authors concluded that consecutive IGB therapy could be offered to those patients who do not feel ready for surgery. Although not performed in high-risk groups, these studies imply that IGB could be used for duration of therapy similar to other endoluminal therapies.

3. Primary obesity surgery endoluminal

Primary endoluminal gastric volume reduction through the use of an endoluminal operating system has been reported in 4 studies [41–44]. In this procedure, the patient is placed under general anesthesia, and the 60-Fr TransPort operative platform (USGI Medical, San Clemente, CA) is placed orally into the stomach for insertion of the instruments. Using proprietary tissue graspers, a tissue approximator, and an anchor delivery system, 2 rows of internal full-thickness tissue plications are used to reduce stomach volume and fundal compliance to incoming food [42]. A distal stomach ridge of 4–5 anchors is created to disrupt the antral mill and presumably delay gastric emptying. Most recently, a small (44 patient), multicenter randomised controlled trials (RCT) from Europe was published [44]. Primary obesity surgery endoluminal (POSE) has been associated with a TBWL of 13%–19% in patients with a BMI of 30–40 kg/m². In the earliest publication, POSE median operative time was 69 minutes. In the RCT, median operative time was 48 minutes with placement of a median of 13 anchors total. Reported safety has been good with this procedure. Within the evidence base of 244 patients, there has been only 1 serious adverse event reported. An event of asymptomatic reduction in hemoglobin was managed without transfusion. As is typical for early feasibility study publications, very low-risk patients were selected for the reported procedures. At this point, there is no evidence base to determine whether this procedure will be appropriate in high-risk individuals. As with most endoluminal therapies, the authors of the largest study (147 patients) noted that the variables effecting outcomes include overall health, ability to exercise, and commitment to dietary guidelines. Furthermore, 50.9% of the patients were considered good responders experiencing at least 15% TBWL. Good responders were significantly younger (42.1 vs 46.7 years) and had a higher BMI (39.7 vs 37.4 kg/m²) than the nonresponders. These variables may be significantly affected in the high-risk patient pool. As the procedure is intended to create full-thickness gastric plications, esophageal and gastric varices would be a relative contraindication

limiting the use in decompensated cirrhotic patients. In addition, any patient would need to be able to tolerate a 1-hour general anesthetic.

4. Endoscopic sleeve gastroplasty

Different than the POSE procedure, the endoscopic sleeve gastroplasty uses the Apollo Overstitch device (Apollo xxx) to create a full-thickness approximation of the anterior and posterior walls of the stomach. The multiple sutures are placed to create a lesser curve based channel. Although the channel does have small gaps between sutures, there appears to be significant restriction when the patient eats solid foods and receives appropriate post-operative counseling [45]. Abu Dayyeh and colleagues reported on 25 patients with 20-month follow-up [46]. Average BMI was 35.5 kg/m². Procedure time decreased from 217–98 minutes when the first 5 patients were compared with the final 5 patients, indicative of a significant learning curve with the procedure. % EWL was 54% and 45% at 12 and 20 months postprocedure, respectively, with significant variation among patients. Further, 3 of the 8 patients with 20-month follow-up had regained all lost weight. Physiologically, endoscopic sleeve gastroplasty resulted in a significant delay in gastric emptying and early satiety. Of 25 patients, 3 had serious adverse events requiring intervention including perigastric fluid collection requiring drainage, pulmonary embolism, and a combined pneumoperitoneum and pneumothorax requiring thoracostomy tube; 32% of treated patients required hospitalization for an average of 1.5 days.

In their 25 patient, 12-month follow-up series from Spain, Lopez-Nava and colleagues note a dramatic correlation between nutritional visits and visits with the psychologist and ultimate weight outcomes [45]. Median procedure time was 80 minutes under general anesthesia. A minimum of 17 nutritional visits and 13 visits with the psychologist were associated with the best results.

5. Aspirational therapy

Gastric aspiration therapy (AspireAssist) was first reported in 2013 [47]. This novel therapy involves endoscopic placement of a large bore percutaneous endoscopic gastrostomy (PEG) tube and a proprietary external drainage system that allows gravity-based evacuation of gastric contents approximately 20 minutes after consuming a meal. As with most endoscopic therapies, Aspire Assist requires a specific behavioral eating pattern for the best results. In the pilot trial, AspireAssist was associated with 18.9% vs 5.6% TBWL vs the randomized control group. Device placement time was not reported. However, other series of PEG placement in obese patients have noted an average placement time of 15 minutes [48]. Although there were many adverse events, none were graded as serious. The most common complaint was pain at the gastrostomy site. A design change was made during the study, transitioning from a reinforced polytetrafluoroethylene tube to a silicon tube to address this complaint.

AspireAssist was approved by the US FDA on June 14, 2016, for use in adults aged 22 years and older with a BMI of 35–55 kg/m². The investigational device exemption pivotal study represents the largest data set available at this time for review [49]. This multicenter RCT comprised 111 treatment patients and 60 controls, and 83% reported at least 1 adverse event. Only 5 events were graded as severe, and no events required operative intervention. The most severe was symptomatic pneumoperitoneum that resolved spontaneously. Mean %EWL was 31.5% in the treatment group and 9.8% in the control group. Further, 56.8% of treated patients achieved at

least 25% EWL. In their conclusions, the US FDA determined that the adverse event rate was comparable to traditional (FDA approved) PEG devices. Thus, the device was determined safe and effective for approval.

As with most devices, the investigational device exemption pivotal trial for AspireAssist excluded many patient groups. Comorbidities including uncontrolled hypertension, diabetes on oral or injection therapy, pulmonary hypertension, and severe heart disease, among others, were excluded. Thus, the evidence base regarding its use in the “high-risk” bariatric populations is lacking. In the United States, placement in a high-risk population is feasible and indicated if the only risk factor is BMI more than 50. Most other risk factors either are, or would likely be, associated with a contraindication. So, although technically feasible, therapy would currently be considered “off label.” The evidence base for safety of PEG in morbidly obese patients is small but comparable to nonobese individual [50]. AspireAssist is likely to be used as both a bridge and a destination therapy in well-selected high-risk individuals in the future, if the clinical experience of the pivotal trial is confirmed with more widespread use.

6. EndoBarrier DJBS

The EndoBarrier duodenal-jejunal bypass sleeve (DJBS) is an impermeable sleeve introduced endoscopically. The sleeve is anchored with titanium barbs to the duodenal bulb. The tubular sleeve then elongates to create a second channel within the lumen of the proximal small intestine. The intent is to separate the flow of ingested material from the pancreatic and hepatic secretions until the material reaches the jejunum. Duodenal exclusion has been theorized as an important method of both weight loss and diabetes control in obese individuals [51].

There are 2 well-performed systematic reviews of the approximately 500 reported EndoBarrier DJBS cases in the literature [17,52]. The ASGE Bariatric Endoscopy Task Force reviewed 11 studies. Meta-analysis revealed the typical heterogeneity in %EWL result that is seen in many endoscopic therapies. EndoBarrier did meet the societies primary weight loss requirement (> 25% EWL) for primary placement in observational studies with 12-month follow-up. Analysis of the 3 studies meeting this reporting requirement combined for a total of 35% EWL. However, analysis of the randomized control trial did not meet the societies' guidelines for recommendation reporting only 9.4% difference in %EWL between treatment and control groups. EndoBarrier DJBS was associated with a 1% improvement in HbA1C compared with controls. Rohde et al [52] also reviewed the EndoBarrier for both weight loss and glycemic control in a meta-analysis, and EndoBarrier DJBS achieved 11.1% greater weight loss than control, again failing to meet the ASGE recommendation guideline of > 15%. In this meta-analysis, the change of HbA1C of -0.9% was not statistically significant. Final therapeutic results from the ENDO US Pivotal trial did show a statistically significant 0.8% improvement in HbA1C and 5.6% greater TBWL as compared with controls [53].

Rhode et al also reported a high number of moderate and severe adverse events associated with EndoBarrier DJBS. Although there are no fatalities in the literature, a 19% early extraction rate because of complication has been reported. Maggi et al [54] in their report of hepatic abscess and complication review hypothesized a relative underrepresentation of severe adverse events in the literature owing to the very short reporting time in many of the studies. Of note, the FDA suspended recruitment of the US pivotal trial because of unexpectedly high hepatic abscess rate [55]. The developer of the EndoBarrier, GI Dynamics, subsequently discontinued the trial. In their press release, the incident rate was 3.5%. This result was significantly higher than the

0.73% rate reported internationally and greater than the 2% threshold for the trial.

7. Conclusion

There are many promising and effective endoluminal therapies currently available and in development. The best studied and lowest risk therapy is the IGB. The IGB is well studied and proven to be beneficial in many high-risk populations. Currently, the main limitation to adoption in the United States is procedural cost. Given the number of new devices under trial, competition should result in decreased cost in the near future. In addition, modification in the technology to reduce the number, or eliminate endoscopic delivery and retrieval altogether, should also accelerate IGB therapy adoption. The proven efficacy of sequential therapy broadens the appeal of IGB therapy for longer-term destination therapy.

Gastric content aspiration therapy is a novel approach that has been met with some controversy. However, the procedural risk appears low, and the weight loss effect is significant. Translation of the weight loss to clinical outcomes is likely but not proven. No high-risk group clinical results are currently available. Although the procedure is likely to be limited in some high-risk groups, longer-term therapy is indicated. If this therapy achieves wider adoption, use in high-risk groups is likely.

POSE and endoscopic sleeve gastroplasty face different challenges. The technical expertise and significant learning curve will likely slow adoption. If the safety profile continues to improve and the operative times continue to decrease with experience, adoption in high-risk groups is likely. The extreme heterogeneity in effect related to nutritional and psychological follow-up visits, however, is of concern. Additional clinical reports and randomized trials should help elucidate the future of this therapy in high-risk groups. At this time, outlook for FDA approval of the EndoBarrier DJBS in the United States is questionable. Future use in high-risk individuals is doubtful.

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