

Bariatric Embolization for Obesity: A New Frontier for Interventional Medicine

Early trial results, procedural technique, and challenges to designing and conducting further trials.

BY MUBIN I. SYED, MD, FSIR, FACR; AZIM SHAIKH, MD, MBA; SUMEET PATEL; ILYAS IKRAMUDDIN, DO; AND KAMAL MORAR, MD, MBA

Obesity has become a worldwide epidemic, not only in the developed world but also in developing countries.¹ In fact, after the United States, China and India have the second- and third-largest obese population, respectively. Obesity leads to many comorbid conditions such as cardiovascular disease, diabetes mellitus, sleep apnea, and stroke; therefore, there is a critical need to find solutions to this widespread problem, which is responsible for one-fifth of all deaths in the United States.² Obesity is defined as a body mass index (BMI) > 30 kg/m², and morbid obesity is defined as a BMI > 40 kg/m² (candidacy for bariatric surgery). Interestingly, these definitions are different for people of Asian ethnicity (BMI > 25 kg/m² for obesity and > 35 kg/m² for candidacy for bariatric surgery).^{3,4}

Produced by cells located mostly (> 90%) in the mucosa of the fundus of the stomach, ghrelin is the only known orexigenic hormone. Gastric sleeve surgery causes a marked sustained reduction in ghrelin production (approximately 40%–50% at 5 years),⁵ and it is believed that this may be a contributing factor to weight loss in gastric sleeve surgery (other than the actual reduction in stomach volume). Therefore, it is logical that embolization of the fundus of the stomach could result in marked appetite suppression and, thus, weight loss. This article reviews study results of initial animal and human studies of bariatric embolization and their limitations, procedural technique, and challenges to conducting trials of gastric artery embolization (GAE) for obesity to confirm its safety and efficacy.

GASTRIC ARTERY EMBOLIZATION FOR OBESITY

GAE has been used since the 1970s to treat life-threatening gastric hemorrhage.^{6,7} This is commonly accepted as standard of care, has been life saving for thousands of patients, and yet has been safe and effective enough to be used empirically in the setting of angiographically negative life-threatening hemorrhage.⁸

Recent animal in porcine and canine models have shown that GAE suppresses ghrelin levels, resulting in weight loss. Arepally et al first described the technique of GAE to reduce weight gain in a controlled study. Sodium morrhuate was used in a porcine model with resultant lower ghrelin levels and significantly blunted weight gain in otherwise rapidly growing young swine.⁹ Paxton et al described using 40- μ m microsphere particle embolization in a similar porcine model, which also resulted in decreased ghrelin levels, reduced weight gain, and no duodenal upregulation of ghrelin.^{10,11} Bawudun et al described a technique of left gastric embolization using a mixture of bleomycin and Lipiodol (Guerbet USA) versus polyvinyl alcohol (PVA) 500- to 700- μ m particles in a canine model. At the end of the 8-week trial, there was significant reduction in plasma ghrelin, body weight, and subcutaneous fat without gastric ulceration (unlike the swine studies where there was ulceration).¹²

Human Experience

A recent retrospective case-controlled study found a 7.9% average decrease in body weight at 3 months in 15 patients who underwent left GAE for life-threatening hemorrhage

compared to 1.2% for age-matched controls who underwent embolization other than the left gastric artery for upper gastrointestinal bleeding ($P = .001$).¹³ In a prospective, single-arm study of five patients in the Georgian Republic, Kipshidze et al showed an average total body weight loss of 16% and 17% at 6 and 24 months, respectively, as well as reduced ghrelin levels after left GAE using 300- to 500- μ m Bead Block (BTG International) compressible microspheres.¹⁴ In the US Food and Drug Administration (FDA)–supervised investigational device exemption (IDE) studies, Weiss et al reported 9% mean excess weight loss at 3 months using 300- to 500- μ m Embosphere Microspheres (Merit Medical),¹⁵ and Syed et al reported a mean 17.2% excess weight loss at 6 months using 300- to 500- μ m Bead Block.¹⁶ However, these prospective human studies have only had short-term follow-up with a very limited number of patients.

This stage of early prospective human experience has shown that the procedure appears to be safe in the intermediate term. In animal studies, when more than one gastric fundal artery was embolized, 40% to 100% of animals developed gastric ulcers using 40- μ m particles (embolized to stasis for five cardiac cycles) at 3 to 5 weeks even with a proton pump inhibitor and sucralfate. Kipshidze et al reported no ulceration at 24 hours and at 1-week postprocedure after using Bead Block (300–500 μ m, embolized to stasis of the distal branches) without gastroprotective agents.¹⁴ Syed et al reported superficial ulcerations in 75% of four patients at day 3 postprocedure endoscopy (all healed by 30 days) after use of 300- to 500- μ m Bead Block (embolized to stasis of the distal branches for at least five cardiac cycles, with proton pump inhibitor and sucralfate).¹⁶ Superficial ulcerations were described by Weiss et al in one of five patients based on endoscopy at approximately 3 weeks, even with use of gastroprotective agents, but they were healed at the time of a 3-month endoscopy. Additionally, there was one episode of transient pancreatitis.¹⁵

Limitations

Although intermediate-term results are promising in small studies, efficacy of GAE for obesity has not yet been established, and the mechanism of action has not been precisely determined. Ghrelin is the obvious player, but other gastrointestinal neuropeptides may be involved. Ghrelin secretion is reduced after bariatric surgery, but other gut hormones/neuropeptides are also stimulated, including glucagon-like peptide-1, peptide tyrosine-tyrosine, and oxyntomodulin.^{17–19} There may also be some type of mechanical effect in addition to appetite suppression and weight loss. Surgical placebo effect has also not been excluded.

It should also be noted that embolizing the left gastric artery may preclude the use of gastric sleeve

surgery in the future for the patient, because the left gastric artery becomes the only supply to the gastric remnant in gastric sleeve surgery. In addition, gastric sleeve surgery and gastric bypass have level 1 evidence to support their efficacy in the morbidly obese population unlike bariatric embolization, and there is no surgical backup procedure available if bariatric embolization fails. Some preliminary animal studies suggest that it may be feasible to perform bariatric embolization solely using the gastroepiploic arteries (EMBARGO procedure), which would have the theoretical advantage of allowing sleeve gastrectomy to be safely performed afterward. Although decreased ghrelin levels were noted at 3 weeks in these swine studies, blunting of weight gain or weight loss was not mentioned.^{20,21}

Future Directions

To date, only patients with a BMI > 40 kg/m² have been allowed to participate in clinical trials per the FDA and European trials. A large population of patients with BMI < 40 kg/m² may potentially benefit from this procedure if its safety and efficacy become further established (eg, patients with a BMI > 35 kg/m² and comorbidities). Obese diabetic patients are another subgroup that should be studied further, because dysglycemia and frank diabetes are directly related to insulin resistance as a result of visceral fat deposition (abdominal obesity). Anecdotally, one diabetic patient underwent bariatric embolization in our GET LEAN study,¹⁶ and hemoglobin A1c levels normalized at 3 months and remained normal at follow-up at 6 months.

TECHNIQUE

Standard microcatheters, guidewires, and embolic agents that are commonly utilized in visceral interventions are also used for GAE. Bead Block compressible microspheres (300–500 μ m), PVA particles (500–700 μ m), and Embosphere Microspheres (300–500 μ m) have been given IDEs for clinical trials by the FDA.

Similar to the uterus, the stomach has a rich collateral arterial supply, which helps prevent complications such as gastric infarction or nonhealing ischemic ulceration. However, visceral vessels are prone to spasm, and therefore, intra-arterial vasodilators are extremely helpful during the procedure.

In addition, anatomic variation commonly occurs in these visceral vessels, and it is critical to have carefully mapped out the anatomy to ensure the target vessel is identified properly. The anatomy of the left gastric artery typically has an S-curve configuration, which makes catheterization rather difficult. Often, a reverse curve catheter (from the femoral approach) is used to leverage the tip into a vertically oriented superior arterial branch off of the



Figure 1. Selective left celiac angiogram in the anteroposterior projection demonstrates angiographic anatomy prior to selection. The left gastric artery is highlighted (arrow).

celiac artery (whereas the main celiac artery trunk may be horizontal or even inferiorly oriented forming an acute angle anteriorly with the aorta). This can be challenging if one is not familiar with this procedure.

Procedure Description

The steps for performing GAE have been previously described by Syed et al.¹⁶ Ultrasound-guided vascular access is either obtained to the right common femoral artery or left radial artery. A pigtail catheter is then utilized to perform an angiogram of the abdominal aorta at the level of the superior margin of T12. The celiac artery is then selected utilizing a 4- or 5-F Simmons 1 catheter or any other appropriate type of reverse curve catheter, which allows visualization of the left gastric artery (Figure 1). A coaxial microcatheter is used to further select the left gastric artery (Figure 2). At this point, the embolic agent is prepared according to the package insert and typically mixed with contrast. Embolic particles are then injected into the left gastric artery and its branches until there is complete cessation of flow (stasis) within the left gastric artery and its branches. Stasis is defined as visualization of contrast within the main left gastric artery for at least five cardiac cycles. Cessation of flow is then confirmed with follow-up contrast injection into the left gastric artery (Figure 3). Celiac arteriography is then performed to confirm occlusion of the left gastric artery and lack of gross nontarget embolization. Patient photographs before and after bariatric embolization are shown (Figures 4 and 5).

CHALLENGES ASSOCIATED WITH GASTRIC ARTERY EMBOLIZATION

Conducting Clinical Trials

Several variables need to be considered when undertaking a trial for GAE in obese patients. First, in the United States, an IDE is required from the FDA to conduct clinical research using experimental devices that may have significant risk, even if the device is already FDA approved for other clinical indications. Presently, embolization particles for bariatric

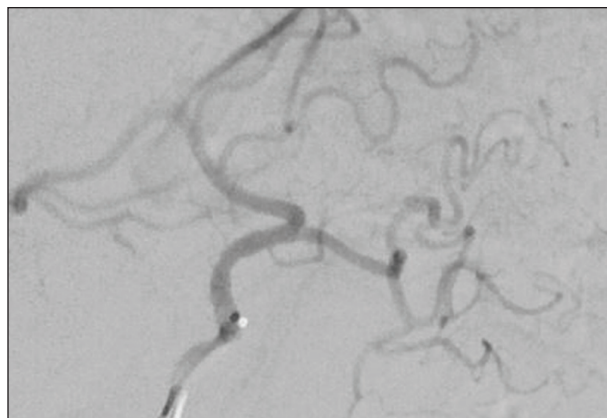


Figure 2. Preembolization selective left gastric arteriogram reveals normal anatomy prior to embolization.

embolization require an IDE for research in human subjects. It is also likely that for trials conducted in Europe, the equivalent European country competent authority approval would have to be obtained. Additionally, investigational review board approval must be obtained worldwide.

One of the unique challenges of designing and constructing a GAE trial is the ethical dilemma of embolizing an otherwise normal organ with no actual pathology. This is far different from any other interventional radiology procedure where a diseased or damaged organ is typically treated. Consequently, any trial would have to have a low threshold for stopping points. The potential for irreversible injury to an otherwise normal organ can be intimidating for any physician. Therefore, a trial must meet and preferably exceed the FDA's expectations for safety; this includes accounting for backup plans for all conceivable worst-case scenarios. Additionally, the FDA will likely mandate the use of a data safety monitoring board for oversight, and the European equivalent may also require a data monitoring committee.

At the same time, there is a conflicting drive to demonstrate efficacy, which would require taking a small amount of risk to "push the envelope," as well as concern for a having a backup plan if a catastrophic complication (eg, stomach perforation/infarction) were to occur that required hospital admission/emergency surgery and/or resulted in significant morbidity or mortality. Costs related to these complications should be considered, as well as insurance coverage in general, as health insurance may not cover experimental procedures. Embolization endpoints also need to be determined; we used stasis of contrast during intra-arterial injection lasting at least five cardiac cycles in the GET LEAN study.¹⁶

Patient selection and recruitment can also be an issue. One must determine patient readiness and motivation, as well as exclude patients with eating disorders and those who



Figure 3. Postembolization selective left gastric arteriogram demonstrates “pruning” of the arterial branches consistent with successful embolization.

eat for psychological comfort, which can drastically affect study results. Unlike animals, humans often eat when they are not hungry. Thus, inclusion of psychologists can be beneficial for patient selection. Additionally, interventional radiologists do not have a bariatric practice, and partnering with a bariatric surgeon/surgery department, although essential, may present its own challenges, such as (1) ethical dilemmas from referring surgeons due to the potential for excluding a patient from an effective and arguably life-saving procedure, especially if bariatric embolization fails; and (2) apprehension on the part of the surgeon regarding how to manage unforeseen and unknown complications should they arise.

Ensuring patient compliance, particularly with dietary follow-up, can be a factor in GAE trials. None of the patients in the GET LEAN trial followed up with the dietician regularly,¹⁶ which is similar to the experience in the BEAT Obesity study group.¹⁵ Another unique challenge is how to manage postembolization syndrome of the stomach, which has never been described in the literature to our knowledge. Postembolization syndrome is usually self-limited and is a combination of symptoms including nausea, vomiting, pain, leukocytosis, and fever. We typically see a similar pattern following embolization of the stomach.

There is also the challenge of how to control for confounding factors of change in diet and exercise patterns (or lack thereof), as well as how to handle unforeseen complications. Results of serum ghrelin can also be a confounding factor because these levels can fluctuate up to 116% within 3 to 4 hours, especially with respect to timing of usual food intake.²² Determining a set number of calories ingested prior to testing and having blood testing for ghrelin performed at a precise time after a meal challenge could help balance this confounding variable.

Psychologic factors include depression, which must be continuously assessed even if the patient has no prior



Figure 4. Patient photograph preembolization of the left gastric artery.



Figure 5. Photograph of the same patient in Figure 4, 2 years after embolization of the left gastric artery (after 33 kg of weight loss).

history of depression. It is known that 50% of morbidly obese patients suffer from depression.²³ Surgical placebo effect is another confounding factor but may not be able to be excluded early in trial experience. There is no way to quantify desired decrease in hunger, and it can only be measured subjectively or indirectly through measurement of dietary intake (that could be inaccurate).

Multidisciplinary Team Considerations

Team formation can also be difficult in terms of finding a gastroenterologist, bariatric medicine specialist, and anesthesia provider. A dietician must be motivated enough to encourage patients to be seen for regular follow-up visits, which can be difficult in this patient population. Explaining a potentially risky procedure to a skeptical referring primary care physician may also be difficult. In our study, one challenge we encountered was that patients often did not mention use of antidepressants and/or a history of prior depression so as not to be excluded from the study. Therefore, records from a primary care physician are critical, and communication with a primary care physician before and after the procedure is also very important. Coordination of the numerous tests, studies, and physician visits before and after the procedure can be complex, and involvement of a conscientious study coordinator is also a must.

SUMMARY

The only proven treatment for obesity when medical therapy fails is bariatric surgery. Currently, there are three main surgeries performed in the United States: laparoscopic gastric banding, laparoscopic sleeve gastrectomy, and Roux-

en-Y gastric bypass. Current practice patterns are favoring laparoscopic sleeve gastrectomy as the first-line surgical treatment. Moreover, recent study results are now showing long-term outcome of laparoscopic sleeve gastrectomy is comparable to Roux-en-Y gastric bypass without as many complications.²⁴ It is estimated that only 0.1% of the obese population undergoes bariatric surgery.²⁵ Thus, there is a tremendous opportunity for an alternative to bariatric surgery.

However, bariatric embolization is still in its infancy. The procedure itself may need to be further refined. This includes factors such as appropriate patient selection, particle size and composition/structure of embolic agents, and technique. Additionally, long-term confirmation of safety and efficacy (phase 2 clinical trials) will be necessary. Until this happens, randomized controlled trials, preferably with a sham procedure, cannot be considered. Intense skepticism and resistance by bariatric surgeons to bariatric embolization can also be expected, even if it becomes a proven modality.

It would be a feat for bariatric embolization to become a proven alternative to the current gold standard of bariatric surgery for treatment of morbidly obese patients. Therefore, long-term results in the 5- to 10-year range may be necessary. Insurance and reimbursement will also be a key factor, and interventional radiologists will need to identify their ideal role in the patient's overall care continuum, which could evolve along with the procedure. Knowledge and certification in obesity medicine would be de rigueur for any interventionist interested in practicing this procedure. ■

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Mubin I. Syed, MD, FSIR, FACR

Dayton Interventional Radiology
Boonshoft School of Medicine
Wright State University
Dayton, Ohio
mubinsyed@aol.com

Disclosures: Partial funding for the GET LEAN trial provided by the SIR Foundation Pilot Research Grant and by the Radiological Society of North America Research Seed Grant.

Azim Shaikh, MD, MBA

Dayton Interventional Radiology
Dayton, Ohio

Disclosures: Partial funding for the GET LEAN trial provided by the SIR Foundation Pilot Research Grant and by the Radiological Society of North America Research Seed Grant.

Sumeet Patel

Dayton Interventional Radiology
Dayton, Ohio
Disclosures: None.

Ilyas Ikramuddin, DO

Boonshoft School of Medicine
Wright State University
Dayton Gastroenterology
Dayton, Ohio
Disclosures: None.

Kamal Morar, MD, MBA

Dayton Interventional Radiology
Boonshoft School of Medicine
Wright State University
Dayton, Ohio

Disclosures: Partial funding for the GET LEAN trial provided by the SIR Foundation Pilot Research Grant and by the Radiological Society of North America Research Seed Grant.