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Left Gastric Artery Embolization: A New Tool in the Armamentarium to Treat Obesity? A Systematic Review

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Background: Relevance of the Problem

In 1997, for the first time, the World Health Organization defined a non-infectious illness, obesity, as an epidemic malady [1]. Obesity is defined by a Body Mass Index (BMI) greater than or equal to 30 [2]. Prevalence of obesity has nearly doubled since 1980 and more than 10% of global adult population is classified as obese. Recent data suggest that obesity may be associated with nearly 20% of all deaths. Obesity is ranked as the fifth leading risk for mortality, being strictly related to numerous comorbidities such as diabetes (18-fold increased risk), hyperlipidemia, heart disease, stroke, obstructive sleep apnea, cancer and depression [3,4]. These obesities related illnesses are responsible for 2.5 million of deaths in the world every year and reduce drastically life expectancy (22% of rate) [5].

Medical care associated with obesity costs the American Health Care System nearly 168 billion of dollars per year and accounts for approximately 16.5% of all expenditures [6]. The main cause of obesity is a discrepancy between calories intake and calories consumption through physical exercise, mainly due to highly caloric food spread and always more sedentary life style [1]. To define severity of obesity Body Mass Index (weight in kilograms divided by the square of height in meters) is used. Three categories are distinguished: mild obesity (BMI between 30 and 35), moderate obesity (BMI between 35 and 40), severe obesity (BMI besides 40) [7].

Treatment Options for Obesity

Management of weight loss starts with lifestyle changes such as caloric reduction and increased physical activity, but despite all patients' efforts, reduction in weight has been shown to be only short-term. Among pharmacological tools against obesity, there are three approved medications: orlistat, lorcaserin and phentermine-topiramate, able to achieve weight loss up to 10%. However, anti-obesity medications are not without significant side effects (headache, constipation, insomnia, dry mouth) and have shown difficulty to maintain weight loss in the long term [8].

Conversely, bariatric surgery has proved to be the only treatment option for morbid obesity producing a significant and durable (up to two years) weight loss and has to be reserved for morbidly obese individuals (defined as BMI more than or equal to 40) or to obese individuals with a BMI more than 35 and an obesity related comorbidity [9]. There are several bariatric surgical techniques, but Roux -En-Y Gastric Bypass (RYGB), Sleeve Gastrectomy (SG) and Adjustable Gastric Banding (AGB) are the most commonly employed. Of these, Roux-en-Y-gastric bypass surgery is most efficacious with a significant and sustained weight loss of 25-30% at 5 years. Unfortunately, surgical interventions for obesity have significant morbidity and mortality with post-operative anastomotic leak (0.1-5.6%), intussusception (1%), gallstones (13-36%) and operative revisions (39-81%).Moreover not all obese patients are suitable for surgery due to having relative or absolute contraindications. Besides, these procedures are expensive, costing on average 38000 dollars, and in case of complications, healthcare costs can even double up [10].

Bariatric Embolization: Rationale and Procedure

Hunger is regulated by a very complex neuronal and endocrine mechanism and the gastrointestinal tract plays an intricate and fundamental role in appetite modulation. Increasing evidence suggests that variation in circulating levels of gut hormones is responsible for weight loss. These alterations include stimulation of glucagon-like peptide 1 and reduction in ghrelin secretion [11]. Ghrelin, firstly described by Kjima et al in 1999 is a 28 amino-acid peptide which is the main regulator of hunger. It is found in highest concentrations within the fundus of the stomach, where nearly three-quarters of the body's ghrelin is produced. Duodenum, pancreas, ovaries, adrenal cortex and brain are secondary sites of ghrelin production. When released, ghrelin induces hunger, increasing gastro-intestinal motility and supressing insulin production. Plasmatic levels of ghrelin rise significantly

before food intake and decrease drastically after meal [12-15].

To decrease ghrelin production, through fundic arteries selective embolization, represents a new and interesting approach to treat obesity [16,17]. Firstly described in humans by Gunn, left gastric artery embolization was retrospective reviewed in patients who underwent the procedure for upper gastrointestinal bleeding, no matter the cause of bleeding; the intervention was demonstrated to lead to weight loss [18] "Bariatric Artery Embolization" (BAE) is a minimally invasive interventional radiology procedure, which consists of percutaneous trans-arterial embolization of the gastric fundus, that is mainly supplied by Left Gastric Artery (LGA) and secondarily by Left Gastroepiploic Artery (GEA) [19]. Patients are mildly sedated during the procedure and a femoral or radial approach is employed. The celiac trunk is selected and a celiac angiography is performed in order to precisely assess the visceral vascular anatomy. Once the fundic arteries are identified (LGA, GEA), embolization is performed by injecting embolic particles until complete cessation of flow for at least five cardiac cycles. A celiac arteriogram is obtained to confirm arterial occlusion [20].

Although the initial BAE used morrhuate sodium to occlude the LGA, there are a large variety of embolic materials such as other sclerosant, colis, particles or gelffoam [16,17,21,22]. One advantage of liquid embolics is their ability to penetrate deeply into the smallest capillaries. One great disadvantage is that many liquid embolics are very caustic and may cause tissue damage. Calibrated microspheres show the benefit of being able to pass into small calibre vessels and provide long-term occlusion to fundal arteries. FDA recommends large beads (300-500 micronm) in order to provide less distal embolization (a wider collateral perfusion of the mucosal tissue is guaranteed). Ongoing studies are investigating small beads to more deeply penetrate into mucosal vessels and to produce a greater reduction in ghrelin. Ulceration risk secondary to small beads remains undetermined [23]. BAE is considered successful when stasis or decreased flow are obtained; if needed an anti-reflux microcatheter is used to prevent retrograde flow during infusion and excessive devascularisation [23].

Patients are prescribed oral proton-pump inhibitor and sucralfate (1 gr four times per day) prior embolization (generally two weeks) and after the procedure (6 weeks). A meal tolerance test is provided in order to establish baseline ghrelin levels before and after a high-calorie-meal. Plasmatic ghrelin is measured at various time points. After BAE all patients are able to begin oral intake of fluids within 4 hours after the procedure and solid food within 12 hours (a low fat and carbohydrate diet is given) [24]. Patients undergo systematic postprocedural visits and endoscopies to assess physical condition, weight measurement and mucosal state [25].

Results (Animal and Human Models)

Technical success, defined as the ability to embolize the gastric fundus, is reported to be 100% in animal and human studies [16,17,18,21,22,25]. Theoretically, all obese patients can be candidate to bariatric artery embolization. In literature no absolute contraindications are found except for pregnancy due to ionic radiations. No major adverse events are reported; mild abdominal discomfort, gastritis and asymptomatic superficial ulcer in fundus/lesser curvature are described as minor adverse events, with no prolonged hospitalization associated and no re-admission. In particular, superficial gastric ulcerations detected by endoscopy undergo to spontaneous solution in about 1 month [26]. Transient pancreatitis, with mild abdominal pain and elevation of plasmatic lipase level, has been described by Weiss in preliminary results of the BEAT Obesity Trial: supportive therapy with antiemetics and intravenous pain medication was done and discharge was at 48 hours [23]. Thanks to its high feasibility and safety BAE can be potentially employed in young patients for whom bariatric surgery is scarcely applicable according to the strict existing guidelines [27].

The expected decrease of plasmatic ghrelin, via percutaneous trans-arterial embolization of LGA, results in an early (1.6 month) loss of 7.3% of initial body weight, significantly greater than control group (2%) as reported by Gunn; at delayed time points (13.6 month) weight loss is an average of 3.5% of the pre-embolization body weight versus 0.3% in the control group ($p<0.0006$). Mean weight reduction is assessed to be 10%, 13%, 16%, 17% and 17% at 1, 3, 6, 12 and 24 - month follow up according Kipshidze [25].

To summarize, theoretic advantages of BAE are:

- feasibility of 100% even in patients with absolute or relative contraindication to bariatric surgery for poor conditions

-high safety: absence of major adverse events and only few minor adverse events noted without sequelae

-mini-invasiveness

-high repeatability: each bariatric embolization is performed after angiographic study of anatomy

-no theoretic contraindication to bariatric surgery after BAE and even bridge therapy to surgery itself

-theoretic lower costs than bariatric surgery.

Limitations

Even if bariatric artery embolization could represent a non-surgical approach for the treatment of severe obese patients, further studies before BAE can be routinely employed in obese patients are needed. Indeed, in literature several important limitations are noted weakening the global procedural effectiveness:

-few studies, mainly retrospective, with small sample size and short follow up

-short-term efficacity of the procedure

-many unanswered questions regarding the procedure and its effects.

In literature, the first to describe that BAE might be effective for humans was Gunn et al with a retrospective analysis of 19 patients who underwent left gastric artery embolization for gastrointestinal bleeding. The study compared patients who underwent LGA embolization and patients who underwent embolization of a different artery for upper gastrointestinal bleeding; patients analysed were not obese. Moreover, the study included patients with bleeding malignancy, therefore weight loss cannot be attributed solely to embolization [18]. The bias of malignancy was eliminated by Anton et al that demonstrated a BMI reduction in LGA embolization group (10 patients) compared to the control group (22 patients) at 4 months (p=0.03), but no statistically significant reduction of BMI at 8 months and 12 months was found. The main limitation is represented by the small sample size, especially at 12 months, affecting statistical power of follow up and of results [8].

The first prospective study was led by Kipshidze who treated 5 patients with LGA embolization and demonstrated mean weight reduction of 10% at 1 month, 13% at 3 months, 16% at 6 months, 17% at 12 and 20 month-follow up. Serum ghrelin levels after an initial drop, 3 months after the procedure, increased at six months to 19%. Several limitations affected the study: the lack of control group and of specific dietary instructions and the small cohort study [25]. To date the only study reporting ghrelin and leptin serum levels, waist circumference and waist-to-height ratio data after LGAE is Bai et al series with the MRI subcutaneous adipose tissue decrease with a 9-month follow up. Even if the study shows that embolization of the LGA is a safe and a promising strategy, the very small cohort and the short term follow up (9 months) are important limitations [28].

There are two ongoing FDA-approved clinical trials: the GET LEAN (Gastric artery Embolization Trial for the Lessening of Appetite Non-surgically) and the BEAT Obesity (Bariatric Embolization of Artery for the Treatment of Obesity) [23,24]. The GET LEAN demonstrated that radial approach is feasible when femoral artery access is not possible. Average weight loss was 8.5% at 6 months with superficial gastric ulcerations, nausea and vomiting as adverse events. To date, the BEAT Obesity trial has enrolled 17 on 20 patients with six-month follow up with a primary safety endpoint of 30-day adverse events and a primary efficacy endpoint of weight loss with 1 year-follow up. No major adverse events have been reported; three minor adverse events including mild pancreatitis and superficial ulcerations have been described.

Future Directions

Bariatric arterial embolization has demonstrated to be a promising strategy to treat severe obesity; an increasing consensus is building toward the influence of modifications of circulating appetite - mediating hormones to determine hunger and consequently, weight gain or loss. At the same time, minimally invasive techniques are widely spreading all over the world because of their low cost and invasiveness together with their high safety. Thus, bariatric embolization, in selected cases, may represent a further therapeutic tool in the armamentarium for the war against obesity but many unanswered questions have to be investigated to routinely employ BAE for bariatric patients.

Acknowledgement

We performed a systematic review of bariatric embolization of the gastric arteries for the treatment of obesity to assess safety and feasibility of the procedure focusing on clinical efficacy, adverse events and costs. The project was part of a Health Technology Assessment (HTA) for the Lumbardy Region Agency for Drugs and Health. Literature was widely reviewed.

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