LABORATORY INVESTIGATION

Bariatric Radioembolization: A Pilot Study on Technical Feasibility and Safety in a Porcine Model

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ABSTRACT

Purpose: To evaluate feasibility of left gastric artery (LGA) yttrium-90 (^{90}Y) radioembolization as potential treatment for obesity in a porcine model.

Materials and Methods: This study included 8 young female pigs (12–13 weeks, 21.8–28.1 kg). Six animals received infusions of ^{90}Y resin microspheres (46.3–105.1 MBq) into the main LGA and the gastric artery arising from the splenic artery. Animal weight and serum ghrelin were measured before treatment and weekly thereafter. Animals were euthanized 69–74 days after treatment, and histologic analyses of mucosal integrity and ghrelin immunoreactive cell density were performed.

Results: Superficial mucosal ulcerations < 3.0 cm^2 were noted in 5 of 6 treated animals. Ghrelin immunoreactive cell density was significantly lower in treated versus untreated animals in the stomach fundus (13.5 vs 34.8, $P < .05$) and stomach body (11.2 vs 19.8, $P < .05$). Treated animals gained less weight than untreated animals over the study duration (40.2 kg $\pm$ 5.4 vs 54.7 kg $\pm$ 6.5, $P = .053$). Average fundic parietal area (165 cm^2 vs 282 cm^2, $P = .067$) and average stomach weight (297.2 g vs 397.0 g, $P = .067$) were decreased in treated versus untreated animals. Trichrome staining revealed significantly more fibrosis in treatment animals compared with control animals (13.0 vs 8.6, $P < .05$). No significant differences were identified in plasma ghrelin concentrations ($P = .24$).

Conclusions: LGA ^{90}Y radioembolization is promising as a potential treatment for obesity. A larger preclinical study is needed to evaluate the safety and efficacy of this procedure further.

ABBREVIATIONS

BAE = bariatric arterial embolization, EBRT = external-beam radiation therapy, GI = gastrointestinal, H&E = hematoxylin-eosin, HPF = high-power field, LGA = left gastric artery, MAA = macroaggregated albumin, NTE = nontarget embolization, TARE = transarterial radioembolization, ^{99m}Tc = technetium-99m, ^{90}Y = yttrium-90

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Ghrelin is a 28-amino acid peptide hormone (1) produced and secreted predominately by mucosal cells lining the gastric fundus in humans and other monogastric animals (2). It binds to receptors in the hypothalamus and stimulates release of neuropeptide Y, increasing appetite. Myriad research over the past 15 years has defined ghrelin as the principal neurohormonal orexigenic (appetite-inducing) stimulus and has shown its influential role in caloric energy balance (3–6). For these reasons, it is referred to as the "hunger hormone" and has been the subject of multiple targeted therapies aimed at achieving the goal of weight loss. Because most human ghrelin production reliably occurs in the perfusion territory of the left gastric artery (LGA), several minimally invasive, transcatheter therapies have been described with the intent of ghrelin reduction, the most promising of which may be bariatric arterial embolization (BAE) (7,8). BAE has shown potential in decreasing serum ghrelin concentration and weight gain in animal models, and phase I human clinical trials are currently underway.

This study explores LGA transarterial radioembolization (TARE) as a potential tool in the management of obesity. Although the most common modern therapeutic uses of radiation are oncologic in nature, radiation therapy has a long history in the management of benign disease. Hyperthyroidism, arteriovenous malformation, chronic synovitis, vascular restenosis, and other conditions have been treated using radiation therapy (9). In this preclinical pilot study, the feasibility of LGA TARE using yttrium-90 (^{90}Y) resin microspheres was evaluated as an entry point to further investigation.

MATERIALS AND METHODS

The University of Tennessee institutional animal care and use committee approved the animal procedures performed in this study. The primary endpoints of this pilot study were to assess the technical feasibility and safety of LGA TARE. Secondary endpoints included use of treatment and control data to evaluate physical changes in stomach size, changes in weight gain, ghrelin immunoreactive cell density in gastrointestinal (GI) tissue, and plasma ghrelin concentration.

Eight young female pigs (approximately 25% American Yorkshire) 12–13 weeks old and weighing 21.8–28.1 kg (mean 24.7 kg) were included. The animals were housed in individual enclosures 1.5 × 2.5 m for the duration of the experiment. After a 3-day acclimation period, each animal was weighed and fasting blood samples were drawn to assess serum ghrelin concentration. These procedures as well as all diagnostic and surgical procedures (**Fig 1**) were performed under general anesthesia. An intramuscular injection of telazol-xylazine (4.4 mg telazol/kg, 2.2 mg xylazine/kg) (Zoetis Inc, Kalamazoo, Michigan; Bayer CropScience AG, Monheim, Germany) was administered before anesthesia. Pigs were maintained with a 1%–5% isoflurane anesthetic inhalant (Baxter Healthcare Corporation, Deerfield, Illinois) with 100% oxygen after endotracheal tube placement. The animals were randomly assigned into 3 groups: diagnostic + treatment, treatment, and control. All pigs that received surgical intervention were administered prophylactic antibiotics (10,000 IU/kg penicillin) (AGRI-CILLIN; AgriLabs, St. Joseph, Missouri) and analgesia (50 μg/h fentanyl transdermal patch) (Duragesic; ALZA Corporation, Vacaville, California).

Treatment Planning

Fluoroscopically guided interventions for both the diagnostic and the treatment procedures were performed on a Philips Veradius Neo (Philips Healthcare, Andover, Massachusetts) vascular C-arm by board certified interventional radiologists (A.A., B.E.P.). Three animals (animals A, C, G; **Table**) underwent a diagnostic mapping procedure. The primary goal of this procedure was to identify the volume of fundal tissue treated in the ensuing ^{90}Y BAE therapy, a necessary component of treatment planning.

Ultrasound guidance was used to obtain percutaneous femoral access. A 5-F Cobra catheter (Surefire Medical, Inc, Westminster, Colorado) was advanced into the celiac artery followed by angiography to map the arteries supplying the gastric fundus. These arteries included the gastric artery arising from the splenic artery and accessory LGA arising from the left hepatic artery. Both arteries were catheterized using 2.8-F antireflux microcatheters (Precision Microcatheter; Surefire Medical, Inc) (**Fig 2a, b**). Nitroglycerin (200 μg) mixed with verapamil (5 mg) was administered to each artery as needed as a spasmolytic, and 120 MBq ± 10 of technetium-99m (^{99m}Tc) macroaggregated albumin (MAA) was infused into each artery. The catheters and sheath were removed, and a 5-F closure device (AngioSeal; St. Jude Medical, St. Paul, Minnesota) was used for hemostasis.

After angiography, each animal was immediately transferred for 4-view planar scintigraphy, performed on a single-head Philips Argus gamma camera (Philips Healthcare) with an acquisition time of 4 minutes per view. Animals then underwent a contrast-enhanced abdominal computed tomography (CT) scan with 0.5-mm slices on a Philips Brilliance (Philips Healthcare) 40-slice system. A dual board–certified diagnostic/nuclear medicine radiologist (Y.C.B.) cross-referenced the 4-view ^{99m}Tc MAA images with the contrast-enhanced CT images to estimate the volume of gastric tissue perfused, which included the gastric fundus and part of the gastric body. Volumetry of perfused tissue was performed directly on sequential 0.5-mm CT slices, with care taken to trace all gastric rugae. A three-dimensional interpolative algorithm determined the final tissue