Orthostatic Intolerance After Bariatric Surgery

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1.0 Background

More than 78 million adults or ≈36% of U.S. adults are obese with medical costs estimated to be $210 billion annually. Bariatric surgery is the only modality that results in sustained weight loss along with reversal of type 2 diabetes mellitus (T2DM), improvements in cholesterol biosynthesis, lipoprotein metabolism, and decreased cardiovascular events.[1] In 2014, nearly 200,000 individuals in the US underwent bariatric surgery and each year the number increases by 22%.

We[2] and others, [3, 4] showed that obesity results in an increased sympathetic (SNS) activity decreased parasympathetic (PNS) activity and altered baroreflex sensitivity. Previous studies showed that bariatric surgery significantly reduces sympathetic activity. Vertical sleeve gastrectomy (VSG) decreases SNS as measured by direct sympathetic nerve recording at 6 and 12 months post-surgery.[5] Roux-en-Y gastric bypass (RYGB), the most common bariatric procedure, also reduces SNS at 3 and 6 months post-surgery.[6] The mechanism underlying these sympatholytic actions are not completely understood but were found to be associated with a decrease in visceral fat[7] and leptin levels.[5] Regardless of the mechanism(s) involved, the reduction in SNS activity induces a decline in blood pressure in post-bariatric surgery patients[8], which can have in some cases deleterious effects. Importantly, a previous study showed mild orthostatic hypotension in otherwise asymptomatic post-bariatric subjects.[9]

Recent retrospective studies and case series reported an orthostatic intolerance (OI) syndrome characterized by symptoms of cerebral hypo perfusion upon standing associated with pre-syncope and recurrent syncope.[10-14] Our recent preliminary data support these findings; in our center, we performed 4,906 bariatric procedures (78.4% RYGB and 19.7% VSG) in the past 20 years. Patient's follow up after surgery is reduced to ≈15% at 5 years. Despite this attrition, 741 post-bariatric surgery patients, reported symptoms of OI. Chart review showed that 98 (13.2%) of these patients, progressed to chronic OI unexplained by anti-hypertensive use, vitamin deficiency or fluid loss. In 17 cases, the OI is so disabling that patients had to be treated with pressor agents such as midodrine and fludrocortisone.

Normally, after assuming the upright position gravitational forces shift about 700 ml of blood volume to the lower part of the body, particularly the splanchnic circulation;[15] to compensate for the decrease in venous return, the SNS is maximally activated to induce vasoconstriction. We, therefore, hypothesize that the decrease in SNS activity in post-bariatric subjects results in insufficient vasoconstriction upon standing, causing patients to have OI.

2.0 Specific Aims

Specific Aim 1: To test the hypothesis that bariatric surgery (RYGB and VSG) impairs sympathetic vasoconstrictor activity and lead to the development of orthostatic intolerance independent of weight changes.

Specific Aim 2: To test the hypothesis that potentiating sympathetic vasoconstrictor activity will reverse the impaired orthostatic tolerance post-bariatric surgery.

3.0 Inclusion/Exclusion Criteria

We will recruit obese patients that will undergo bariatric surgery and medical weight loss from the Vanderbilt Center for Weight Loss (VWL). We will study three groups before and after 10% weight loss (15 RYGB, 15 VSG, and 15 medical weight loss).

Inclusion criteria

- Obese subjects that will undergo bariatric surgery or medical weight loss.
- Age 18-65 years
- BMI >35 kg/m^2
- Weight < 400 lbs

Exclusion criteria:
Subjects presenting with any of the following will not be included in the study:

- Diabetes type 1
- Use of an alpha blockers, clonidine, beta-blockers.
- Pregnancy or breast-feeding. Women of childbearing potential will be required to have undergone tubal ligation or to be using an oral contraceptive or barrier methods of birth control.
- The use of any strong CYP2D6 inhibitor (e.g., fluoxetine, paroxetine, quinidine, tipranavir).
- Use of selective NET inhibitors.
- Use of monoamine oxidase inhibitors.
- Cardiovascular disease such as myocardial infarction within six months prior to the study, presence of angina pectoris, significant arrhythmia, congestive heart failure (left ventricular hypertrophy acceptable), deep vein thrombosis, pulmonary embolism, second or third degree heart block, mitral valve stenosis, aortic stenosis or hypertrophic cardiomyopathy
- History of serious neurologic disease such as cerebral hemorrhage, stroke, or transient ischemic attack
- Hematocrit < 34%
- Any underlying or acute disease requiring regular medication which could possibly pose a threat to the subject or make implementation of the protocol or interpretation of the study results difficult
- Mental conditions rendering a subject unable to understand the nature, scope and possible consequences of the study
- Inability to comply with the protocol, e.g., uncooperative attitude, inability to return for follow-up visits, unlikelihood of completing the study, and investigator discretion

4.0 Enrollment/Randomization

Recruitment and informed consent:

We will recruit obese patients that will undergo bariatric surgery and medical weight loss from the Vanderbilt Center for Weight Loss (VWL). The VWL clinic is the largest bariatric surgery facility in Tennessee and annually performs ≈500 bariatric surgeries. We may also recruit persons willing to participate in the Jenny Craig weightloss program for 6 weeks. We will use research match and subject locator as well as an online pre-screening survey. We will use printed consent and e-consent to consent the subjects, for the two, parallel-arm, placebo-controlled portion of the study**.** We will randomize 1:1 to either placebo vs. the NE-transporter inhibitor, atomoxetine, at doses of 0.5 mg/kg/day.

5.0 Study Procedures

Pre-screening survey: Potential participants may choose to complete a pre-screening survey that will better evaluate their eligibility. Subjects may complete the survey on their own or while in clinic.

Screening evaluation: Patient will be consented by phone. We will review the pre-surgical evaluation to assess for inclusion/exclusion criteria and we will invite to complete additional visits in the center for surgical weight loss or the autonomic cardiovascular suite.

Visit 1: Baseline (pre-surgery, RYGB/VSG) or pre-hypocaloric diet (medical weight loss).

Visit 2: After 10% weight loss. The time is variable (RYGB/VSG= 10-12 days; medical weight loss group= ~30-40 days).

Visit 3 (only for RYGB and VSG groups): 3-months after the bariatric procedure.

Visit 4 (only for RYGB and VSG groups): After 3-days on stable doses of Strattera (atomoxetine) vs. matching placebo. For the two, parallel-arm, placebo-controlled portion of the study**.** We will randomize 1:1 to either placebo vs. the NE-transporter inhibitor, Strattera (atomoxetine), at doses of 0.5 mg/kg/day.

Visits 1-4 specific procedures:

In supine position, we will measure: 1) plasma volume assessment; 2) continuous beat-to-beat blood pressure, and heart rate monitoring; 3) muscle sympathetic nerve activity (MSNA) with microneurography (at the physician's descretion), 4) blood volume assessment; and 5) supine plasma catecholamines and metabolites.[2, 16] We will assess orthostatic tolerance using tilt table testing.[17, 18] We will perform a 60º head-up tilt (HUT) for 30 min until pre-syncope (defined as systolic BP (SBP, mm Hg) <80 or SBP>90 and pre-syncopal symptoms (nausea, lightheadedness, dizziness).[19] We will repeat plasma catecholamines at the end of the 30 min HUT and hemodynamic measurements throughout the HUT. The supine and 60º HUT plasma catecholamines will provide information on orthostatic-induced sympathetic neuro-hormonal activation**.** We will use the ratio dihydoxyphenylglycol (DHPG) to NE as the biomarker for NET inhibition as we previously reported.[20] We will repeat the serum pregnancy test (if applicable).

We will wait 24 hours to perform visits 1-4 if the patient has received IV fluids for clinical care.

Our primary endpoint (orthostatic tolerance, OT) is defined as the time between the start of the 30º HUT until pre-syncope

Justification for Strattera dose and frequency. We selected a weight-adjusted dose (0.5 mg/kg/day or equivalent to 40 mg/day) because body weight has a significant impact on Strattera pharmacokinetics.[21] The weight-adjusted dose will provide comparable exposure between patients of different body sizes, which is of particular importance in the obese post-bariatric population. The T½ of atomoxetine is 5.6 hours,[21] hence we will study subjects after 3-day treatment to achieve stable concentrations. Specific procedures for visit 4 will be performed two hour after intake of blinded study medication. Atomoxetine reaches maximum plasma concentration within two hours after administration.

The PI (Dr. Cyndya Shibao) holds an IND (117394) for the use of Strattera (atomoxetine) for indication other than attention deficit hyperactivity disorder.

6.0 Risks

Blood Draws: Subjects may experience discomfort, bruising, and/or bleeding, or infection at the needle insertion site after a blood draw. Rarely, some people faint. Frequent blood sampling may cause anemia. We will exclude subjects with hematocrit <34%

12-hour fast: Participants may experience hunger during a 12-hr fast, however this is a standard requirement by clinicians for accurate blood testing.

Study medication: NET blockade such as Strattera can cause severe hypertension when taken together with monoamine oxidase inhibitors. For this reason, subjects will be asked to wear a medical alert bracelet stating that they should not be given a monoamine oxidase inhibitor without first contacting the PI. Common (>10%) side effects associated with Strattera are headaches (2% to 19%), insomnia (2% to

15%), somnolence (4% to 11%), xerostomia (21%), nausea (7% to 21%), abdominal pain (7% to 18%), appetite decrease (11% to 16%), and vomiting (3% to 11%). Research subjects will be informed of all the potential side effects associated with the drug. All potential adverse events will be ranked according to severity and will be reported according to the data and safety-monitoring plan described below.

Strattera has been associated with suicidal ideation in children. The frequency of suicidal ideation is 0.37% (5/1,357) based on a recent meta-analysis. Because subjects will only receive acute doses of Strattera, the risk of suicidal ideation is minimal.

Intravenous Cather Insertion:
Inserting a plastic catheter into the vein may cause a brief amount of pain and possibly a small bruise at the site, but will allow us to draw blood without repeated sticks throughout the study. It is also possible to develop an infection at the location of the catheter. It is uncomfortable to have the intravenous catheter in place for any length of time because it causes discomfort when the patient moves their arm.

Tilt table testing:
The potential risks associated with this procedure are: 1) subjects **may** experience low back pain after lying down on the tilt table test; 2) there is a risk of syncope and/or low blood pressure. These events, however are expected considering that the procedure intend to cause evaluate orthostatic intolerance. We have specific rules for when to stop the procedure and move subjects to recumbent position (pre-syncope defined as SBP<80 mmHg or SBP>90 mmHg and pre-syncopal symptoms (nausea, lightheadedness, dizziness).

Muscle Sympathetic Nerve Activity:
The potential risk associated with this procedure are: 1) numbness sensation and/or pain in the area of nerve stimulation and/or needle insertion; 2) discomfort when the patient moves his/her leg; 2) potential risk of infection in the site of needle insertion. We will minimize these potential risks by applying sterile technique for needle insertion. Dr. Shibao has significant experience in the use of this technique and will choose which subjects will have the procedure.

Blood volume assessment:
As part of this research study, participants will receive a small amount of radioactive substance called Iodine-131. Iodinated I-131 albumin (Volumex®), injected intravenously for determination of total plasma volume, is a radiopharmaceutical and, as such, requires that care be taken to ensure minimum radiation exposure consistent with proper patient management. Each 1 ml dose of Volumex® contains 25 microcuries in a pre-filled injection kit. This radioactive substance will expose participants to a small amount of radiation (x-rays). The radiation dose that they will receive from each procedure is about the same amount that they would receive over a period of four months from natural background radiation. Natural background radiation comes from naturally occurring radioactive material that is present in everyone's body, from outer space (cosmic radiation), and from naturally occurring radioactive material in soil, rocks, and building materials. This procedure will be performed a maximum of two times at an interval of at least several weeks. I-131 tagged human albumin is a human blood product. This product has been screened and heat-treated for at least 10 hours at 60°C. Experts demonstrated that this treatment kills the encapsulated viruses (like HIV and Hepatitis C). Recent studies have shown that the risk of getting a disease from human blood products such as this is extremely small. However, some individuals may not want to receive human blood products for religious or other ethical concerns.

Breach of Confidentiality:
In the event of a security breach, confidential information may be stolen. We have strong security procedures in place to minimize the possibility of a breach. Although we cannot provide a 100%

guarantee that the participant's data will be safe, our procedures minimize the chance that a breach would take place.

There is no benefit of the proposed research to the subjects per se.

7.0 Reporting of Adverse Events (AEs) or Unanticipated Problems involving Risk to Participants or Others

All protocols will be reviewed and approved by the Vanderbilt Institutional Review Board (IRB) before enrolling any subject. Any untoward medical event will be classified as an AE, regardless of its causal relationship with the study. The PI will be responsible for ensuring both data integrity and for ensuring that study participants are safely cared for, and that all AEs are noted, followed, and reported to the IRB, the DSMO, and the FDA.

We will use the Guidance for Industry and Investigators for safety reported requirements for INDs and BA/BE studies published in the FDA website:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

Definitions:
Adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not consider drug related. Suspected AE means any AE for which there is reasonable possibility that the drug caused the AE; "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE.

An AE will be considered unexpected if it is not listed in the investigator brochure.
Serious AE means any AE that: a) results in death, b) is life-threatening, c) requires inpatient hospitalization or prolongation of existing hospitalization, d) results in persistent or significant disability or incapacity, e) is a congenital anomaly or birth defect.

Serious adverse events will be reported to the Chairman of the Data and Safety Monitoring Board (DSMB), the IRB, and the FDA no later than 7 calendar days after the PI's initial receipt of the information.

Suspected AE interpretable as single case (uncommon and strongly associated with drug exposure) will be reported to the FDA within 15 days from initial receipt.

Non-serious, unexpected adverse events will be reported to the IRB at the time of the annual continuing review.

The Data Safety Monitoring Officer (DSMO), Dr. Cheryl Laffer, Director of the Vanderbilt Hypertension Service, a patient-oriented investigator with experience in clinical research, will serve as DSMO and consultant for this grant. We will provide annual reports to the IRB and the DSMO regarding recruitment, safety reporting, data quality, and efficacy.

Incidents of non-compliance with the protocol will be reported at the time of continuing review.

8.0 Study Withdrawal/Discontinuation

Criteria for study withdrawal/discontinuation

- Drug-related toxicity
- Requirement for prohibited concomitant medications (see exclusion criteria)
- Pregnancy
- Request by subject to terminate treatment
- Clinical reasons believed to be life threatening by the physician, even if not addressed on the potential risk section

9.0 Statistical Considerations

Sample size justification: For aim 1, we will compare primary endpoint (OT) between each surgery group (RYGB and VSG) and the medical weight loss group. Based on the literature,[22] we expect a 48.5% reduction in orthostatic tolerance (OT) after RYGB/VSG (normal baseline OT is 36.7±7.3 (mean±SD) versus poor OT 18.9±5.96.[22]) After weight loss, we estimated a ≈25% reduction in OT (baseline 36.7±7.3 to 27.5 ±7). This is a 25% difference in OT between surgical versus medical weight loss. We need n=15 per group to have 90% power to detect the difference between 18.9 and 27.5 using SD of 7 with type I error rate of 0.05. We plan to enroll 15 subjects in each of the 3 groups. For aim 2, in visit 3 we will randomize these 30 RYGB/VSG subjects with 1:1 ratio to the Strattera and placebo groups. We will compare OT between the placebo and the Strattera groups. We expect that OT is 18.9±5.96 (mean±SD) for the placebo group (similar to the surgery group in aim 1) and the Strattera group will improve by ≈50% or 28.35±7 (mean±SD). With 15 in each group in aim 2, we will have excellent (96%) power to detect the difference.

Data Analysis Plan: the primary analyses will focus on the comparison of the primary endpoint, OT. In aim 1 between RYGB vs. medical weight loss, and between VSG vs. medical weight loss; in aim 2: between Strattera versus placebo groups. Secondary endpoints include changes in hemodynamics (blood pressure, heart rate) during HUT and HUT+LBNP, orthostatic changes in plasma catecholamines, and MSNA. We will assess continuous outcomes for normality. If normality is violated, we will apply data transformation or non-parametric analysis methods. We will provide summary statistics for both numerical and categorical variables by study arms and assess comparability among randomization groups. In both aims, we will estimate the direct between-group difference by means with its 95% confidence interval (CI), which will be tested using either two-sample t-test or Wilcoxon Rank Sum test. A multivariate general linear model will be used to evaluate the group or treatment effects while adjusting the baseline measure of the endpoint. Model over fitting will be avoided using the rule of thumb of 10 observations per parameter in the model. Analyses of secondary endpoints and other exploratory analyses will be conducted similarly. We will test all hypothesis at the level of α=0.05. We will use SPSS for Windows (Version 22.0, SPSS, Chicago) and the open source statistical package R (version 3.4.3, R Core Team, 2017) for analyses (https://www.R-project.org.)

10.0 Privacy/Confidentiality Issues

All data will be collected specifically for the proposed research project. A unique identification case number will be used to protect the confidentiality of the study participants. Only case numbers will be included in spreadsheets used for the statistical analysis. PHI and access to the key for the ID numbers will only be viewable by members of the research team. Members of the research team will have access to the patient's medical record during the screening visit and throughout the study until the patient completes her participation in the study or meets any of the criteria for study withdrawal/discontinuation.

11.0 Follow-up and Record Retention

Research records will be maintained for at least three (3) years from the date the research is closed with the Vanderbilt University IRB. All research records will be accessible for inspection and copying by authorized representatives of the IRB, federal regulatory agency representatives, and the department or agency supporting the research.

All Health Insurance Portability and Accountability Act (HIPAA)-related documentation will be maintained for at least six (6) years from the date of the last use or disclosure of the Protected Health Information (PHI).

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