

Lessons Learned from a Randomized Controlled Trial of Bariatric Surgery versus Intensive Lifestyle Modification for Individuals with Type 2 Diabetes

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Abstract

Objective: Relatively few Randomized Controlled Trials (RCTs) have compared bariatric surgery to lifestyle modification for weight loss and improvements in type 2 diabetes. The Surgery or Lifestyle Intervention for Diabetes (SOLID) RCT was designed to address this insufficiency by comparing

- (1) Roux-en-Y Gastric Bypass surgery (RYGB),
- (2) Adjustable Gastric Banding surgery (AGB), and
- (3) A non-surgical Intensive Lifestyle Modification (ILM) for weight loss on changes in weight and diabetes status.

Methods: SOLID was a RCT for the first 24 months, but due to low enrollment, was modified to a prospective observational study for the last 12 months.

Results: In total, 1,290 individuals inquired about the study and completed initial screening. Of these, 209 were eligible, however only 18 were enrolled in the trial (3 RYGB, 3 AGB, 12 ILM). Multiple barriers to patient enrollment were identified, including issues related to the eligibility criteria, reluctance to accept random assignment to the three interventions, and lack of insurance coverage or availability of funds to pay for the bariatric procedures.

Conclusion: These issues warrant thoughtful attention from investigators who are planning future RCTs in this area.

Keywords: Type 2 diabetes; Bariatric surgery; Randomized controlled trial

Introduction

There have been few Randomized Controlled Trials (RCTs) that have compared the benefits and risks of bariatric surgical procedures to each other or to an intensive non-surgical weight loss intervention [1-3]. The American Recovery and Reinvestment Act of 2009 designated \$200 million for a National Institutes of Health initiative for Challenge Grants in Health and Science Research [4]. In response to the demand for higher quality evidence for bariatric surgery as a potential treatment option for type 2 diabetes, particularly among those with a Body Mass Index (BMI) <35 kg/m², three separate RCTs were funded by the American Recovery and Reinvestment Act of 2009. This paper describes the challenges we encountered in the design and conduct of our RCT, titled Surgery or Lifestyle Intervention for Diabetes (SOLID), which was initially proposed to compare the effectiveness of (1) Roux-en-Y Gastric Bypass Surgery (RYGB), (2) Adjustable Gastric Banding surgery (AGB), and (3) non-surgical Intensive Lifestyle Modification for weight loss (ILM) on rates of diabetes remission.

Methods

The SOLID study initially was designed to randomly assign individuals with type II diabetes and a BMI of 30-40 kg/m² to one of three treatment conditions: (1) RYGB; (2) AGB; or (3) ILM. The primary outcome was the rate of diabetes remission at 1 year, which was defined as glycated hemoglobin (HbA1c) <6.5% and a fasting blood glucose <126 mg/dL in the absence of antidiabetic medications. Secondary aims of this study were to: (1) determine the effects of the three treatment conditions on glucoregulatory gut hormones and

their corresponding effects on postprandial insulin release and insulin sensitivity after a weight loss of 10% was achieved; and (2) compare other benefits (e.g., changes in dietary intake and physical activity) as well as risks (e.g., hypoglycemia) of the interventions. The proposed sample size was 32 individuals (10 RYGB, 10 AGB, 12 ILM). The study was initially designed to detect differences in type 2 diabetes remission between treatment groups (from baseline to 12 months) with 80% power. The study was approved by the Institutional Review Board of the University of Pennsylvania. All participants provided written informed consent.

Eligibility, recruitment, screening, and enrollment of study participants

Individuals 18 to 65 years of age with a BMI of 30-40 kg/m² and diagnosis of type II diabetes (defined by an existing diagnosis confirmed

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by the primary care provider, the use of antidiabetic medications (orals or injectables), a fasting plasma glucose >126 mg/dL on two occasions or a fasting glucose >126 mg/dL with a 2-hour postprandial glucose >200 mg/dL, HbA1c >6.5%, or an oral glucose tolerance test) were eligible for participation.

The primary method to identify patients involved using two mailing lists of individuals with diabetes in the Philadelphia metropolitan area—the Pennsylvania Integrated Clinical and Administrative Research Database (PICARD) as well as an Aldata list obtained from a commercial company (Lorton Data, Arden Hills, Minnesota). When PICARD patient mailing lists were used, we obtained provider authorization, gauged potential eligibility through BMI and diabetes status, as listed in the PICARD database, and providers signed the recruitment letters. Letters were followed by telephone calls to pre-screen those who could be reached for eligibility.

To further promote the study, we posted study advertisements on external websites, including Craigslist, Clinical Trials.gov, and Google, as well as websites housed at the University of Pennsylvania. We posted fliers throughout the University of Pennsylvania Health System and in public places throughout West Philadelphia. We also purchased advertisements in local newspapers and on a local radio station.

A research coordinator conducted a preliminary telephone screen on individuals who expressed interested in participation. Individuals who met the enrollment criteria during the telephone screen were asked to attend a free bariatric surgery program information session to learn more about bariatric surgery. If they remained interested in participating after the information session, potential participants scheduled an initial consultation with a surgeon. They were subsequently scheduled for routine preoperative tests (e.g., upper gastrointestinal series, sleep study, and psychological evaluation) to confirm medical appropriateness for bariatric surgery as consistent with their insurance company's requirements for surgery. Once approved for surgery by their insurance company, individuals who met these criteria were consented, randomized, and placed in the queue for study enrollment.

Results

Recruitment and enrollment

The vast majority (1,081 (83.8%)) of individuals who completed a telephone screen did not meet the inclusion criteria. As shown in Table 1, the most common reasons for exclusion were: BMI>40 kg/m² (24.3%); type II diabetes for over 10 years (19.2%); unwillingness to be randomized to a bariatric surgical procedure (12.2%); no type II diabetes diagnosis (9.5%); unresponsiveness to outreach from study personnel (8.2%), and lack of insurance coverage for bariatric surgery (7.2%).

Among the 209 individuals who met the inclusion criteria during the phone screen, 160 (76.6%) failed to complete the next steps in the enrollment process. As shown in Table 2, the two most common reasons were failing to attend the initial bariatric surgery information session (63.8%) and failing to attend an initial consultation with a bariatric surgeon following the information session (20.6%).

In the first two years of recruitment, from September 2009 to August 2011, 990 individuals completed an initial phone screen. Only 172 (17.4%) successfully cleared the screen and were directed to the bariatric information session. Twenty-six individuals (2.6%) attended this session, subsequently completed all of the clinical assessments

prior to bariatric surgery, and consented to participate in the study. Seven (0.7%) of these individuals were randomized and 4 (0.4%) subsequently enrolled (Table 3).

As lack of insurance or other financial coverage for bariatric surgery appeared to be a significant barrier to enrollment, we, in consultation with study staff at the National Institute of Diabetes and Digestive and Kidney Diseases, agreed to modify the trial design to a prospective observational study. This change allowed participants to choose between the RYGB, AGB, and ILM weight loss treatments.

In the third year of recruitment, from August 2011 to August 2012, 300 individuals completed an initial telephone screen. Thirty-seven individuals (12.3%) were deemed eligible, 23 (7.7%) consented, and 14 (4.7%) enrolled (see Table 3). Of those who enrolled, 11 (78.6%) selected the ILM group.

Failure Reason [#]	¹ Year 1-2		² Year 3		³ Total	
	n	(%)	n	(%)	n	(%)
BMI too high	258	(23.5)	92	(26.7)	350	(24.3)
Type 2 diabetes > 10 years	209	(19.1)	68	(19.8)	277	(19.2)
Not willing to be randomized*	174	(15.9)	0	(0.0)	176	(12.2)
No type 2 diabetes	101	(9.2)	36	(10.5)	137	(9.5)
Unresponsive to messages	80	(7.3)	39	(11.3)	119	(8.2)
No insurance coverage	69	(6.3)	35	(10.2)	104	(7.2)
Other	48	(4.4)	28	(8.1)	76	(5.3)
Distance	61	(5.6)	13	(3.8)	74	(5.1)
BMI too low	43	(3.9)	7	(2.0)	50	(3.5)
Age	23	(2.1)	10	(2.9)	33	(2.3)
Medication	20	(1.8)	7	(2.0)	27	(1.9)
Unable to contact	11	(1.0)	9	(2.6)	20	(1.4)
ILM full, uninterested in surgery†	0	(0.0)	2	(0.6)	2	(0.1)

[#] These data include only first screens and not those who were later re-screened, and individuals that failed the phone screen for multiple reasons.

¹ 09/10/2009 to 08/18/2011 (RCT design)

² 08/19/2011 to 08/31/2012 (observational study design)

³ 09/10/2009 to 08/31/2012

* Only collected for RCT design.

† Only collected for observational study design.

Table 1: Reasons for SOLID trial phone screen failure.

Exclusion Reason	¹ Year 1-2		² Year 3		³ Total	
	n	(%)	n	(%)	n	(%)
Lost before information session	83	(62.4)	19	(70.4)	102	(63.8)
Lost after information session	33	(24.8)	0	(0.0)	33	(20.6)
Lost before initial surgery consult	4	(3.0)	2	(7.4)	6	(3.8)
Lost after initial surgery consult	13	(9.8)	0	(0.0)	13	(8.1)
Lost before screening visit	0	(0.0)	4	(14.8)	4	(2.5)
Uninterested in surgical treatment*	0	(0.0)	2	(7.4)	2	(1.3)
Total	133	(100.0)	27	(100.0)	160	(100.0)

¹ 09/10/2009 to 08/18/2011 (RCT design)

² 08/19/2011 to 08/31/2012 (observational study design)

³ 09/10/2009 to 08/31/2012

* ILM group was full.

Table 2. Reasons for SOLID trial exclusion after passing phone screen.

Recruitment Stage [#]	¹ Year 1		² Year 2		³ Year 3		TOTAL	
	n	(%)	n	(%)	n	(%)	n	(%)
Phone Screened	551	(100.0)	439	(100.0)	300	(100.0)	1290	(100.0)
Passed Phone Screen	111	(20.1)	61	(13.9)	37	(12.3)	209	(16.2)
Consented	19	(3.4)	7	(1.6)	23	(7.7)	49	(3.8)
Randomized	1	(0.2)	6	(1.4)	0	(0.0)	7	(0.5)
Enrolled	0	(0.0)	4	(0.9)	14	(4.7)	18	(1.4)

¹ 09/10/2009 to 08/31/2010 (RCT design)

² 09/01/2010 to 08/18/2011 (RCT design)

³ 08/19/2011 to 08/31/2012 (observational study design)

[#] These data include only first screens and not those who were later re-screened.

Table 3. Yearly recruitment breakdown.

Among the 49 individuals who consented to participate (26 within the RCT design and 23 within the observational study design), 29 (59.2%) did not complete their baseline assessment. The most common reasons for not completing the assessment were loss to follow up after consent (34.5%), change of mind regarding willingness to be randomized (20.7%), baseline HbA1C out of study range (17.2%), and inability to be randomized due to lack of insurance or other funding for the surgeries, or medical/psychological reasons (10.3%).

Discussion

Recruitment for the SOLID study was uniquely challenging, particularly when the study was structured as a RCT. Failure to achieve enrollment goals, both as a RCT and subsequently as a prospective observational trial, is attributable to several factors. These include potential participants having a BMI > 40 kg/m², having type II diabetes for greater than 10 years, unwillingness to be randomized to a surgical procedure for weight loss, and lack of insurance coverage or other financial resources for bariatric surgery.

The SOLID study was able to recruit 12 individuals for the ILM group, which filled this study arm. The majority of ILM participants (11/12, 92%) were enrolled after the change in study design from a RCT to an observational study. This observation suggests that many of those interested in participating (and who met other eligibility criteria) were unwilling to risk being randomized to a surgical intervention, and only wanted to participate if they could choose the ILM group.

The number of participants in the RYGB and AGB surgery groups could have been increased in two ways: (1) securing health insurance coverage for the cost of bariatric surgery and/or (2) obtaining other funding to cover the cost of surgery for those without insurance coverage. One hundred and four (7.2%) screen failures occurred because of a lack of health insurance coverage for the cost of surgeries. If this barriers to participation were eliminated and one-third of these individuals enrolled, the trial would have been filled.

Financial support for bariatric surgery appears to be essential for the successful completion of RCTs in this area. The STAMPEDE trial (Cleveland Clinic) was supported by funding from Ethicon Endo-Surgery to cover the cost of the surgical procedures for those participants without insurance coverage [5]. The ongoing TRIABETES Study (University of Pittsburgh) used the same three arm randomization model as the SOLID Study and had financial support for the surgical procedures from the host institution [6].

Other study design considerations also may contribute to successful enrollment. The SLIMM-T2D Study (Brigham and Women's Hospital) used a two arm model that compared either RYGB vs. ILM or AGB vs. ILM. This allowed participants to first choose either RYGB or AGB before potential randomization to ILM [7]. Such a model applied to the SOLID RCT may have been appealing to those who would have wanted ILM if they did not receive their surgery of choice and, as a result, enhanced enrollment.

In summary, issues related to the specificity of the inclusion criteria, apprehension of the participants to accept randomization to all three interventions, and the lack of financial support for the surgical procedures are critical issues for investigators to consider prior to launching future RCTs in this area.

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Conflict of Interest Statement

Dr. Sarwer has served as a paid consultant for Allergan, BAROnova, EnteroMedics, and Ethicon Endo-Surgery, which are manufacturers of products for bariatric surgery. He also served on the board of directors of the Surgical Review Corporation, which created the International Center of Excellence for Bariatric Surgery program to evaluate bariatric surgeons and hospitals around the world, and also managed Center of Excellence programs on behalf of several bariatric surgery professional societies.

Dr. Wadden discloses that he has relationships with Novo Nordisk, Orexigen, Vivus, Nutrisystem, Guilford Press, and the Cardiometabolic Support Network.

The remaining authors have no conflicts of interest.

References

- Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, et al. (2008) Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA* 299: 316-323.
- Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, et al. (2012) Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med* 366: 1567-1576.
- Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, et al. (2012) Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 366: 1577-1585.
- National Institutes of Health Office of Extramural Research (2010) National Institutes of Health Challenge Grants in Health and Science Research.
- Kashyap SR, Bhatt DL, Schauer PR; STAMPEDE Investigators (2010) Bariatric surgery vs. advanced practice medical management in the treatment of type 2 diabetes mellitus: rationale and design of the Surgical Therapy And Medications Potentially Eradicate Diabetes Efficiently trial (STAMPEDE). *Diabetes Obes Metab* 12: 452-454.
- ClinicalTrials.gov (2010) The TRIABETES Study: A Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes
- Joslin Diabetes Center (2010) Clinical Trial Compares Leading-Edge Treatments for Obesity and Diabetes.