Laparoscopic Gastric Bypass versus Sleeve Gastrectomy to Treat Morbid Obesity (SLEEVEPASS)

Trial protocol 19.2.2008

Paulina Salminen, MD, PhD

A prospective randomized multicenter study: laparoscopic gastric bypass versus laparoscopic sleeve gastrectomy in the treatment of morbid obesity

Purpose of the study

In recent years morbid obesity has been recognized a serious worldwide health crisis. In the US obesity in considered the second most common cause of premature death after smoking. It has been estimated that 400 000 deaths per year are related to obesity and its complications [13]. Body mass index (BMI) of Finnish people has been increasing and obesity has become more common during the last two decades. In 2002 the mean BMI was 27,0 kg/m² among working age males and 25,9 kg/m² among females in Finland. 66 % of the males and 49 % of the females had BMI ≥ 25 kg/m² and every fifth had BMI ≥ 30 kg/m² [10].

Obesity is related to increased morbidity and mortality. The increased mortality in mainly caused by obesity related comorbidities such as insulin resistance, type 2 diabetes, hypertension and dyslipidemia. [13] In addition to this, obesity is related to many other diseases such as metabolic syndrome, coronary artery disease, stroke, obstructive sleep apnea, gout, gall stones, fatty liver disease, arthritis, asthma and certain cancers (postmenopausal breast, uterus, colon and kidney cancer [2].

Bariatric surgery is considered superior to conservative treatment regarding weight loss and resolution of comorbidities in patients with BMI ≥ 40 kg/m² [12]. In two recent studies bariatric surgery decreased common morbidity compared to conservative treatment [3, 17]. Death by heart disease, diabetes and cancer was less common after gastric bypass operation compared to control group [3].

The most common operative technique worldwide is gastric bypass (65 % of all procedures) and over half of these are performed by laparoscopy [6]. In this operation a small 30 ml gastric pouch is created, the biliopancreatic limb is measured (approximately 50 cm) by graspers and an antecolic end-to-side gastrojejunostomy is created (circular or linear staplers). The alimentary limb is measured by graspers at 150 cm and a side-to-side jejuno-jejunostomy is created.

The weight loss is based on limited food intake by the small gastric pouch, partial malnutrition by the ileal bypass and possible hormonal changes. [12] Mean excessive weight loss (%) after gastric bypass is 25 % at ten-year follow-up. In the same SOS study at ten-year follow-up regarding conservative treatment equaled 1,6 % excessive weight gain. Surgery was also superior to conservative treatment considering diabetes, hypertriglyseremia, low high density lipoprotein, hypertension and hyperuricaemia. [17] Mortality after gastric bypass is 0,5 – 2,5 % and morbidity is 10 – 20 % [4, 12].

Laparoscopic sleeve gastrectomy is a relatively new operative technique. It was originally intended as a bridge procedure for high-risk super obese patients (BMI > 60) preceding the definitive

bariatric procedure [15]. Sleeve gastrectomy is created narrow along a 33-35 Fr calibration bougie using linear staplers preserving the majority of the antrum. The weight loss is based on limited food intake by the narrow gastric tube created in the procedure and decrease of ghrelin hormone secreted from the resected fundus of the stomach. In the last few years sleeve gastrectomy has been used as a single procedure for patients with BMI 35 – 60. The initial promising results in terms of weight loss and the resolution of comorbidities have been comparable to gastric bypass at short-term follow-up. However, long-term results of sleeve gastrectomy are very scarce [9, 14].

Morbid obesity by itself increases risk for venous thrombosis and pulmonary embolism. After bariatric surgery, possible serious complications are hemorrhage, anastomotic or staple line leakage and related infection and stricture of the anastomosis. Some of these complications must be treated by reoperation. After laparoscopic gastric bypass the risk for serious complication is 0.9–5.1 % [7, 8, 16] and mortality is 0,16 % [5]. The risk for serious complication after laparoscopic sleeve gastrectomy is 2,9 % [11], but studies regarding mortality and long-term results are lacking.

Aim of the study

The aim of the study is to compare two different operative techniques regarding weight loss, resolution of comorbidities and complications. The primary endpoint is weight loss evaluated by %EWL (excessive weight loss, %). The secondary endpoints include resolution of associated comorbidities, improvement of QOL, mortality and morbidity of the procedures.

Design of the study

The study is carried out at three centers, Turku University Hospital, Vaasa Central Hospital and Helsinki University Hospital (Peijas). The patients evaluated for enrollment are assigned to undergo surgical treatment for morbid obesity and their treatment follows established treatment protocols.

Inclusion criteria:

- BMI ≥ 40 or BMI ≥ 35 with a significant obesity related comorbidity
- Age 18 – 60 years
- Previous successfully instituted and supervised but failed adequate diet and exercise program

Exclusion criteria:

- BMI > 60
- Significant psychiatric disorder
- Severe eating disorder, active alcohol or substance abuse
- Active gastric ulcer disease
- Difficult GERD with a large hiatal hernia
- Previous bariatric surgery

Preoperative evaluation

All the patients undergo a thorough multidisciplinary evaluation (an endocrinologist, a dietician, and a bariatric surgeon), and a psychiatric evaluation is obtained, if considered necessary. All patients undergo upper gastrointestinal endoscopy and abdominal ultrasound examination. Possible Helicobacter pylori infection and associated gastric ulcer disease are treated before surgery. Only symptomatic gallstones are considered an indication for laparoscopic cholecystectomy at the time of the bariatric procedure. After the clinical decision of proceeding to bariatric surgery for treating

morbid obesity is reached, patient eigibility for this RCT is evaluated according to the inclusion and exclusion criteria. A written informed consent is received and the patients are randomized by a closed envelope method either to undergo laparoscopic sleeve gastrectomy or laparoscopic gastric bypass. Preoperative quality of life is measured by the Moorhead-Ardelt questionnaire at the same visit.

Postoperative treatment

Postoperative treatment is carried out according to established treatment protocols. Oral fluids are initiated on the first postoperative day and patients are discharged from the hospital from the second postoperative day onward depending on recovery. All patients are placed on multivitamins postoperatively and proton pump inhibitors are routinely used for the first three months. The postoperative control visits at surgical outpatient clinic are planned at 3, 6, 12, 18 months, 2, 3, 4, 5, 7, 10 and 15 years. At these visits the patients are measured for weight, checked for blood samples according to normal treatment protocols and asked to fill the Moorehead-Ardelt quality of life questionnaire. Plastic surgery consultation is obtained, if needed.

Current state of the study

The statement for approval by the ethics committee of Turku University Hospital will be submitted ann the approvals by the ethics committees of Vaasa Central Hospital and Helsinki University Hospital will also be applied. The randomization for the study will be started during spring 2008 after the approvals by the ethics committees. The researchers (Paulina Salminen, Jari Ovaska, Mika Helmiö, Mikael Victorzon, Pekka Tolonen, Pipsa Peromaa, Anne Juuti and Marja Leivonen) will be personally responsible for the preoperative visits, operations and postoperative visits.

Hypothesis and meaning of the study

The results of this current RCT study enable comparison on the long-term data between the current golden standard of laparoscopic gastric bypass and laparsocopic sleeve gatrectomy. The hypothesis of the study is that as sleeve can be considered less traumatic and easier and faster to perform compared to RYGB, it could become the procedure of choice in treating morbid obesity provided that long-term results of SG were comparable with those of RYGB. The results can directly be applied to patient care.

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Laparoscopic Gastric Bypass versus Sleeve Gastrectomy to Treat Morbid Obesity (SLEEVEPASS)

Statistical Analysis Plan 19.2.2008

Saija Hurme, Biostatistician, MSc

A prospective randomized multicenter study: laparoscopic gastric bypass versus laparoscopic sleeve gastrectomy in the treatment of morbid obesity

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Hypothesis and meaning of the study

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Sample size calculation

Sample size calculations are based on test of mean difference of bypass and sleeve operation in excessive weight loss (EWL) in one year. The mean of 60 and standard deviation of 20 in bypass group were assumed and α-level of 0.05 were used in calculations. By using a equivalence design with a margin of equivalence of 15% (-9 to 9) a sample size of 108 patients per group is needed for 90% power. When 10% drop out is taken account, 120 patients per group were recruited for the study.

Statistical analyses

Continuous variables will be characterized by treatment and time-point using means and standard deviations (SD) or medians and range of values, and in case of categorical variables frequencies and percentages will be used.

Primary endpoint of the study is weight loss evaluated by %EWL (excessive weight loss, %) and groups will be compared using equivalence trial setting. For comparing groups the 90% confidence intervals (90% CI) for the difference between the study groups will be calculated in every time-point and the equivalence will be evaluated using the pre-defined margins of equivalence -9 to 9. When the data from the longer follow-up will be analyzed, repeated measurements ANOVA will be used and confounding factors will be taken into account in the analyses if needed.

In analyses of secondary outcomes associations between categorical variables will be tested using Pearson's χ^2 -test and in case of small frequencies Fisher's exact test will be used. Differences between groups in normally distributed continuous variables will be tested using independent samples t-test and in case of non-normally distributed variables Mann-Whitney U test will be used. When the data from the longer follow-up will be analyzed, repeated measurements ANOVA techniques will be used to analyze continuous variables and confounding factors will be taken into account in the analyses if needed.

Additional sub-group analyses will be performed for the data if it appears to be needed.

Two-tailed p-values will be used and p-values less than 0.05 will be considered statistically significant. The main analyses will be based on the intention-to-treat principle. Missing data will be excluded from the analyses. Statistical analyses will be performed using SAS System for Windows, Version 9.2 or later (SAS Institute Inc., Cary, NC).