

Protocol for a randomised clinical study comparing the effect of Roux-en-Y gastric bypass and sleeve gastrectomy on reactive hypoglycaemia in morbidly obese subjects

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ABSTRACT

Introduction: Roux-en-Y gastric bypass (RYGB) is the most performed bariatric operation. Reactive hypoglycaemia is a frequent late complication occurring in about 72% of RYGB patients, which can present with various intensities up to the serious form of neuroglycopenia. However, it seems to occur also after sleeve gastrectomy (SG) although much more rarely.

Methods and analysis: A single centre, open, 1-year randomised trial to compare the incidence of hypoglycaemia after RYGB or SG. A secondary objective is the assessment of the comparative ability of the two surgical procedures in determining the improvement or normalisation of insulin sensitivity, given the established relevance of insulin resistance in the cardiometabolic syndrome of obesity.

Ethics and dissemination: The study will be published and presented to international meetings and, due to the safety issue, it will represent a relevant information for national healthcare systems. *The protocol was approved by the Catholic University Ethical Committee (A1534/CE/2012).* Clinicaltrials.gov Registration n. NCT01581801.

INTRODUCTION

The overall prevalence of grade 2 and 3 adult obesity (body mass index, BMI>35 kg/m²) derived from the 2009–2010 National Health and Nutrition Examination Survey (NHANES) exceeded 15% and grade 3 obesity (BMI>40 kg/m²) accounted for 6.3%.¹ The dietary approach is of limited value in the short term and weight regain is practically the rule in the long run, as a consequence of the poor compliance to the diet shown by obese subjects. In fact, in a recent study,² where different types of diets were assigned to a population of overweight and obese subjects (BMI from 25 to 40 kg/m²), an

ARTICLE SUMMARY

Article focus

- To compare the incidence of reactive hypoglycaemia in sleeve gastrectomy with respect to Roux-en-Y gastric bypass, within 1 year after bariatric surgery.
- To assess the modifications in insulin sensitivity and secretion of these two bariatric operations.

Key messages

- Reactive hypoglycaemia is a late complication of gastric bypass, although it seems to occur also after sleeve gastrectomy. However, no study assessing the incidence of reactive hypoglycaemia after these operations is available in the literature. This randomised study aims at investigating the incidence of this complication and the changes in insulin sensitivity and secretion.

Strengths and limitations of this study

- The strength of this study is its randomised design. A limitation might be the fact that this is a short term study with 1 year time frame; however, in the secondary aim we foresee to follow the patients up to 5 years.

average of 6 kg, corresponding to 7% of initial body weight, was lost in the first 6 months, but most of the weight was regained after 1 year and at 2 years, only 31–37% of the participants had maintained a weight loss of at least 5% of their initial weight.

Bariatric surgery has long been recognised as an effective treatment for grades 3 or 2 obesity associated with complications³ and, accordingly, the number of bariatric operations in the USA is growing over time from ca. 10 000 in the early 1990s to 103 000 in 2003.⁴

Bariatric surgery may determine type 2 diabetes remission,^{5 6} while improving several other serious comorbidities.⁷ Among bariatric

surgery procedures, Roux-en-Y gastric bypass (RYGB) was shown to account for 41% of all bariatric operations at least in the USA.⁸ Sleeve gastrectomy (SG), which was originally conceived as a first step before performing RYGB or biliopancreatic diversion with duodenal switch in super-obese patients,⁹ has recently gained a place as first-choice restrictive bariatric procedure.¹⁰ It was noted that SG determines weight loss similar to that achieved after RYGB¹¹ and larger than that following laparoscopic adjustable gastric banding.^{12 13}

Reactive hypoglycaemia is a late complication of RYGB, although it seems to occur also after SG.

After RYGB, early insulin secretion is enhanced during an oral glucose tolerance test (OGTT)¹⁴ or after a meal,^{15 16} which fact might explain the later reactive hypoglycaemia. An increasing number of reports highlight the occurrence of severe hypoglycaemia after RYGB, including cases of neuroglycopenia attributed to nesidioblastosis.^{17–20} Roslin *et al*²¹ found that 72%, that is, 26 of 36 patients who underwent RYGB 6 months earlier, had reactive hypoglycaemia at 2 h during OGTT (100 g of glucose), which was defined as ‘an absolute serum glucose level ≤ 60 mg/dl, or a drop of 100 mg/dl in serum glucose level in 1 h’.

As compared with RYGB, SG seems to have a much lower occurrence of reactive hypoglycaemia, ca. 3%, that is, 1 of 31 patients studied at 6 weeks after the operation in one series.²²

Fortunately, the frequency of severe hypoglycaemia or related symptoms requiring hospitalisation after RYGB is pretty low, the adjusted HRs were in fact 2.7 for hypoglycaemia, 2.8 for confusion, 4.9 for syncope, 3.0 for epilepsy and 7.3 for seizures in a Swedish retrospective cohort study on 5040 cases based on national registries.²³

However, until now no prospective studies have investigated the incidence of hypoglycaemia after RYGB and no randomised studies have been undertaken to compare the effect of SG to that of RYGB in terms of incidence of hypoglycaemic episodes.

The primary aim of the present study was to conduct a 1-year randomised trial to compare the incidence of hypoglycaemia after RYGB or SG. A secondary objective of great interest is the assessment of the comparative ability of the two surgical procedures in determining the improvement or normalisation of insulin sensitivity in this class of subjects, given the established relevance of insulin resistance in the cardiometabolic syndrome.

STUDY OBJECTIVE

Primary objective

The primary objective of the study is to compare the incidence of reactive hypoglycaemia in SG with respect to RYGB, within 1 year after bariatric surgery.

Secondary objectives

- ▶ To quantify the relative contribution of changes in insulin sensitivity and insulin secretion during an OGTT on the glycaemic effects of bariatric surgery, and to determine if differences exist between the two surgical treatments.
- ▶ To determine whether treatment is associated with body weight, BMI and abdominal circumference loss, with body composition changes, as assessed by DEXA (dual-energy x-ray absorptiometry), and with lipid profile modifications.
- ▶ To compare between SG and RYGB the incidence of severe hypoglycaemia or related symptoms (shakiness, sweating, dizziness or light-headedness, difficulty speaking, weakness, confusion, syncope, epilepsy and seizures) within 5 years after surgery.

EXPERIMENTAL DESIGN

This is a randomised study of gastric bypass as compared with SG. Since there is no agreement and no consensus about the criteria for the selection of a certain type of bariatric operation in relation to other types, the randomisation does not have ethical implications.

The protocol was approved by the Catholic University Ethical Committee (A1534/CE/2012).

Study endpoints

Primary endpoint

The primary endpoint of the study is the incidence of reactive hypoglycaemia at 1 year after bariatric surgery.

Secondary endpoints

- ▶ Changes at 1 year in insulin sensitivity and insulin secretion during an OGTT.
- ▶ Changes at 1 year in body weight, BMI, abdominal circumference, body composition and lipid profile.
- ▶ Incidence of severe hypoglycaemia or related symptoms (shakiness, sweating, dizziness or light-headedness, difficulty speaking, weakness, confusion, syncope, epilepsy and seizures) within 5 years after surgery.

Experimental plan

This is a monocentric prospective controlled randomised clinical trial designed to investigate the difference in incidence of reactive hypoglycaemia between SG and RYGB within 1 year after surgery.

At the moment of the screening visit subjects will be randomised to undergone either SG or RYGB.

Study design diagram

The diagram of the study plan is as follows:

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screening visit (-3 months)	Baseline visit (-1 month)	Follow-up visit (+1 month)	Follow-up visit (+3 months)	Follow-up visit (+6 months)	Follow-up visit (+9 months)	Follow-up visit (+12 months)
Written informed consent	x	x					
Demographic data	x						
Medical and surgical history	x	x					
Physical examination*	x	x	x	x	x	x	x
Height	x						
Weight, BMI	x	x	x	x	x	x	x
Waist and hip circumference	x	x	x	x	x	x	x
DEXA		x		x	x	x	x
Blood pressure and HR	x	x	x	x	x	x	x
ECG	x	x	x	x	x	x	x
Laboratory assessments†	x	x	x	x	x	x	x
OGTT	x	x	x	x	x	x	x
Adverse events (AE) recording			x	x	x	x	x
Concomitant medication	x	x	x	x	x	x	x

*See box 1 related to the physical examination and DEXA.

†See table 1 related to the Laboratory assessments.

An overview of all planned blood samples, including volumes and purpose is provided in [table 1](#).

Study duration

Subjects will be studied from the time of screening visit to 1 year after the surgical procedure. The study will undergo four distinct phases:

- ▶ Screening visit (month 3)
- ▶ Baseline visit (month 1)
- ▶ A follow-up period after the surgical treatment (1 year of duration, months 1, 3, 6, 9 and 12)
- ▶ A further limited yearly follow-up period after study conclusion (4 years of duration)

Screening visit

At month 3, eligible patients will be identified and the written informed consent for enrolment will be obtained. Demographic data, anthropometric measures, physical examination variables, information about medical history and concomitant medications, as well as variables related to inclusion criteria will be collected.

Basal visit

At month 1 enrolled patients will be asked to give their informed consent to randomisation. Study compliance will be assessed during the screening and baseline periods using attendance at appointments and completion of questionnaires. Baseline anthropometric

measures, body composition, blood pressure and biochemical data (levels of fasting plasma glucose, glycated haemoglobin (HbA1c), C-peptide and serum insulin, lipid profile and OGTT) are measured.

Follow-up period

At 1 month after bariatric surgery and every 3 months until 1 year after surgery (hence at month 1, 3, 6,

Box 1 Variables recorded during the physical examination and included in DEXA

Physical examination
 Appearance in general
 Skin
 Head and neck
 Lymph nodes
 Thyroid
 Cardiovascular system
 Respiratory systems
 Abdomen
 Concomitant medication
 Other
 DEXA
 Total-body bone mineral density
 Lean body mass
 Fat mass
 Percentage of weight body fat

Table 1 Blood samples planned during the enrolment and control visits

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screening visit	Baseline visit	Follow-up visit (+1 month)	Follow-up visit (+3 months)	Follow-up visit (+6 months)	Follow-up visit (+9 months)	Follow-up visit (+12 months)
Glucose disposal and insulin secretion							
Fasting plasma glucose	x	x	x	x	x	x	x
Fasting insulin and C-peptide	x	x	x	x	x	x	x
HbA1c	x	x					x
3-h OGTT	x		x	x	x	x	x
Special							
Total cholesterol	x	x			x	x	x
HDL-cholesterol	x	x			x	x	x
Triglycerides	x	x			x	x	x
Safety		x	x				
Haematology profile	x	x	x		x	x	x
Chemistry panel	x	x	x	x	x	x	x
Serum pregnancy test*		x					
Total blood samples (ml)	80	80	80	80	800	800	80

*In female patients of childbearing potential before operation.

HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test.

9 and 12) variables collected at baseline will be recorded again, and an OGTT will be performed. AE will be recorded at each follow-up visit.

Study conclusion and further follow-up period

At the conclusion of the study, a conclusion form will be filled in. The patients will then be tracked up to 5 years after the surgical treatment, assessing lipid and carbohydrate metabolism where possible.

STUDY POPULATION

Sample size

The sample size depends on the magnitude of the difference in reactive hypoglycaemia incidence as derived from previous studies.^{21 22} The study is designed to detect a more conservative absolute difference in the occurrence of hypoglycaemia of 50%, expecting an incidence of 70% in the RYGB group versus an incidence of 20% in the SG group. A more conservative approach has been chosen, given the limited information available and the inhomogeneous diagnostic criteria used in the different studies. A sample size of 19 patients per group would be required for this clinical trial to detect a difference between treatments at a significance level of 0.05 (two-tailed) with a power of 0.90. Considering an attrition rate of approximately 25% over the course of the study, a total of 50 subjects (25 for each group) will be enrolled.

Study population

Patients will be recruited from the Obesity Outpatient Clinics and Day Hospital, Catholic University School of Medicine, Rome, Italy. The study will be subject to revision and approval by the Ethical Committee (EC) of the

above Institution, in accordance with the guidelines of the National Health Ministry and the Helsinki Declaration, as revised in 2000. All participants will provide written informed consent to participate in the study. Additional written informed consent will be obtained prior to the surgical procedure.

Inclusion criteria

Patients will be eligible if aged between 25 and 65 years included, if they have a BMI between 35 to greater than 40 kg/m² (in the presence of complications such as sleep apnoea, severe coxarthrosis or gonarthrosis, severe hypertension) and if they are able to understand and comply with the study process.

Exclusion criteria

- ▶ History of type 1 diabetes or secondary diabetes
- ▶ Previous bariatric surgery
- ▶ History of medical problems such as mental impairment
- ▶ Cancer
- ▶ Major cardiovascular disease: severe heart valve disease; heart failure; myocardial infarction; endocarditis; atrial fibrillation or flutter; third-degree block
- ▶ Major gastrointestinal disease: liver cirrhosis; inflammatory bowel disease; severe hiatal hernia
- ▶ Major respiratory disease: pulmonary embolism; pulmonary fibrosis; severe chronic respiratory failure
- ▶ Hormonal disorders: pheochromocytoma; Addison's disease; Cushing; Conn's syndrome; Graves's disease; pituitary adenoma with mass effect symptoms or secreting pituitary adenoma
- ▶ Infections: HIV; tuberculosis; acute infections

- ▶ History of drug addiction and/or alcohol abuse
- ▶ Internal malignancy
- ▶ Pregnancy
- ▶ Impaired glucose tolerance or type 2 diabetes mellitus
- ▶ Suspected or confirmed poor compliance
- ▶ Lack of informed consent
- ▶ Participants will be excluded if they did not attend at least two initial information visits

TREATMENT

Surgical program

Within 1 month of randomisation the patients will undergo RYGB or SG.

Roux-en-Y gastric bypass

This laparoscopic operation includes the division of the stomach in two parts. A proximal, smaller pouch (20–25 ml), is connected to the rest of the gastrointestinal tract through a gastro-jejunal anastomosis, whereas the distal gastric pouch is left behind, but excluded, from the transit of food.

An entero-entero anastomosis, with a Roux-en-Y type of reconstruction, allows the bile and pancreatic juices to mix with the nutrients at about 100–150 cm from the gastro-jejunal connection.

Sleeve gastrectomy

Laparoscopic SG involves a longitudinal resection of the stomach on the greater curvature from the antrum starting opposite of the nerve of Latarjet up to the angle of His. The final gastric volume is about 100 ml.

Randomisation process

Automatic dynamic allocation of the treatment to the patients will be performed via a web-based software. The randomisation procedure via the internet is an automatic and flexible mechanism that on one hand guarantees random allocation and on the other reduces imbalance with respect to the two treatment groups over the two considered stratification factors: gender and age (18–40 and 40–60 years). The procedure may be accessed from any web-connected computer; it clears the user for data access (user id/password); it requires the user to specify the screening number of the subject about to be randomised; it verifies inclusion/exclusion criteria and acquires stratification information; it finally assigns the subject to a treatment, and delivers the corresponding unique randomisation number. The procedure optimises the overall balance of treatments among each stratification cell. The allocation algorithm will be verified by the statistician responsible for the study, who will have continuing access to the randomisation statistics throughout the duration of the study.

Criteria for discontinuation and/or withdrawal

- ▶ Withdrawal of informed consent
- ▶ Subject uncooperative

- ▶ Safety reasons as judged by principal investigator
- ▶ Non-compliance to the protocol
- ▶ Incorrect enrolment
- ▶ Subjects who could not be operated laparoscopically
- ▶ Conditions requiring medication that could interfere with the outcome of the study, except for those for intercurrent illnesses or adjustment of antihypertensive therapy, as judged by the principal investigator
- ▶ Subjects with severe complications due to surgery, as judged by the principal investigator
- ▶ Bleeding related to surgery that makes it impossible to draw blood samples

Subjects may be discontinued from the study at any time, at the discretion of the investigator. Subjects are free to discontinue their participation in the study at any time. Subjects who discontinue from the study should always be asked about the reason(s) for the discontinuation. If possible, they should always be seen and assessed by an investigator. AE will be followed up according to Italian Health Ministry guidelines.

If a subject discontinues participation in the study, then her/his enrolment number cannot be issued to another subject.

EFFICACY EVALUATION

To evaluate the effect of the SG versus the RYGB on glycaemic control the following parameters will be considered.

Primary endpoint

Primary endpoint: incidence of reactive hypoglycaemia at 1 year after bariatric surgery. According to the American Diabetes Association, a ‘true’ hypoglycaemic episode is defined as a plasma glucose value <3.9 mmol/l with or without accompanying symptoms. This cut-off will be used after either an OGTT or a glucose profile.

Secondary endpoints

- ▶ Changes at 1 year of insulin sensitivity and insulin secretion during an OGTT
- ▶ Changes at 1 year of body weight, BMI, abdominal circumference, body composition and lipid profile
- ▶ Incidence of severe hypoglycaemia or related symptoms (shakiness, sweating, dizziness or light-headedness, confusion, difficulty in speaking, weakness, syncope, epilepsy and seizures) assessed by questionnaire and blood glucose measurement (glucometer) or medical report within 5 years after surgery

Evaluation methods and timing

During the experimental study the following clinical evaluations will be performed:

- A. Demographic data (month 3)
 - ▶ Date of birth
 - ▶ Gender
 - ▶ Ethnicity

- B. Medical and surgical history (month 3, month 1)
- C. Anthropometric measurements (month 3, month 1, months 1, 3, 6, 9 and 12)
- ▶ Body weight (will be measured to the nearest 0.1 kg on a balanced beam scale in the morning before breakfast after a visit to the lavatory, with the subjects in their underwear).
 - ▶ Height (will be measured to the nearest 0.5 cm using a stadiometer)
 - ▶ Waist circumference (will be measured at the part of the trunk midway between the most caudal part of the lateral costal arch and the iliac crest in the morning before breakfast, after lavatory, visit with the person standing with feet about 25–30 cm apart. The measurer will stand beside the individual and fit the tape snugly, without compressing any underlying soft tissues. The circumference will be measured to the nearest 0.5 cm, at the end of a normal expiration).
 - ▶ Hip circumference (will be measured as the maximal circumference over the buttocks)
 - ▶ BMI (will be computed as weight (kg)/height (m²))
- D. Physical examination (month 3, month 1, months 1, 3, 6, 9 and 12)
- ▶ General appearance
 - ▶ Skin
 - ▶ Head and neck
 - ▶ Lymph nodes
 - ▶ Thyroid
 - ▶ Cardiovascular system
 - ▶ Respiratory system
 - ▶ Abdomen
 - ▶ Other
- E. Cardiovascular parameters (month 3, month 1, months 1, 3, 6, 9 and 12)
- ▶ Blood pressure
 - ▶ Heart rate
 - ▶ (blood pressure and heart rate will be measured in sitting position in duplicate after 15 min rest)
 - ▶ ECG (recorded under resting conditions. It will be performed according to standard routine at bariatric surgery)
- F. Biochemical analysis (month 3, month 1, months 1, 3, 6, 9 and 12)
- ▶ Fasting plasma glucose
 - ▶ Fasting plasma insulin
 - ▶ Fasting plasma C-peptide
 - ▶ HbA1c
 - ▶ Total cholesterol
 - ▶ High-density lipoprotein cholesterol
 - ▶ Triglycerides
 - ▶ Haematology profile
 - ▶ Chemistry panel
- G. OGTT (month 3, month 1, months 1, 3, 6, 9 and 12)
- At 8:00–9:00 h, after a 12 h overnight fast, an intravenous catheter is placed in one antecubital vein to draw blood samples. A 75 g of oral glucose bolus is administered in 10 min maximum and blood

samples are obtained at –20, –5, 5, 10, 20, 30, 40, 60, 80, 100, 120, 140, 160 and 180 min relative to the administration of the bolus. Samples are placed in heparinised tubes, and plasma is separated within 20 min and stored at –70°C.

- H. The patients will be asked to monitor their blood glucose by a seven-point glucose profile (ie, before and 2 h after breakfast, lunch and dinner plus one control before bedding) randomly performed once a week.

Analytical methods

Plasma glucose will be measured by the glucose-oxidase method (Beckman, Fullerton, California, USA). Plasma insulin will be assayed by microparticle-enzyme immunoassay (Abbott, Pasadena, California, USA) with a sensitivity of 1 µU/ml and an intra-assay CV of 6.6%.

C-peptide will be assayed by radioimmunoassay (MYRIA; Technogenetics, Milan, Italy): minimal detectable concentration=17 pmol/l and interassay and intra-assay CVs of 3.3–5.7% and 4.6–5.3%, respectively.

Mathematical modelling

Empirical indices of insulin sensitivity²⁴ and secretion (AUC_I/AUC_G (area under the curve) ratio) will be computed. Glucose and insulin concentrations will be fitted by the oral glucose minimal model after the OGTT. Insulin secretion will also be computed via a deconvolution approach on C-peptide measurements.

- A. DEXA variables (month 1, months 6, 9 and 12)

- ▶ Body composition will be measured by DEXA (Lunar Prodigy), which provides results on total and regional (trunk, arms, legs, pelvis) fat mass, fat-free mass and bone mass. The following will be recorded:
 - ▶ Total body bone mineral density
 - ▶ Lean body mass
 - ▶ Fat mass
 - ▶ Percent weight body fat

- B. Concomitant medications (month 3, month 1, months 1, 3, 6, 9 and 12)

SAFETY AND TOLERANCE EVALUATION AND ASSESSMENT

The safety of the surgical procedures will be evaluated at the end of the study, analysing all the information recorded in the Case Report Form (CRF) designed for the study, according to the timing and modalities described in other sections of the present protocol.

Information to assess safety will include: objective exam, patient's symptoms related to the operation, occurrence of AE.

Safety parameters

Adverse events

The clinical tolerability will be evaluated by recording the occurrence of AE as reported by the patient or observed by the medical investigator. Any AE occurring after surgery will have to be recorded in the CRF.

Definitions

An AE) is any untoward medical occurrence in a patient or clinical investigation subject undergoing a treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal product, or related to the surgical procedure. Preexisting events, which increase in frequency or severity, or change in nature during or as a consequence of use of a drug in human clinical trials, will also be considered AEs.

A serious adverse event (SAE) is defined as any AE regardless of causality that

- ▶ Leads to death.
- ▶ Leads to a serious deterioration in the health of the subject that
 - results in life-threatening illness or injury,
 - results in permanent impairment of a body structure or a body function,
 - requires inpatient hospitalisation or prolongation of existing hospitalisation.
- ▶ Results in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.
- ▶ Leads to fatal distress or death.

Adverse event reporting procedures

If the investigator identifies the occurrence of an AE or SAE, the corresponding report form must be completed and transmitted to the coordinating investigator within 24 h. The form will be part of the study documentation. Any fatal or life-threatening event should be reported immediately to the coordinating investigator: this preliminary report will be followed within 24 h by detailed documentation including the completed SAE form, copies of hospital case reports, autopsy reports and other documents, when requested and applicable.

Minimal information contained in the AE/SAE report form should include:

- ▶ Identification of the subject or patient
- ▶ Type of surgical treatment
- ▶ An identifiable reporting source
- ▶ All related AE
- ▶ All medications used

Follow-up of SAEs that occur during the study will continue until satisfactory resolution or stabilisation, as judged by the investigator. The coordinating investigator may request that certain AE be followed until resolution.

If and when supplementary information is available, a follow-up SAE Report Form must be completed by the investigator and delivered within 24 h to the coordinating investigator.

The coordinating investigator must inform the Ethics Committee if the serious AE is likely to affect the safety of the subjects or the conduct of the study.

Moreover, it will be the responsibility of the coordinating investigator to inform in writing all clinical

investigators about all serious AE occurring during the study. This information shall be sent to the clinical investigators based on perceived risk.

DIRECT ACCESS TO ORIGINAL DOCUMENTATION

The investigator will allow the national Regulatory Authority, and the staff possibly indicated by the EC or by coordinating investigator, direct access to the complete original documentation, including informed consent and the clinical records or outpatient registers. People who have direct access to this documentation will have to take all reasonable precautions to avoid disclosure of the patient identity and of all information which is the property of the coordinating investigator, in compliance with applicable laws.

QUALITY ASSURANCE PROCEDURES

The organisation, monitoring and quality assurance of the present study will be under the responsibility of the coordinating investigator.

Clinical monitoring

The clinical monitoring will be carried out by qualified persons assigned by the coordinating investigator and will be conducted according to the guidelines of the ICH GCP. In addition, the monitoring activities will include the verification of the correct completion of the CRFs and, when applicable, the consistency between source documents and stored electronic data are used for the randomisation procedures. The coordinating investigator will ensure the practical training for the personnel involved in the study.

Data review and audits

Data review and audits will be carried out by qualified persons assigned by the coordinating investigator.

The CRFs will be tracked and periodically updated.

Moreover, audit visits to Hospital wards may be planned in order to verify that:

- ▶ Compliance with the protocol is maintained
- ▶ Any deviation from the protocol are discussed with the coordinating investigators and documented
- ▶ Study staff and facilities are qualified to conduct the study safely and effectively
- ▶ Informed consent forms have been obtained
- ▶ The procedures for recording and reporting AE are followed
- ▶ EC approvals have been obtained and protocol amendment notifications have been carried out
- ▶ Randomisation procedures have been followed
- ▶ Subject withdrawals have been documented and discussed with the coordinating investigator

The audit is a check of the study activities and documentation aimed at verifying if the study activities have been conducted and the data have been recorded and transmitted in accordance with the protocol, with the GCPs, with institutional SOPs and with applicable laws.

Audit visit reports will be produced and communicated to the study investigators and to the ec.

CRF structure

For the investigator three main phases will be foreseen: enrolment of a new patient (at the screening visit), randomisation procedure (at the basal visit), further data insertion of a randomised patient's data (at the follow-up visits). For the first and third phase a standard paper CRF will be completed. The randomisation procedure will be carried out by means of an electronic procedure.

- ▶ Enrolment of a new patient. In this phase preliminary information will have to be recorded (such as patient screening number, gender, age, date of admission, concomitant medications and the presence of risk factors) in order to assess the eligibility of the patient and to include her/him in the study protocol. Each time an investigator will admit a new patient a consecutive screening number will be assigned.
- ▶ Randomisation procedure. After the patient's demographic and basal characteristics have been collected, a randomisation procedure will be performed by an electronic system according to the procedure described above. After entering the patient screening number and the information needed for stratification, the treatment will be randomly assigned by the system.
- ▶ Data recording. The investigators will record all subjects' study data in a paper CRF identified with that patient's screening number.

All necessary documentation containing the instructions for the web access and for the electronic randomisation procedure will be provided to the investigators prior to the beginning of the study.

Data management

The verification of the experimental data will be made according to the following procedure:

- ▶ The monitor will verify the correct and complete transcription of the experimental data in the CRF and will verify the correspondence with the source documents in the Experimental Centre;
- ▶ If necessary, queries will be generated, and changes and/or comments will be required of the investigators.

STATISTICAL ANALYSIS

Study populations

There are two analysis populations, which will be used in evaluating treatment differences: *intent-to-treat* (ITT) (which coincides with the *safety-analysable population*) and the *efficacy-evaluable* (*completer-complier* or *per-protocol*, EE).

The ITT population consists of all randomised patients.

The EE population consists of all patients who completed the study, that is, all patients where the primary endpoint was measured.

Efficacy analysis

Primary efficacy analysis

The primary analysis will test if the SG surgical treatment determines a lower incidence of reactive hypoglycaemia than the RYGB surgical treatment. The analysis will be performed by means of Fisher's exact test. The type I error will be set at 0.05 (two-tailed).

Secondary efficacy analyses

The statistical analyses on the secondary endpoints will have an explorative character, so, for each analysis, the type I error will be set to the nominal level of 0.05.

All the categorical variables (binary or with more than two modalities) will be analysed by means of a χ^2 test or a Fisher exact test when appropriate. For continuous variables relative δ s will be computed (as difference between values at 1 year and values at baseline, over basal values) and will be analysed by means of a t test for independent samples or an equivalent non-parametric test as appropriate. Differences between groups and trends over time will be analysed by means of an analysis of variance for repeated measurements.

Safety and tolerability analysis

All patients who undergo the surgical treatment will be included in the safety analysis. Safety analyses will include tabulation of type and frequency of any recorded AE. Between-group differences in the proportion of patients reporting an AE will be analysed using Fisher's exact test whereas all continuous safety laboratory evaluations will be summarised using descriptive statistics, and relative δ s will be computed as above. Relative δ s will be analysed by means of the Mann-Whitney U test or the t test as appropriate.

ETHICAL ASPECTS

All the involved parts in the study agree and will verify that the experimental study is conducted in compliance with ethical principles originating from the Helsinki Declaration, with the guidelines of Good Clinical Practice (GCP) and with applicable laws.

Ethical authorisations

The coordinating investigator has the responsibility of submitting the present clinical protocol to the local EC for approval, before enrolling patients. The coordinating investigator will have to provide the EC with all necessary documents for obtaining approval.

Informed consent

Before the start of the study, the Informed Consent forms to be provided to the patients will be submitted to the EC for examination and approval, along with the

protocol. The signed Informed Consent will be obtained after having informed the patient of all aspects of the trial as reported in the guidelines of the GCP.

ADMINISTRATIVE PROCEDURES

Changes in the study conduction or in the planned analyses

Each change in the conduction of the study is defined 'Amendment to the Clinical Protocol'. This term is referred to any change brought to the experimental protocol after the EC has given its final approval.

Amendments to the protocol are changes of a legal document which has a binding value and therefore must be approved in writing and signed in two copies by the same signatories of the protocol.

All amendments to the protocol must be submitted to the assessment of the EC who approved the study protocol, before being applied.

The coordinating investigator has the responsibility of submitting the amendment to the EC in order to obtain an approval in writing. The approval will be delivered and kept with the same modalities as the study protocol.

When changes are referred only to administrative or logistic aspects of the study, the related amendment must simply be notified to the EC.

It must be considered that whenever the amendment significantly alters the study design or the potential risks to which patients are exposed, each patient will have to be informed and will have to put down in writing her/his intention to continue the study. An appropriate form will be prepared by the coordinating investigator and will be approved by the EC.

Study suspension/interruption

Complete suspension of the study

The coordinating investigator will have the power of suspending/interrupting the study whenever:

The rate of patient enrolment will be shown to be ineffective:

- ▶ The clinical investigators do not respect the requirements of the study, particularly where the evaluation of the patient inclusion/exclusion criteria is concerned.
- ▶ The Experimental Centre is not capable of meeting the requirements specified in the guidelines of GCP (GCP-ICH DM n. 162 del 15/07/97):

The coordinating investigator will inform the EC of the early interruption of the study, justifying the decision made.

Suspension of the study by the EC

The study can also be suspended by the EC. A detailed explanation in writing of the conclusion or suspension of the study will be provided.

Archiving

The coordinating investigator is responsible for the conservation of the study documents in compliance with applicable laws. The coordinating investigator will take all measures necessary to avoid accidental or early document destruction.

Confidentiality

Individual subject medical information, obtained as a result of this study, is considered confidential and disclosure to third parties is prohibited. Such medical information may be given to the subject's physician or to other appropriate medical staff responsible for the subject's well-being.

Financing of the study

No financial aspects must be taken into account because no funding is foreseen for the present study.

RESPONSIBILITY OF THE INVESTIGATOR

The investigators are responsible towards the coordinating investigator for all actions carried out by their staff involved in the conduction of the study. Except when specifically required, the term 'investigator' used in this protocol and in the CRF is referred to the investigator or to a qualified person designed by him/her to carry out all the activities related to the clinical trial and to sign in his/her stead the study documents. The investigator must be responsible for the safety and well-being of the human subjects involved in the clinical investigation and must conduct the study in compliance with the study protocol, and with the Helsinki Declaration (1964) and subsequent revisions.

FINAL REPORT OF THE STUDY

Within 3 months from the end of the study, a Study Final Clinical Report, including the clinical comments based on the results of the statistical analysis, will be drafted by the coordinating investigator and/or by a delegated person.

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