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STUDY PROTOCOL

Study Title: **GASTRIC MYOELECTRICAL ACTIVITY WITH WATER LOAD SATIETY TEST AS A PREDICTOR OF INDIVIDUAL SUCCESSFUL RESPONSE TO TREATMENT BY VARIOUS BARIATRIC PROCEDURES**

Promoted by GETTEMO-SEED

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Summary

Background: Total body weight loss (TBWL) after Bariatric Endoscopy (BE) is variable. Gastric emptying may be normal, rapid or delayed in patients with obesity and be a factor in variable BE outcomes. Gastric myoelectrical activity (GMA) reflects gastric pacemaker activity which controls gastric contractions. The non-invasive electrogastrogram (EGG) uses standard electrodes positioned on the abdominal surface to record GMA. There is currently a lack of studies in a population with obesity utilizing EGG to determine GMA patterns. We postulate that GMA patterns recorded with EGG will reflect subgroups in regards to stomach electrical physiology in obesity and that these subgroups will be useful in selecting patients for various BE procedures to maximize success of the procedures.

Hypothesis: We postulate that GMA patterns recorded with Pre-intervention EGG can predict clinical success and adverse events after bariatric interventions.

1.- INTRODUCTION

1.1. Severe obesity as a health problem

Obesity, defined as a body mass index (BMI) of 30 kg/m2, is increasing worldwide at alarming rates and is a cause of comorbidity and death. Nearly 2.8 million people die each year from obesity and being overweight according to the World Health *Organization.* In developed countries, the prevalence is more than 25%, with a high load of chronic comorbidities (hypertension, diabetes, atherogenic dyslipidemia, sleep apnea syndrome, hepatic steatosis, osteoarthritis, cancer, etc. *(1)*.

In Europe it is known by the European Association for the Study of Obesity (EASO) that, in the last decade, in countries such as Spain 30% of its children population (7-11 years) was obese and that there was, respectively, a prevalence of overweight of more than 39% and 15% in adults between 25 and 60 years. This year the prevalence of overweight could amount to > 70% of the population and that of obesity, to > 40 and it is worst after the lockdown because of covid-19 pandemic. Adulthood obesity prevalence forecasts (2010–2030) predict that in 2020, 27% of men and 19% of women will be obese. By 2030, the model predicts that 36% of men and 21% of women will be obese *(1)*. In addition, it is severe and morbid obesity that grows proportionately the most (with prevalence > 5-10 % of the population) and the costs of this disease have a cost of almost 10% of the total health budget in the European Union. Thus, the socio-health impact is greater since medical treatments, based on lifestyle changes, are less effective. In this scenario, bariatric techniques (endoscopic or surgical), at present is the only effective long-term treatment that can offer significant weight loss (> 15-20%) and a parallel reduction in associated comorbidities *(2)*.

More than 135 million individuals are obese in India. The prevalence of obesity and central obesity varies from 11.8% to 31.3% and 16.9% to 36.3% respectively.(36) The prevalence of obesity is higher among the urban population, higher socioeconomic status, and south India.(35)

In addition to preventing the development of obesity it is necessary to individualize therapies for each obese patient by selecting the most appropriate BE treatment, based on

gastric physiology as described below, in order to increase the likelihood of successful total body weight loss (TBWL) and maintenance.

1.2. Bariatric Techniques:-

Bariatric techniques can be divided into three categories: restrictive, malabsorptive and mixed. In the first one, the procedures can be surgical or endoscopic. Malabsorptive techniques act on gastric capacity and perform complex anatomical short circuits that aim to reduce body weight significantly in very obese patients (BMI < 45 kg/m2), at the expense of producing a "controlled malabsorption" picture of nutrients, vitamins and minerals. Gastric bypass has been the "gold-standard" technique in bariatric surgery for decades, due to its long-term efficacy and it combines a restrictive procedure with another maldigestive, allowing average weight loss of around 30%, without side effects of intestinal malabsorption.

As a restrictive bariatric surgery technique, sleeve gastrectomy is the procedure of choice today, which due to its relatively low technical difficulty and results close to those of gastric bypass, is displacing other surgical techniques at the international level. worldwide Technically, a gastric tubular reservoir is created guided by a Fouchet orogastric tube calibrated at 42 Fr (14 mm), sectioning the greater gastric curvature from 6 cm proximal to the pylorus to the bottom. In this way the gastric volume is reduced by approximately 70-80%. This technique allows full maintenance of gastric functions, gastric emptying through the pylorus and without the need to act on the absorption of nutrients at the intestinal level.

According to 2019 data from the International Federation for the Surgery of Obesity (IFSO), SG is the preferred technique used in Europe (43%), compared to gastric bypass (35%), which came in second place. In Spain, gastric bypass continues to occupy first place (43%), compared to GV (34%), followed by biliopancreatic diversions (13.6%), mini-gastric bypass (6.2%), gastric band adjustable (1.1%) and gastric plication (0.9%). As for India in the year 2014, the percentage distribution of different procedures performed was 68% for LSG, 16% for LRYGB, and 14% for MGB-OAGB. In 2018, 48% of the procedures performed were LSG, while MGB-OAGB and LRYGB were at 34% and 15%, respectively.(37)

Bariatric endoscopy (BE) techniques have emerged as safe and effective treatment that include restrictive endoscopic techniques: Intragastric balloons (IGB), endoscopic sleeve gastroplasty (ESG), primary surgery obesity endoluminal (POSE) or Endo-Sleeve (GESP or POSE 2.0) procedures; malabsorptive techniques: endoluminal bypass (endobarrier), duodenal mucosa resurfacing; extraction methods (Aspire); electrical stimulation: gastric pacemaker, vagal blockage and other procedures including botulinum toxin, magnetic compression anastomosis or the novel endozip *(2, 3, 4,5,6).*

1.3. Gastric motility, electrogastrography, weight control and bariatric techniques

Total body weight loss (TBWL) in response to these therapies is variable. The pathophysiological mechanisms involved behind bariatric techniques go beyond restrictive capacity and malabsorption secondary to anatomical changes caused by different therapeutic procedures that help explain the improvement of metabolic disorders (diabetes, insulin resistance, dyslipidemia, improvement of hepatic steatosis, etc.). even before weight loss has been clearly evident with cambios in the secretion and regulation profile of gastrointestinal hormones, bile acids, pro-inflammatory cytokine pattern, immune capacity, intestinal microbiota, etc *(7)*.
The combination of hormonal and gastric electrophysiological changes due to weight loss has physiological significance in light of the association between obesity and accelerated gastric emptying (GE) and the fact that GE delay of solids is an important determinant of fullness and satiety in humans *(8)*.

The stomach is a complex neuromuscular organ that receives, mixes and empties ingested food. The neuromuscular work of the stomach is coordinated by the gastric pacemaker which controls the frequency and propagation of gastric peristaltic waves. For normal emptying of liquids and solids from the stomach into the duodenum integrated coordination of corpus-antral-pyloric contractions are required.

There are neurogenic factors (parasympathetic afferents -efferents, intrinsic gastric pacemaker function), hormonal and biochemical factors (cholecystite, gamma-aminobutyric acid, ghrelin, etc.), all of which have feedback mechanisms that affect gastric motility. There are also anatomical factors such as structural alterations or inflammatory conditions that affect motility and here is remarkable the role of interstitial cells of Cajal (ICCs). ICCs are the pacemaker cells and interface between enteric nerves and smooth muscle cells and the key to gastric motility. ICCs create the rhythmic 3 cpm electrical conduction system that coordinates the three per minute gastric peristaltic waves that results in normal gastric emptying *(9)*.

Variable weight loss and intolerance of BE procedures are appreciated. For this protocole we define Failure of BE methods when patient only obtain less than 25% of EWL after 6 months of BE, according to the Part 1 of the BAROS (Bariatric Analysis and Reporting Outcome System) scale adapted to endoscopic treatment *(2)* (Table 1).

After BIG placement, patients present intolerance such vomit and abdominal pain in 70-90% of cases at the first week but these effects can be extended up to three weeks (18%) and removal of the balloon in 4% of patients *(3)*. Gastric emptying measured by gastric scintigraphy breath test or stable isotope breath tests show that there are physiological predictors of intolerance and response to BIG placement *(10)*. Many studies show that patients after ESG at 6 months achieved a mean of 50% of EWL or more with rate of severe adverse events around 2% , including pain or nausea requiring hospitalization, upper gastrointestinal bleeding and peri-gastric leak or fluid collection *(11)*.
After SEG……

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Table 1 . BAROS (BARIATRIC ANALYSIS AND REPORTING OUTCOME SYSTEM) ADAPTED TO BARIATRIC ENDOSCOPY

1. Percentage of excess weight loss (%EWL):
   (Initial weight – Current weight) / (Initial weight – Ideal weight) x 100
   (-1): Weight gain
   (0): Weight loss 0-24%
   (+1): Weight loss 25-49%
   (+2): Weight loss 50-74%
   (+3): Weight loss > 75%
2. Comorbidity:
   (-1): Aggravated
   (0): Unchanged
   (+1): Improved (unresolved)
   (+2): Improved: one major resolved, others improved
   (+3): Improved: all majors resolved, others improved
3. Quality of life questionnaire:
   (much worse, worse, unchanged, better, much better)
   Self-esteem (scale -1, -0.5, 0, +0.5, +1)
   Physical (scale -0.5, -0.25, 0, +0.25, +0.5)
   Social (scale -0.5, -0.25, 0, +0.25, +0.5)
   Work (scale -0.5, -0.25, 0, +0.25, +0.5)
   Sex (scale -0.5, -0.25, 0, +0.25, +0.5)
4. Complications:
   (-0.2): Per minor complication
   (-1): Per major complication
   (-1): In case of repeat endoscopy or surgery

Final score (sum total of above 4 items)

- No comorbidities:
  Failure: 0 or less
  Fair: 0-1.5
  Good: 1.5-3
  Very good: 3-4.5
  Excellent: 4.5-6
- Comorbidities:
  Failure: < 1
  Fair: 1-3
  Good: 3-5
  Very good: 5-7
  Excellent: 7-9

Thus, a fuller understanding of gastric physiology before undertaking BE treatments may lead to better patient selection for each procedure.

An important aspect of gastric emptying and physiology is GMA which reflects the gastric pacemaker activity that coordinates gastric peristaltic contractions. The GMA is measured with electrogastrography methods that will be used in this study.

Electrogastrography is a non-invasive method of recording GMA that is used to diagnose gastric dysrhythmias in patients with intractable chronic nausea and vomiting, gastroparesis and gastroesophageal reflux *(15,16,17)*. Electrogastrography signals are recorded using standard EKG-type electrodes placed on the surface of the upper stomach. 3CPM Company developed the first patented, non-invasive FDA-approved diagnostic device that records and displays the EGG signal and provides analysis of the GMA signal for clinical diagnosis.

Gastric dysrhythmias (tachygastria, 3.7 to 10 cpm, bradygastria, 1.0-2.5 cpm) and mixed dysrhythmias (combinations of tachygastria and bradygastria) are recorded with electrogastrography *(17,18,19)*. In addition, patients with gastroparesis may have normal (2.5 to 3.7 cpm) or hypernormal GMA. These patients have antro-pyloro-duodenal

outflow dysfunction and respond well to endoscopic or surgical therapies *(20)*. The pattern(s) of GMA in response to the WLST in obese patients who will undergo BE procedures is unknown. In addition, the volume of water ingested in 5 minutes during the WLST indicates gastric capacity or accommodation which may be an important variable in patient selection for BE. Finally, in patients with functional dyspepsia or gastroparesis, symptoms induced by the WLST include nausea, fullness, bloating and pain and and are scored on a VAS. These symptoms, if elicited in the obese patients, may also represent an important variable for patient selection *(21, 22, 23)*.

The position of the electrodes on the upper abdominal surface, skin preparation and test meals influence the GMA recordings. Interestingly, neither age nor sex has a definitive impact on the parameters for in adults or children *(24, 25, 26)*.

Controversial findings on the correlation between EGG and GE have been reported in the literature. Different authors have said that a normal 3 cpm GMA may not predict normal GE and dysrhythmic GMA may be present in delayed GE but is also present in functional dyspepsia. Patients with delayed GE and abnormal EGG have more severe symptoms and more tachygastria in pre and post-prandial states than patients with normal *GE*. 80% of the non-obese population has normal EGG and 20% have variability *(27 28, 29, 30)*. There is only one preliminar study of GMA with WLST before BE techniques in obesity (31), but has not been studied in before and after BE procedures to determine subtypes of GMA and whether or not subtypes will predict successful bariatric outcomes.

Therefore, we propose a study to evaluate the GMA in response to the WLST in patients who have agreed to BE procedures. We hypothesize that GMA patterns in response to the WLST, the volume of water ingested and the array of symptoms elicited will help to predict successful outcomes of the bariatric procedures and thus help with patient selection for these procedures.

2.- WORKING HYPOTHESIS

Weight loss and long-term maintenance may be conditioned by changes in GMA, as well as by anatomical modifications induced by the bariatric procedure.

Since anatomical modifications of the stomach by the BE procedures are related to weight loss, our purpose is to determine whether different procedures to reduce gastric capacity will result in substantial changes in GMA and in the water load volume ingested. No studies that have studied obese population before and after such BE procedures are available.
Therefore, an important question is whether obese patients have the GMA that is similar to those with functional dyspepsia and normal weight *(32)*. Also, the usefulness of electrogastrography as a new tool to customize choice of Bariatric therapies by determining success or failure based on GMA and WLST results has not been studied. GMA measures the normal or depleted gastric ICCs and the WLST measures gastric capacity, objective measures that may be important to predict success of Bariatric procedures and thus to help with patient selection to maximize efficacy and minimize side effects *(32)*.

Hypothesis Question: Pre-intervention EGG can predict clinical success and adverse events after bariatric interventions?.

Demonstrate the usefulness of EGG meizuring the GMA by identifying subtypes with the Water Load Satiety Test (WLST) in obese adults to predict individual successful responses to BE treatments: Intragastric Balloon (IGB) placement and Apollo Endoscopic Sleeve Gastroplasty (ESG) method.
Demonstrate the usefulness of EGG meizuring the GMA by identifying subtypes with the Water Load Satiety Test (WLST) in obese adults to predict individual successful responses to BE treatments: Intragastric Balloon (IGB) placement and Apollo Endoscopic Sleeve Gastroplasty (ESG) method

3.- OBJECTIVES

3.1.- Primary Objective –

. Pre-intervention EGG parameters and/or changes in EGG parameters (one/three months) after bariatric intervention can predict clinical success at the end the of follow up

a. Pre-intervention EGG parameters and/or changes in EGG parameters after the bariatric intervention can predict adverse events at the end of follow-up.

3.2. Secondary:

a. Secondary Objective
   To predict suitable bariatric intervention for patients depending upon a pre-intervention EGG.
b. EGG is a feasible diagnostic tool in obese population with reproducible and predictible results

4.- STUDY DESIGN AND METHODOLOGY

4.1. Type of study: Multicenter,prospective, observational study in patients with body mass index (BMI) at 30 kg/m2 prior and after one, and three, six and 12 months of an bariatric procedure. All tests will be analyzed by one blinded specialist.

4.2. Study design: This is a pilot study, involving 2 hospitals in Spain and India, , where 4 groups of patients will be recruited.

a) Group of 50 patients who will undergo BIG placement

b) Group of 50 patients who will undergo Endoscopic Sleeve Gastroplasty (ESG) Apollo method.

c) Group of 50 patients who will undergo Surgical Sleeve Gastrectomy (SEG) Apollo method

d) Group of 50 patients who will undergo RYGB method

The protocol will be carried out in the run-up to the BE procedure until 12 months after of follow up. As a control group, 50 people (of the same age and gender) will be selected, with BMI less than 25% who voluntarily agree to participate in the protocol and have the same criteria of inclusion or exclusion of patients that belongs to all the groups, except BMI.

Duration – 18 months to 24 months

4.3. Characteristics of subjects:

Voluntary patients with obesity will be recruited among those patients who will be given any of the four types of bariatric procedures described above, at the time before and after the first, third, sixth and 12 months of performing the bariatric methods. Patients will be recruited in AIG Hospitals, Gachibowli, Hyderabad

Inclusion criteria:

1. Men and women, aged between 18-65 yrs
2. IMC basal ≥ 30 kg/m^2
3. Patient undergoing bariatric intervention willing to participate in the study
4. Informed consent (oral and written) for the tests to be carried out.

Exclusion criteria:

1. Presence of severe cardiac, renal, hepatic, or neurological disease
2. Long term use of medication that alter gastric motility (> 4 weeks)
3. Significant alcohol or opioids or narcotics or tobacco
4. Active malignancy
5. Pregnancy
6. Uncontrolled Diabetes Mellitus with glycosylated hemoglobin (HbA1c) levels ≥ 6.5% or glucose level more than 270 mg/dL.
7. Uncontrolled hypothyroidism (High TSH with low levels of Free T4)

4.4. Collection of data and variables to be studied

Anamnesis: Collection of clinical data in the medical history: history of obesity, evolution of weight, associated comorbidities, personal and family history. Dietary history.

Anthropometric data: Weight, size, waist circumference, BMI.

Electrogastrography data: clínical diagnosis, percentage distribution, ratios

4.5. EGG registration

Instruments: The 3CPM electrogastrography device will be used to record GMA before and after the WLST to record GMA. 3CPM EGGSAS GMAT Threshold software will be used for signal analysis. The data will be collected prospectively in a virtual log for blind analysis. (Figure 1)

Figure 1

On the morning of the EGG and water load satiety test, the subject will arrive fasting after midnight. Participants may take their usual medications (e.g antihypertensive medications) with a small amount of water (up to 4 oz) up to two hours prior to the study, but should refrain from coffee, tea, or juice.

At home, the skin of the abdomen should be shaved before for better placement of the electrodes. The typical recording process usually takes a total of 1 hour: A 15 minutes baseline recording, 5 minutes of ingestion of water until "completely full, and a 30 min post-ingestion recording.

Electrogastrographic signals are recorded from electrodes placed in the midline midway between the xiphoid appendage and the umbilicus. The other electrodes are placed in the left and right upper quadrant, respectively, from a straight line from the midpoint of the clavicle and a point 2-3 cm below the left and right -costal border. The belt to record respiration rate is placed above nipples of the chest level and is firmly fixed.

Patients should be seated in a comfortable chair, reclining at about 30-45 degrees and will remain motion-free throughout the test (Fig.2.3).

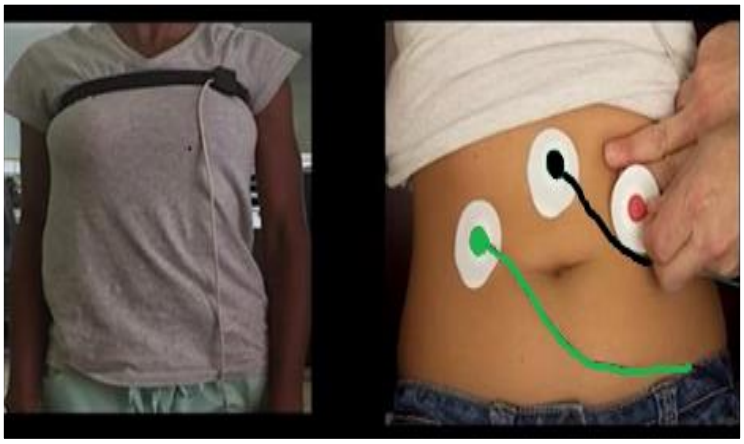


Figure 2

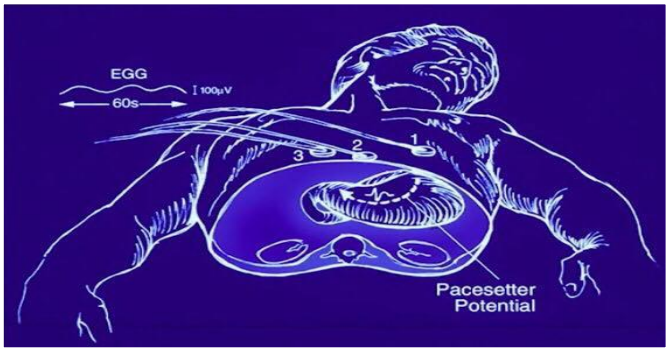


Figure 3

A 15 min baseline EGG recording is obtained and then the WLST is given.

Water at from a tap is placed into a 1-liter container from which the patient will drink as directed below. The patient must be given the following instruction about the WLST in precisely the words below:

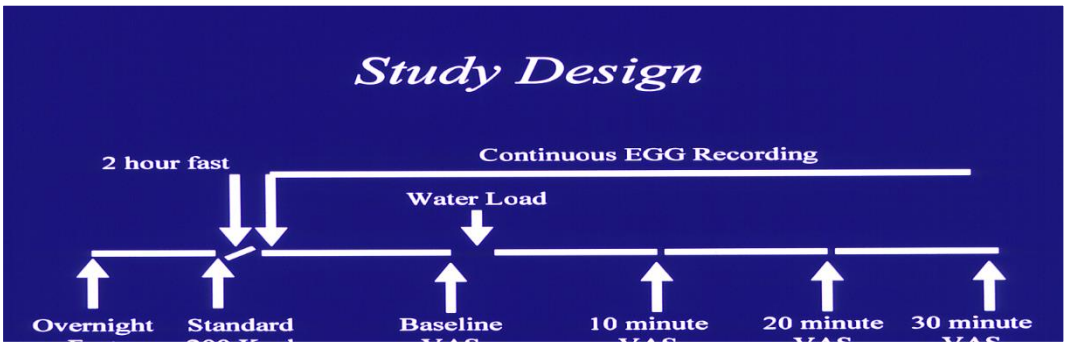
Diabetic participants' blood glucose level should be checked to ensure it is less than 270 mg/dL. If the participant's blood glucose level is greater than 270 mg/dL, it is either treated and rechecked before proceeding or the EGG and water load satiety test will be rescheduled for another day under better glucose control.

Baseline symptoms prior to EGG recording are obtained using 100 mm visual analog scales (VAS) for stomach fullness, hunger, nausea, bloating, and abdominal discomfort. The patient marks each symptom line with a vertical line to indicate how they currently feel in terms of that symptom. Once the EGG and respiratory signals are stable, the baseline EGG recording period can begin.

After the 15 min baseline EGG recording is completeds the participants will begin the Water Load Satiety Test. For this, participants will sit upright. During the test, participants

will drink cool water from the 1 liter container (Figure 4). They will drink for a 5-minute period only and until they feel "completely full."

Figure 4



A continuous 30 minute EGG recording is then obtained after the water is consumed. The participant's symptoms are recorded using VAS at 10, 20, and 30 minutes after ingestion of the water (at the end of the 0-10 minute, 11-20 minute, and the 21-30 minute periods after the water load ingestion) (Figure 5). The test is completed after the 30-minute recording period and the electrodes are removed).

Figure 5.- Water Load Stress Test and Visual Analogue Scale

It is important that the research associate at each site gives each subject the very same instructions as follows:

"I want you to drink water from this container until you feel completely full. You have up to five minutes to reach the feeling of completely full. You may stop at any time, up to the five-minute time limit, when you feel completely full. This is not a test to see how much you can drink, but to drink until you are completely full in the five minute period. Do you have any questions about this?"

The total volume of water consumed will be recorded.

4.7. EGG signal analysis

EGG signal is reviewed for movement artifacts. Artifact – free minutes are chosen for blinded computer analysis (at baseline, three, six and 12 months recordings and for each type of BE procedure). The selected minutes of EGG are analyzed by spectral analysis

by computer applications. 3CPM EGGSAS GMAT Threshold software will be used for signal analysis. EGG data will be organized by clinical diagnosis. Water load volumes ingested that are <238 ml are considered abnormally low *(33*).

5.- STATISTIC

The normal distribution of the variables will be confirmed by the kolmogorov-Smirnoff test. Quantitative variables shall be expressed as mean s/e d or means (interquartile range). Comparison between groups will be performed by parametric or nonparametric tests, depending on the distribution of the variables. Spearman or Pearson correlation will be used for the study of correlations. The possibility of multivariate logistic regression analysis will be explored. An SPSS statistical programme will be used. EGG data will descriptive in terms of overall clinical EGG diagnosis and normal or abnormal water load volume ingested. Symptom data before and after the WLST will be tabulated. These measures will be calculated before and 3 and 6 months after the BE procedures.

6.- STUDY LIMITATIONS

Recruitment of the number of subjects should not be a problem due to the high number of patients performed in the different centers and will allow the selection of those with the most approximate clinical results between groups.

A strength of the study is to have a control group of non-obese subjects, which will allow us to know the normal pattern of GMA in response to the WLST and whether it is similar to those worldwide reported in healthy individuals.

All tests will be carried out by the same expert operator in the medical center and analyzed by one specialist in EGG that received the blinded information from all the centers because it is a multicenter study, but the bariatric procedures will be performed by different operators from every center.

7.- STAGES OF DEVELOPMENT AND DISTRIBUTION OF THE AREAS OF ALL RESEARCH EQUIPMENT

The clinical study will be conducted simultaneously in AIG hospitals, Hyderabad,India. and Gastrodex, Dexeus University Hospital center in Spain. The task layout of the study team members will be as follows:

Eduardo Espinet-Coll (Coordinator of Digestive and Bariatric Endoscopy Unit at Gastrodex, Dexeus University Hospital)

Director General and Coordinator of the study at the Dexeus Hospital, patient monitoring and responsible for performing BE techniques (IGB, endoscopic gastroplasty), dta analysis and participation in the drafting of research articles.

Carmen Bautista-Altamirano (Gastroenterologist, researcher. Digestive and Bariatric Endoscopy Unit at Gastrodex, Dexeus University Hospital Medical university)

General Coordinator: Responsible for Inter-hospital coordination and supervision of patients selection, compliance with patient indications, water-load stimulation test, data collection, monitoring, coordination of EGG registration. Blinded interpretation of results, participation in the drafting of research articles.

Rakesh Kalapala (Director of Endoscopy, Bariatric and Metabolic Therapy at AIG Hospitals India).

Principal Investigator of the study at AIG Hospitals India, patient recruitment, responsible for performing BE techniques (IGB, endoscopic gastroplasty) and participation in the drafting of research articles.

Nitin Jagtap (Senior Consultant Interventional Endoscopy at Asian Institute at Gastroenterology, India)

Co- Investigator of the study at Asian Institute of gastroenterology India, patient recruitment, responsible for performing Bariatric techniques (IGB, ESG, SEG) and participation in the drafting of research articles.

Neeraj Singla (Senior Consultant, Interventional Endoscopy and GI motility at AIG Hospitals, India)

Co- Investigator of the study at AIG Hospitals India Medical center, patient recruitment, responsible for performing bariatric techniques (IGB, ESG and SEG) and participation in the drafting of research articles.

David Mark Noar (Gastroenterologist at John Hopkins University Hospital Maryland, USA)

Supplier of 3CPM electrogastrography and 3CPM EGGSAS GMAT Threshold software. Responsible for validating the blinded Interpretation results of EGG studies.

Ajit Kolatkar (Director, GastroLab India Pvt Ltd, India)

Co-ordinator and Supplier of 3CPM electrogastrography and 3CPM EGGSAS GMAT Threshold software. Responsible for validation and blinded Interpretation results of EGG studies.

8.- STUDY EXECUTION TIME

Considering that this is a prospective study with a predetermined number of non-high subjects, an execution time - from the baseline EGG, at three and six months post-procedure - is foreseen or approximately 18 months after the approval of the Ethics Committees Corresponding. In another 3 months, statistical analysis, interpretation of results and writing of the manuscript will be carried out.

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