STUDY PROTOCOL

(Investigator initiated study)

Study Title:

TO STUDY THE ELECTROGASTROGRAPHY (EGG) ABNORMALITIES IN HEALTHY SUBJECTS AND IN PATIENT'S WITH IDIOPATHIC AND DIABETIC GASTROPARESIS: A PROSPECTIVE SINGLE CENTER STUDY

1.0 TITLE PAGE

Protocol No:	
Product Name:	NA
Type of Study:	Investigator Initiated study
Date:	June 25, 2022
Principal Investigator:	Dr. Rakesh Kalapala Consultant Gastroenterologist & Therapeutic Endoscopist, Director - Endoscopy (Center for Obesity & Metabolic Therapy) Email: drrakesh.kalapala@aighospitals.com
Investigator:	Dr Neeraj Singla

- **INTRODUCTION**

Electrogastrogram (EGG) is a non-invasive method for recording myoelectric activities by placing electrodes on the abdomen surface (1). Many studies suggested EGG measures the gastric slow wave frequency effectively; the relative change in EGG signal amplitude would reflect the contractility of the stomach. Thus, this technique is used to study the pathophysiological processes of diseases such as functional dyspepsia and many more (2).

The present study aims to study the EGG pattern in healthy individuals in Indian population and the factors associated with it.

- **RATIONALE**

EGG is an authentic method to detect gastrointestinal diseases accompanied by gastric motility abnormalities (3). The present study would help to determine the normatic values of EGG in healthy population and EGG changes in patients with idiopathic gastroparesis. This pilot study would provide findings/abnormalities seen in study population and may be helpful in providing a comparative data for proper treatment and a better quality of life patients suffering from dyspepsia.

4.0 STUDY OBJECTIVES

4.1 Primary Objective

- To study the EGG abnormalities in healthy subjects and in patients with Diabetic and Idiopathic Gastroparesis

4.2 Secondary Objective

- To study factors associated with abnormalities noted in EGG

➢ **Primary Endpoint**

- Number and percentages of various EGG abnormalities like Dysrhythmias, Bradygastria/ Tachygastria, and delayed gastric emptying.

➢ **Secondary Endpoints**

- Measuring association of factors (disease characteristics, co-morbidity etc.) with abnormal gastric myoelectrical activity like EGG dominant frequency (DF) and other EGG abnormalities

- Number and proportion of subjects with adverse events (AEs) and serious adverse events (SAEs) if any post procedure
- Number and proportion of subjects with Abnormal laboratory parameters

● INVESTIGATIONAL PLAN

5.1 Eligibility Criteria

5.1.1 Inclusion Criteria

Subjects must meet the following criteria to be included in the study:

Healthy subjects

- 20 Males and 20 females subjects atleast one will be taken from each group [18-20,20-30,30-40,40-50,50-60,60-70years]
- Absence of previous upper gastrointestinal surgery anytime in past.
- Absence of drugs which affect the upper gastrointestinal system in 3 months.
- Absence of diabetes,thyroid disorder or neuromuscular disorder.
- Subject who has read the informed consent form, has understood the relevant aspects of the study, and grants his/her authorization to participate by signing the informed consent form before the inclusion in the study and the performance of any procedure
- Subject willing to use appropriate method of contraception as per investigator's discretion, throughout the study

Idiopathic Gastroparesis

- Male and female subjects above 18 to 70 years of age.
- Subject who has read the informed consent form, has understood the relevant aspects of the study, and grants his/her authorization to participate by signing the informed consent form before the inclusion in the study and the performance of any procedure
- Subject willing to use appropriate method of contraception as per investigator's discretion, throughout the study
- Patient's having symptoms of dyspepsia based on ROME IV Criteria and not having a known cause of gastroparesis like endocrine, neurological, rheumatological disorder.

➢ ROME IV criteria for Functional Dyspepsia* (Diagnostic criteria**): One or more of the following

- Bothersome postprandial fullness
- Bothersome early satiation
- Bothersome epigastric pain
- Bothersome epigastric burning
- AND
- No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms
- *Must fulfill criteria for Postprandial Distress Syndrome (PDS) and/or Epigastric Pain Syndrome (EPS)
- **Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Diabetic Gastroparesis

- Male and female subjects above 18 to 70 years of age.
- Subject who has read the informed consent form, has understood the relevant aspects of the study, and grants his/her authorization to participate by signing the informed consent form before the inclusion in the study and the performance of any procedure
- Subject willing to use appropriate method of contraception as per investigator's discretion, throughout the study
- Patient's having symptoms of dyspepsia based on ROME IV Criteria and Diabetes mellitus of any duration.

5.1.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

A. For Idiopathic Gastroparesis

1.Subjects suffering from Diabetes

2. Subjects with history of any bariatric procedures/ gastric surgeries in the past

3.Females who are pregnant

4.Subjects taking following medications within 72 hours to the start of the study: Opioids, TCA, Calcium channel blockers, anti-psychotics, anti-cholinergic, steroids, L-Dopa

5.Subjects with electrolyte abnormalities like hypokalaemia, hypomagnesemia

6.Subjects with known cases of thyroid disorder (hypo or hyperthyroidism)

7.Subjects who are unsuitable for any other reason to participate in the study in the opinion of the investigator

B. For Diabetic Gastroparesis

1. Subjects with history of any bariatric procedures/ gastric surgeries in the past

2..Females who are pregnant

3.Subjects taking following medications within 72 hours to the start of the study: Opioids, TCA, Calcium channel blockers, anti-psychotics, anti-cholinergic, steroids, L-Dopa

4.Subjects with electrolyte abnormalities like hypokalaemia, hypomagnesemia

5.Subjects with known cases of thyroid disorder (hypo or hyperthyroidism)

6.Subjects who are unsuitable for any other reason to participate in the study in the opinion of the investigator.

5.2 Number of Subjects to be Enrolled

40 healthy subjects, 50 subjects with Idiopathic Gastroparesis and 50 subjects with Diabetic Gastroparesis who meet eligibility criteria will be recruited from the clinic.

5.3 Study Duration

The total duration of subject recruitment in study will be 3 Months and total duration of study completion including data analysis will approximately be 6 months.

5.4 Study Conduct

- For Healthy Controls- Subjects with no previous medical history (healthy volunteers) will be assessed for eligibility criteria.
- For Idiopathic Gastroparesis- Patients with symptoms of Gastroparesis based on ROME IV criteria and not having a known cause of gastroparesis like endocrine, neurological, rheumatological disorder.
- For Diabetic Gastroparesis- Patients with symptoms of Gastroparesis based on ROME IV criteria and Diabetes mellitus of any duration.
- There is no follow up visit.
- Eligible subjects will be offered enrolment into the study. After written informed consent is obtained, subjects will assess with EGG. Subjects will be monitored throughout the study procedure for any adverse events. Study will be conducted in compliance with ICH guidelines and Good clinical practice.

5.5 Investigational Study Procedure

All the eligible subjects will undergo study procedure i.e. EGG. The study procedure will conduct as per standard study protocol. EGG is a non-invasive, painless method for the measurement of gastric myoelectrical activity. EGG takes around two hours to complete the procedure and no side effects reported. Following steps are included in the procedure

- Subject lie on back on a procedure table.
- Investigator or technician tapes electrodes to Subject's abdomen (belly). The electrodes are similar to those used for other tests, such as an ECG (electrocardiogram). The electrodes measure electrical signals coming from stomach muscles. They send the signals to a computer that records the signals as a graph.
- Investigator or technician records a test while Subject's stomach is empty. An hour later, Subject have something to eat and drink. Investigator or technician then records a second test. The test and electrodes are painless.
- The electrodes are removed. EGG test is completed at this point.

5.6 Description of Study Activities

After IEC approval, Subject will be approached. Subjects who willingly agree to participate in the study will be offered enrolment in this study. All Subjects will be required to sign an informed consent form detailing protocol procedures, possible risks and benefits. After written informed consent is obtained, Subjects will be screened for inclusion and exclusion criteria. Subjects who meet the eligibility criteria will be recruited to undergo study procedures (EGG).

Study Visit

Subjects who have signed written Informed Consent Form after a full explanation about the participation in this study and after meeting the eligibility criteria, the following study assessments will be performed at this visit:

- Assignment of subject ID number
- Recording of prior personal/medical/surgical history
- Recording of prior medication history
- Collection of demographic data, including age, gender
- Weight, height, and body mass index (BMI)
- Waist to hip ratio
- Family history
- Recording of concomitant medication
- Laboratory investigations (including haematology and biochemistry parameters: CBP, Serum electrolytes (serum potassium, magnesium, calcium), Lipid profile, Thyroid profile, FBS, PLBS, HbA1C, ESR, CRP)
- Physical examination
- Vital signs
- If any discomfort or if any AE/SAE recording

5.7 Study Procedure Discontinuation

A Subject will be discontinued or withdrawn from study procedure under the following circumstances:

- If the attending physician thinks a subject is not co—operative or suitable for the study procedure and not to continue with the procedure is in the best interest of the subject
- If Subject wants to withdraw from the study

5.8 Withdrawal Criteria

Subjects will have the right to withdraw consent from the study at any time and for any reason without prejudice to his/her future medical care by the investigator. Withdrawal of consent means that the Subject does not wish to or is unable to continue further study participation and thereby, willingly decides to discontinue from any further study procedures. The investigator will discuss with the Subject the most appropriate way to withdraw from the study to ensure the Subject's health and safety.

In case of premature withdrawal, the reason for procedure discontinuation will be recorded in the CRF and End of the study procedures will be performed. The reasons for premature withdrawal may include:

- Withdrawal of consent
- Per investigator's discretion, continuation in the study will be detrimental to the Subject's well-being
- Significant protocol deviation
- Subject non-compliance to study procedures
- AE or SAEs
- Use of prohibited medications

5.9 End of study

Subjects will be considered off study if any of the following occur:

- Termination of the study
- Withdrawal of consent (Subject will not be contacted and no further information will be collected). If the Subject withdraws consent, then no additional data will be collected without his/her explicit consent; all data collected prior to withdrawal of consent may be used in the data analysis.
- Death

5.10 Visit Schedule and Evaluations

Study Procedures	**Single Visit**
	V1

	Day 1
Assignment of subject ID number	✓
Informed consent	✓
Inclusion/exclusion criteria	✓
Prior medical/surgical history	✓
Prior medication history	✓
Demographics	✓
Body weight (kg)	✓
Height (cm)	✓
Body mass index [a]	✓
Medication	✓
Laboratory (biochemistry and hematology) investigations [b]	✓
Physical examination	✓
Vital signs [c]	✓
Adverse events / serious adverse events	✓
EGG procedure and Overall compliance check of study procedure	✓

[a]BMI will be calculated as (weight in kg)/(height × height in m^2).

[b]All the laboratory investigations will be done in the local laboratory.

[c]Vital signs, including pulse rate (beats/minute), BP (SBP and DBP) measurement (mmHg); will be recorded in supine position after 5 minutes of rest.

Prior and Concomitant medications

Each subject will be questioned on use of concomitant and prohibited medications.

Prohibited Medications include: Opioids, TCA, Calcium channel blockers, anti-psychotics, anticholinergic, steroids, L-Dopa

5.11. Study Evaluations

EGG findings as procedure report (pattern of gastric myoelectric activity) will be analyzed for abnormalities reported for participating subjects

The clinical severity of gastroparesis will be ranked as:-

Grade 1: Mild gastroparesis (mild symptoms relatively controlled)

Grade 2: Compensated gastroparesis (symptoms only partially controlled with medications)

Grade 3: Refractory gastroparesis (refractory symptoms that are not controlled).

- AEs will be collected and evaluated for their relatedness to study procedure, severity, seriousness, and outcome
- Vital signs (after 5 minutes of rest in supine position)
- Pulse rate (beats/minute)
- BP (mm Hg) (systolic BP and diastolic BP)
- Physical examination
- Nervous system
- Respiratory system
- Cardiovascular system
- Abdomen
- Head-eyes-ear-nose-throat
- Musculoskeletal system
- Genitourinary system

Others, as applicable

- Following clinical laboratory tests will be performed or anything additional as per investigator discretion
- Hematology
- Complete blood count/picture (hemoglobin, hematocrit, red blood cell counts, white blood cells, including differential counts, HbA1c and platelets)
- Biochemistry parameters
- Serum electrolytes (serum potassium, magnesium, calcium)
- Lipid Profile
- Fasting blood sugar (FBS)
- Thyroid Profile
- PLBS
- ESR
- CRP

6.0 PHARMACOVIGILANCE RELEVANT INFORMATION

6.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject under clinical investigation after administration of a study procedure. The AE does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease, temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal product.

All AE and relevant abnormal laboratory findings (serious/non-serious, expected/unexpected, related/non-related), whether previously known or unknown, will be recorded in the Case Report Form. All SAEs

should be recorded in the Appendix XI of Schedule Y with clear description, severity, action taken, duration, outcome and opinion about causal relationship to study procedure.

All AE will be assessed for severity:

Mild: Symptom barely noticeable to subject; does not influence performance or functioning; prescription drug not normally needed for relief of symptom but may be given because of personality of subject.

Moderate: Symptom of sufficient severity to make the subject uncomfortable; performance of daily activities influenced; subject is able to continue in the study; treatment for the symptom may be needed.

Severe: Symptom causes severe discomfort; may be of such severity that the subject cannot continue; severity may cause cessation of treatment with Investigational product (IP); treatment of the symptom may be given and/or the subject hospitalized.

6.2. Serious Adverse Event

A SAE is defined as an AE that:

- Results in death
- Is life-threatening*
- Requires in-subject hospitalization or prolongation of an existing hospitalization**
- Results in a persistent or significant disability or incapacity***
- Results in a congenital anomaly or birth defect
- Required intervention to prevent permanent impairment or damage
- Does not fit the other outcomes, but the SAE may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

6.3 Recording of Adverse Events

Investigator should record all AE on the AE form of the CRF. All SAEs will be recorded on the third Schedule of New Drugs and Clinical Trials Rules, 2019.9.1.5 Reporting safety information to IEC

The Investigator is responsible for complying with all applicable local regulations with respect to the documentation, assessment, and reporting of safety data, including but not limited to the submission of expedited and periodic reports to concerned regulators and Ethics Committees.

7.0 ETHICS AND QUALITY

7.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB) Review

The IEC will review the ethical, scientific and medical appropriateness of the study before it is conducted. The final study protocol, including the final version of the Written Informed Consent Form, must be approved or given a favorable opinion in writing by an IEC. Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study.

The principal investigator is responsible for informing the IEC of any amendment to the protocol. In addition, the IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IEC annually, as local regulations require.

Progress reports and notifications of serious unexpected adverse events will be provided to the IEC according to local regulations and guidelines.

7.2 Ethics Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

7.3 Written Informed Consent

The investigator will ensure the Subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The Subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The investigator must store the original, signed Written Informed Consent Form. A copy of the signed Written Informed Consent Form must be given to the Subject.

7.4 Subject Confidentiality

Subject confidentiality will be maintained at all times. All information generated as part of the study (subject's medical records) will be kept confidential by the participating site Investigators and respective research team. The data and information will not be used by the Investigators, Co Investigators, etc. for any purpose other than conducting the study.

7.5 Registration of the Study

The study will be registered on clinical trial registry (Link: www.ctri.nic.in)

8. DATA HANDLING AND RECORD KEEPING

8.1 Case Report Forms

A case report form (CRF) is required and must be completed for each included subject. The completed dataset is the sole property of the investigator and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities

Subject data will be collected using defined paper CRF's. A unique identifier will be given to each subject enrolled. Personal identifiers such as name, address and date of birth that can be linked back to subjects will be kept confidential with access restricted to the investigator and the site team.

8.2 Record Retention

To enable evaluations and/or audits from Health Authorities or third parties, the investigator must agree to keep records, including the identity of all participating subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all CRF's, and detailed records of EGG procedure as per local regulatory requirements.

8.3 Data Processing

Completed CRFs will be then analyzed by the study data management center. Subsequently, multilevel review process will be initiated to validate the data. Data will be entered in a format that is suitable for analysis.

9. STATISTICAL ANALYSIS PLAN

9.1 Sample size calculation

Approximately 40 healthy subjects and 50 subjects with Idiopathic Gastroparesis will be enrolled in the study. If they are willing to participate in this study, they will be offered enrolment and written informed consent will be taken. No formal sample size calculations done for the study.

9.2 Analysis plan

The process of data quality check, along with query resolution, will be carried out. Post data lock approval, data analysis, table-listing-graph (TLG) will be prepared. Descriptive and summary statistics will be calculated to gain a general perspective of the data. The primary and secondary outcome measures will be summarized as N, Mean, SD, Median/percentile, Min and Max as per applicability. For the Gastroparesis Cardinal Symptom index (GCSI) scores, best fit summary statistics will be reported for overall scale. Student t-test/Chi-square/ Wilcoxon signed-rank tests test will be used to measure significant change across various groups at the 5% level of significance, if necessary. Statistical analyses will be carried out using IBM SPSS statistics software version 20 and Microsoft excel.

10 FINAL REPORT AND PUBLICATION

10.1. Publication

The data generated from this study would be compiled in a final study report, in collaboration with the principal Investigator. The Investigator will provide a final report to the IEC/IRB following the conclusion of the study.

Researchers will have no access to subject's identifiers. Individual results will not be reported to anyone, not directly involved in this research other than for regulatory purposes. Aggregated information from this study may be used in scientific publications or presented at medical conventions. Information will be published or presented only in a way that does not identify any individual subjects.

11 REFERENCES

12 Riezzo G, Russo F, Indrio F. Electrogastrography in Adults and Children: The Strength, Pitfalls, and Clinical Significance of the Cutaneous Recording of the Gastric Electrical Activity. BioMed Research International. 2013 May 25;2013:e282757.

13 Chacón M, Curilem G, Acuña G, Defilippi C, Madrid AM, Jara S. Detection of subjects with functional dyspepsia using wavelet transform applied to their electrogastrogram. Braz J Med Biol Res. 2009;8.

14 Qi HB, Luo JY, Zhu YL, Wang XQ. Gastric myoelectrical activity and gastric emptying in diabetic subjects with dyspeptic symptoms. World J Gastroenterol. 2002 Feb 15;8(1):180–2.

15 Al Kafee A, Akan A. Analysis of gastric myoelectrical activity from the electrogastrogram signals based on wavelet transform and line length feature. Proc Inst Mech Eng H. 2018 Apr 1;232(4):403–11.