A prospective, randomized, double-blind, placebo-controlled trial of the effects of magnesium sulfate on postoperative esophageal spasm-associated pain following peroral endoscopic myotomy

Protocol Number
58859

Clinicaltrials.gov Number
04638881

Version 1.0

Date
International date format: 12 November 2020

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Study Product: *Magnesium Sulfate*

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List of Abbreviations

ESQ – Esophageal symptoms questionnaire
NMDA - N-methyl-D-aspartate
POEM - Peroral endoscopic myotomy
SHC – Stanford Hospital & Clinics

Study Summary

Title	A prospective, randomized, double-blind, placebo-controlled trial of the effects of magnesium sulfate on postoperative esophageal spasm-associated pain following peroral endoscopic myotomy
Short Title	MgPOEM
Protocol Number	58859
Methodology	Randomized, double-blind, placebo-controlled prospective trial
Study Duration	2 years
Study Center(s)	Single-center
Objectives	This study hypothesizes that among patients having peroral endoscopic myotomy, intraoperative magnesium sulfate infusion will reduce the severity of postoperative pain while decreasing perioperative opioid requirements.
Number of Subjects	100
Diagnosis and Main Inclusion Criteria	Diagnosis: Esophageal motility disorder, including achalasia Main Inclusion Criteria: Patient undergoing peroral endoscopic myotomy
Study Product, Dose, Route, Regimen	Magnesium sulfate. 50 mg/kg (based on lean body weight) intravenous over 15 minutes at start of mucosal incision, followed by 25 mg/kg/hr infusion that is turned off at patient extubation
Duration of administration	Only limited to surgery duration, from start of mucosal incision to patient extubation
Reference therapy	Reference is placebo (normal saline)
Statistical Methodology	Chi-square test to compare primary outcome (postoperative pain) Chi-square test, Fisher's exact test, or Mann-Whitney U test to compare secondary outcomes (intraoperative opioid usage, postoperative opioid usage, pain at 24 hours, esophageal symptoms questionnaire results)

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Since its initial description in 2010, POEM has been suggested to be a safe and effective surgery for achalasia and other esophageal motility disorders.1,2 Compared to patients who undergo the traditional laparoscopic Heller myotomy, patients managed with POEM experience shorter procedure times, longer myotomies, lower adverse events, and improved functional outcomes.3 However, postoperative retrosternal pain and regurgitation due to residual carbon dioxide and/or increased intraoperative esophageal exposure to gastric acid remain common. Dual innervation of the esophagus by vagal and spinal afferent fibers is present along the entire length of the esophagus, accounting for patients' reports of vague discomforts and localized retrosternal sensations, respectively.4 Pain management has largely been based on opioids, which may contribute to worsened symptoms associated with achalasia.5 Postoperatively, most patients typically experience mild to moderate pain requiring modest doses of opioids.6

1.2 Investigational Agent

We recently published a case report on opioid-free anesthesia for POEM surgery utilizing magnesium not only for its analgesic,7 but also antispasmodic properties.8,9 Magnesium has been recognized as an antinociceptive agent since 1916, but its mechanism of action remains poorly elucidated. Two of its functions were considered for this anesthetic plan. First, magnesium is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that can decrease visceral hyperalgesia.7 Second, magnesium induces smooth muscle relaxation by decreasing intracellular calcium concentrations in both smooth muscle and the adrenal gland, the latter causing a decrease in circulating catecholamines.10 Magnesium has been well characterized in obstetrical management of preeclampsia.8. The antispasmodic potential of magnesium was recently studied in the context of bladder surgery, where intraoperative magnesium administration was associated with decreased catheter-related bladder discomfort and improved patient satisfaction.9 In POEM procedures, insufflation with carbon dioxide for visualization can lead to postoperative subcutaneous or mediastinal emphysema. Residual carbon dioxide along the esophagus can also lead to referred pain that translates as postoperative esophageal spasm and regurgitation. Magnesium may adequately relax esophageal smooth muscle and desensitize afferent nerve endings to decrease these symptoms. In other words, the mechanisms underlying magnesium provide a physiologically and anatomically targeted therapy for esophageal pain.

1.3 Preclinical Data

None

1.4 Clinical Data to Date

Magnesium has been extensively studied for its nonopioid analgesic properties across multiple different types of surgeries and procedures in the anesthesia literature.11 Its smooth muscle relaxant properties have been also documented in the context of preeclampsia management in obstetrics.12 We also recently published a case report that highlighted the role of magnesium in decreasing postoperative pain specific to esophageal spasms and reflux.13

1.5 Dose Rationale and Risk/Benefits

The magnesium bolus dosing of 50 mg/kg emulates the dose used in a recent urologic study that explored the effect of magnesium to decrease bladder catheter-associated discomfort.9 Furthermore, this bolus dose and the infusion rate are the most frequently reported dose/rate in a meta-analysis of 20 randomized controlled trials.12 The aforementioned meta-analysis found no major adverse events associated with magnesium toxicity, whilst finding a statistically and clinically significant decrease in postoperative pain. The medication is administered intravenously as part of the intraoperative anesthetic regimen. The POEM surgery lasts on average 1 to 2 hours, which is the maximum duration of the magnesium infusion. This will limit the risk of magnesium toxicity. Hence, the study will be safely investigating a nonopioid analgesic that has been shown to be efficacious in similar populations undergoing a diverse range of surgeries, with the hope of clarifying the antispasmodic potential of magnesium.

2 Study Objectives

Primary Objective
To assess the efficacy of magnesium sulfate on decreasing esophageal spasm-associated pain as measured by subjective pain scores and the esophageal symptoms questionnaire score.14

Secondary Objective
To assess the efficacy of magnesium sulfate on decreasing intraoperative opioid usage.
To assess the efficacy of magnesium sulfate on decreasing postoperative opioid consumption.
To assess the efficacy of magnesium sulfate on decreasing discharge opioid prescription.
To assess the efficacy of magnesium sulfate on decreasing postoperative pain as measured by the esophageal symptoms questionnaire score at 24 hours.

3 Study Design

3.1 General Design

- Prospective randomized, double-blind, placebo-controlled trial
- Expected duration of subject participation: 2 days

3.2 Primary Study Endpoints

This study will evaluate the efficacy of magnesium sulfate on decreasing esophageal spasm-associated pain as measured by subjective pain scores and the esophageal symptoms questionnaire score.

3.3 Secondary Study Endpoints

This study will assess the efficacy of magnesium sulfate on decreasing intraoperative opioid usage, postoperative opioid consumption, discharge opioid prescription, and on decreasing postoperative pain as measured by the esophageal symptoms questionnaire score at 24 hours.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

i) Ages 18 and over
ii) Subjects capable of giving informed consent, or have an acceptable surrogate capable of giving consent on the subject's behalf
iii) Planned peroral endoscopic myotomy

4.2 Exclusion Criteria

i) cannot give consent
ii) patients who are clinically unstable and/or require urgent/emergent intervention
iii) previous esophageal myotomy
iv) preexisting hypermagnesemia
v) end-stage renal disease
vi) neuromuscular disease, including but not limited to Guillain-Barre syndrome, myasthenia gravis, congenital myopathy, and muscular dystrophy
vii) preexisting heart failure
viii) severe ventricular systolic dysfunction (left or right ventricle)

4.3 Subject Recruitment and Screening

No patient health information will be collected prior to enrollment. When possible, the primary endoscopist/surgeon or other health care provider(e.g. nurse practitioner, nursing staff) will inform eligible participants of the study. If the patient expresses interest they will be approached by research study personnel. If they decline they will not receive any further information about the study. In cases where it is not feasible for an endoscopist to inform the patients of the study, or the patient has not yet met the endoscopist, a research personnel will screen for eligibility using chart review. Eligible patients will be approached about the study if history review reveals a potential candidate for the study. If the family expresses interest, the research personnel will proceed with consent and protocol. If patient decline interest, we will respect their decision and will not pursue the family any further for this study. Participants will be asked if they are participating in other studies. They will be allowed to participate in more than one study if it can be determined that this poses no increased risk to the participants or the integrity of the data collected for either study.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Patients will be informed that they may withdraw from the study at any time, for any reason, with no consequences for withdrawing, and the standard clinical care and procedures will continue as normal.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

All data will be de-identified and stored in Stanford-secured encrypted devices, only accessible to research personnel. For withdrawn subjects, we will attempt to seek permission for magnesium levels drawn during the defined follow-up period (postoperative days 0 and 1). This is related to the safety profile of the study drug. Otherwise, all other data related to the withdrawn subject will be destroyed, and no further follow-up information will be collected.

5 Study Drug

5.1 Description

Magnesium sulfate is the second most plentiful electrolyte in human intracellular fluids. It has NMDA antagonist and smooth muscle relaxant properties. The medication will appear as magnesium sulfate USP 50%, a sterile, concentrated solution of magnesium sulfate in water. In the vial, each milliliter contains 500 mg magnesium sulfate heptahydrate.

5.2 Treatment Regimen

A loading dose of 50 mg/kg (based on lean body weight) will be administered intravenously over 15 minutes at start of mucosal incision, followed by 25 mg/kg/hr infusion intravenously that is turned off at patient extubation. The expected treatment duration is 1 to 2 hours.

5.3 Method for Assigning Subjects to Treatment Groups

Randomization codes will be generated using web-based randomization software (RStudio) with block sizes of four and an allocation ratio of 1:1 for either intravenous magnesium sulfate (magnesium group) or intravenous normal saline as control (control group). These randomization codes will be enclosed in sequentially numbered, identical, opaque, and sealed envelopes. They will be kept in a closed box during the entire study period. The envelopes will be provided in sequence to the anesthesia team.

5.4 Preparation and Administration of Study Drug

The anesthesia team will prepare the study treatment based on the instructions within the envelope. Specifically, the anesthesia team will be instructed to draw up 10 g (20 ml) of the study drug within a 20 ml syringe, or to draw up 20 ml of normal saline within a 20 ml syringe. Although both medications are colorless and transparent, and thus are indistinguishable to the endoscopist, the syringes will be labeled as “study” to minimize drug error during the intraoperative anesthetic management. These medications will be administered using a syringe pump (Alaris; Becton, Dickinson and Company, New Jersey, USA) available in all SHC operating rooms. Instructions to manually program the syringe pump will be provided. Specifically, the anesthesia team will be instructed to enter 10 g of the study drug in 20 ml of volume, and to enter the patient’s lean body weight. The team will enter the infusion rate as 25 mg/kg/hr, and save these settings.

When the endoscopist announces that she/he will start the mucosal incision, the syringe pump will be programmed to bolus 50 mg/kg over 15 minutes. After the bolus is administered, the syringe pump will default to the infusion rate of 25 mg/kg/hr. The anesthesia team will stop the infusion at extubation.

5.5 Subject Compliance Monitoring

The anesthesia team will be documenting the drugs in the intraoperative anesthesia medication record. The research staff will review the records to ensure compliance with administration of the study drug. There is no compliance monitoring necessary for the study participant as they will not be administering the drug to or by themselves.

5.6 Prior and Concomitant Therapy

Information on their preoperative medications will be collected, including use of multivitamins, herbal supplements, or magnesium-containing supplements, and use of acid-reducing medications such as H2-receptor antagonists or proton pump inhibitors.
During the study, the patients will be expected to receive standard anesthetic care including hypnotics, narcotics, neuromuscular blockers (e.g. succinylcholine/rocuronium), antiemetics, vasopressors, antihypertensives, and anesthetics as needed at the anesthesia team's discretion.
In the rare case of magnesium toxicity, all healthcare providers will have access to calcium chloride/gluconate therapy to reverse the cardiorespiratory and musculoskeletal effects.

5.7 Packaging

As described above, the magnesium sulfate is packaged in 2 ml vials, each containing 1 g (500 mg/ml). Multiple vials are already available in the anesthesia medication carts in every operating room. In addition, the normal saline vials are packaged in 10 ml vials.

5.8 Blinding of Study Drug

The study drug will be blinded to the endoscopist and patient. While the study or control drug is being prepared by the anesthesia team, the endoscopist will not be present in the operating room environment. The 20 ml syringe in which the drug is prepared will be labeled as "study" for the purpose of minimizing drug error during the course of intraoperative management.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

The magnesium sulfate and normal saline are already available for use in the anesthesia drug carts.

5.9.2 Storage

The drugs are maintained at room temperature with no particular light protection requirements in every anesthesia drug cart. The special handling requirements are necessary.

5.9.3 Dispensing of Study Drug

The anesthesia team will follow instructions provided to them to prepare the study drug, using multiple vials of the drug already available for use in the anesthesia drug cart.

5.9.4 Return or Destruction of Study Drug

By the completion of the anesthetic, the drug's bolus and infusion will be documented in the electronic anesthetic record. The ususued study drug remaining in the syringe will be wasted and destroyed.

6 Study Procedures

6.1 24 to 72 hours prior to scheduled surgery

6.1.1 Patients undergoing per-oral endoscopic myotomy (POEM) in the SHC operating rooms will be identified, and screened by phone whether or not they agree to the study.

6.2 Day of surgery

6.2.1 In the preoperative holding area, all enrolled patients will have preoperative plasma calcium and magnesium levels drawn and complete the esophageal symptoms questionnaire (ESQ), a validated survey to assess symptoms of dysphagia, globus, and reflux.

6.2.2 The patient will proceed to the OR for anesthetic care.

6.2.2.1 Patients will undergo rapid sequence induction of general anesthesia. In the control group, the anesthesia team will use ketamine, propofol, succinylcholine, and esmolol and/or opioids at their discretion. In the treatment arm, the anesthesia team will use ketamine and propofol using lean body weight (LBW) dosing, and succinylcholine at total body weight (TBW) dosing. After endotracheal tube placement and confirmation, sevoflurane in air and oxygen will be used for maintenance of general anesthesia. The anesthesiologist will ensure adequate neuromuscular relaxation throughout the case.

6.2.2.2 In the treatment arm, the anesthesia team will prepare a magnesium sulfate infusion within a 20 ml syringe. Patients will receive a magnesium sulfate bolus of 50 mg/kg lean body weight over 15 minutes, followed by a magnesium sulfate infusion at 25 mg/kg/hr when the endoscopist begins mucosal incision. In addition, the patients will receive dexamethasone 0.1-0.2 mg/kg at the start of case, and ondansetron 4 mg at the end of case. The magnesium infusion will be discontinued at extubation. After surgery, patients will be admitted to the postanesthesia care unit. For mild pain reported as a numeric score ranging from 1 to 3, acetaminophen 1000 mg IV will be offered. For pain greater than a score of 3, opioids (fentanyl and hydromorphone) will be available. For nausea and vomiting, prochlorperazine and haloperidol will be provided. Calcium gluconate and a code cart with emergency drugs and airway equipment will be made available in case of symptoms concerning for magnesium toxicity.

6.2.2.3 In the control arm, the anesthesia team will prepare a normal saline infusion within a 20 ml syringe. Patients will receive a normal saline bolus of 50 mg/kg lean body weight over 15 minutes, followed by a normal saline infusion at 25 mg/kg/hr when the endoscopist begins mucosal incision. Opioids (fentanyl and hydromorphone) will be administered for analgesia at the discretion of the anesthesia team. In addition, patients

will receive dexamethasone and ondansetron in the aforementioned doses. After surgery, patients will be admitted to the postanesthesia care unit, where opioids (fentanyl and hydromorphone) and antiemetics (anesthesia team's discretion) will be available for further pain and nausea management.

6.3 All study participants will repeat the ESQ in the PACU when the nursing team deems the patient's recovery appropriate enough to participate.

6.4 Postoperative Day 1

6.4.1 The ESQ and serum calcium/magnesium levels will be reobtained in the morning of POD1.

7 Statistical Plan

7.1 Sample Size Determination

Unpublished data at our institution reveals an 60% incidence of esophageal spasm-related pain. We assume that magnesium might decrease the incidence of esophageal spasm-related pain by 30%. Based on this assumption, our calculation show that 45 patients in each group would be necessary to acquire statistical significance, with a two-sided $\alpha = 0.05$ and $\beta = 0.20$. Considering a 10% dropout rate, 50 patients are necessary for each group.

7.2 Statistical Methods

Data will be expressed as means ± SD, number (proportion), relative risk, 95% CI, absolute risk reduction, or number needed to treat.

The primary outcome is the incidence of esophageal spasm-related pain at 0 h postoperatively, compared using the chi-square test.

The secondary outcomes of the incidence of esophageal spasm-related pain at 24 hours postoperatively, intraoperative opioid usage, postoperative opioid consumption, and discharge opioid prescription will be compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables will be compared using the Mann–Whitney *U* test. Categorical variables will be compared using the chi-square test or Fisher's exact test as appropriate.

Post hoc subgroup analyses will be conducted regarding the incidence of esophageal spasm-related pain according to achalasia type (e.g. type 1, 2, or 3), preoperative H2-receptor antagonist use, preoperative proton pump inhibitor use, and intraoperative opioid usage. *Post hoc* subgroup analysis will be further conducted on postoperative magnesium levels and the incidence of esophageal spasm-related pain at 24 hours.

All *P* values will be two-sided, and a value of $P < 0.05$ will be considered statistically significant.

Comparisons of postoperative pain between the two groups at time 0 h and time 24 h will be analyzed using the Mann–Whitney *U* test and performed using an adjusted significance level of 0.0125 (0.05/4) after *post hoc* analysis using the Bonferroni method.

Statistical analyses will be performed using R version 4.0.3.

7.3 Subject Population(s) for Analysis

Enrollment will cease when the target sample size is obtained. Analyses will be performed on an intention-to-treat basis. All patients who are enrolled and randomly allocated for treatment will be included in the analysis.

8 Safety and Adverse Events

8.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events

8.3.1 Study Sponsor Notification by Investigator

A serious adverse event must be reported to the study sponsor by telephone within 24 hours of the event. A Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and secure email to:

Richard K. Kim, MD 347-586-9661 rkwkim@stanford.edu

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor

8.3.2 EC/IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the EC/IRB within 10 working days. Copies of each report and documentation of EC/IRB notification and receipt will be kept in the Clinical Investigator's binder.

8.3.3 FDA Notification by Sponsor

The study sponsor shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information. Other serious, unexpected adverse events associated with the use of study drug shall be reported to the FDA no later than 15 calendar days from the sponsors' original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

8.4 Unblinding Procedures

Postoperative magnesium levels evaluated after surgery will reveal those among study participants who received magnesium or normal saline. If a study participant experiences a serious adverse event postoperatively, including cardiorespiratory arrest, unblinding will occur to ensure the patient's safety by evaluating if the patient would benefit from administration of calcium chloride therapy. The patient's randomization envelope contents will be shared with the care team. Documentation of this will be indicated in our data collection spreadsheets. The sponsor will be notified of each participant who was unblinded within 24 hours by phone or email, followed by a written narrative of the event within 48 hours.

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why

- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan in Attachment ___. The investigator will allocate adequate time for such monitoring activities. The Investigator will also

ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment ___ for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This study is financed solely through divisional and departmental funds from the Division of Regional Anesthesia and Acute Pain Medicine of the Department of Anesthesiology, Perioperative and Pain Medicine at Stanford University School of Medicine, and the Division of Gastroenterology and Hepatology of the Department of Medicine at Stanford University School of Medicine.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Stanford University investigators will follow the University conflict of interest policy.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

14 References

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15 Attachments

- Sample Consent Form
- Sample Protocol for Magnesium Treatment Group
- Sample Esophageal Symptoms Questionnaire