A randomized controlled trial of metoclopramide versus placebo during gastrojejunostomy tube placement for facilitating guidewire advancement through the pylorus

NCT03331965

Protocol Identifying Number: Pro00081892

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Funded by: Duke Radiology Putman Seed Fund

November 21, 2018

1. Protocol Title:

A randomized controlled trial of metoclopramide versus placebo during gastrojejunostomy tube placement for facilitating guidewire advancement through the pylorus.

2. Purpose of the Study:

The goal of this study is to determine whether use of promotility agents to stimulate gastric peristalsis can reduce fluoroscopy time and procedure time during gastrojejunostomy (GJ) tubes placement in interventional radiology (IR). We hypothesize that increased gastric peristalsis will aid in advancing a guidewire through the pylorus, a time consuming and tedious step required during GJ tube placement. In order to maximize scientific rigor and clinical practice impact, we aim to answer this question through a blinded, randomized, placebo controlled trial.

Specific Aim 1: To test the hypothesis that a single dose of IV metoclopramide immediately prior to GJ tube placement reduces the fluoroscopy time required to advance a guidewire through the pylorus. (Primary outcome for which the trial will be specifically powered to assess.)

Specific Aim 2: To determine whether a single dose of IV metoclopramide immediately prior to GJ tube placement reduces total procedure fluoroscopy time, air kerma and total procedure time. (Secondary outcomes.)

Specific Aim 3: To assess the safety of a single dose of promotility agent prior to GJ tube placement by assessing rates of adverse events in the periprocedural period in patients receiving IV metoclopramide versus placebo. (Safety outcomes.)

3. Background & Significance:

Gastrojejunostomy tube placement is a commonly performed procedure for providing nutritional support in patients unable to tolerate gastric feeds due to gastric outlet or duodenal obstruction or severe gastroesophageal reflux[1]. When performed percutaneously, this procedure involves advancing a guidewire from the gastrostomy skin entry site through the pylorus. Based on data collected for quality improvement purposes we have found that this step accounts for approximately one half the total fluoroscopy time and radiation dose during GJ tube placement and approximately one third of the total physician time in the procedure. Specifically, crossing the pylorus required on average 5.3 minutes of fluoroscopy time out of a total of 9.3 minutes for the entire procedure, and accounted for 92.2 mGy air kerma out of 201.7 mGy for the entire procedure. Furthermore, inability to advance a wire into the duodenum due to refractory pylorospasm is among the most common reasons for aborting GJ placement. Specifically, in approximately 1.5% of GJ placement procedures the pylorus cannot be crossed and a gastrostomy tube is placed instead. Only colonic interposition, in which GJ tube placement is not attempted, accounts for a larger fraction of failed procedures (3%). A variety of wire, catheter, and device related techniques have been described to facilitate wire intubation of the pylorus[2], but this remains a rate limiting step in the procedure. In order to reduce radiation doses to both the patient and interventional radiologist to levels that are as low as reasonably achievable and to maximize procedural success rates, adjunctive methods to aid in wire intubation of the pylorus are needed.

Previous meta-analyses of randomized controlled trials have found that a single dose of erythromycin or metoclopramide is effective at emptying the stomach of blood and improving visualization during endoscopy for upper gastrointestinal tract bleeding[3,4]. Similarly, a previous

randomized controlled trial demonstrated that a single dose of metoclopramide or domperidone increases the rate at which nasoenteric tubes spontaneously pass through the pylorus from 27 to 55%[5]. Single dose metoclopramide is also indicated for reducing transit time during small bowel follow through examinations[6]. Drug related adverse events in these studies were rare.

Although single dose promotility agents are established in the above described settings, they have not been studied for GJ tube placement. We hypothesize that use of promotility agents may facilitate advancement of the guidewire through the duodenum and into the proximal jejunum during GJ tube placement by enhancing gastric peristalsis, pylorus relaxation, and small bowel motility. Single doses of commercially available promotility agents such as metoclopramide are inexpensive (approximately $1.02 per dose), easily administered at the time of the procedure, and have very favorable safety profiles[3-6]. Therefore, promotility agents may represent a simple, effective, and readily feasible means of reducing radiation dose and procedure time during GJ tube placement, thus improving the safety and efficiency of this common IR procedure.

4. Design & Procedures:

We plan to enroll patients undergoing GJ tube placement as part of their routine, clinically indicated care. A total of 110 Duke University Hospital inpatients will be randomized in 1:1 fashion to receive a one-time dose of a commercially available promotility agent (10 mg metoclopramide IV) or placebo at the time of GJ tube placement. Given the paucity of published data on use of promotility agents to facilitate wire advancement through the pylorus, as well as reports of the potential benefit of the antiperistaltic agent glucagon to facilitate gastric insufflation during GJ placement procedures[7], it is possible that promotility agents may hinder GJ placement. Therefore, a placebo control is necessary to rigorously test the study's hypothesis. Although other promotility agents are available, metoclopramide is routinely used in both the US and abroad for this indication, and has previously been shown to be safe and efficacious at promoting gastric peristalsis in a variety of settings[4-6].

The randomization key will be created and maintained by the PI using Microsoft Excel. Randomization will be performed in two equal blocks to facilitate the preplanned interim analysis as described below. Specifically, for the first block of 55 patients, there will be 23 placebo assignments and 22 metoclopramide assignments. These assignments will be "shuffled" to generate a random order by pairing each assignment with a uniformly distributed pseudorandom number, and sorting the associated assignment in order of ascending pseudorandom number. A similar procedure will be performed for the second block of 55 patients with 22 placebo and 23 metoclopramide assignments. Once the assignments are shuffled, sealed envelopes containing the assignments will be made.

During the GJ tube placement procedure, after the "Time Out" when the initial doses of routine procedural sedation medications are administered, metoclopramide or placebo will also be administered intravenously. The corresponding sealed envelope will be delivered to a dedicated IR nurse. Both sedation medications and the study drug will be administered by the dedicated IR nurse whose sole responsibility during the procedure is patient monitoring and medication administration. The patient and IR physician performing the procedure will be blind to medication assignment.

After administration of metoclopramide or placebo, the GJ placement procedure will be performed in identical fashion in both groups using conventional technique[1,7]. An IR technologist

observing the procedure will record the fluoroscopy time, air kerma, and chronological time will be recorded by an IR technologist at the following routine events during GJ tube placement procedures: 1) start of gastric insufflation, 2) needle access to the stomach, 3) wire intubation of the duodenum, 4) wire intubation of the jejunum, 5) and procedure completion. This will allow determination of the primary outcome (fluoroscopy time at wire intubation of the duodenum minus fluoroscopy time at needle access to the stomach). Secondary outcomes will include total fluoroscopy time, total air kerma, and total chronological time, measured at procedure completion minus start of gastric insufflation.

Any symptoms of potential adverse drug reactions including arrhythmias, hyper or hypotension, dyspnea, extrapyramidal side effects, pruritus, and nausea or vomiting will be recorded during the procedure. After GJ tube placement procedures, patients are routinely followed by the interventional radiology service to identify complications. Complications will be graded according to Society of Interventional Radiology reporting standards[1].

5. Selection of Subjects:

Potential subjects will be identified at the time that referral is placed for GJ placement. A designated member of the study team will screen for study eligibility. Adult patients over the age of 18 who are undergoing de novo GJ placement as part of their routine clinical care will be considered for enrollment. Females of child bearing age are routinely screened for pregnancy status prior to undergoing IR procedures in accordance with Radiology Department protocol. Specifically, females ages 12-50 are asked if they could be pregnant. Patients who answer “no” are asked to provide the reason that best describes their situation: prior hysterectomy, postmenopausal, premenarche, menstrual period within 28 days, not sexually active with males, on birth control, or other (specified). Women who are unsure about their pregnancy status or who cannot support their non-pregnant status with one of the above undergo a urine pregnancy test. Pregnant females will be excluded from the study. Contraindications to metoclopramide including allergic reaction, pheochromocytoma, QTc prolongation, history of seizure disorder, or extrapyramidal symptoms will represent additional exclusion criteria. Potential subjects with an absence of a pylorus from prior whipple surgery or other post-surgical incontinuity between stomach and duodenum will be excluded from participation.

6. Subject Recruitment & Compensation:

A total of 110 inpatients at Duke University Hospital undergoing GJ placement as part of their routine clinical care will be recruited. Prior to the GJ procedure, potential subjects will be approached by a designated member of the study team to determine whether the patient is interested participating. Subjects will have a minimum of 1 hour and up to a day (or longer) depending on when they are scheduled for their procedures to decide whether or not they would like to participate. Subjects who decide to participate will be provided a signed and dated copy of the study consent form for their records. No compensation will be offered for study participation.

7. Consent Process – see Section 14 of the e-IRB submission form and complete the questions in that section.

See Section 14.

For those patients who elect to participate, informed written consent will be obtained prior to the GJ procedure by a designated member of the study team in the patient's private hospital room or in a private room in the IR suite. The potential risks and complications will be discussed with the patient, as well as the implications of the study and future benefits to the patient and the medical literature. A minimum of 1 hour will be allotted for this discussion.

8. Subject's Capacity to Give Legally Effective Consent:

Informed written consent will be obtained from individuals able and willing to give consent. In patients unable to give legally effective consent, as deemed by the clinical team caring for the patient, the patient's legal representative providing consent for the GJ procedure itself will provide consent for the study. A significant fraction of patients undergoing GJ tube placement are either critically ill and require nutritional optimization while on ventilatory or circulatory support, or have impaired swallowing due to neurologic disorders. Therefore, excluding these potentially cognitively impaired groups would substantially hinder the ability to recruit. Given the short duration of study intervention, no reassessment of ability to provide consent will occur.

9. Study Interventions:

A one-time dose of promotility agent (metoclopramide 10 mg in 10 mL saline IV), or a placebo (10 mL saline IV) will be administered at the time of GJ placement. After administration of the pro-motility drug or placebo, no further study intervention will occur.

10. Risk/Benefit Assessment:

Potential risks of the study include allergic reaction or adverse reaction to promotility agent. In a recent randomized placebo controlled trial utilizing a one-time dose of 10-20 mg metoclopramide IV, among 100 patients receiving this agent there were 4 drug associated events (lethargy n=2, dysphoria n=1, tremor n=1) which were not significantly different in frequency compared to the placebo group[5]. Potential benefits of the study include the possibility of reduction in fluoroscopic radiation dose and procedure time as a result of promotility agent.

11. Costs to the Subject:

No costs will be incurred by the subjects. The costs for promotility drug or placebo will be covered by the research grant.

12. Data Analysis & Statistical Considerations:

For Aim 1, the primary outcome of the study, the fluoroscopy time required for wire intubation of the duodenum will be determined by subtracting the fluoroscopy time when the wire first enters the stomach at the time of gastrostomy needle placement from the fluoroscopy time when the wire first enters the duodenum. We will test the following hypothesis:

$$H_0: \mu_1 = \mu_2 \text{ vs } H_1: \mu_1 \neq \mu_2$$

where μ_1 represents the mean fluoroscopy time among patients in the placebo group and μ_2 represents the mean fluoroscopy time among patients in the promotility drug group. The test of $H_0: \mu_1 = \mu_2$ vs $H_1: \mu_1 \neq \mu_2$ will be performed using a two sided T-test. For sample size calculations

we estimate, based on results from an internal IR quality improvement database, that $\mu_1 = 5.3$ minutes and that $\sigma_1 = \sigma_2 = 5.7$. In order to provide a clinically meaningful reduction in fluoroscopy time, we assume that $\mu_2 - \mu_1 = 3$ minutes. We therefore estimate that 55 patients in the promotility group and 55 patients in the placebo group would be required to produce 80% power to achieve a p-value < 0.05 in a two sided T-test[8].

For Aim 2, the secondary outcomes, the total fluoroscopy time, air kerma, and chronological procedure time will be determined by subtracting these values at the start of gastric insufflation from the values at the completion of the procedure. As in Aim 1, the tests of H_0: $\mu_1 = \mu_2$ vs H_1: $\mu_1 \neq \mu_2$, where μ_1 and μ_2 represent the placebo and promotility group means, will be performed using two sided T-tests.

For Aim 3, the safety outcomes, counts of total adverse events and of individual categories of adverse events will be compared in the placebo and promotility groups using Fisher's exact test.

Based on an internal IR quality improvement database, in 2016, 315 enteral access placement procedures were performed, approximately 75% of which were GJ tube placements. Allowing for CRC availability and potential patients declining participation, we expect to accrue approximately 50 patients per year.

A planned interim analysis will occur after accrual of 55 patients. Based on the Heybittle-Peto approach[9], a p-value < 0.001 will be utilized to stop for efficacy. At this interim analysis if conditional power to detect an effect size of $\mu2 - \mu1 = 3$ for the primary outcome falls below 0.2, the study will be stopped for futility[10].

13. Data & Safety Monitoring:

Important safety concerns include adverse drug events. As part of routine care during and after GJ placement, patients are closely monitored by IR nursing staff to identify complications. In the event of a severe unexplained adverse event occurring during the GJ placement procedure, which is thought to be due to the study medication, blinding will be broken to determine which medication was administered to ensure appropriate treatment. Any such protocol deviations will be promptly reported to the Duke University IRB.

14. Privacy, Data Storage & Confidentiality – see Section 12 of the e-IRB submission form and complete the questions in that section.

See Section 12.

Informed consent will be obtained in a private room to maintain confidentiality. Consent documents, case report forms, and any other paper documents with PHI will be stored under the care of the CRC. The door to this office area is locked during non-business hours. All data for analysis will be stored on a secure network drive maintained by DHTS.

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