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Effect of Oral Naloxone in Relieving Post-operative Ileus in Patients Undergoing Spinal Fusion

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I. Abstract

Postoperative ileus and opioid induced constipation are well-known post-operative complications. Previously, research has shown that using peripherally acting opioid antagonists can help alleviate the condition.[1] There has not been a prospective study to investigate whether use of peripherally acting opioid antagonists are effective in preventing post-operative ileus in patients having spinal fusion surgeries.

II. Background and Significance/Preliminary Studies

Post-operative ileus is a well-recognized entity and can significantly prolong a patients' length of stay in the hospital.[2] Anterior surgical approaches and duration of surgery for spinal fusion have been shown to increase the incidence of post-operative ileus with no successful intervention identified that reduces the incidence of ileus.[2]

Naloxone is an opioid antagonist which is FDA approved as an intravenous agent for the reversal of adverse effects associated with synthetic and naturally occurring opioid agonists.[3] Enteral administration of naloxone has been investigated for the reversal of opioid induced constipation.[4-7] Naloxone administered via the enteral route has been shown to antagonize the effect of opioid medications peripherally without affecting pain control.[4-7] There was a significant increase in bowel movements and reduction in laxative use without a significant impact on pain control.[4-7]

I. Study Aims

The current study will assess the safety and efficacy of an enteral formulation of the opioid antagonist naloxone in prevention of post-operative ileus and opioid induced constipation.

I. Administrative Organization

This is a single center study to be completed at Loyola University Medical Center. Participants may be located on a number of different in-patient units including Neurosciences Intensive Care Unit (2W), Surgical Intensive Care Unit (4N/S/WICU), Cardiac Care Unit (3HTU), Progressive Care unit (2N/PCU), and medical-surgical wards (2E or 4T).

I. Study Design

This is a prospective, historically controlled observational trial of enteral naloxone use in patients admitted for spinal fusion surgery and receiving opioids for pain management.
Primary outcome: Time to first bowel movement (hours)
Secondary outcomes:

- Hospital length of stay
- Incidence of post-operative ileus. Post-operative ileus will be diagnosed through a combination of clinical exam and radiographic (X-ray) findings
- incidence of post-operative constipation (defined as 3 days without a bowel movement)
- average numerical pain scale (Adult Nonverbal Pain scale or Visual Analog Scale) on post-operative days 0, 1, 2, and 3
- average daily opioid requirement on post-operative days 0, 1, 2 and 3 (morphine equivalents)
- number of naloxone doses administered
- average number of daily bowel movements,
- number of medication escalations required (defined as use of an as needed laxative medication or addition of a new order for a laxative medication)
- Incidence of adverse effects
- Incidence of study drug discontinuation

II. Study Procedures

Inclusion/Exclusion Criteria

Patients will be included if they are having an in-patient spinal fusion procedure, are 18 years or older, post and post-operative pain control plan includes opioid medications. Patients will be excluded if they are pregnant, nursing, under the age of 18, have an allergy to naloxone or its related products, or if they are having an outpatient procedure.

Study recruitment

Recruitment will take place prior to surgery. Initial contact with prospective participants will occur in the pre-operative clinic visit which occurs 1 – 12 weeks prior to surgery. A member of the study team will provide the patient with a copy of the informed consent document to review and take home. The patient will be given an opportunity to ask any questions they may have about the study. Patients will then be approached on the day of surgery to sign the consent form when surgical consent is obtained. Consent will be obtained by one of the neurosurgery residents involved with the study.

Screening procedures

Patients will be screened at the pre-operative clinic visit based on the inclusion and exclusion criteria.

Historical controls will be identified by a report of patients undergoing spinal fusion procedures

identified via ICD9 codes in the previous 3 years. ICD-9 codes include a short fusion surgery (81.06, 81.62) with 3 or fewer vertebral body segments, long fusion surgery (81.63, 81.64), more than 4 vertebral segments, anterior approaches (81.06) and posterior approaches (81.07) in the thoracic and lumbar spine. The historical controls will be matched to active participants based on age, gender, Charleston co-morbidity index, complexity of surgery, and duration of surgery.

Study Intervention

Active study agents: Naloxone
Blinding/labeling/preparation of agents: No blinding is required in this study. The study drug will be prepared, unit dose labelled, and patient labelled according to institutional protocols.
Storage: Secured at room temperature in the central pharmacy then dispensed as a patient specific supply and stored at room temperature the automated dispensing cabinet. No more than a 24 hour supply will be dispensed at any given time.
Administration: 4 mg of a 1 mg/ml oral solution administered enterally (oral, nasogastric, orogastric, gastrostomy, or jejunostomy) every 8 hours for 48 hours

Toxicities and guidelines for adjustments

Potential adverse effects associated with the use of enteral naloxone have been associated with abrupt reversal of opioid activity with the most uncomfortable or dangerous of these being antagonism of central opioid activity and loss of pain control. Additional adverse effects include nausea, vomiting, diarrhea, hypertension, tachycardia, diaphoresis, and mental status changes. Patients will be monitored for adverse effects via routine vital signs, pain score, and neurological assessment every 1 – 4 hours and evaluation for emesis, bowel movements, and diaphoresis. Study drug will be discontinued in patients who meet any three of six criteria within 1 hour of study drug administration:

1. Heart rate increases > 20 beats per minute for > 5 minutes
2. Respiratory rate increases to > 20 breaths per minute
3. Diaphoresis
4. Pain score increases by > 50%
5. Emesis
6. Diarrhea (defined as > 1 large, liquid bowel movement within 1 hour)

Study Assessments and Activities

All patients will undergo the scheduled operation per routine. Post operatively, all usual medications for pain control and bowel movements will be ordered according to institutionally approved and reviewed post-operative order sets. All home medications will also be reconciled and restarted as deemed clinically appropriate by the interdisciplinary care team. Oral naloxone 4 mg enterally every 8 hours will be initiated on post-operative day 1 at 0900. Study drug will be discontinued as described in the study protocol, after 48 hours, or upon discharge whichever is sooner.

III. **Safety Monitoring Plan**

Definition of adverse events, serious adverse events

Adverse event: Any reported or observed event that is not part of the usual post-operative clinical course.

Serious adverse event: Any event that requires discontinuation of the study drug

Any serious adverse events will be reported immediately to the IRB. All identified adverse events will be reported in the final analysis of this study. Upon completion of data collection, all adverse events will be evaluated by study personnel and adjudicated for their relation to study drug.

What procedures will be used to monitor subject safety

Patients will be monitored for adverse effects via routine vital signs, pain, and neurological assessment every 1 – 4 hours and evaluation for emesis, bowel movements, and diaphoresis. These evaluations do not represent an additional burden to the patient since they are a part of routine post-operative care.

Protected health information and data security

All protected health information associated with the historical cohort will be stored in a password protected Microsoft Excel file on the SSOM Research secured drive. De-identified patient information will be entered into a RedCap database for data collection. All signed consent forms will be collected and securely kept in the patients' medical record through EPIC.

I. Analysis Plan

Power Analysis

Power estimates for this study were based on prior work by Lee et al.[8] In their study, patients were randomly assigned to receive morphine with naloxone or morphine without naloxone. They found that those who received naloxone had a shorter time to first postoperative passage of flatus (*M* = 51.9hr, SD = 16.6hr) versus control (*M* = 87.0hr, SD = 19.5hr). Similarly, the authors found that time to first feces was faster in the naloxone cohort (*M* = 95.3hr, SD = 25.0hr) than control group (*M* = 132.9hr, SD = 29.4hr). However, their study duration was exceedingly long with a maximum duration of approximately 160-180 hours. One goal of this study is to estimate the effect of naloxone on time to first feces within the first 120 hours (5 days) following treatment. In this study, patients who require a second intervention or who do not experience flatus or feces by Day 5 will be censored.

The null hypothesis is that the bowel movement (BM) rate is identical in the two groups (control and naloxone). Power is computed to reject this null hypothesis. Computation of power is based on a hazard ratio of 1.508. Specifically, it assumes instantaneous BM rates of 0.160 for the control group versus 0.241 for the naloxone group. This is equivalent to a median time of no BM of 4.34 days for the control group versus 2.879 days for the naloxone group. At 5 days, it is hypothesized that 45% of the control cohort versus 30% of the naloxone cohort will require a second intervention because they have not experienced a BM.

With a total of 150 patients entered into the naloxone group and a total of 150 historical controls, the study will have power of 80.1% to yield a statistically significant result. The

criterion for significance (alpha) is set at 0.050, and the test will be 2-tailed meaning an effect in either direction will be interpreted.

Analysis Plan

Two different approaches will be used for the primary aim. First, a paired *t*-test will be used to estimate the mean difference in hours to first feces between the active cohort and historical control cohort. For this analysis, the origin of time for both groups is start of surgery. If necessary, a Wilcoxon signed ranks test will be used to compare the two distributions.

A second approach will compare the instantaneous rates of bowel movements between the active and control cohorts using a Frailty survival model that allows for clustering of patients within their matched strata. In this analysis, control patients who required treatment for ileus will be censored at the time of such treatment, and active patients who require an additional treatment beyond receipt of naloxone will be censored at the time of such treatment. All patients who do not achieve BM by 120 hours will also be censored. Hours to first feces for both groups will be start of surgery. While we assume there is no immortal time bias between start of surgery and receipt of naloxone for the active cohort, a conditional landmark method may be used to account for the amount of hours between surgery and receipt of naloxone.[9] The proportional hazards assumption for all predictors will be tested using Martingale residuals as described by Lin, Wei, and Ying.[10]

Regarding the secondary aims, a linear mixed effects model will be used to compare LOS between the two groups. A generalized linear mixed effects model will be used to compare the two groups on all other secondary outcomes. In these models, random intercepts will be allowed for each case-control matched strata in order to account for the correlation between cases and controls based on age, gender, Charleston co-morbidity index, and operation time under anesthesia.

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