Double-Blind, Randomized Trial of Peri-operative Subcutaneous Methylnaltrexone Versus Placebo for Postoperative Ileus Prevention after Adult Spinal Arthrodesis

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SIGNATURE PAGE

TITLE: Double-Blind, Randomized Trial of Peri-operative Subcutaneous Methylnaltrexone Versus Placebo for Postoperative Ileus Prevention after Adult Spinal Arthrodesis

Protocol Number:
Date:

The signatures of the investigator and representative of the sponsor below constitute their approval of this protocol and provide the necessary assurances that this Clinical Trial will be conducted according to Good Clinical Practices and to all stipulations, clinically and administratively, as stated in the protocol, including all statements as to confidentiality.

It is agreed that the protocol contains all necessary information required to conduct the Clinical Trial as outlined in the protocol.

It is agreed that all participants in this study will provide written informed consent and/or a HIPAA Authorization and agree to the Clinical Trial procedures as approved by the Institutional Review Board, as applicable.

PRINCIPAL INVESTIGATOR:

_____
Print Name

_____ _____
Signature Date

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1 INVESTIGATIONAL PLAN

1.1 Purpose

The purpose of this randomized controlled trial is to assess and compare the effect of peri-operative administration of Methylnaltrexone (MNTX) versus placebo on post-operative ileus (POI) following lumbar spinal fusion procedures.

2 INTRODUCTION

2.1 Background

POI refers to the transient interruption of propulsive motor activity of the gastrointestinal (GI) tract that prevents effective movement of its contents and tolerance of oral intake. Although POI is generally considered to significantly increase hospital stays and inpatient costs after spinal surgery, the incidence, associated risk factors, and effective preventative strategies remain poorly characterized.

POI was recognized as a complication of abdominal and other major surgeries as early as the late 1800s. The proposed etiologies underlying POI are broad and remain incompletely characterized. They include postsurgical sympathetic nervous system activation, inflammatory factors, and the effects of analgesics on GI tract motility [1, 2]. Treatment often consists of aggressive bowel regimens, nasogastric tube insertion for decompression, and the application of various laxatives, suppositories, and enemas. The widespread use of these measures is unfortunately not supported by high level evidence.

The incidence of POI after spinal fusion is reported to range between 0.6 to 16.7% [3]. This estimated range likely represents a gross underestimate of POI given the retrospective nature of studies undertaken to date. Fineberg and colleagues reported that the risk increases nearly 3-fold following anterior lumbar spinal fusions as compared to posterior surgeries [4]. Furthermore, the only risk factors they identified to be correlated with POI is male gender, ≥ 3 fusion levels, alcohol abuse, anemia, electrolyte abnormalities, and weight loss. Kiely and colleagues [3] found that ileus was associated with the administration of certain intravenous solutions such as lactated ringers and sodium chloride. Interestingly, they found that albumin administration was associated with a reduced incidence of ileus postoperatively. Lee and colleagues evaluated POI following orthopedic surgery and reported an incidence of 2.1% [5]. They found that patients who developed POI were more likely to be older, had higher blood loss during surgery, and also

had higher rates of preoperative constipation. This study, however, included all types of orthopedic surgeries (not limited to spinal fusion).

2.2 Drug Background

Early clinical studies evaluated the effectiveness of MNTX in treating opioid-induced constipation (OIC). Several clinical trials confirmed that MNTX was well tolerated and counteracted the GI effects of opioids, thereby enhancing gut motility without inhibiting their analgesic properties [8-10]. Only two studies to date have evaluated the potential effectiveness of MNTX in reducing the incidence of POI following GI surgery [11, 12]. Both studies were unfortunately hampered by serious design flaws. Most importantly, neither study included pre-operative administration of MNTX, which was a characteristic of the alvimopan studies that showed clinical benefit [13-15]. As such, MNTX remains at this time approved only for chronic OIC based on two double-blind, randomized, placebo-controlled trials conducted in patients with advanced illness wherein MNTX rapidly induced laxation as compared to placebo [16, 17].

In 2001, alvimopan, a related peripherally acting μ-opioid receptor (PAM-OR) antagonist that selectively targets GI μ-opioid receptors, was noted to significantly reduce the time to first flatus passage, time to first bowel movement (BM), and time to discharge in a cohort of 78 patients undergoing either partial colectomy or total hysterectomy [18]. Wolff and colleagues found similar results in a larger cohort of 469 patients undergoing bowel resection or hysterectomy [19]. These results led to approval by the FDA in 2008 of alvimopan as the first (and still only) drug for POI treatment after partial small or large bowel surgery. Unfortunately, however, alvimopan is contraindicated in patients that have taken opioids the week prior to surgery, which significantly limits its application to spinal surgery patients who are often taking opioid analgesics at relatively large doses.

As such, there is a glaring paucity of clinical evidence regarding the potential benefits of PAM-OR antagonists for POI prophylaxis. Specifically, no studies have been undertaken to date evaluating MNTX in relation to POI prophylaxis after spinal fusion. A critical clinical need therefore needs to be addressed for spinal surgery patients who suffer from POI and its associated complications and costs.

3 TRIAL DESIGN

3.1 Design

This randomized controlled trial will prospectively evaluate the clinical benefit for subcutaneous MNTX in counteracting the obstipatory effects of spinal surgery without increasing narcotic usage or otherwise disrupting the recover course of patients. Using a double-blind randomized design, either subcutaneous MNTX (0.15 mg/kg rounded to 8 mg or 12 mg) or placebo will be administered starting before surgery and then daily for three days.

3.2 Primary / Secondary Outcomes

The primary outcome will be the time from the end of surgery to the first bowel movement (BM; in hours). A sample size of 43 randomly assigned patients per study group (86 subjects in total) was calculated to detect a treatment effect of MNTX (90% power; alpha = 0.05). This calculation was performed with the assumption that subjects who experience their first BM by day three comprise 50% in the placebo group and 85% in the treatment group. A 10% lost-to-follow up rate was also included in the calculation. The secondary outcomes will be the time to discharge and the time to discharge eligibility (in hours). Finally, exploratory outcomes will include the amount of daily narcotics (in morphine milli-equivalents) administered during the first 4 days or up to hospital discharge. Administration of drug/placebo will be stopped should the patient experience frequent stools, defined as greater than 3 BMs per day.

3.3 Inclusion Criteria

Subjects will be considered for inclusion in this trial if they satisfy the following criteria:

1. Subject is scheduled to undergo a 1 – 3 level lumbar spinal fusion for degenerative spinal conditions including neurogenic claudication and/or lumbar radiculopathy with stenosis and/or spondylolisthesis.
2. Subject must be over the age of 18 years old.
3. Subject has been unresponsive to conservative care for a minimum of 6 months.
4. The subject must in the investigator’s opinion, be psychosocially, mentally, and physically able to fully comply with this protocol and have the ability to understand and give written informed consent.

3.4 Exclusion Criteria

Subjects will be excluded from this trial if they satisfy any of the following criteria:

1. Previous treatment with MNTX

2. History of mechanical gastrointestinal obstruction
3. History of OIC refractory to outpatient medical management
4. Presence of a peritoneal catheter for intraperitoneal chemotherapy or dialysis
5. Clinically relevant active diverticular disease
6. Recent history of bowel surgery (past 1 year)
7. Use of vinca alkaloids within previous 4 months
8. Renal failure defined as EGFR <30 ml/min per 1.73 m^2 or requires dialysis
9. Known or suspected allergy to MNTX or similar compounds (e.g. naltrexone or naloxone)
10. Participation in a study with investigational products within 30 days before first dose of MNTX
11. Pregnant or nursing
12. Clinically important abnormalities that may interfere with participation or compliance to the study, as determined by investigator

4 STUDY PROCEDURE

4.1 Screening Assessments

4.1.1 Informed Consent

Subjects will be provided with an informed consent and will be given ample opportunity to review the consent and ask questions. The signed informed consent will be obtained before any study specific procedures are initiated that are not part of the investigator's standard of care. A copy of the informed consent will be given to the subject. All subjects who meet all of the entry criteria will be considered for inclusion in this trial. Any subject meeting any of the exclusion criteria will be excluded from the trial.

All subjects who have agreed to participate in this study, have signed the informed consent and who meet the inclusion/exclusion criteria will be considered enrolled and assigned a subject ID number. Once a Subject ID number has been issued, it cannot be reassigned or used for another subject.

4.1.2 Medical History and Demographic Data

Within 30 days prior to the surgery date, the following information will be collected:

- Demographic data
- Medical history, including a complete history of spinal disorder(s) (non-operative or operative treatments performed)
- Physical examination (including height, weight)
- Current pain medications and other drug therapies.

- Primary diagnosis and any associated assessments collected per standard of care

4.2 Recruitment and Randomization

All subjects will be randomized in the trial to receive either subcutaneous MNTX (0.15 mg/kg rounded to 8 mg or 12 mg) or placebo to be administered starting before surgery and then daily for three days. Subjects and investigators alike will be blinded to their group status for the duration of the study assessments and procedures (1 month post-operatively).

A sample size of 43 randomly assigned patients per study group (86 subjects in total) was calculated to detect a treatment effect of MNTX (90% power; alpha = 0.05). This calculation was performed with the assumption that subjects who experience their first BM by day three comprise 50% in the placebo group and 85% in the treatment group. A 10% lost-to-follow up rate was also included in the calculation.

Potential participants will be identified by the principal investigator (HFF), co-investigators, and study personnel through the review of medical records during outpatient clinic visits at the Ohio State University Comprehensive Spine Center. A partial waiver of HIPAA authorization has been requested for this purpose. Given historical surgical numbers, a sufficient number of patients who are candidates for lumbar fusion procedures and potentially eligible for study enrollment are expected to be evaluated during the study period.

4.3 Perioperative and Postoperative Management

Enrolled patients will be given MNTX (0.15 mg/kg rounded to 8 mg or 12 mg) or placebo prior to surgery in the pre-operative holding area and every 24 hours for 3 days following surgery (a total of 4 doses). This dosing matches the FDA approved dosing for the use of MNTX in patients effected by opioid induced constipation.

Following surgery patients' BMs will be closely monitored and the time to first BM will be recorded in hours. Patients will receive routine post-operative orders including early mobilization with a physical therapist on the first post-operative morning, intravenous patient controlled anesthesia for 1-2 days transitioned thereafter to an oral opioid regimen, as well as a bowel routine comprising Docusate Sodium, Senna Glycoside, Polyethylene Glycol 3350, and Bisacodyl

suppositories (started on post-operative day 2, if needed). All patients are also routinely discharged on a tapering oral opioid regimen.

Administration of drug/placebo will be stopped should the patient experience frequent stools, defined as greater than 3 BMs per day. If a treating physician choses to prescribe the off-label use of Methylnaltrexone for the management of post-operative ileus, the subject will be unenrolled from the study. Abdominal X-rays and CT will be collected and analyzed only if performed as standard of care to evaluate the GI tract following surgery. Additional review of concomitant medications, patient-reported pain levels (NRS), and adverse/serious adverse events will be reviewed daily for up to 96 hours following surgery and at 30 days post-operatively.

4.4 Schedule of Events

	Screening/ Enrollment (-30 days of procedure)	Immediately Pre-operative	Post-operative Day 1	Post-operative Day 2	Post-operative Day 3	30 Days Post-operative
Informed consent	X					
Medical History	X					
Demographics	X					
Concomitant medications review	X	X	X	X	X	X
Randomization		X				
Clinical Safety Labs (Chem7, CBC)		X	X	X	X	
MNTX/Placebo administration		X	X	X	X	
Vital Signs		X	X	X	X	
Numeric Pain Rating Scale	X	X	X	X	X	X
X-rays and CT Scan**			X**	X**	X**	
AE/ SAE review		X	X	X	X	X
**X-rays and CT scans are only to be collected if done as standard of care as determined by subject's clinical care team						

4.7 Success Criteria

4.7.1 Primary Measure of Effectiveness

A subject will be considered a success if a BM is achieved within 3 days of surgery. The primary outcome measure of effectiveness will be determined by the comparative rate of patients achieving BM and evading POI in the MNTX group versus placebo.

4.7.2 Secondary Measure of Effectiveness

Secondary measures of effectiveness will be determined by the comparative average time to discharge eligibility and/or discharge in hours for the MNTX group versus placebo.

4.7.3 Tertiary Measure of Effectiveness

Tertiary measures of effectiveness will include the effect of MNTX on the amount of daily narcotics administered (in milli-equivalents) during the first 4 post-operative days or up to hospital discharge.

4.8 Subject Withdrawal

It is recognized that the subject's participation in this trial is entirely voluntary, and that she/he may refuse to participate and may withdraw from participation at any time without jeopardy to any future medical care. It is also recognized that the investigator, at his/her discretion, may withdraw a subject from this study based upon his/her professional judgment.

Other Conditions for Withdrawal:

Any subject who develops a severe concurrent medical illness during the trial should be withdrawn. This type of illness is defined as any illness that would hinder the subject's ability to return for scheduled follow-up appointments. Such a withdrawal will not be counted for the purposes of determining success or failure.

5 STATISTICAL ANALYSIS PLAN

Efficacy analyses will be based on a modified intent-to-treat population including all subjects randomly assigned and having received at least one dose of study drug. The distribution of the primary efficacy end point time of first BM will be estimated via the Kaplan-Meier product-limit method and compared between treatment groups using the log-rank test. Secondary efficacy end points will be evaluated at the alpha = 0.05 level of significance without adjustment for multiple comparisons.

This study will attempt to identify not just relevant demographic and clinical risk factors for POI following spinal fusion, but also will quantify peri-operative opioid use in this patient population in order to determine whether an increased use of opioids increases the risk of POI.

Finally, safety will be assessed by monitoring adverse events (AEs), concomitant medications, vital signs, physical examination findings, ECG findings, and laboratory test results. Withdrawals owing to AEs will be evaluated as a safety end point. Treatment-emergent AEs, potentially clinically important laboratory measurements, and premature study discontinuations will be compared between groups by use of the Fisher exact probability test.

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