COVERSHEET

TITLE: A randomized, double-blinded, placebo-control trial of IV ondansetron to prevent pruritus in children who receive intrathecal morphine.

NCT03262038

Version Date: 7/3/2018

CLINICAL PROTOCOL

A randomized, double-blinded, placebo-control trial of IV ondansetron to prevent pruritus in children who receive intrathecal morphine.

Study Agents: Ondansetron (Zofran)

HUM #: 00124202

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Institution: University of Michigan

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PROTOCOL SYNOPSIS

Sponsor: Department of Pediatric Anesthesiology
Name of Investigational Study Agent: Ondanestron (Zofran)
Study Title: A randomized, double-blinded, placebo-control trial of IV ondansetron to prevent pruritus in children who receive intrathecal morphine.
Study Phase: 4
Primary Objective: Demonstrate efficacy of Ondansetron (Zofran) to reduce incidence and intensity of pruritus as a side effect of IntraThecal Morphine (ITM)
Study Design: Prospective, randomized, double-blind, placebo controlled
Study Population: ages 3-17 inclusive
Diagnosis and Main Criteria for Inclusion Each subject must meet the following criteria to be enrolled in this study: Scheduled for any procedure necessitating ITM for pain management. Wt </= 100kg Ability to use verbal or pictorial scoring scales Parental informed consent Subject informed assent, as applicable Subjects who meet any of the following criteria will be excluded from study: Inability to use verbal or pictorial scoring scales (developmental delay) Hypersensitivity to selective 5-HT_3 receptor antagonists Diagnosed congenital long QT syndrome Severe hepatic impairment Pregnancy and nursing mothers Use of serotonin specific reuptake inhibitors within 14 days Use of serotonergic-nonadrenergic reuptake inhibitors within 14 days Current use of any medications that prolong QT interval
Test Product; Dose; and Mode of Administration: **Intervention group:** This arm will receive (in a blinded fashion) 0.1 mg/kg of Ondansetron IV diluted in normal saline to a volume of 5 mLs intra-operatively and Ondansetron IV 0.1 mg/kg diluted in normal saline to a volume of 5 mLs every 6 hours for 24 hours postoperatively (not to exceed 40 mg in 24 hours).

Reference or Placebo Therapy; Dose; and Mode of Administration:

Control group:
This arm will receive (in a blinded fashion) a volume-matched placebo (normal saline) intraoperatively as well as IV every 6hrs for 24 hours postoperatively.

Duration of Treatment: Intraoperative time period plus 24 hours from end of surgery.

Statistical Methods:
Data will be summarized using descriptive methods. Parametric data will be analyzed between groups using unpaired t tests or Mann Whitney U, as appropriate. Rankings of pruritus and PONV will be coded as none-mild vs. severe and Chi-squared and Fishers' Exact tests will be used to compare these outcomes between groups. Significance will be accepted at the 5% level.

1 INTRODUCTION

1.1 Indication

Pruritus is one of the most common and bothersome side effects of intrathecal morphine (ITM) in children, with a reported incidence of 30-70% (1, 2, 13, and 15). We previously found a 40% incidence of pruritus in young children who received intrathecal morphine for major urologic surgery (2) (retrospective review, n= 77, anti-pruritic treatment required in 31 cases). Clinicians, who have witnessed unbearable itching and scratching in their young patients after intrathecal morphine, may be reluctant to offer this effective pain control to future patients, for fear of these unpleasant sequelae.

1.2 Background and Rationale

The mechanism of morphine-induced itch is not fully elucidated. (1, 16, 19). However, neuraxial opioids induce more frequent and intense itch than peripherally administered doses (26). Centrally located Mu-opioid receptors, in the medullary dorsal horn, may play a role, and activation of this site with an opioid injection induced a dose related scratch frequency in primates (23). The mu opioid receptors, but not other opioid receptor subtypes, appear to mediate the neuraxial opioid-induced itch as opposed to intravenously administered opioids (21, 22, 25). However, the physiology is more complex, as morphine induced pruritus is not always reversed with naloxone (13) and effective treatments for neuraxial induced pruritus include partial opioid agonists (1, 13), 5HT3 antagonists (4-7), propofol (13, 24), and prostaglandin modulation (19).

1.3 Hypothesis

Pre-emptive and continued blocking of 5HT3 receptors with the 5HT3 receptor antagonist ondansetron, given intravenously prior to ITM and 6 hourly thereafter, will reduce the incidence and intensity of pruritus as a side effect of morphine, in our pediatric patients.

Secondary outcomes to be studied: Post-operative nausea and vomiting and any adverse events.

1.4 Previous Human Experience

5HT3 antagonists are considered among the first line of treatments for morphine-induced nausea as well as pruritus in adult, particularly obstetric, populations (4, 7, 8, 19). A review of placebo RCTs, using prophylactic 5HT3 antagonists for pruritus in neuraxial opioids, found NNTT = 7 to reduce pruritus in adults (29). 5HT3 antagonists block the effects of morphine in animal studies (3). There is a high density of 5HT3 receptors in the nucleus of the facial and trigeminal nerve (20, 25). An “itch center” has been proposed at the spinal tract nucleus of the trigeminal nerve (18). More specifically, pre-emptive (27, 28) and around-the-clock ondansetron (28) dosing with ondansetron has been shown to reduce itch (both incidence and intensity), in adults who received intrathecal opioids.

In the pediatric population, case reports (9-11) suggest ondansetron is an effective treatment for pruritus, but to date there are no data to support the efficacy of 5HT3 antagonists in preventing or treating ITM-related pruritus in children.

In contrast, antihistamines such as diphenhydramine, while used in many pediatric settings, have been shown to be ineffective on opioid-related pruritus, in recent reviews (1, 13). This is corroborated by research in primates (23).

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

- Incidence and severity of pruritus in both study groups
- Incidence and severity of nausea and vomiting in both study groups

2.2 Endpoints

2.2.1 Primary Endpoint

Incidence and severity of pruritus within 24 hours post-operatively

2.2.2 Secondary Endpoint

- Post-operative nausea and vomiting within 24 hours post-operatively
- Adverse events intra-operatively and within 24 hours post-operatively

3 STUDY DESIGN

After obtaining IRB approval and informed consent, we will recruit children ages 3-17 years (able to use verbal or pictorial scoring scales) who are scheduled to intrathecal morphine for a surgical procedure and weigh less than or equal to 100kg.

We will recruit 130 children, and randomize using a random numbers table, stratifying for female gender. The patients who have consented to take part in the study, their families and caregivers, their medical team and the trained observers will be blinded to the treatment being given.

Our proposed ondansetron regime comprises an intra-operative bolus dose of ondansetron, 0.1mg/kg IV, prior to intrathecal morphine injection, followed by around-the-clock ondansetron doses, of 0.1mg/kg IV every 6 hours. We will compare this to a standardized control regime comprising an intra-operative bolus dose of saline placebo and around the clock placebo for 24 hours. 56 patients will comprise each group. All children in both groups will be cared for using a standard, current practice, which includes intra-operative anti-emetics per our departmental algorithm for PONV (Postoperative nausea and vomiting), described below.

Rescue orders for pruritus and PONV are also summarized below. See the attached protocol flowsheet for an overview. Naloxone is routinely ordered, to be given as needed for the treatment of respiratory depression or over-sedation only. We will compare our study group with the control group over the 24 postoperative hours with blinded observers / interviewers.

STANDARD OF CARE FOR PONV PREVENTION

As per standard of care, all subjects will receive dexamethasone and diphenhydramine intra-operatively for PONV prevention. For patients who fall into the "High Risk for PONV" category (according to departmental standard of care algorithm), anesthesiologist may, at their discretion, consider any of the following: pre-operatively aprepitant; fluid bolus 30ml/kg; Total Intravenous Anesthesia (TIVA); Sub-hypnotic dose propofol of 1mg/kg infused at 20mcg/kg/min.

STUDY PROCEDURES Pre-Operatively, Intra-Operatively and Post-Operatively**:**

- **Pre-op:** Patients will be consented in clinic whenever possible or on the day of surgery and randomized, with gender stratification. Patients, their families and health care professionals will be blinded as to whether the patient is in the treatment or control group.

- **Intra-op:** Induction of general anesthesia per standard of care. Syringe of drug labeled "Anti pruritic study drug" to be given IV, prior to intrathecal morphine administration, by anesthesiologist in the OR:

    - Study group: Syringe contains ondansetron 0.1mg/kg, diluted to a volume of 5 mls (not to exceed 5 mg/dose).

- Control group: Syringe contains normal saline, 5 mls.

- **Post-op:** Syringe of drug labeled "Anti pruritic study drug" to be given IV, q6h for 24 hours by RN on the floor:

    - Study group: Syringe contains ondansetron 0.1mg/kg, diluted to a volume of 5 mls (not to exceed 40 mg in 24 hours or 10 mg/dose).

    - Control group: Syringe contains normal saline, 5 mls.

STANDARD OF CARE FOR POST-OPERATIVE RESCUE TREATMENT OF PRURITUS AND PONV

Regardless of study group, all subjects will receive standard of care treatment for pruritus and or PONV should it be required at any time post-operatively.

Standard of Care rescue medications for pruritus:

- First line: PRN nalbuphine.
- Second line PRN diphenhydramine.

Standard of care rescue medication for PONV:

- First line: PRN prochlorperazine.
- Second line:. promethazine

4 SUBJECT SELECTION

4.1 Subject Recruitment

4.1.1 Inclusion Criteria

1. Age: 3-17 years, inclusive and wt </= 100kg

2. Scheduled for any procedure necessitating ITM

3. Ability to use verbal or pictorial pain assessment tools and techniques

4. Informed consent and assent (if applicable)

4.1.2 Exclusion Criteria

1. Inability to use verbal or pictorial scoring scales

2. Hypersensitivity to selective 5-HT_3 receptor antagonists

3. Diagnosed congenital long QT syndrome
4. Current use of any medications that prolong QT interval
5. Severe hepatic impairment
6. Pregnancy or nursing mothers
7. Use of serotonin specific reuptake inhibitors within 14 days
8. Use of serotonergic-noradrenergic reuptake inhibitors within 14 days

5 STUDY TREATMENTS

5.1 Allocation to Treatment

Subjects will be randomized via previously generated random numbers table and stratifying for female gender.

5.2 Breaking the Blind

The randomization can be broken, if necessary per the physicians caring for the subject to ensure subject safety. In the case of such a medical emergency, the blind will be broken by the study pharmacist or pharmacy designee.

5.3 Drug Supplies

5.3.1 Formulation, Preparation and Dispensing

All study drugs for this study are available on formulary. The study pharmacist will have access to the random numbers table denoting group assignment and will prepare the blinded study drug for each patient and deliver it the appropriate operating room on the day of surgery.

5.3.2 Drug Storage and Drug Accountability

All study medications are stored in accordance with Mott OR Pharmacy standards. Drug accountability will be maintained by the study pharmacist and designated and trained Mott OR Pharmacy staff.

6 STUDY PROCEDURES

6.1 Screening

Subjects will be identified 2 ways:

1. Review of the applicable clinic schedules
2. Review of the daily Operating Rooms schedule

6.2 Treatment Study Period

6.2.1 Day of Surgery through 24 hours post-operative

Preoperatively, the medical history will be reviewed to confirm that no exclusion criteria have developed since informed consent.

In the operating room, the subject will receive an intra-operative bolus dose of study drug labeled “antipruritic study drug” (ondansetron, 0.1mg/kg or placebo) IV, prior to intrathecal

morphine injection, followed by around-the-clock study drug labeled “antipruritic study drug” (ondansetron doses, of 0.1mg/kg or placebo) IV every 6 hours for 24 hours from OR end time.

Subjects in the operating room, recovery room, and PACU will be monitored as per standard clinical care.

Data collection

For the first 24 hours after surgery, subjects will be visited in the Post Anesthesia Care Unit (PACU), the evening of surgery, the next morning and at 24 hours postoperatively (not between the hours of 10p-7a) to obtain the presence and degree of adverse effects, our primary outcomes. Pruritus will be scored similar to previous pediatric studies, as 0 = none; 1 = mild/tolerable/not requiring treatment; 2 = severe/intolerable/requiring treatment (12). We will use a similar method to quantify the amount of nausea/vomiting each patient experiences (0 = no nausea/vomiting; 1 = mild/tolerable nausea/vomiting not requiring treatment; 2 = severe/intolerable nausea/vomiting requiring treatment) (14). The following data will also be collected: all analgesics, antiemetic, and antipruritic agents used.

SCHEDULE OF ACTIVITIES

Protocol Activity	Screen	Day of surgery	Follow-up: OR end +24 hrs
Informed Consent	X		
Review of medical history	X	X	
Vitals	X	X	
Randomization		X	
Treatment with study agent		X	X
Pruritus and PONV assessment			X
Adverse Event Assessment		X	X
Concomitant Medication	X	X	X

Note: Pregnancy test is performed as standard of care for all post-menarchal females scheduled for surgery at C. Mott Children's Hospital.

7 ASSESSMENTS

7.1 Primary Endpoint Assessments

For the first 24 hours, subjects will be visited in the PACU, the evening of surgery, the next morning and at 24+/-3 hours (not between the hours of 10p-7a) to obtain the presence and degree of adverse effects, our primary outcomes. Pruritus will be scored similar to previous pediatric studies, as 0 = none; 1 = mild/tolerable/not requiring treatment; 2 = severe/intolerable/requiring treatment (12).

7.2 Secondary Assessments

We will use a similar method to quantify the amount of nausea/vomiting each patient experiences (0 = no nausea/vomiting; 1 = mild/tolerable nausea/vomiting not requiring treatment; 2 = severe/intolerable nausea/vomiting requiring treatment) (14).

8 ADVERSE EVENT REPORTING

Adverse Event Definition
An adverse event (AE) is any untoward medical occurrence in a subject participating in an investigational study or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory and vital sign findings), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

These events may be:

a. *Definitely related:* clearly associated with study drug/treatment
b. *Probably related*: likely associated with study drug/treatment
c. *Possibly related*: may be associated with study drug or other treatment
d. *Unlikely to be related*, or
e. *Definitely not related* to the study drug/treatment

For reporting purposes, an AE should be regarded as definitely or probably related to the regimen if the investigator believes that at least one of following criteria are met:

a. There is a clinically plausible time sequence between onset of the AE and the administration of the study drug or treatment.
b. There is a biologically plausible mechanism for the study drug or treatment causing or contributing to the AE.
c. The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.
d. A potential alternative cause does not exist.

Serious Adverse Events (SAE): An adverse drug experience occurring at any dose that results in any of the following outcomes:

a. Death
b. A life-threatening adverse drug experience
c. Inpatient hospitalization or prolongation of existing hospitalization
d. A persistent or significant disability &/or incapacity
e. A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A serious adverse experience includes any experience that is fatal or immediately life threatening, results in a persistent or significant disability/incapacity, requires or prolongs in-patient hospitalization, or is a congenital anomaly, cancer, or overdose.
Other important medical events that may not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously.

Expected adverse events are those adverse events that are listed in the protocol, the Investigator's Brochure (current edition) or in the study informed consent document.

Unexpected adverse events are those that:

a. are not described in the labeling for Ondansetron
b. are not anticipated in the study informed consent. This includes adverse events for which the specificity or severity is not consistent with the description in the informed consent.

Unanticipated problem: Per FDA Procedural Guidance for Clinical Investigators, Sponsors, and IRBs (January 2009), A serious problem that has implications for the conduct of the study (requiring a significant and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent or investigator's brochure).

Unanticipated problem Reporting: Per 21 CFR 312.66, 312.53 (c)(1)(vii), and 56.108(b)(1), should an Unanticipated problem occur during the investigation, the investigator will promptly report all unanticipated problems involving risks to human subjects or others to IRBMED.

The severity or grade of an adverse event may be measured using the following definitions:

Mild: Noticeable to the subject, but does not interfere with subject's expected daily activities, usually does not require additional therapy or intervention, dose reduction, or discontinuation of the study.

Moderate: Interferes with the subject's expected daily activities, may require some additional therapy or intervention but does not require discontinuation of the study.

Severe: Extremely limits the subject's daily activities and may require discontinuation of study therapy, and/or additional treatment or intervention to resolve.

Event reporting: The study will comply with the IRB reporting requirements and guidelines.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until hospital discharge. AEs and serious adverse events (SAEs) will be recorded in the subject's source documents. All SAEs must be reported to the IRB according to the University of Michigan IRB reporting requirements.

9 DATA ANALYSIS/STATISTICAL METHODS

9.1 Sample Size Determination

Anticipating study drug to result in 50% decrease in pruritus from current rate of pruritus for those patients receiving ITM, we need to enroll 56 patients per group to achieve 80% power.

9.2 Data Analysis

Data will be summarized using descriptive methods. Parametric data will be analyzed between groups using unpaired t tests or Mann Whitney U, as appropriate. Rankings of pruritus and PONV will be coded as none-mild vs. severe and Chi-squared and Fishers' Exact tests will be used to compare these outcomes between groups. Significance will be accepted at the 5% level.

10 MONITORING

10.1 Data Safety and Monitoring Board (DSMP)

This study has a DSMP. An interim analysis will be done when we have reached 20 patients per group. At this point, the statistician will break the blind, and the PI Dr. Elizabeth Putnam along with Co-I Dr. Rebecca Hong will review the incidence of pruritus and nausea and vomiting in both groups to examine whether it is higher than expected.

Events will be reported to the IRB according to the "Standard Adverse Event Reporting Guidelines for INTERNAL AEs Occurring at UM". Accordingly, any non-serious unrelated AE, will be reported in aggregate at the IRB continuing review. Serious adverse events (SAEs) will be reported within 14 calendar days if related to the study. SAEs that are NOT related to study participation will be reported in aggregate at scheduled continuing review. Any study-related SAE will be reported within 14 calendar days of becoming aware of the event. Any SAE resulting in death or life-threatening outcome will be reported as soon as possible but not later than 7 calendar days of becoming aware of the event.

DATA HANDLING AND RECORD KEEPING

10.2 CRFs / Electronic Data Record

We will use paper CRFs and data entry will be performed using StatView in a password protected, UM maintained computer. CRFs will be kept in a cabinet in locked research office in the department of pediatric anesthesiology.

10.3 Record Retention

Records will be retained according to IRBMED Guidelines for record retention.

11 ETHICS

11.1 Institutional Review Board (IRB)

Before implementing this study, the protocol, the proposed informed consent form and other information to be provided to subjects, must be reviewed by a properly constituted Institutional Review Board (IRB). Any amendments to the protocol must be reviewed and approved by IRBMED.

11.2 Ethical Conduct of the Study

Subject Information and Consent

The study team member will explain to each subject and parental unit/s (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject's parent will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect subsequent medical treatment or relationship with the treating physician.

This parental informed consent will be given by means of a standard written statement, written in non-technical language. The subject's parent should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject's parent cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient's parent could not read or sign the documents. No patient can enter the study before parental informed consent, as well as child assent, if applicable, has been obtained.

Subjects age 10 years and older will be provided an assent document. An age appropriate discussion of the study will take place and the child will have opportunity to have all questions answered and will sign the document if he/she agrees to participate. A copy will be given to the parent. If the child refuses assent, the subject will not be included in the study.

The informed consent form and pediatric assent forms are considered to be part of the protocol, and will be submitted for IRB approval.

11.3 STUDY DISCONTINUATION CRITERIA

11.3.1 Stopping Rules for Safety reasons

The Study team will review all Serious Adverse Events (SAEs) and make recommendations regarding the continuation or discontinuation of the study, as appropriate.

11.3.2 Rules for Discontinuation of a Subject

In the event a patient drops out of the study or is discontinued due to protocol violations, all attempts will be made to exit the patient in accordance with the protocol requirements.

12 REFERENCES

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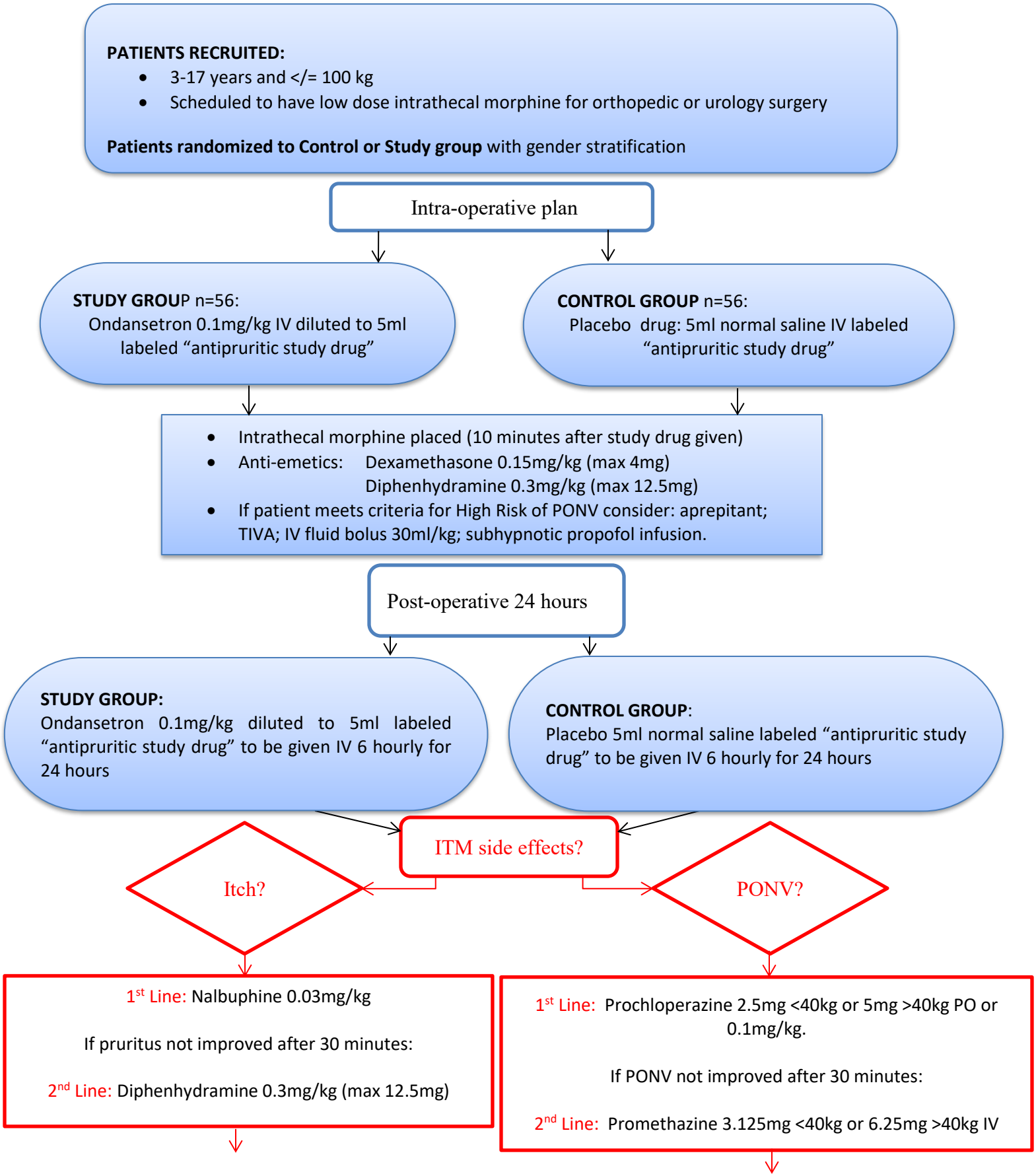
APPENDIX A – Protocol Algorithm



If symptoms still inadequately treated, contact MD (APS Fellow). Further orders at provider's discretion.