

Intravenous Versus Oral Acetaminophen for Postoperative Pain Control After Cesarean Delivery

NCT02487303

August 31, 2015

|

**Medical University of South Carolina
Protocol**

PI Name: Sylvia H. Wilson

Study Title: Efficacy of Intravenous versus Oral Acetaminophen for Postoperative Pain Control after Cesarean Delivery

Once protocol is complete, save it as a Word document. Go back to the IRB application and upload the protocol.

TABLE OF CONTENTS – Prepare a table of contents based on the following outline, including page numbers, and insert here.

- A. Specific Aims: Page 1
- B. Background and Significance: Page 2
- C. Preliminary Studies: Page 2
- D. Research Design and Methods: Page 2
- E. Protection of Human Subjects: Page 3
 - E1. Risks to Subjects: Page 3
 - E2. Adequacy of Protection Against Risks: Page 5
 - E3. Potential Benefits of the Proposed Research to the Subjects and Others: Page 5
 - E4. Importance of Knowledge to be Gained: Page 6
 - E5. Subject Safety and Minimizing Risks: Page 6
- F. References/Literature Citations: Page 7

A. SPECIFIC AIMS

List the broad, long-term objectives and the goal of the specific research proposed, e.g., to test a stated hypothesis, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, or develop new technology.

The purpose of this study is to evaluate the efficacy of intravenous (IV) acetaminophen when compared to oral (PO) acetaminophen.

B. BACKGROUND AND SIGNIFICANCE

Briefly sketch the background leading to the present application, critically evaluate existing knowledge, and specifically identify the gaps that the project is intended to fill. State concisely the importance and health relevance of the research described in this protocol by relating the specific aims to the broad, long-term objectives. If the aims of the study are achieved, state how scientific knowledge or clinical practice will be advanced.

There is established efficacy of IV acetaminophen for perioperative pain control [1-3]; however, there is very little prospective literature comparing IV acetaminophen to oral formulations in the surgical populations. Multimodal and narcotic sparing pain control strategies have been shown to improve outcomes. [1-2] IV acetaminophen represents a potential benefit to parturients to improve postoperative pain control, decrease narcotic side effects, and improve patient safety and satisfaction. The literature suggests that the slowing of gut motility in the perioperative setting may limit the absorption and efficacy of oral formulations of acetaminophen. [3-4] This study will evaluate if there is a clinically significant improvement in pain control, in addition to improvement in other outcomes such as patient satisfaction, ambulation time, and readiness for discharge, for post-cesarean parturients when IV acetaminophen is used.

IV acetaminophen has a proven quick onset of action of 15 minutes versus 1 hour for the oral formulation. [4] There is also a higher peak plasma concentrations in IV formulation, and CSF levels are linearly related to plasma levels, which may provide overall improved efficacy in the parenteral formula. In addition, gut motility decreased perioperatively, causing onset of oral acetaminophen to be delayed for

up to 60-80 minutes. [2] The only prior study to compare IV to oral acetaminophen examined patients with tooth extractions. [5] Study subjects were given one dose of either oral acetaminophen 45 minutes preoperatively or IV acetaminophen after anesthesia induction. This study found equivalent VAS scores at 1 hour postoperatively. However, this was a minimally invasive procedure with little effect on gut motility, limited evaluation of postoperative pain control, and poor generalization to our parturient population.

One prior study has evaluated the use of IV acetaminophen for postoperative pain following Cesarean delivery.[6] In this study, they compared IV acetaminophen to oral ibuprofen. VAS scores and cumulative opiate consumption were similar in both groups. Our study would differ since all of our patients would receive ketorolac IV as part of their postoperative care and then be randomized to oral, IV or no acetaminophen.

If we successfully find that IV acetaminophen is superior to oral formulations it would become an additional modality for postoperative pain control that would be valuable in the post-cesarean population.

The primary aim of the study would evaluate total opiate consumption in morphine equivalents in the first 24 hours postoperatively following cesarean delivery. Subjects would receive either IV acetaminophen, oral acetaminophen, or no acetaminophen. All subjects would receive our institution's current standard of care for post-operative pain control regimen in this setting. Secondary outcomes will include VAS measurements, side effects to opiates (nausea, vomiting, prutitus), patient satisfaction, time to discharge criteria and 48 hours opiate consumption. We hypothesize that IV acetaminophen will provide superior postoperative pain control, decreased opioid consumption, improved patient quality measures, and overall improved patient satisfaction with pain control when added to this institution's current standard of care.

C. PRELIMINARY STUDIES

Provide an account of the principal investigator's preliminary studies pertinent to this protocol and/or any other information that will help to establish the experience and competence of the investigator to pursue the proposed project.

Dr. Wilson has performed numerous prior prospective and retrospective studies examining analgesia and patient comfort in relation to systemic analgesics, regional analgesia and obstetric anesthesia.

D. RESEARCH DESIGN AND METHODS (including data analysis)

Describe the research design and the procedures to be used to accomplish the specific aims of the project. Include how the data will be collected, analyzed, and interpreted and specify what statistical methods will be used. Describe any new methodology and its advantage over existing methodologies. Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims. As part of this section, provide a tentative sequence or time-table for the project. Point out any procedures, situations, or materials that may be hazardous to personnel and the precautions to be exercised.

This study will compare IV versus oral acetaminophen for postoperative pain in parturients after scheduled, elective Cesarean delivery. It is designed as a randomized, open label, controlled trial. All patients will receive a standardized spinal anesthetic for operative anesthesia and will be randomized into one of three groups: (group 1) 1 gram IV acetaminophen every 8 hours for three doses, (group 2) 1 gram oral acetaminophen every 8 hours for three doses, or (group 3) no acetaminophen. This will be a computer generated randomized, open label study. The study drugs will be stored and dispensed by MUSC's Investigational Drug Services Pharmacy.

All patients will receive the standard of care for Cesarean delivery intraoperatively and postoperatively. Intraoperative anesthetic care will be standardized to intraoperative spinal anesthetic with 12mg of 0.75% bupivacaine, 15mcg of fentanyl, and 0.2mg of preservative-free morphine. This is our standard practice and also a well studied anesthetic care for Cesarean delivery. [7-9]

Following delivery, postoperative pain control will be standardized to include IV ketorolac 30 mg every 6 hours for 24 hours and oral oxycodone and IV morphine as needed for breakthrough pain control. In the post anesthesia care unit (PACU), study participants will receive the first dose of IV ketorolac and, as randomized, their first dose of either oral or IV acetaminophen (groups 1 and 2) or no acetaminophen (group 3). Once transferred to the floor, all patients will continue to receive the randomized scheduled study drug and scheduled IV ketorolac. Patients are eligible to receive an as needed standardized opiate pain control regimen including oxycodone 5-10 mg orally (5 mg for pain scales of 4-6 and 10 mg for pain scales of 7-10). Pain will be reassessed one hour after oral

oxycodone. If pain is poorly controlled then patients are eligible to receive IV morphine 2 mg every 2 hours for rescue pain control in the first 12 hours post-operatively. From 12-24 hours postoperatively, IV morphine will be given after assessment by an anesthesia provider to ensure patient safety due to the bi-modal metabolism of morphine and the concern for delayed respiratory depression seen with intrathecal morphine administration, consistent with our current institutional practice. Patients' respiratory rate and level of sedation will be monitored every 1 hour for 12 hours and then every 2 hours for the following 12 hours while on the ward.

Primary outcome for this study will be total opiate consumption in first 24 hours postoperatively. Secondary outcomes include: time to first narcotic rescue dose, subjective pain rating using visual analogue scales (VAS) at 24 hours postoperatively at rest and with ambulation, opiate consumption at other time points (12, 36, and 48 hours) time to first ambulation, overall patient satisfaction with pain control, time to meet discharge criteria (ambulation, oral diet, voiding/foley removal, and satisfactory pain control), and presence of opiate side effects (nausea, vomiting, and pruritus).

Inclusion/Exclusion Criteria will be determined by chart review and patient interview during their anesthesia work up.

Inclusion criteria consist of any parturient 18 years and older undergoing elective Cesarean delivery under spinal anesthesia who is able to consent to the study and participate in the follow-up.

Exclusion criteria include: weighing under 50 kgs, any known allergy to acetaminophen, general anesthesia, urgent or emergent cases, any bleeding diathesis or other coagulopathy, known G6PD deficiency, any known liver disease, known alcohol abuse or dependence, HELLP syndrome, thrombocytopenia or known platelet dysfunction, history or active gastrointestinal bleeding, acute kidney injury or chronic renal insufficiency, contraindication/refusal to spinal anesthetic, chronic pain, chronic narcotic use, illicit drug use or allergy to any study related medications.

Power analysis:

Based on a study conducted by Wong et al. [7], we expect mean morphine consumption at 24 hours to be 45 +/- 35 mg. A sample size of 47 subjects per group would achieve 80% power to detect a 30% difference (~ 13.5 mg) in morphine consumption between groups at a Bonferroni adjusted significance level of alpha = 0.033 using 4 repeated measures and assuming a first-order auto-regressive correlation structure with moderate correlation of 0.3 and assuming the standard deviation is 35 mg. Therefore, the study will require a sample size of 141 patients.

E. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics

- *Describe the proposed involvement of human subjects.*
- *Describe the characteristics of the subject population, including their anticipated number, age range and health status.*

141 subjects will be enrolled in this study. All subjects will be 18 years old or over and scheduled for cesarean delivery.

Risks include allergic reaction, hepatotoxicity and skin reactions.

Risk of allergic reaction to acetaminophen may include: hives, difficulty breathing, swelling of your face, lips, tongue, or throat.

Risk of hepatotoxicity may include: dark urine, jaundice, increased liver enzymes. These symptoms are usually associated with acetaminophen toxicity or use of acetaminophen with liver disease or alcoholism.

Skin reactions may include: acute generalized exanthematous pustulosis, Steven-Johnson Syndrome and toxic epidermal necrolysis.

There is a risk of loss of confidentiality.

Targeted/Planned Enrollment Table

Total Planned Enrollment 141

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	20	0	
Not Hispanic or Latino	121	0	
Ethnic Category: Total of All Subjects*	141		
Racial Categories			
American Indian/Alaska Native	0		
Asian	2		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	55		
White	84		
Racial Categories: Total of All Subjects*	141	0	141

*The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects".

- Identify the criteria for inclusion or exclusion of any subpopulation.
- Explain the rationale for the involvement of special classes of subjects, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins.
- If you propose to exclude any sex/gender or racial/ethnic group, include a compelling rationale for the proposed exclusion. For example, 1) the research question addressed is relevant to only one gender or 2) evidence from prior research strongly demonstrates no difference between genders.
- Provide either a description of the plans to include children or, if children will be excluded from the proposed research, then you must present an acceptable justification for the exclusion. For example, 1) the condition is rare in children as compared to adults or 2) insufficient data are available in adults to judge risk in children.
- List any collaborating sites where human subjects research will be performed, and describe the role of those sites in performing the proposed research.

Subjects will neither be selected nor excluded based on ethnicity. The only reason for exclusion based on ethnic category is the inability to speak English. Our interpreters service are limited in time and availability. Parturients less than 18 years of age will also be excluded since they are not able to consent for themselves.

b. Sources of Materials

- Describe the research material obtained from living human subjects in the form of specimens, records, or data.
- Describe any data that will be recorded on the human subjects involved in the project.
- Describe the linkages to subjects, and indicate who will have access to subject identities.
- Provide information about how the specimens, records, or data are collected and whether material or data will be collected specifically for your proposed research project.

The following data will be collected from the subjects medical record or interview: time to first narcotic rescue dose, subjective pain rating using visual analogue scales (VAS) at 24 and 48 hours postoperatively at rest and with ambulation, opiate consumption at (12, 36, and 48 hours). The time to first ambulation, overall patient satisfaction with pain control, time to meet discharge criteria (ambulation, oral diet, voiding/foley removal, and satisfactory pain control), and presence of opiate side effects (nausea, vomiting, and pruritus).

Upon enrollment, subjects will be assigned a randomized numerical identifier for the remainder of the study. This number will be used to label charts and paperwork associated with the subject. An electronic enrollment log will link patient name and MRN with his/her study ID number. All paper information will be kept in a locked cabinet in a locked office. All electronic data will be kept on MUSC's password protected server.

c. Potential Risks

- *Describe the potential risks to subjects (physical, psychological, social, legal, or other), and assess their likelihood and seriousness to the subjects.*
- *Where appropriate, describe alternative treatments and procedures, including the risks and benefits of the alternative treatments and procedures to participants in the proposed research.*

Risk: Acetaminophen can damage the liver if given in large amounts. Consequently, we will utilize only 75% of the maximum daily dose. (The maximum daily dose is 4g. We will administer only 3g given as 1g every 8 hours for 24 hours.) Subjects will also not be given any other acetaminophen during the study period. We will also exclude subjects with a history of or current liver dysfunction or alcohol abuse.

Alternative: Patients may choose to not participate or withdraw from the study at any time.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

- *Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.*
- *Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent.*

A study team member will inform a potential participant of the study prior to elective Cesarean delivery. This may be done at the preoperative visit or on the day of surgery. Participants will be given time to read the informed consent/HIPAA and have all of their questions answered prior to enrollment. If subjects choose to participate, consent will be documented in writing. All participants will be 18 years old or older and able to consent.

b. Protection against Risk

- *Describe planned procedures for protecting against or minimizing potential risks, including risks to confidentiality, and assess their likely effectiveness.*
- *Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects.*
- *Studies that involve clinical trials (biomedical and behavioral intervention studies) must include a description of the plan for data and safety monitoring of the research and adverse event reporting to ensure the safety of subjects in Section 4 below.*

Acetaminophen is an FDA approved medication however; too much acetaminophen can harm the liver. The recommended maximum daily dose is 4g in 24 hours. While the IV formulation was only approved by the FDA in the last 3 years, it has been utilized in Europe for decades with excellent safety. Therefore, we are utilizing only 75% of the maximum dose (3g administered as 1g every 8 hours for 3 doses over 24 hours) and excluding patients with a history of hepatic disease or alcohol abuse.

Allergic reaction to acetaminophen is possible. Any reaction to the study drug will be treated per MUSC protocol for drug reactions and the medication will be discontinued. Any potential participant with an allergy to acetaminophen will be excluded from the study.

If any of the listed skin reactions (please see E1) occur the study drug will be stopped immediately.

The study team will make every effort to prevent a loss of confidentiality. All study team members will be properly trained on the procedures necessary to protect the participants information by keeping data in a locked cabinet, in a locked office and electronic data will be kept on a MUSC password protected server.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

- *Discuss the potential benefits of the research to the subjects and others.*
- *Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.*

Establishing the efficacy of IV acetaminophen over the oral formulation is relevant in order to improve postoperative pain control following abdominal surgery. All patients will receive the standard of care at MUSC. Patients also receiving any acetaminophen may experience improved analgesia without increased exposure to opiates or opiate related side effects. Subjects receiving IV acetaminophen may experience further analgesia if it is superior to the oral formulation.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

- Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.
- Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.
- NOTE: Test articles (investigational new drugs, devices, or biologicals) including test articles that will be used for purposes or administered by routes that have not been approved for general use by the Food and Drug Administration (FDA) must be named. State whether the 30-day interval between submission of applicant certification to the FDA and its response has elapsed or has been waived and/or whether use of the test article has been withheld or restricted by the Food and Drug Administration, and/or the status of requests for an IND or IDE covering the proposed use of the test article in the research plan.

There is established efficacy of IV acetaminophen for perioperative pain control [1-3]; however, there is very little prospective literature comparing IV acetaminophen to oral formulations in the surgical populations. Multimodal and narcotic sparing pain control strategies have been shown to improve outcomes. [1-2] IV acetaminophen represents a potential benefit to parturients to improve postoperative pain control, decrease narcotic side effects, and improve patient safety and satisfaction. The literature suggests that the slowing of gut motility in the perioperative setting may limit the absorption and efficacy of oral formulations of acetaminophen. [3-4] This study will evaluate if there is a clinically significant improvement in pain control, in addition to improvement in other outcomes such as patient satisfaction, ambulation time, and readiness for discharge, for post-cesarean parturients when IV acetaminophen is used.

5. SUBJECT SAFETY AND MINIMIZING RISKS (Data and Safety Monitoring Plan)

*Studies that involve *clinical trials (see description below) must include a description of the plan for subject safety and minimizing risks of the research, including data monitoring and adverse event reporting to ensure the safety of subjects. The complexity of the plan should be determined by the level of risk to subjects. The plan should specify: 1) what will be monitored, 2) how frequently the monitoring will occur, 3) who will be responsible for the monitoring, and 4) study endpoints.*

Data and safety monitoring will be performed by the research study committee in the Department of Anesthesia and Perioperative Medicine on a quarterly basis. The committee is comprised of several attending anesthesiologists, the chairmen of anesthesiology and an emeritus dean of medicine. Any adverse events will be reported to MUSC's IRB per protocol and will be evaluated by the committee. The primary endpoint of this study is to determine the efficacy of IV acetaminophen in post cesarean pain.

***Clinical Trials**

A clinical trial is a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective. Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits these criteria of a clinical trial. Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision-making for the subject or the test itself imposes more than minimal risk for subjects.

F. REFERENCES/LITERATURE CITATIONS

List all references. Each reference must include the title, names of all authors, book or journal, volume number, page numbers, and year of publication. The reference should be limited to relevant and current literature. It is important to be concise and to select only those literature references pertinent to the proposed research.

1. Macario A, Royalf M. A Literature Review of Randomized Clinical Trials of Intravenous Acetaminophen (Paracetamol) for Acute Postoperative Pain. *Pain Pract* 2010;11(3):290-96.
2. Smith HS. Perioperative Intravenous Acetaminophen and NSAIDs. *Pain Med* 2011;12(6):961-81.
3. Wininger SJ, Miller H, Minkowitz HS, Royal MA, Ang RY, Breitmeyer JB, Singla NK. A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Repeat-Dose Study Of Two Intravenous Acetaminophen

Dosing Regimens For The Treatment Of Pain After Abdominal Laparoscopic Surgery. Clin Ther 2010;32(14):2348-69.

4. Singla NK, Parulan C, Samson R, Hutchinson J, Bushnell R, Beja EG, Royal MA. Plasma and Cerebrospinal Fluid Pharmacokinetic Parameters After Single-Dose Administration of Intravenous, Oral, or Rectal Acetaminophen. *Pain Pract* 2012;12(7):523-32.
5. Fenlon S, Collyer J, Giles J, Bidd H, Lees M, Nicholson J, Dulai R, Hankins M, Edelman N. Oral vs intravenous paracetamol for lower third molar extractions under general anaesthesia: Is oral administration inferior? *Br J Anaesth* 2013;110(3):432-7.
6. Alhashemi JA, Alotaibi QA, Mashaat MS, Kaid TK, Mujallid RH, Kaki AM. Intravenous acetaminophen vs oral ibuprofen in combination with morphine PCA after Cesarean delivery. *Can J Anesth* 2006;53(12):1200-6.
7. Wong J, Carvalho B, Riley E. Intrathecal morphine 100 and 200 microgram for post-cesarean delivery analgesia: A trade-off between analgesic efficacy and side effects. *Int J Obstet Anesth* 2013;22(1):36-41.
8. Singh SI, Rehou S, Marmai KL, Jones AP. The Efficacy of 2 Doses of Epidural Morphine for Postcesarean Delivery Analgesia. *Anesth Analg* 2013;117(3):677-85.
9. Beatty N, Arendt K, Niesen A, Wittwer E, Jacob A. Analgesia after Cesarean delivery: A retrospective comparison of intrathecal hydromorphone and morphine. *J Clin Anesth* 2012;25(5):379-83.

G. CONSULTANTS

Where applicable, attach electronic versions of appropriate letters from all individuals confirming their roles in the project. Go to the application under “additional uploads” to attach this information.

H. FACILITIES AVAILABLE

Describe the facilities available for this project including laboratories, clinical resources, etc.

I. INVESTIGATOR BROCHURE

If applicable, attach the electronic version of the investigator brochure. Go to the application under “additional uploads” to attach this information.

J. APPENDIX

Attach any additional information pertinent to the application, such as surveys or questionnaires, diaries or logs, etc. Go to the application under “additional uploads” to attach this information.