Improving Post-Operative Pain and Recovery in Gynecologic Surgery

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Michaela Beynon, MD
Sareena Singh, MD
Ob/Gyn Department
Aultman Health Foundation
2600 6th St SW
Canton, OH 44710

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1.0 INTRODUCTION

The objective of this research project is to demonstrate that acetaminophen, whether administered rectally or intravenously, reduces post-operative pain, use of opioid medications, and thus improves the overall recovery process after minimally invasive gynecologic surgery.

1.1 Abstract

This is a clinical investigation to determine the efficacy of rectal versus intravenous acetaminophen in patients undergoing a minimally invasive hysterectomy. All women will receive acetaminophen either rectally or intravenously immediately postoperative, prior to extubation. Patient's will be randomly assigned to either the rectal acetaminophen or the intravenous acetaminophen group. Patient outcomes will be measured through a Numeric Rating Scale (NRS) from 0-10 for pain scores, and total opioid consumption measured in morphine milligram equivalent (MME) for the first 24 hours following surgery, or upon discharge, whichever comes first.

1.2 Background/Rationale

Patient's undergoing major gynecologic surgery require effective postoperative pain management in order to enhance recovery and ultimately allow patients to return to their preoperative functional state. Traditionally, acute postoperative pain control has been achieved largely with the use of opioid medications. Excessive use of opioids can have adverse effects on the recovery process. Side effects include, but are not limited to dizziness, sedation, nausea/vomiting, respiratory depression, euphoria, constipation, and abuse (1). In addition, opioid monotherapy can delay post-operative ambulation, contribute to prolonged hospital stay and resumption of activities of daily living, and furthermore, have long-term sequelae for individuals as well as society at whole (1).

Over the past decade, a multimodal approach to pain management has been explored in attempts to optimally treat acute postoperative pain (1-3). This approach is one of the keys to improving the recovery process.

Acetaminophen is a non-opioid analgesic with a well-established safety and tolerability profile that is commonly used in multimodal approach to treating surgical pain. It is available in oral, rectal and Intravenous (IV) formulation. IV acetaminophen in particular is increasingly used for pain control after surgery as it has demonstrated a significant analgesic benefit in a variety of surgery types by reduction in pain intensity while decreasing total opioid use (3,4). Many studies have evaluated the efficacy of acetaminophen based on route of administration. A systematic review demonstrated that there is no clear indication for intravenous acetaminophen for patients who can tolerate an oral dosage as there was no difference if efficacy outcomes (5). This is valuable information as the cost of IV acetaminophen is exponentially more than the oral form. Although the oral form of acetaminophen is as efficient as controlling pain when compared to IV, and is notably cheaper, it is not the best option for the nauseated patient or patients whom are restricted from oral intake following surgery. Rectal acetaminophen is therefore a feasible alternative option in such patients.

Data on the use of rectal acetaminophen in adults for postoperative pain management is limited. Pettersson and colleagues (2005) compared oral, rectal and IV paracetamol in day surgery patients. Although they demonstrated significantly higher plasma paracetamol concentrations in patients who received oral and IV formations at multiple

time points, there was no difference in pain ratings. In another study, rectal paracetamol was shown to have a significant morphine-sparing effect after hysterectomy (7).

At this time, there has been no study in the gynecologic literature to compare IV to rectal acetaminophen in terms of pain control and effect on overall opioid use in the acute post-operative period.

The rationale for this study is to determine the optimal way of managing post-operative pain in gynecologic surgery in attempt to improve the overall recovery process. More specifically, this study will determine if the route of administration of acetaminophen has an effect on post-operative pain and use of opioid medication following a minimally invasive hysterectomy. The results of this study may guide post-operative pain management after gynecologic surgery, and help limit the amount of opioid use, while potentially reducing pharmacological costs for patients and hospitals.

2.0 OBJECTIVES/STUDY AIMS

2.1 Primary Objective: To demonstrate that rectal acetaminophen is not inferior to intravenous acetaminophen in decreasing subjective acute postoperative pain after a minimally-invasive hysterectomy.

2.2 Secondary Objective: To demonstrate that rectal acetaminophen is not inferior to intravenous acetaminophen in decreasing opioid use during the hospital admission.

3.0 SUBJECT SELECTION [ELIGIBILITY]

The study population will consist of all patients undergoing a minimally-invasive simple hysterectomy (total laparoscopic hysterectomy with or without robotic assist) for benign or malignant conditions.

3.1 Inclusion Criteria

Patients eligible for inclusion in this study have to fulfill the following criteria:

- Female patients age ≥ 18 years old
- Willing to consent
- Amendable to receive either rectal or intravenous acetaminophen
- Planned hospital stay for at least 24 hours

3.2 Exclusion Criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study:

- Patients unable to provide informed consent
- Patients with a history of regular opioid use prior to surgery based on their current home medication list.
- Patients who have required regular opioid intake for the 7 days preceding surgery
- Patients with known hypersensitivity to acetaminophen
- Patients with a baseline preoperative liver function enzymes (AST and ALT) that are greater than twice the upper limits
- Unable to complete procedure as planned

4.0 SUBJECT ENROLLMENT

4.1 Where will recruitment occur?

Recruitment will occur prior to the day of surgery. Patient's will be screened to ensure they are eligible for inclusion based on inclusion and exclusion criteria. The study will be discussed with patients who are eligible, and patients will be given a copy of the consent form to take home and review. This encounter will be documented in the patient's medical record.

4.2 Where and when will consent be obtained?

After the patient has had ample time to review the consent form and have all questions answered, the consent will be signed. This will be done in the office or in the Same Day Surgery Unit at Aultman Hospital prior to the start of the operation, and prior to admission of any sedating medications.

4.3 Who will obtain consent?

Either Dr. Singh, or Dr. Beynon, or any other investigator involved in the study, will obtain consent.

4.4 What procedures will be used for screening?

Dr. Singh's office schedule will be reviewed to identify patients that are scheduled for a minimally-invasive simple hysterectomy. Patients will be evaluated during a pre-operative visit to determine if they are eligible to participate in the study.

4.5 What happens with screen failures (including any data gathered during screening)?

Any patient that does not receive protocol prescribed acetaminophen will not be included in the final analysis.

5.0 STUDY DESIGN/PROCEDURES

5.1 Potential Subject Identified

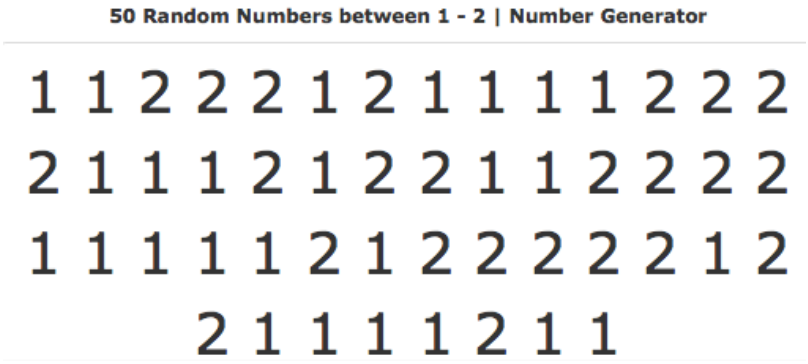
Dr. Singh's office schedule will be reviewed to identify patients that are scheduled for a minimally-invasive simple hysterectomy. When a potential patient is identified, Dr. Singh and Dr. Beynon will be notified and proceed with a more in-depth patient interview during a pre-operative visit.

5.2 Obtain Informed Consent

Either Dr. Singh or Dr. Beynon, or any other investigator involved in the study, will obtain consent after the patient has reviewed the entire consent and all questions have been answered. Consent will be documented by having the patient sign the consent document and authorization for use of protected health information. After consent has been obtained, the subject will be assigned to the rectal acetaminophen group or the intravenous acetaminophen group. The signed consent form will remain part of the patients' medical record.

5.3 Pre-operative Randomization

Patients will be randomly assigned to receive rectal acetaminophen or intravenous acetaminophen using a random number generator. Patients randomly assigned to group 1 will be in the rectal acetaminophen study group. Patients randomly assigned to group 2 will be in the intravenous acetaminophen study group.



5.4 Pre-operative Orders

Pre-operative orders will be standardized and include VTE prophylaxis with SCDs and preoperative antibiotics with a first generation cephalosporin or an appropriate alternative.

5.5 Medication administration

Patients will receive either rectal or intravenous acetaminophen at the end of the surgery, just prior to extubation and awakening. Patients receiving the rectal acetaminophen will receive two 650mg suppositories rectally for a total dose of 1300mg, which has been used in prior pharmacokinetic studies (7). Patients receiving intravenous acetaminophen will receive one dose of 1000mg. The route of administration will be recorded in the patient's medical record. Patients will be blind to their study group. Storage and dispensing of medication will be under the direction of the Aultman Pharmacy department pursuant to physician order.

5.6 Post-operative Orders

All patients included in the study will receive the same post-operative order set. Patients will not have access to additional non-opioid medications, such as acetaminophen or ibuprofen products for pain control for the first 24 hours post-op, or until discharge whichever comes first. Patients will have oral Oxycodone available upon patient request. Intravenous Morphine or an appropriate alternative (i.e., Dilaudid) will be available for breakthrough pain. Patients will receive opioid medications based on their reported pain level using a standardized 0-10 pain scan.

5.7 In-Hospital Evaluation

While in the hospital, all participants will be evaluated regularly by a registered nurse. Patients will be asked to report their pain level using a standardized pain scale from 0 (no pain) to 10 (worst pain) every 4 hours, which is standard protocol. Patients will receive medication if they request it and based on the pain level reported. For example, patients will receive Oxycodone 2.5mg PO for pain scale 1-3, Oxycodone 5mg PO for pain scale 4-6, and Oxycodone 10mg PO for pain scale 7-10. Pain level and medication administration will be recorded in the Electronic Medical Record. If needed, the investigatory team can alter the frequency and amount of opioids available in order to control pain. If pain cannot be controlled with opioid medications, the investigatory team can administer other non-opioid anesthetics at their discretion. However, in cases where non-opioid anesthetics are administered to adequately control pain, data from these patients will not be included in final analyses.

5.8 Discharge Medication

Patients will be discharged with prescription medication(s) at the request of the attending Physician, which may include a combination of opioids and non-opioid medication.

5.9 Data Collection

Baseline data to be obtained includes age, height, weight, BMI, indication for surgery (benign vs. malignant), and medical comorbidities. Comorbidities that will be documented include diabetes mellitus, hypertension, thyroid disease, pulmonary disease, anxiety/depression on medication, and obesity as defined as BMI ≥ 30. Procedure-related data includes estimated blood loss, operative time. Data collection regarding opioid medication administration will begin as soon as surgery is complete and after acetaminophen has been administered. Pain medications administered intraoperative by anesthesia will not be included in data collection and further analyses. Complications while in the hospital, adverse effects to acetaminophen, and the length of hospital stay will be recorded. Morphine milligram equivalents will be calculated from the electronic medical record. Data collection will conclude at 24 hours post-operatively or at discharge, whichever comes first.

Data	At Entry	Postoperatively	At Discharge
Age	X		
BMI	X		
Indication for Surgery	X		
Comorbidities	X		
Route of Acetaminophen Administration	X		
Estimated Blood Loss		X	
Operative Time		X	
Pathology		X	
Complications While in Hospital			X
Morphine Milligram Equivalents			X
Length of Hospital Stay			X
Adverse Effects to Acetaminophen			X

5.10 Chart Review Procedures

A list of patients (name, medical record number) by subject number separate from the data will be maintained only until the data has been verified. Subject number will identify data only. Once the data has been verified, the patients name and medical record number will be deleted.

After 24 hours post-operatively or at discharge, which ever comes first, a chart review will take place that will used to determine the patient-reported pain score and the total amount of opioids used in morphine milligram equivalents. Additional information will be obtained, including length of hospital stay, complications while in the hospital and reported adverse effects to acetaminophen. Chart review will conclude at the end of the study, which is 24 hours post-operatively or at discharge, whichever comes first.

5.11 Adverse Reactions and Management

This section should include the following segments:

5.11.1 Reporting Adverse or Unanticipated Events

All serious adverse events and unanticipated problems will be collected until 24 hours post-operatively or at discharge, whichever comes first. The only non-serious adverse event that will be collected are adverse reactions related to acetaminophen use, whether severe allergic reactions (hives, anaphylaxis, etc…) or significant side effects that requires withholding future use.

5.11.2 Anticipated Reactions

Allergic reactions, such as itching or rash, neither of which should cause significant distress and will be managed symptomatically. Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis. In such cases, the use of acetaminophen will be discontinued immediately.

5.11.3 Reaction Management

Any patient with an allergic reaction to the included analgesics will be treated per standard management (Benadryl, Epinephrine, etc.) Whether the patient remains on said analgesics, transitioned to different analgesics, or removed from the study will be determined by the severity of the reaction, patient input and investigator digression. Any severe reactions may require consultation with Internal Medicine and other specialties throughout the hospital. The Research Faculty Advisor will supervise all care.

5.12 Safety Management

5.12.1 Data Safety Monitoring Plan

The investigator will ask the HRRB/Compliance Office to assign a data safety monitor to review adherence to the protocol, occurrence of adverse events, and accuracy of the data. The first review will be conducted after enrolling the first patient. The second review will occur after enrollment of the fifth patient. Upon study completion a final review will occur. Unscheduled random chart audits may also be performed to ensure data integrity. Any deficiencies found during these reviews will be addressed and reported to the PI, HRRB, and federal agencies as indicated.

6.0 STATISTICAL CONSIDERATIONS

For a medium effect size, alpha level (p value) 0.05 and power of 0.95, a total sample size of 36 (18 per study group) is needed. A total of 40 participants (20 per study group) would be ideal to account for patients who drop out or are excluded from the study.

The mean and median post-operative pain scores between groups across time will be compared. The value for the median morphine milligram equivalents of post-operative opioids will be compared between the two study groups.

Differences between the study groups in baseline characteristics and outcome variables will be assessed with chi-square tests for normal variables, *t* tests for normally distributed continuous variables, or Mann-Whitney *U* tests for non-normal continuous variables.

A statistician will assist in organizing data and conducting analyses.

7.0 REGULATORY REQUIREMENTS

7.1 Informed Consent – It is the investigator's responsibility to obtain written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. This will take place before the procedure and after the patient has had ample time to review the consent. The research subject must be given a copy of the signed informed consent document. The original signed copy of the informed consent must be retained in the research records.

7.2 Patient Confidentiality – Documents will be kept in strict confidence by the investigator. Any use of personally identifiable data or private health information (PHI) will be used per the subject's consent.

8.0 REFERENCES

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9.0 APPENDICES

Consent Document