RESEARCH PROTOCOL

Date	3/1/2018
Title	Comparison of Outcomes when Patients Receive Preoperative IV Acetaminophen versus Preoperative Oral Acetaminophen
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Purpose of Study

In the fall of 2016, there was a change implemented in the clinical care of patients undergoing surgery at Bethesda Butler. Previously, intravenous Acetaminophen was routinely ordered for surgical patients and administered preoperatively, either by the RN, or by anesthesia personnel prior to the surgical incision. A system-wide change occurred, and routine use of preoperative intravenous Acetaminophen ceased; instead, patients were given oral Acetaminophen prior to surgery. Anecdotally, recovery room nurses at Butler have noticed negative patient outcomes after this change in care was implemented. An extensive literature search was undertaken, and no research was found that compared the different administration routes of Acetaminophen in surgical patients. The current study proposes to fill this gap in the literature, and examine the trend that nurses have experienced during clinical care, to determine if there is a significant difference in outcomes related to the **administration route** of preoperative Acetaminophen. Specifically, the study will compare the following outcomes of surgical patients who receive IV Acetaminophen with surgical patients who receive oral Acetaminophen: postoperative pain, postoperative opioid dose, postoperative nausea and vomiting, length of stay in recovery room, and patient satisfaction with pain control. Ultimately, we would plan to use the results of this study to advocate for best preoperative care for patients to improve patient outcomes and experience with care.

Hypotheses or Research Questions

Hypothesis 1: Patients who received IV Acetaminophen preoperatively will report decreased pain in the PACU compared to patients who received oral Acetaminophen preoperatively.

Hypothesis 2: Patients who received IV Acetaminophen preoperatively will receive decreased opioid doses compared to patients who received oral Acetaminophen preoperatively.

Hypothesis 3: Patients who received IV Acetaminophen preoperatively will experience less negative effects of pain medications (including postoperative nausea and vomiting, respiratory depression, and need for reversal agents) compared to patients who received oral Acetaminophen preoperatively.

Hypothesis 4: Surgery patients who received IV Acetaminophen preoperatively will have a shorter length of stay in the recovery room compared to surgical patients who received oral Acetaminophen preoperatively.

Hypothesis 5: Surgery patients who received IV Acetaminophen preoperatively will report higher satisfaction with their pain control compared to surgical patients who received oral Acetaminophen preoperatively.

Background

Anecdotally, nurses noticed negative patient outcomes after a change in care was implemented from patients receiving Acetaminophen intravenously preoperatively to patients receiving Acetaminophen orally before surgery. To assess clinical care before and after this practice change, a template was created through coordination with an assigned Lead Applications Programming Analyst from the Information Technology Department to pull retrospective data at Bethesda Butler. An Epic report was generated to examine outcomes of surgical patients before and after the change in practice (no patient identifiers were included). The report, completed at the end of June, 2017, contained information mined from Epic from 2016, and included over 2000 surgical patients who had surgical procedures under general anesthesia, and received either IV or oral Acetaminophen. However, we were unable to draw conclusions based on this data because of missing documentation and variations in documentation; more than one third of the data (885/2609, or 34%) had to be thrown out. Additionally, the actual amount of opioids given (total mg or mcg) was not discoverable.

To determine whether there was evidence around this practice change, a literature search was also completed. Several studies examined the relationship between giving IV Acetaminophen preoperatively, compared to not administering IV Acetaminophen (or administering a placebo), and found benefits including a reduction in reported pain (McNicol et al., 2011; Salihoglu et al., 2009), a reduction in postoperative opioid consumption (Jebaraj et al., 2013; Maund et al., 2011; McNicol et al., 2011; Moon et al., 2011; Remy, Marret, and Bonnet, 2005; Salihoglu et al., 2009; Song, Melroy, & Whipple, 2014), a reduction in postoperative nausea and vomiting (Song, Melroy, & Whipple, 2014), a reduction in length of stay (Hansen et al., 2016; Song, Melroy, & Whipple, 2014), and a reduction in hospitalization costs (Hansen et al., 2016). These studies report important benefits to patients receiving IV Acetaminophen preoperatively compared to not receiving Acetaminophen at all. However, the debate is not whether to administer IV Acetaminophen or no Acetaminophen. Oral Acetaminophen is currently being administered in an attempt to achieve the same outcomes that have been shown after IV Acetaminophen administration. This translation from research supporting IV Acetaminophen administration to clinically administering oral Acetaminophen is not evidence-based. To date, there have been no studies evaluating the use of oral Acetaminophen to achieve these same outcomes, and no studies comparing the effect of patients receiving IV Acetaminophen to oral Acetaminophen preoperatively. Experts in the field have called for randomized studies that take the current evidence a step further and compare the route of Acetaminophen administration

preoperatively (Boggs, 2017). **The current study proposes to address this gap in the literature by determining if there is a significant difference in patient outcomes related to the administration route of preoperative Acetaminophen (IV vs oral)**. Specifically, the study will compare the following outcomes of surgical patients who receive preoperative IV Acetaminophen with surgical patients who receive preoperative oral Acetaminophen: postoperative pain, post-operative opioid dose, postoperative nausea and vomiting, length of stay in recovery room, and patient satisfaction with pain control.

Research Plan

Study Design

This study will use a randomized, double-blind, controlled design with two arms:
Arm 1: Scheduled IV Acetaminophen provided preoperatively
Arm 2: Scheduled PO Acetaminophen provided preoperatively

Setting for the study

This study will take place at Bethesda Butler Hospital in the perioperative department. This unit consists of 12 preoperative bays, 8 operating rooms, and 9 postoperative recovery bays. The department provides care for patients undergoing procedures including (but not limited to) arthroscopy, ear/nose/throat, gynecology, laparoscopy, ophthalmology, orthopedic total joint replacement, plastics, and podiatry.

Before the study begins, the study staff will provide education to all of the nurses working in the perioperative department involved in patient care. This education will include information about the study design, the intervention, the inclusion/exclusion criteria, and the data collection forms. Letter to Patients will be provided to surgeons to hand out to their patients during the pre-surgical visit. Additionally, the presurgical services staff who call the patients before surgery will be provided a script to read describing the study. Both the letter and the phone script will be used to provide information about the study to patients, but will not be used to determine eligibility or consent. By offering information about the study before the day of surgery, we are hoping to decrease the anxiety involved when study staff approach the patients the morning of surgery.

Participants

This study will enroll patients who meet the inclusion/exclusion criteria and who consent to the study.

Inclusion criteria:

- 18 years old or older

- Admitted to Bethesda Butler Main Perioperative Services for an outpatient surgical procedure performed under general anesthesia

Exclusion criteria:

- Allergy to Acetaminophen
- Lactose intolerance or lactose allergy (placebo capsules contain lactose)
- Hepatic disease
- Having taken a product containing acetaminophen within 6 hours of scheduled surgery time
- Pregnant
- Weight less than 60kg
- Opioid addiction – admits to current opioid addiction and/or substance abuse disorder, and/or currently in treatment for opioid addiction or substance abuse
- Emergent or on-call procedures
- Inpatient surgery

Each day, the study staff will review the patients scheduled for surgery to determine potential subjects. In addition, the study staff expects that the staff education provided before implementation of the research study may result in clinical nurses notifying study staff when an eligible patient is identified. By reviewing daily census and involving the clinical staff in identifying potential subjects, the study staff hopes to approach the majority of the potentially eligible patients. When a patient appears to be eligible, study staff will complete the *Inclusion/Exclusion Criteria Checklist*. If the patient is eligible, a study staff member will meet with the patient and describe the study and answer any questions. If the patient is interested in enrolling in the study, the study staff will review the *Informed Consent Form* and *HIPAA form* and obtain written informed consent. Patients will receive a copy of their signed Informed Consent form and HIPAA form.

Sample Size Determination: No studies were found examining the impact of IV versus oral Acetaminophen on the listed dependent variables. Therefore, a power analysis was conducted using G*Power (version 3.1.9.2) with a default medium effect size (0.5), power of 0.8, and level of significance 0.05. It was determined that 53 patients would be needed in each group, for a total sample size of 106 patients. We plan to enroll 120 patients (60 patients in each group) to allow for any missing data or withdrawals. Additionally, 120 patients will provide adequate power to detect a clinically significant (2 point difference on a 0-10 pain rating scale) mean difference in pain scores between two groups.

Procedures

Randomization:

After obtaining informed consent, the subject will be randomized into one of two groups:

1. IV Acetaminophen
2. Oral Acetaminophen

To randomize the subject, the study staff will assign the patient the next study ID number on a list. The pharmacy will have a list of subject ID numbers with corresponding randomization assignments. This list will be created from a computerized simple random number generator (1:1 randomization) prior to the start of the study. Only the pharmacists will have access to this information.

The Study ID number will be added to the top of the *Data Collection Form.* Study staff will add the patient's name to the *Enrollment Log* that connects the subject ID number to the patient's name. This is the only list that will connect patient identifiers to study ID numbers. Beginning with selection of the envelope, all documents will be labeled with only subject ID number and no patient identifiers.

Intervention or experimental aspect of the study

Once the patient has been randomized, the nurse will provide study ID number to the pharmacist who will provide the correct IV and oral medications:

- Patients randomized to Arm 1 (IV Acetaminophen group) will receive IV Acetaminophen 1000mg in 100mL once and a PO placebo pill preoperatively
- Patients randomized to Arm 2 (Oral Acetaminophen group) will receive IV saline 100mL once and Acetaminophen 1000 mg PO once preoperatively

Patients and nurses will be blinded about which of the IV solution and capsule is active and which is a placebo. The pharmacists will have access to the randomization scheme and will be able to unblind medication administration in case the information is needed for clinical care.

Patients in both arms of the study will receive standard postoperative care including assessment and management of postoperative pain. All care received, except route of preoperative Acetaminophen, will follow standard of care.

<u>Data Collection</u>

The following variables will be collected:

- Independent variable:
    - Route of Acetaminophen administration (IV or oral)
- Dependent variable:
    - Postoperative pain score – patient's self-report of pain using a 0-10 pain scale as documented by clinical nurse in the patient's electronic medical record
    - Amount of postoperative opioid pain medication administered – this will be documented by clinical nurse in the patient's electronic medical record when administered
    - Postoperative nausea and vomiting – As documented by the clinical nurse in the patient's electronic medical record
    - Occurrence of respiratory depression – As documented by low O2 saturation in the patient's electronic medical record

  - Administration of reversal agent – As documented by the clinical nurse in the patient's electronic medical record
  - Length of stay in recovery room – Duration of length of stay in PACU is routinely recorded on all patients' electronic medical record (this will include both Phase I, and Phase II when applicable)
  - Patient satisfaction with pain control – This question will be asked of patients during the post-operative telephone call, which generally takes place 1 day (3 days if the procedure is performed on Friday) after surgery. The patients will be asked: On a scale of 1-10 (with 1 being extremely dissatisfied and 10 being extremely satisfied), how satisfied were you with your pain control on the day of surgery?
- Potentially confounding variables: These variables are routinely documented in patients' electronic medical record. The study team will record this data from the medical records.
  - Age
  - Gender
  - Weight
  - Medications
  - Type of surgery
  - Length of surgery
  - Baseline pre-operative pain level
  - Postoperative nausea and vomiting risk score
  - Prophylactic anti-emetic administered
  - Nerve block given
  - Local medication injected
  - Additional preoperative medications given (ie. Celebrex, Oxycontin, Neurontin) for pain management

Each day, the study team members will review the Enrollment Log from the previous day and the study team nurses will make the clinical postoperative discharge telephone calls for patients were enrolled in the study. The telephone call will follow the standard script used clinically for all patients and then one additional question will be asked at the end of the call: On a scale of 1-10 (with 1 being extremely dissatisfied and 10 being extremely satisfied), how satisfied were you with your pain control on the day of surgery? The patient's response to this question will be recorded on the Enrollment Log.

To collect the remaining outcome data, a paper data collection form will be placed on the patient's chart. The RN caring for the patient post-operatively will be asked to complete the form at the time of patient care. The form includes: Times of Acetaminophen/Placebo (IV and oral) administration, postoperative pain scores (before and after pain medication administration), opioid medications administered (including cumulative dose of each medication administered), any occurrence of postoperative nausea, any occurrence of postoperative vomiting, any low O2 saturations (<92%), and any reversal medications administered. The study team will conduct a review of the medical records of all patients

enrolled in the study and complete the following information on the data collection sheet: Time surgery started, time surgery ended, time into recovery room and time discharged from recovery room (includes Phase I, and Phase II when applicable), age, gender, weight, type of surgery, baseline preoperative pain score, postoperative nausea and vomiting risk score, prophylactic anti-emetics administered, preoperative nerve block given, any local injected, additional preoperative medications given for pain management.

Additionally, any adverse events experienced by patients will be documented and communicated to the patient's clinical team. The pharmacist(s) will be able to unblind Acetaminophen route administration if needed for clinical care of the patient. All adverse events will be reviewed by the study team and reported to the Institution Review Board (IRB) following IRB guidelines.

Statistical Analysis

Data will be recorded on paper data collection forms with only subject ID and no identifiers. Data from these forms will be entered into a password protected database. Only study team members will have access to the database. No personal information will be entered into the electronic database. Data will undergo range checks when entered into the database, and quality control procedures will be performed to ensure accuracy of the data in the electronic database.

Statistical analyses will be performed using SPSS statistical software. Descriptive statistics (frequencies for categorical data; means and standard deviations and ranges for continuous data) will be used to describe the sample. The following analyses will be performed to address each hypothesis:

Hypothesis 1: Patients who received IV Acetaminophen preoperatively will report decreased pain in the PACU compared to patients who received oral Acetaminophen preoperatively.

To compare the effects of the intervention, a Mann-Whitney U test will be used to compare mean pain scores for patients who received IV Acetaminophen to the mean pain scores of patients who receive oral Acetaminophen. A level of significance of $\alpha=0.05$ will be used. Secondary analyses will be planned using multiple regression modelling to adjust for the potential confounding variables.

Hypothesis 2: Patients who received IV Acetaminophen preoperatively will receive decreased opioid doses compared to patients who received oral Acetaminophen preoperatively.

To compare the effects of the intervention, an independent samples t-test will be used to compare mean dose of opioids received for patients who received IV Acetaminophen to the mean dose of opioids received among patients who receive oral Acetaminophen. A level of significance of $\alpha=0.05$ will be used. Secondary analyses will be planned using multiple regression modelling to adjust for the potential confounding variables.

Hypothesis 3: Patients who received IV Acetaminophen preoperatively will experience less negative effects of pain medications (including postoperative nausea and vomiting, respiratory depression, and need for reversal agents) compared to patients who received oral Acetaminophen preoperatively.

To compare the effects of the intervention, a Chi Square test will be used to compare occurrence of postoperative nausea and vomiting for patients who received IV Acetaminophen to patients who receive oral Acetaminophen. A level of significance of α=0.05 will be used. Secondary analyses will be planned using multiple regression modelling to adjust for the potential confounding variables.

To compare the effects of the intervention, a Chi Square test will be used to compare occurrence of postoperative respiratory depression for patients who received IV Acetaminophen to patients who receive oral Acetaminophen. A level of significance of α=0.05 will be used. Secondary analyses will be planned using multiple regression modelling to adjust for the potential confounding variables.

To compare the effects of the intervention, a Chi Square test will be used to compare occurrence of administration of reversal agents for patients who received IV Acetaminophen to patients who receive oral Acetaminophen. A level of significance of α=0.05 will be used. Secondary analyses will be planned using multiple regression modelling to adjust for the potential confounding variables.

Hypothesis 4: Surgery patients who received IV Acetaminophen preoperatively will have a shorter length of stay in the recovery room compared to surgical patients who received oral Acetaminophen preoperatively.

To compare the effects of the intervention, an independent samples t-test will be used to compare mean length of PACU stay for patients who received IV Acetaminophen to the mean length of PACU stay for patients who receive oral Acetaminophen. A level of significance of α=0.05 will be used. Secondary analyses will be planned using multiple regression modelling to adjust for the potential confounding variables.

Hypothesis 5: Surgery patients who received IV Acetaminophen preoperatively will report higher satisfaction with their pain control compared to surgical patients who received oral Acetaminophen preoperatively.

To compare the effects of the intervention, a Mann-Whitney U test will be used to compare mean satisfaction rating for patients who received IV Acetaminophen to the mean satisfaction rating of patients who receive oral Acetaminophen. A level of significance of α=0.05 will be used. Secondary analyses will be planned using multiple regression modelling to adjust for the potential confounding variables.

Ethical Considerations

Informed consent

All study staff will complete CITI training. A study staff member will meet with potentially eligible patients and describe the study and answer any questions. If the patient is interested and meets all the inclusion/exclusion criteria, the study staff will review the *Informed Consent Form* and *HIPAA form* and obtain written informed consent. Patients will receive a copy of their signed Informed Consent form and HIPAA form.

Informed Consent forms and HIPAA forms will be stored in a locked cabinet that only study staff will have access to. After the study closes, the signed Informed Consent forms and HIPAA forms will be boxed and sent to off-site storage and securely stored for 10 years. At that time, the hard copy forms will be shredded.

Privacy information

Personal identifiers will be recorded on the Informed Consent, on the HIPAA forms, and on the Enrollment Log. All other data collection forms and electronic database of final data will include study ID number only.

Hard copy forms (including Informed Consent forms, HIPAA forms, and data collection sheets) will be stored in locked cabinets that only study staff will have access to. Electronic data (including Enrollment Log and data entered into an electronic database) will be stored on a password-protected folder on the U drive. Only study staff will have access to the electronic study documents. After data analysis and dissemination is completed, hard copy forms will be boxed and sent to secure storage for 10 years at which time they will be shredded. After data analysis and dissemination, electronic data and forms will be de-identified and transferred to a password-protected flash drive which will be sent to secure storage for 10 years at which time it will be destroyed.

Cost/Budget

Pharmacy Costs:

- IV acetaminophen, $31.61/dose x 60 subjects $1896.60
- IV normal saline 100 mL bag, $1.40 /dose x 60 subjects $84.00
- Empty bottles, $5.13 x 120 subjects $615.60
- Bottle hangers, $1.20 x 120 subjects $144.00
- TriHealth Pharmacy fee, waived for staff study (per Steve Shepherd) $0.00
- Compounding Pharmacy fee (Tristate Compounding Pharmacy & Kunkel Pharmacy) total from below $420.00
  - Colored/Opaque Capsules (#120 = $20)
  - Acetaminophen 1000mg capsules (#60 = $210)
  - Placebo Capsules (#60 = $180.00)

Dissemination Costs:
National experts have stated a study comparing IV and oral Acetaminophen is needed. Disseminating this information to a surgical audience will help patients even outside TriHealth and will allow TriHealth to be at the forefront of disseminating this new knowledge. Ultimately the work will be published, but because of time required for publication, we are requesting presentation at a professional organization conference (likely the American Society of PeriAnesthesia Nurses, or ASPAN, 2019 conference) first to impact patients as quickly as possible. Attendance at the (ASPAN 2019) conference is a requirement for poster submission and presentation.

- Poster development = $70.00
- Conference fees for 2 presenters = $1000.00
  (cost estimated based on 2017 conference registration fees:
  $400 member/$600 non-member)
- Travel costs for 2 presenters - mileage to Nashville from Bethesda Butler = 298 miles x $0.535 (current TriHealth mileage reimbursement) = 159.43 on way, roundtrip = $318.86
- Hotel for 2 presenters ($250/night x 3 nights) = $750.00

Total **$5299.06**

(Grant funding has been approved by the Bethesda Foundation)

Estimated Period of Time to Complete Study	
When will study begin?	January 1, 2018 (date awards dispersed)
Protocol Development Completed	2 weeks
Admin Review Time	2 weeks
IRB Approval	6 weeks
Data collection	3 months
Data analysis	2 weeks
Presentation development (if applicable)	2 weeks
Manuscript Development (if applicable)	1 month
Journal submission process (if applicable)	3 months
Study closure	1 month

When and how will results be disseminated?

Results will be disseminated internally to the Bethesda Butler surgery leadership and system-wide through the TriHealth Research Council. Results will be disseminated nationally through presentation at a professional organization conference. Finally, results will be disseminated nationally and internationally by publication in a relevant peer-reviewed journal.

References

Boggs, W. (2017). IV acetaminophen curbs need for narcotics after C-section. *Medscape,* http://bit.ly/2q1vKY3

Hansen, R.N., Pham, A., Strassels, S.A., Balaban, S., & Wan, G.J. (2016). Comparative analysis of length of stay and inpatient costs for orthopedic surgery patients treated with IV Acetaminophen and IV opioids vs IV opioids alone for post-operative pain. *Advances in Therapy, 33*, 1635-1645.

Jebaraj, B., Maitra, S., Baidya, D.K., & Khanna, P. (2013). Intravenous paracetamol reduces postoperative opioid consumption after orthopedic surgery: A systematic review of clinical trials. *Pain Research and Treatment*. http://dx.doi.org/10.1155/2013/402510

Maund, E., McDaid, C., Rice, S., Wright, K., Jenkins, B., & Woolacott, N. (2011). Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side effects after major surgery: A systematic review. *British Journal of Anaesthesia, 106*, 292-297.

McNicol, E.D., Tzortzopoulou, A., Cepeda, M.S., Francia, M.B.D., Farhat, T., & Schumann, R. (2011). Single-dose intravenous paracetamol or propacetamol for prevention or treatment of postoperative pain: A systematic review and meta-analysis. *British Journal of Anaesthesia, 106*, 764-775.

Moon, Y-E, Lee, Y-K, Lee, J., & Moon, D-E. (2011). The effects of preoperative intravenous acetaminophen in patients undergoing abdominal hysterectomy. *Archives of Gynecology and Obstetrics, 284*, 1455-1460.

Remy, C., Marret, E., & Bonnet, F. (2005). Effects of acetaminophen on morphine side-effects and consumption after major surgery: Meta-analysis of randomized controlled trials. *British Journal of Anaesthesia, 94*, 505-513.

Salihoglu, Z., Yildirim, M., Demiroluk, S., Kaya, G., Karatas, A., Ertem, M., & Aytac, E. (2009). Evaluation of intravenous paracetamol administration on postoperative pain and recovery characteristics in patients undergoing laparoscopic cholecystectomy. *Surgical Laparoscopy Endoscopy & Percutaneous Techniques, 19*, 321-323.

Song, K., Melroy, M.J., & Whipple, O.C. (2014). Optimizing multimodal analgesia with intravenous acetaminophen and opioids in postoperative bariatric patients. *Pain Management Pharmacotherapy, 34*, 14S-21S.