Comparative Efficacy of Intravenous Acetaminophen vs. Oral Acetaminophen in Ambulatory Surgery
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Mount Sinai	Protocol Name:	Comparative Efficacy of Intravenous Acetaminophen vs. Oral Acetaminophen in Ambulatory Surgery
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HRP-503 PROTOCOL TEMPLATE

Brief Summary of Research (250-400 words):

There is limited research on the outcome differences between two different routes of administration for acetaminophen (brand name Tylenol). Acetaminophen can be administered to humans in various forms before or during surgery, with injections into human veins (intravenous or IV) or taken orally by mouth (or Per Os or PO) forms being the most common. There are alleged reported differences with onset, duration, cost, metabolism seen with different forms of administration but little is substantiated by literature or clinical evidence. With the costs of injection of acetaminophen through human blood vessels or veins (IV) sometimes being almost 100 times the cost of intake by mouth (PO), it is not only important fiscally but also clinically to differentiate the benefits of IV versus PO acetaminophen. The proposed research study is to determine the advantages of IV vs PO acetaminophen during the post-operative recovery time for ambulatory surgery patients by analyzing differences in time to first opioid delivery, pain scores, and patient satisfaction. This will not affect the subject's cost of participation since both forms of acetaminophen is currently administered to most eligible ambulatory surgical patients as part of perioperative protocol. The medications used are both part of standard of care and no extra cost will be incurred by the research study.

1) Objectives

Research Question:

Are there clinical benefits of IV vs PO acetaminophen in the post-operative period in ambulatory surgery patients?

The objective of this study is to determine the clinical advantage of IV vs PO acetaminophen.

2) Background

In previous literature it has been shown that compared to placebo, IV acetaminophen can improve postoperative pain scores and reduce opioid requirements (Remy C, et al. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. Br J Anaesth 2005;94(4):505-13).

In addition, IV acetaminophen has several pharmacokinetic properties that may be beneficial when compared to PO acetaminophen. IV acetaminophen has been shown to achieve a more rapid and higher maximum plasma concentration as well as higher cerebrospinal fluid concentrations. Comparative effectiveness trials of IV vs PO administration have not conclusively demonstrated improved clinical

outcomes despite the proposed pharmacokinetic benefits (Jibriil F, et al. Intravenous versus oral acetaminophen for pain: Systematic review of current evidence to support clinical decision making. Canadian Journal of Hospital Pharmacy 2015:68(3)238-47). More research needs to be conducted to determine possible clinical advantages of PO acetaminophen when compared to IV acetaminophen.

3) Setting of the Human Research

The research study will take place at Mount Sinai West hospital and Mount Sinai St. Luke's hospitals. The site PI is Yan Lai, MD.

4) Resources Available to Conduct the Human Research

For n=100, the feasibility of recruitment is easily manageable. With the HIPAA waiver requested, the surgeon will provide the investigators (all three of whom are physicians within the Dept of Anesthesiology) with information of eligible patients. Subjects will be called by the Dept of Anesthesiology when their surgery is scheduled, and they will be told about the study then. After the operating room schedule has been reviewed for potential participants in the study the contact information will be obtained through the surgeon's office. A member of the research team will then contact the patient and notify him/her of the study. The staff members on this protocol are all employees of Mount Sinai and will either be a resident or attending physicians that are included on the IRB protocol. There are three primary members of the research personnel: The study team plans to obtain the placebo directly from pharmacy. The study team team is working directly with pharmacy for the supply required to conduct the human research. Since the use of IV APAP is not restricted within the Dept of Anesthesiology, it is frequently used for patients intraoperatively. If there is any objection to allowing IV APAP being removed from the pyxis for the patients the Dept of Anesthesiology has volunteered to cover the costs associated with using IV APAP to obtain the data.

Yan Lai, MD, MPH – Roles for Dr. Lai in this study include serving as primary investigator responsible for study design and planning, data collection, subject recruitment, manuscript writing and preparation, data analysis, safety monitoring, and responding to adverse events and/or complications. He is certified in PPHS/IRB protocols, all Citi/IRB required training in human subject protection, and has prior clinical research experience. He is also a board certified anesthesiologist and assistant professor of anesthesiology with the Icahn School of Medicine and the Mount Sinai Health System.

Poonam Pai, MD – Roles for Dr. Pai include serving as primary research coordinator involved in data collection, subject recruitment, manuscript writing and preparation, data analysis, safety monitoring, and responding to adverse events and/or complications. She has completed all of her required CITI training to be IRB certified and has experience in clinical research. In addition she

has been a resident physician in anesthesiology with the Icahn School of Medicine in good standing for the previous three years going on her fourth.

Brittany Reardon, MD - Roles for Dr. Reardon include serving as research assistant involved in data collection, subject recruitment, manuscript writing and preparation, data analysis, safety monitoring, and responding to adverse events and/or complications. She has completed his CITI training to be IRB certified and has experience in clinical research. In addition, she has been a resident physician in anesthesiology with the Icahn School of Medicine in good standing for the previous year going on her second.

There are institutional processes to ensure that all persons assisting with the protocol will be well informed. The research personnel will conduct regular meetings and department email updates to review the results and safety data of the study. The research personnel will initiate the formation of a safety monitoring board for adverse effects, complications, or complaints from patient subjects.

5) Study Design

a) Recruitment Methods

Potential subjects will be ambulatory surgery patients at Mount Sinai West and St. Luke's hospitals. Patients who are listed as ambulatory surgery patients that meet inclusion and exclusion criterion will be selected. With the HIPAA waiver requested, the surgeon will provide the investigators (all three of whom are physicians within the Dept of Anesthesiology) with information of eligible patients. Subjects will be called by the Dept of Anesthesiology when their surgery is scheduled, and they will be told about the study then. All patients will be provided with copies of the IRB protocol and consent if they wish to have it. Send a copy of the consent form in a secured e-mail to the potential subject. The e-mail will be secured by entering in [SECURE] in the e-mail subject line. Once recruited the blinding assessments will be done by the study team.

b) Inclusion and Exclusion Criteria

Inclusion criteria include: ASA scores I-III, ambulatory surgery patients, ages 18-75, surgeries requiring general anesthesia

Exclusion: Patients with contraindications to acetaminophen (history of end organ liver dysfunction), known allergy to acetaminophen, emergency surgery, patients who were not fasted, patients who cannot tolerate PO, surgery anticipated to last longer than 3 hours or requiring re-dose of acetaminophen, pregnancy, weight less than 50kg, chronic daily narcotic use, patients who's anesthetic plan requires regional anesthesia, patient refusal to participate or do not have capacity to provide consent.

(NOTE: You may not include members of vulnerable populations as subjects in your research unless you indicate this in your inclusion criteria.).

c) Number of Subjects

We intend to have an n=100. Based on a confidence level of 95% with a Z score of 1.96, standard deviation of .5 and a confidence interval of 10% our sample size should be 96. For ease of statistical calculations we rounded up to 100 patients. Based on previous literature pertaining to acetaminophen usage, we found studies included anywhere from 46 to 105 patients which is consistent with our calculations.

$$ss = \frac{Z^2 * (p) * (1-p)}{c^2}$$

Where:

Z = Z value (1.96 for 95% confidence level)

p = percentage picking a choice, expressed as decimal (.5 used for sample size needed)

c = confidence interval, expressed as decimal (e.g., .01= ±1)

Sample size= [(1.96^2)(.5)(.5)]/(.1^2)=96 subjects

For effect size, we expect a Cohens d medium effect of 0.5. The estimate for sample sizes was obtained by using the first set of pain scores obtained in the PACU.

d) Study Timelines

The subject's participation will be from time of enrollment in the pre-operative period until the 24 hour post discharge from the hospital. Estimated date of enrollment completion will be when n=100 (1-2 months.) Estimate date for study completion will be June 2017.

e) Endpoints

The primary endpoints will be PACU pain scores (arrival, 1 hour, and discharge), time to first narcotic use, and total narcotic use in PACU.

Secondary endpoints will be PACU LOS, patient reported total narcotic use post-discharge, and patient satisfaction.

f) Procedures Involved in the Human Research

This will be a prospective randomized observational study. All patients will be randomized to receive either pre-operative PO acetaminophen or IV acetaminophen intraoperatively. Patients will not be at additional risk and all standards of care will be met. A standard dose of PO Acetaminophen 975mg (3 pills) will be given to all patients about 15 minutes prior to entering the operating room. A standard dose of IV Acetaminophen 1000mg will be given to all patients after standard induction doses. Randomization will be performed with a computing software. All patients who are randomized to have IV acetaminophen will take placebo pills preoperatively to standardize all patients and blind patients to treatment. Due to the pharmacologic absorption differences between the PO and IV forms the PO form will be given when the patient is evaluated in the holding area about 15 minutes prior to entering the OR. Because the IV form of a medication in general has a faster onset it is given at a later time in the operating room and not in the holding area.

According to pharmacokinetic literature on IV and PO acetaminophen, the maximal plasma effect of IV acetaminophen is 15 minutes after administration and 45 minutes for PO administration. We will attempt to standardize the effects of PO vs IV by giving IV APAP 30 minutes after the other group receives the PO APAP. For example, if the PO group receives PO APAP 15 minutes prior to going into OR, then the IV APAP group will receive the IV APAP 15 minutes after they are in the OR, which allows for a difference of 30 minutes between the two groups. This allows for the peak effect of the IV and PO to coincide.

We do not intend on giving any other preoperative oral medications to patients, however all patients will have intra-venous access prior to entering the operating room. The subject will meet his/her anesthesia provider on the day of their surgery. The pain score will be on PACU arrival, 1 hour after PACU arrival, and at discharge from PACU. Should the patient experience post operative pain the patient will receive additional opioid medications. The time to first opioid medication administration after arrival to PACU and the total of amount of opioid medications administered will be recorded. If the subject no longer wishes to take part in the trial at any point no further data will be recorded. Additional acetaminophen can be administered four hours after the first dose of IV or PO acetaminophen. Opiod medication may also be given if needed for pain.

Oral acetaminophen is given prior to surgery since it cannot be given intra-operatively while the patient is under general anesthesia. The decision was made to given intravenous acetaminophen after induction so the absorption profile of oral vs intravenous will be similar. Giving the intravenous acetaminophen upon induction of anesthesia will also allow for the shortest time between the administration of the two drugs.

Ambulatory surgeries usually consist of minor procedures such as hysteroscopies, hernia repairs, cystoscopies and laparoscopic procedures such as cholecystectomy and ovarian cystectomy. Due to the relatively minor incisions required in these types of procedures patients tolerate being discharged without significant pain. All patients will receive general anesthesia with either laryngeal mask airway (LMA) or endotracheal intubation.

The patients pain scores will be assessed by the Post-Anesthesia Care Unit (PACU) nurses at arrival, 1 hour after and at discharge from PACU as part of routine patient care by PACU nurses. Intraoperative care of the patient will be provided by an anesthesia team member who is a part of the Mount Sinai System. The anesthesia provider will be aware of the randomization of the patient.

Standard post-operative orders will be written for patients during their time in the PACU. Orders include oxycodone, fentanyl and hydromorphone. Acetaminophen can only be re-administered after four hours from first dose.

g) Specimen Banking

No specimen will be needed for the study.

h) Data Management and Confidentiality

The information included in the data will be medical record number, age, gender, ASA class, type of surgery, type of acetaminophen used, pain score assessments, time to first narcotic, total narcotic use and satisfaction/pain 24 hours after discharge from PACU. Only the research personnel will have access to the data. Only the research personnel will have knowledge of which method of acetaminophen subjects will be receiving. The data will be stored as hard copy files and on a secure spreadsheet. The research personnel is responsible for the receipt of the data. The PI will keep the hard copies secure and any electronic data will be encrypted. No personal identifiers will be used. The data will undergo statistical analysis

i) Provisions to Monitor the Data to Ensure the Safety of Subjects

Part I: Elements of a Data and Safety Monitoring Plan

MSSM Principal Monitor:

Indicate whether this person is the PI, a Team Member, or is Independent:
Last Name: Lai
First Name: Yan
Academic Title: Attending Physician, Assistant Professor
Department: Anesthesiology
Mailing Address: Mount Sinai West 1000 10th Avenue, New York, NY 10019
Phone: 212-523-6915

Fax:
E-mail: ylai@chpnet.org

MSSM Additional Monitor:
Indicate whether this person is the PI, a Team Member, or is Independent:
Last Name: Pai
First Name: Poonam
Academic Title: Research Personnel, Physician
Department: Anesthesiology
Mailing Address: Mount Sinai West 1000 10th Avenue, New York, NY 10019
Phone: 212-523-6915
E-mail: Poonam.PaiBantwalHebbalasankatte@mountsinai.org

The principal monitor is a board certified anesthesiologist thus minimizing the risk to the subjects and further optimizing their health and wellbeing. Adverse events are unlikely (potential side effects of acetaminophen use) and will be monitored as a standard of care everyone receives regardless of participation in the study. The safety and data information will be reviewed on a daily basis until the desired sample size is achieved. All temporary and/or permanent suspensions will be reported.

j) Withdrawal of Subjects

Patients may withdraw from the study at any given time by contacting any member of the research study group. Data will not be collected on patients who wish to withdraw. Patient do not need to withdraw consent in writing.

6) Risks to Subjects

Acetaminophen is a commonly used over the counter medication with minimal foreseeable risks when used at the recommended dosages. As with any medication, there is a possibility of an allergic reaction. There is a risk of liver damage with acetaminophen use regardless of the route. There is no risk of grogginess. There is no risk of pain or bruising with IV acetaminophen administration. When given either PO acetaminophen or placebo the subject will be given a small amount water. Although oral intake prior to surgery can increase risk of aspiration, the minimal amount of water given will not increase the risk of aspiration should an LMA or endotracheal breathing tube be required for the surgery. Oral medications are routinely given immediately prior to many procedures to help with analgesia intra- and post-operatively.

7) Provisions for Research Related Harm/Injury

If you are injured or made sick from taking part in this research study, medical care will be provided. Generally, this care will be billed to you or your insurance in the ordinary manner and you will be responsible for all treatment costs not covered by your insurance, including deductibles, co-payments

and coinsurance. This does not prevent you from seeking payment for injury related to malpractice or negligence. Contact the investigator for more information.

8) Potential Benefits to Subjects

It is important to know that you may not get any benefit from taking part in this research. Others may not benefit either. However, possible benefits may be improved knowledge about how the different forms of acetaminophen affect pain control.

9) Provisions to Protect the Privacy Interests of Subjects

Patients will be appropriately educated about the research study. Any questions or concerns they have will be adequately addressed and patients will have the option to decline participation. Patients will be given as much time as they need to review the consent form. The study personnel will be approaching the subjects. Privacy will be maintained by not including any identifiers such as names or addresses in the data collected.

10) Economic Impact on Subjects

Patients will not incur any additional cost for participating in the study. The medications used are part of a standard anesthetic regimen that will be billed to subject's insurance as bundled standard of anesthesia care. The cost of the procedure is overall unaffected. The cost of Acetaminophen IV will be provided by the Dept of Anesthesiology.

11) Payments to Subjects

Patients will not be be reimbursed for their participation.

12) Consent Process

Both the HRP-090 (SOP) Informed Consent Process for Research and the HRP-091 (SOP) Written Documentation of Consent will be followed by the study team. These documents are both available at http://icahn.mssm.edu/research/resources/program-for-the-protection-of-human-subjects/irb-members-palette.

13) Process to Document Consent in Writing

The patients will receive a paper copy of the IRB approved consent packet and will sign in the designated areas to confirm consent of participation. They will have the option of have a copy of the consent and may ask for a personal copy of the consent.

14) Vulnerable Populations

Indicate specifically whether you will include (target) or exclude each of the following populations:

Include	Exclude	Vulnerable Population Type

	x	Adults unable to consent
	x	Individuals who are not yet adults (e.g. infants, children, teenagers)
	x	Wards of the State (e.g. foster children)
	x	Pregnant women
	x	Prisoners

15) Multi-Site Human Research (Coordinating Center)

This study will be performed within the Mount Sinai West and St. Luke's Hospitals. No additional centers will be involved.

16) Community-Based Participatory Research

This does not apply to our study.

17) Sharing of Results with Subjects

Results will not be shared with the patients since the study will take time to complete. Patients can request results if they contact the PI by writing.

18) External IRB Review History

This does not apply to our study.

19) Control of Drugs, Biologics, or Devices

Acetaminophen IV and PO are stored within the Pyxis drug storage system at Mount Sinai West and St. Luke's.