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A multi-center, randomized, double-blind, pilot study on the effect of intravenous multi-dose acetaminophen on readiness for discharge in patients undergoing surgery with general anesthesia

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Background Information

Delays in the post-anesthesia care unit (PACU) account for an increase in both patient morbidity and hospital cost (1). Some have estimated that a single extra minute of delay in the PACU can account for a $20 increase in cost (2). It has been shown that PACU delays place patients at an increased risk of severe adverse events due to insufficient medical and nursing coverage, inadequate communication, and lack of visiting facilities for patients' families (1). Additionally, as delays stack up throughout the day, a bottleneck in OR departure occurs further escalating costs owing to the expense of "recovering" patients in the operating room (3). These delays are attributable to any number of hospital factors such as unavailability of transport, scarcity of resources, OR holds, lack of ward space, and indetermination as to when a PACU patient can be discharged to another unit (4-7). These factors are oftentimes hard to correct as they are dependent on numerous services and multiple levels of hospital infrastructure, however there are some patient-specific factors such as the patients cardiovascular and pulmonary status, nausea, vomiting, pain, and the type of anesthetic used, which are modifiable, and could contribute to a more streamlined and efficient perioperative process.

Fast tracking patients has been used as a streamlining strategy to minimize PACU delays, decrease healthcare cost, and improve patient morbidity. It allows stable patients to be discharged from same day surgeries sooner as long as they meet criteria set forth by a variety of validated assessments (8-10). Appropriate patient fast tracking is associated with earlier ambulation, return to intestinal motility, and liberation from tubes, catheters, and drains (11). This strategy has shown substantial cost-savings with no change in patient outcomes and no significant rates of reoperation or readmission (11-13). Interventions that would allow a greater number of patients to be appropriately fast tracked could demonstrate cost savings as they would help prevent delays in the system.

A potential intervention lies in administering IV acetaminophen, a non-opioid analgesic drug indicated for patients with mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and for reduction of fever (14). It demonstrates a rapid onset of action, a serum peak concentration at the end of the 15 minute infusion and a total duration between 4-6 hours, all ideal for ambulatory surgery (14-17). The intravenous form is associated with twice the plasma and effect site concentrations when compared to the oral version of the drug (18) and is especially helpful when patients are unable to tolerate enteral formulations. When used perioperatively, IV acetaminophen has been shown to reduce postoperative nausea and vomiting, reduce postoperative opioid consumption, and improve early pain outcomes at rest and during movement (17, 19-22). Such improvements are of particular interest as these are oftentimes the very reasons why patients do not meet early PACU discharge criteria (7, 23).

Study Rationale Both single- and multiple-dose IV acetaminophen regimens have been separately researched. Since most studies demonstrate numerous benefits, it is difficult to determine which regimen is optimal in the perioperative period. Both regimens have shown efficacy in improving pain scores, decreasing narcotic consumption, decreasing postoperative nausea/vomiting, and decreasing time to ambulation (17, 19-22, 24-32). In addition, preoperative/prophylactic vs. therapeutic regimens of IV acetaminophen have also been investigated. It has been shown that, when started postoperatively, or continued throughout that period, IV acetaminophen reduces morphine consumption, increased time to rescue medication, decreases pain intensity, decreases pain scores, and improves global assessment (17, 24, 26, 27, 31). The preoperative trials evaluating earlier administration (i.e. prior to surgical incision), have also demonstrated similar results with a significant reduction in nausea and vomiting, improved pain outcomes, decreased narcotic requirements, and faster recovery (25, 32-34).

However, some studies show that when given after the onset of pain, IV acetaminophen has been found to have "no significant impact" on PONV (19). Although it has been demonstrated that receiving 1,000 mg every 6 hours did not show a statistically significant difference from dosing the drug at 650 mg every 4 hours (21), the study was powered to investigate the difference in outcomes compared to the drug dose not the interval. Subsequently it has also been shown that any single dose over 1000mg is not associated with improved outcomes (20) and is therefore not manufacturer or FDA recommended to exceed this single dose. To date, however, no study has compared the standard Q6 hour dosing to the alternate of 1gm Q4 hour (up to the allowable 4 gm per day maximum) which is the minimal allowable dosing interval as set forth by the FDA and is perhaps a more ideal dosing regimen for quicker, ambulatory procedures allowing for steadier plasma concentrations (14) and a possible clinical and economic benefit.

Despite the numerous benefits of IV acetaminophen, many of the studies thus far have not been able to make a correlation between some of the primary and secondary outcomes, such as with the presumed reduction in opioid consumption being the cause of decreased incidence in PONV (19). This suggests that an alternative mechanism exists and could potentially be explained by IV acetaminophen unknown effect on perioperative stress. It is well established that patients undergoing surgery have a surge of cortisol, epinephrine, norepinephrine, as well as C-reactive protein (CRP) (35). In response, sympathetic activation, free radical production, complement system activation, and a shift towards metabolic catabolism all occur to keep the body in homeostasis (35, 36). Furthermore, it is well known that increases in these stress markers are associated with common postoperative complications, such as with pain and gastrointestinal distress, and with physiologic changes like increased cardiac demand and impaired pulmonary function (37). These responses are the focus of management in the PACU as their augmentation could hasten recovery. As benefits in prophylactic IV acetaminophen have been implicated, a decrease in this stress surge remains to be proven.

IV acetaminophen has proven benefits in managing some of the most common patient problems such as nausea, vomiting, pain, and functionality, all of which when not under control have negative impacts on patient recovery. By administering the drug prior to noxious stimuli, therefore allowing peak concentrations at surgical incision, and continuing treatment throughout the entire perioperative period via multiple frequent dosing the drug, IV acetaminophen may mitigate surgical stress response, achieve better pain control, and prevent the negative outcomes which halt patients from a speedy recovery. Subsequently, any interval of time saved in patient recovery translates into more efficient hospital management with improved cost savings and possibly improved patient satisfaction.

Study Objective

The aim of the proposed study is to examine the effect of Q4 hour multidose IV acetaminophen on patients' readiness for discharge. In doing so we will also investigate the various factors that could potentially contribute to a patient's readiness for discharge such as overall opioid consumption, time to rescue medication, incidence of postoperative nausea and vomiting, pain scores, and perioperative stress markers and their overall correlation with IV acetaminophen intake.

Methods

i. Overall Study Design and Plan:

This is a randomized, double-blind, placebo-controlled, two-arm parallel study.
Ninety subjects (45 in each arm) will be enrolled. Subjects, over the age of 18, undergoing same-day laparoscopic cholecystectomy under general anesthesia will be screened for eligibility to participate in the study. Subjects will be screened, recruited, and randomized during the preadmission visit or the day of surgery. Eligible subjects will be randomized to one of the two treatment groups in a 1:1 ratio to receive either IV acetaminophen or matching placebo. Both men and women will be recruited, and there is no limitation as to racial and ethnic origin. Participation in the study will not alter the patient's anesthetic management. Routine anesthesia monitors used during general anesthesia will be applied as per ASA guidelines. Patients 50kg or more will receive either 1000mg IV acetaminophen or placebo with the first dose given preoperatively in the holding area followed by re-dosing

every four hours from that point up to a maximum of 4 doses or 4000mg in 24 hours. Patients <50 kg will receive 12.5mg/kg to a maximum of 75 mg /per kg/per day as per the label dose with repeat dosing Q4 hours.
After pre-oxygenation, general anesthesia will be induced with lidocaine (1 mg/kg Ideal Body Weight), propofol (1-2 mg/kg **Actual** Body Weight), and fentanyl (up to 2 mcg/kg **Actual** Body Weight). Additionally all subjects with receive 2 mg midazolam. Tracheal intubation will be facilitated with rocuronium (0.6 – 1.2 mg/kg Actual Body Weight). Anesthesia will be maintained with air/oxygen (60%/40%) and desflurane. A remifentanyl infusion (0.05-2mcg/kg/min **Ideal** Body Weight) will be continued throughout the entire case with no further analgesics being administered. All patients will receive ondensentron 4 mg prior to the end of operation as well as additional antiemetics in the PACU as judged by the attending anesthesiologist. Patients will be awakened and extubated in the OR meeting standard extubation criteria. Once extubated all patients will then be transferred to the PACU where they will be assessed via the SPEEDs criteria 5 minutes after arrival and then every 15 minutes for the duration of their PACU stay. While in the PACU, all patients will be assessed for pain using the Visual Analog Scale. Pain will be treated as per our protocol with 0.2mg IV hydromorphone for mild pain (VAS 1-3), 0.4 mg IV hydromorphone for moderate pain (VAS 4-6), and 0.6 mg IV hydromorphone (VAS 7-10). As soon as a patient meets all the SPEEDs criteria he/she will be transferred to phase II of the recovery. In phase II, if need be, pain will be managed according to the following orders: 0.2mg intravenous hydromorphone for mild pain (VAS 1-3), 0.4 mg intravenous hydromorphone for moderate pain (VAS 4-6) and 0.6mg intravenous hydromorphone for severe pain (VAS 7-10).

ii. Sample Size Justification:

The primary outcome of the study is the proportion of patients achieving discharge-readiness status at end of 2-hours post-surgery. It is a categorical variable with binary outcomes (yes vs. no). The study hypothesizes that among those who received multiple doses of I.V. acetaminophen a higher proportion of patients would be ready for discharge at 2-hours post-surgery compared to patients who received routine care.
For the purposes of sample size calculation we assumed that about 50% patients in the control arm would be ready for discharge by end of 2-hr post-surgery. We used a two-sided alpha error rate of 5% (or significance at alpha of <0.05 level) and a power of 80%. With these inputs, we computed that we will need a total of 78 patients, 39 in each arm to detect a difference of at least 30% between the two arms i.e. about 80% or more patients in I.V. acetaminophen arm will be ready for discharge at 2-hours post-surgery. We will be enrolling 45 patients in each arm (total of 90 patients). At an alpha of 0.05, this study will have 86% power in detecting at least 30% difference between the two treatment arms.

iii. IV Acetaminophen Administration:

The study drug will be given via intravenous infusion beginning after a placement of the IV line in the holding area once the patient is checked in the day of surgery. The dose will be fixed at 1000mg for those over 50kg while patients under 50kg will receive 12.5mg/kg all infused over 15 minutes.

iv. <u>Inclusion criteria:</u>

1. Male and female patients 18 years of age or over.
2. Undergoing ambulatory laparoscopic cholecystectomy.
3. ASA physical status 1, 2, or 3.

v. <u>Exclusion criteria:</u>

1. Cognitively impaired (by history) and unable or unwilling to consent
2. Chronic steroid or opioid user (as prescribed for a chronic systemic illness)
3. Pregnant
4. Patients who have been informed by a physician that they have liver or kidney disease

5. History of substance abuse (alcohol or drug)
6. Diagnosis of obstructive sleep apnea
7. Allergy to acetaminophen
8. Chronic use of other products that contain acetaminophen

vi. Endpoints:

The patient's readiness for discharge will be our primary outcome. Each patient will be assessed within 5 minutes of arriving in the PACU and then every 15 minutes thereafter until subject reaches maximum score. The assessment will be done using the SPEEDs criteria, which has recently been shown to be as specific and more sensitive for phase 1 nursing interventions and therefore more accurate in predicting which patients are fast-track eligible as compared to the standard Modified Aldrete 2 and Fast-Track criteria (38).
The secondary outcomes will include:

a) Post-operative pain scores
    a. Assessed every 15 minutes during the recovery period using the Visual and Numerical Analog Scales for 2 hours and then every 4 hours thereafter until discharge.
b) Time to first rescue medication
    a. 0.2mg intravenous hydromorphone for mild pain (VAS 1-3)
    b. 0.4mg intravenous hydromorphone for moderate pain (VAS 4-6)
    c. 0.6 mg intravenous hydromorhone for severe pain (VAS 7-10)
c) Total dosage of post-operative opioids given.
d) Incidence of post operative nausea and vomiting and need for additional antiemetics.
e) Phase II satisfaction survey:
    a. This will focus on three of the following factors rated on a scale of 1 to 5, with 1 being dissatisfied/unlikely while 5 being most satisfied/very likely.
        i. How satisfied are you with the overall experience?
        ii. How likely are you to recommend this anesthetic and analgesic to others?
        iii. How likely would you ask for a similar anesthetic and analgesic in the future if need be?
f) Concentration of the plasma stress/inflammatory markers including cortisol, norepinephrine, epinephrine, interleukins 6, 8, 10 and CRP.
    a. Changes in mediator levels in the IV acetaminophen versus placebo groups will be compared. Plasma samples will be collected before administration of any drug (after placement of IV lines), before incision, and 60 minutes after arrival in PACU. Blood [15mL] will be collected at the time points described above from an additional intravenous catheter placed in the patient's arm. These specimens will be placed in vacutainer tubes with no anti-coagulant. Blood will be drawn

with a syringe attached directly to the angiocatheter which has been placed intravenously. To prevent hemolysis, blood will be transferred without a needle, to a vacutainer whose top has been removed. The vacutainer top will be replaced and specimens labeled with study name, subject's study ID number, sample number (1, 2, 3,), and dated. Bloods from the first two time points will be kept refrigerated until the final sample is obtained postoperatively. They will be centrifuged, serum removed, aliquoted and stored at -80 degrees C until analysis. All samples will be run in duplicate on with plates and reagents of the same lot. Any samples varying greater than 15% between duplicates will be repeated. Serum collected by NewYork-Presbyterian Methodist Hospital will be transported to Rutgers – NJMS, MSB. Samples will be placed into dry ice and transported by car in compliance with IATA regulations by person with IATA Shipping Training.

vii. Methods and Procedures

1. Data monitoring plan: Adverse events will include events reported by the subject or noted by the medical staff and thought to be associated with the research. Unanticipated problems and adverse events will be gathered by study investigators. Adverse events will be evaluated at each study visit. Any serious adverse effects will be reported to the IRB according to regulatory requirements.

   The principal investigator Dr. Michal Gajewski will be primarily responsible for monitoring the study. The study principal investigator will evaluate the data to determine whether to continue the study or to change the protocol to decrease risk.

2. Data Storage: All of the patient data used in this study will be kept confidential and will be used for professional purposes only. Patient records will be coded and kept in locked files within locked rooms or in password protected computers. Only those investigators directly involved in the protocol will have access to these records. Though the information collected in this study may be published, no patient will be identified by name. After completion of the study data will be kept for six years before secure disposal.

3. Risk/Benefit Assessment: Other than general risk of anesthesia and surgery, there are a few risks associated with the study drug, mainly nausea, vomiting, headache and insomnia as reported on the Ofirmev Prescribing Information (reference). Anyone with an increased risk for hepatotoxicity has been excluded from the study. The risks from the blood draws are the risks of any routine blood draw. These include discomfort or minor swelling at the site. There are no risks to the questionnaires.

   Acetaminophen is a non-opioid analgesic which may be of benefit during as well as after surgery. This study will elucidate whether a standing dose given every four hours will have a beneficial effect on patient recovery after surgery and which factors may be of greatest importance.

4. Subject Identification, Recruitment, and Consent: Study flyers approved by the IRB will be distributed to the surgeons' offices and given to patients who come to Pre-Admission Testing. After a general discussion regarding the study and the informed consent, patients will be approached when they arrive at same-day admission and we will formally obtain consent after answering their questions and concerns about the study. In addition, this study in particular poses little risk to the patient. Patients will be approached if possible at pre-surgical testing but more likely on the day of their procedure and spoken to in a closed room or a private area. The patient may have family included, if he/she prefers. We will be approaching all subjects (male and female) who are undergoing same-day laparoscopic cholecystectomy and who, from the OR schedule, are at least 18 year of age. A verbal explanation of

the study will be given followed by a written consent form. Study staff members are experienced at consenting patients for anesthesiology studies. One is an MD anesthesiologist with clinical research experience and another is an experienced coordinator with over 5 years of experience.

Subjects who do not have the capacity to consent for surgery will not be recruited. All other subjects will be recruited. For any patient who might be illiterate, consents will be read to him or her and witnessed by available staff or family member.

5. Costs to the subject

   All study related costs will be paid by Departmental Internal funding. After IRB approval we will apply for funding from the Mallinckrodt Research Grant.
   Patients will not receive payment for participation in the study.

viii. Statistical Analysis

Data will be sent to the Department of Surgery, Rutgers University-New Jersey Medical School for analyses by an independent biostatistician (A.D.). To assess the success of randomization patients' demographic and clinical characteristics, values of biological markers (drawn before drug administration or induction) will be compared using Student's t-tests for continuous measures (where assumptions of normality are met); Mann Whitney U tests for ordinal data; Pearson chi-square or Fishers exact test for categorical data. Using Mann Whitney U test will be used to compare pain scores upon arrival in PACU, at intervals of 30-minutes, 1-hour, 2-hours, 4-hours, and at discharge. Serum epinephrine, serum norepinephrine, C reactive protein, and serum cortisol levels will be compared before induction, end of surgery, and prior to discharge using Student t-tests. In addition, to account for baseline values, ANCOVA models will also be used. Fisher's exact test will be used to compare proportion of patients who received rescue hydromorphone, oxycodone, and anti-emetics. Additionally, Student t-tests will be used to compare total dosage of rescue hydromorphone and oxycodone used by patients in the two arms. All statistical tests will be two sided with statistical significance at alpha of 0.05. SAS 9.4 statistical software will be used for data analysis.

ix. Study drug storage

In accordance with University hospital policy all study medications and placebo will be dispensed by the research pharmacist.

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