Effect of Intravenous Acetaminophen on Postoperative Opioid-related Complications

– FACTOR –

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1. INTRODUCTION

1.1 Background

A. Postoperative pain

Pain is a psychological sensory experience which is caused by various factors. Surgery results in tissue damage which leads to postoperative pain. Studies in recently developed animal models of postoperative pain have advanced our knowledge of the mechanisms of pain resulting from surgical incision and associated tissue injury. Postoperative pain results from a of combination of nociceptive and inflammatory components.(1) The nociceptive component results from activation of peripheral sensory neurons damaged by surgical incision, and fades gradually as tissues heal. The inflammatory component enhances pain sensitivity via release of mediators from the surgically injured tissue. Central neuronal sensitization also seems to contribute to postoperative pain and hyperalgesia. (1, 2) Due to aforementioned mechanisms pain is present in spontaneous resting at the site of surgery plus surrounding tissues. Movement or touching of the wound site, breathing, coughing, and gastrointestinal motility can all evoke pain.

Unrelieved postoperative postoperative pain leads to multiple physiological and psychological consequences which worsen outcomes. For example, inadequate perioperative analgesia is associated with myocardial ischemia, impaired wound healing, delayed gastrointestinal motility, atelectasis, and postoperative pneumonia. (3, 4,5) Furthermore, poorly controlled acute pain is strongly associated with development of persistent incisional pain which can be devastating for patients. (6, 7)

B. Multimodal Postoperative Analgesia With Non-steroidal Anti-inflammatory Drugs

Postoperative pain management has improved, but remains a major problem. Patients still report that 31% of them suffer from severe pain and 47% from moderate pain after surgery.(8) Researchers have estimated that only one in four surgical patients in the USA received adequate relief of acute pain. Consequently, postoperative pain remains the major preoperative concern for patients having surgery. (9)

Pain involves multiple mechanisms and is thus ideally treated with a variety of analgesic techniques with additive or synergistic effects. (1) In theory, at least, combining techniques improves overall analgesia while reducing side effects. Consistent with this

theory, studies indicate that multimodal analgesia shortens hospitalization times, improves recovery and function, and decreases health care costs. (1, 10)

Multimodal analgesia can be achieved by combining many different classes of drugs. (1,10,11) But the most common approaches are a combination of an opioid and non-opioid with or without regional anesthesia-analgesia.(11) The main goal is to decrease opioid use and consequently decrease the incidence of opioid related side effects. Non-opioid analgesics used in this setting are generally insufficient to treat postoperative pain by themselves, but have substantial opioid-sparing effects and thus presumably reduce opioid-related complications. While logical, there is in fact limited evidence that reducing opioid consumption actually decreases opioid-related complications — especially life-threatening complications such as respiratory depression.

The most common drug groups used for multimodal analgesia are non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, and the distinction is important. NSAIDs are antipyretic and anti-inflammatory, but provoke surgical and gastrointestinal bleeding, renal impairment; they also impair bone healing. (11, 12,13) In contrast, acetaminophen is a “pure” analgesic with few side effects, and none likely to harm surgical patients. It is beyond question that acetaminophen is opioid-sparing; however, there are no large randomized trials evaluating whether opioid sparing actually reduces complications as expected.(13)

C. Opioid Analgesics and side effects

Opioids are the most common treatment for postoperative pain. Opioids produce analgesia and other effects by binding to specific opioid receptors in the peripheral and central nervous system. Three types of opioid receptors and their subtypes have been discovered: mu, delta, and kappa receptors. The most commonly used opioids bind to mu receptors. The mu_1 receptor is responsible for the production of opioid-induced analgesia, whereas the mu_2 receptors are related to the respiratory depression, cardiovascular effects, and inhibition of gastrointestinal motility commonly seen with opioids.(14,15,16)

There is a persistent misconception that pain, no matter how severe, can always be effectively relieved by opioids. That is certainly not the case at doses which can be safely used postoperatively, and numerous studies show that postoperative analgesia remains inadequate in a striking fraction of patients. (8) Acute tolerance and opioid-induced hyperalgesia increase opioid requirements, in turn increasing the risk of side effects.

The most serious opioid-induced complication is respiratory depression which results from a dose-dependent reduction in responsiveness of brainstem respiratory centers to carbon dioxide (Pco_2) with opioids. This is clinically manifested as an increase in resting Pco_2 and a shift in the CO_2 response curve. (17,18) Respiratory depression is

the main fatal hazard of opioid use and has been identified as a safety target by the Joint Commission on Hospital Accreditation (19). Supporting this concern, a study conducted in United Kingdom ranked opioids as the second most common cause of adverse events in hospitalized patients.(20) The current national goal of better controlling postoperative pain by making it a quality indicator is likley to increase opioid use — and almost surely also increase associated complications.

Sedation is another serious consequence of excessive opioid use, and often impairs patient mobility and postoperative recovery. For example, sedation decreases ambulation and thus promotes atelectasis and respiratory depression.(21) There are currently no widely accepted guidelines or monitoring practices for opioid-related sedation and the respiratory depression. The Anesthesia Patient Safety Foundation suggests using continuous monitoring of pulse oximetry in patients receiving patient-controlled analgesia (PCA).(22) However, continuous pulse oximetry is in fact rarely used.

Postoperative nausea and vomiting (PONV) is the most common opioid-related complication and is caused by stimulation of the chemoreceptor trigger zone of the medulla.(23) Furthermore, opioids enhance sphincter tone and reduce peristaltic contraction. Delayed gastric emptying is caused by decreased motility, increased antral tone, and increased tone in the first part of the duodenum. Delay in passage of intestinal contents leads to greater absorption of water, increased viscosity, and desiccation of bowel contents — which in turn causes constipation and contributes to postoperative ileus.(24) Postoperative ileus, with an incidence of 4.5%, prolongs hospital stay and increases hospital costs.(25) Opioids also inhibit urinary bladder function, thus increasing the risk of urinary retention.

In summary, opioids provoke numerous severe complications that cause substantial patient morbidity. They also delay discharge from hospital, increase the cost of care, and reduce patient satisfaction.

D. Acetaminophen

Acetaminophen is a derivative of p-aminophenol. It is also known in many countries by the name *paracetamol*. Acetaminophen is a centrally acting analgesic and antipyretic agent which has been in use for decades. Acetaminophen centrally inhibits prostaglandins via the COX pathway, by selective inhibition of COX-2-dependent prostaglandin E2 formation (13,26). The drug reinforces descending serotonergic inhibitory pain pathways (26,27), indirectly activates cannabinoid CB1 receptors (13, 27, 28), and inhibits nitric oxide pathways (8) through N-methyl-D-aspartate or substance P (29). Acetaminophen also appears to be a TRPV-1 agonist.

Acetaminophen is generally considered to be analgesic, without anti-inflammatory properties. However, recent human studies identify anti-inflammatory effects similar to those of ibuprofen; animal studies similarly indicate that acetaminophen inhibits

inflammation and edema.(13) Acetaminophen is thus now thought to provide weak anti-inflammatory properties compared to other NSAIDs.

The recommended dosage of acetaminophen is 1 g every 6 hours, or 650 mg every 4 hours, with maximum of 4 g/day. Acetaminophen IV reaches maximum concentration (C max) at the end of a 15-minute infusion. The C max ranges from 28 to 31 µg/mL. The clearance ranges from 0.27 to 0.34 L/hour/kg, and the volume-of-distribution ranges from 0.8 to 1.2 L/kg. Acetaminophen IV has low plasma protein binding and thus distributes widely through the body tissues except to fat.(13,30,31,32,33)

Acetaminophen has a mean half-life of 2.4 ± 0.6 hours and is metabolized primarily in the liver, with 5% of free drug excreted in urine. Use of acetaminophen in perioperative settings is relatively new, but is becoming more common now that an intravenous formulation is available. There are numerous reasons to prefer acetaminophen to traditional NSAIDs. Among the most important is that recommended doses of acetaminophen do not interfere with platelet function, and thus do not promote bleeding. And unlike NSAIDs, acetaminophen has little effect on the kidney and gastrointestinal system.(13,30,31,32,33)

Several metanalyses summarize available studies of perioperatrive intravenous acetaminophen use. Remy et al. (34) evaluated the morphine sparing effect of intravenous acetaminophen after major surgery in 7 clinical trials and demonstrated a significant 10-mg decrease in morphine consumption on first postoperative day. The decrease was not associated with reduction in opioid-related adverse event, although the total number of patients included in the analysis was limited. In another metanalysis, Elia et al. (35) evaluated opoid sparing with various NSAIDs and acetaminophen. they included 10 trials of acetaminophen analgesia after major surgery and identified a significant 8-mg reduction in morphine consumption, but again no significant decrease in opioid-related side effects. Finally, a recent metanalysis by Apfel, Turan, and colleagues (36) included 30 studies, and demonstrated a significant reduction in pain and opioid use with intravenous acetaminophen, along with a significant reduction in PONV. The most likely reason previous acetaminophen studies failed to identify significant reductions in opioid-related complications is that all were small, and many did not includes rigorous methodology for detecting rare (but serious) complications.

E. Rationale of the study

Previous studies with acetaminophen have shown consistent and clinically important opioid-sparing effects; however these studies were unable to demonstrate significant reductions in opioid-related adverse events, largely because sample sizes were inadequate and because complications were poorly monitored. Most notably, no previous studies of perioperative acetaminophen used continuous pulse oximetry which is probably the only reliable way to detect potentially serious respiratory compromise.

One barrier to using intravenous acetaminophen in the perioperative period is that it is relatively expensive compared to other NSAIDs. However, the complications including respiratory depression associated with increased opioid usage are extremely costly. The costs of using intravenous acetaminophen for preventing opioid related side effects and the costs of treating the associated complications has not been addressed. Furthermore, available studies and calculations regarding cost are not based on actual decreases in opioid-related side effects, but instead on unverified assumptions, making the results unconvincing. Therefore, assessing the cost-effectiveness of intravenous acetaminophen needs to be investigated as well.

We thus propose to evaluate the opioid-sparing effect of intravenous acetaminophen and, more importantly, the reduction in opioid-related complications. Specifically, we propose to test the primary hypothesis that total duration of hypoxia (defined as time with SpO_2 < 90%) is less in patients given intravenous acetaminophen than placebo. Our secondary hypotheses are that intravenous acetaminophen: 1) decreases postoperative opioid consumption; 2) decreases postoperative pain; 3) decreases nausea and vomiting; 4) decreases sedation; 5) improve activity; and 6) reduces fatigue.

The impact of postoperative opioid related complications is not only important from a clinical perspective, but also from an economic standpoint. The additional cost attributable to opioid side effects has not been well defined and usually depends on estimates rather than solid data. Our study will provide data to support a full cost-benefit analysis, so the financial benefits of acetaminophen can be concretely evaluated.

Opioids and analgesics have been separately shown to reduce MAC values in previous studies (37, 38). Acetaminophen and NSAIDs have been implicated in decreased anesthetic requirements, but there is no concrete evidence to support this theory (39, 40, 41). Measurement of BIS values during surgery will help shed some light on the MAC-sparing effect of acetaminophen if it exists.

2. Study Objectives

Using a randomized design and blinded assessments, our goal is to determine the effect of intravenous acetaminophen (versus placebo) infusion on a variety of important opioid-related complications and outcomes in postoperative patients. The proposed research will have the following aims, all of which will be assessed over 48 hours or the duration of hospitalization if shorter:

Primary Aim. To assess whether intravenous acetaminophen decreases postoperative opioid-related respiratory depression.

Hypothesis. Our primary hypothesis is that total duration of hypoxia (defined as time with SpO_2 < 90%) is less in patients given intravenous acetaminophen than placebo.

Secondary Aims.

Secondary Aim 1. To evaluate the role of intravenous acetaminophen on postoperative opioid consumption.

Hypothesis. Total opioid consumption is reduced by intravenous acetaminophen infusion.

Secondary Aim 2. To evaluate the role of intravenous acetaminophen on postoperative pain.

Hypothesis. Intravenous acetaminophen decreases time-weighted postoperative pain scores.

Secondary Aim 3. To evaluate whether intravenous acetaminophen decreases nausea and vomiting.

Hypothesis. The incidence of postoperative nausea and vomiting is reduced in patients given intravenous acetaminophen.

Secondary Aim 4. To evaluate whether intravenous acetaminophen decreases sedation.

Hypothesis. The incidence of postoperative sedation is reduced in patients given intravenous acetaminophen.

Secondary Aim 5. To assess the effect of intravenous acetaminophen on activity after surgery.

Hypothesis. Intravenous acetaminophen increases the time spend sitting and upright rather than lying down.

Secondary Aim 6. To assess the effect of intravenous acetaminophen on fatigue after surgery.

Hypothesis. Postoperative fatigue scores are reduced in patients given intravenous acetaminophen.

Secondary Aim 7. To assess the cost-effectiveness of intravenous acetaminophen after surgery.

Hypothesis. Intravenous acetaminophen reduces total cost of care from the societal perspective by decreasing opioid-related complications and hospital length-of-stay.

Secondary Aim 8. To evaluate the role of intravenous acetaminophen on postoperative opioid-related respiratory parameters.

Hypothesis. Intravenous acetaminophen reduces respiratory depression (defined by decrease in tidal volume, minute ventilation and respiratory rate) compared to placebo.

Secondary Aim 9. To evaluate the MAC-sparing effect of acetaminophen intraoperatively.

Hypothesis. Intravenous acetaminophen reduces MAC requirements when given intraoperatively.

3. Method and Study Design

A. Study Overview

We propose to assess opioid-related side effects in patients recovering from elective non-cardiac surgery who will be randomly assigned to intravenous acetaminophen or placebo for 48 hours postoperatively. The design will be a randomized, double-blind, placebo-controlled trial of intravenous acetaminophen in adults having elective major abdominal surgery. The study will be performed at the Cleveland Clinic hospitals.

B. Setting and Population

Inclusion criteria:

(1) Written informed consent;

(2) 18-85 years old;

(3) ASA Physical Status 1-3;

(4) Scheduled for elective open or laparoscopic abdominal surgery, including colorectal, prostate, and hysterectomy surgeries;

(5) Patients with anticipated hospitalization of two nights;

(6) Expected to require parenteral opioids for at least 48 hours for postoperative pain;

(7) Able to use IV PCA systems.

Exclusion criteria:

(1) Hepatic disease, e.g. twice the normal levels of liver enzymes;

(2) Kidney disease, e.g. twice the normal level of serum creatinine;

(3) Epidural analgesia or regional blocks (including TAP block);

(4) Acetaminophen sensitivity or known allergy;

(5) Female patients who are pregnant or breastfeeding;

(6) Patients taking warfarin.

C. Withdrawal Criteria

Patients will be free to withdraw from study at any time. Patients will also be removed from study at any time for adverse events, or deemed necessary for patient safety.

D. Administration of Acetaminophen

The investigational drug for this study is Acetaminophen 1 g per dose. The placebo control is 0.9% sodium chloride prepared in equal volume and infused at same rate and duration of acetaminophen. The Pharmacy team will have the appropriate randomization in case of a safety or emergency situation, and the study drug label will mention that it is "Acetaminophen or Normal saline".

E. Protocol

Patients must meet all inclusion and exclusion criteria to be eligible for the study. After eligibility is confirmed, patients will receive complete information about the study both verbally and in writing. Informed consent must be obtained from the patients prior to randomization and study-specific procedures. Research fellow will also apply an 8 item STOP-BANG questionnaire.

Anesthetic management will follow pre-established clinical and institutional guidelines. Patients will be pre-medicated, and induced per institutional routine according to attending anesthesiologist discretion. General anesthesia will include the standard monitoring for the given operation, and induction will occur after the electrocardiogram and monitoring equipment are placed on the patient. Induction agents may include sodium pentothal, propofol, or etomidate, fentanyl, rocuronium, and oxygen. Anesthesia will be maintained with sevoflurane or isoflurane in oxygen and air; rocuronium or atracurium will be given per judgment of the attending anesthesiologist. Prophylactic antibiotics will be given per surgical routine.

Randomization (1:1) will be web-based and initiated at induction of anesthesia; allocation will thus be concealed from investigators. Randomization will be stratified based on chronic opioid use. Chronic opioid use will be defined as opioid use for more than 30 consecutive days, at a daily dose of 15 mg or more of morphine or equivalent, within the 3 months before surgery. The treatment groups will be intravenous acetaminophen and normal saline placebo.

Acetaminophen or placebo infusion will be initiated as soon as practical in the operating room with 1 g (or equivalent volume) and repeated every 6 hours for the earlier of 48 postoperative hours of hospital discharge. Intraoperative opioids and benzodiazepines will be left to discretion of the anesthesiologist. However, fentanyl will be recommended for intraoperative analgesia, and hydromorphone for postoperative analgesia.

In the PACU, patients will be given intravenous PRN bolus of hydromorphone or fentanyl as necessary. Subsequently, patients will be given hydromorphone or fentanyl

PCA with standard clinical settings, with the option of fentanyl or hydromorphone for breakthrough pain. The blinded clinicians, according to current standard clinical protocols, will make adjustments for the opioid analgesic dose. Patients will be titrated to comfort (pain score of <4) in the PACU and ward using allowed opioids.

Clinical evaluators for the outcomes will be blinded to group allocation and Pharmacy personnel not involved in evaluations will prepare the study drugs. Patients will be continuously monitored and recorded with a wireless pulse-oximeter starting after extubation in the operating room. A respiratory volume monitor will be used continuously for the study period and information will be recorded. Clinicians including nurses will be blinded to monitoring and will be required to perform their standard of care management after surgery.

Other anti-inflammatory drugs will not be used intraoperatively or for the initial 48 postoperative hours. A single dose of dexamethasone (4-8 mg) will be permitted for PONV prophylaxis, and inhaled steroids will be permitted as necessary to treat reactive airway disease. Other opioid sparing medications like gabapentin, pregabalin, ketamine or lidocaine patch will also not be permitted through the initial 48 postoperative hours.

Patients will be allowed to receive prophylactic anti-emetic (first choice ondansetron) intraoperatively based on the risk assessment for nausea and vomiting. Postoperative anti-emetics for symptomatic treatment will also be allowed; again ondansetron will be the first choice.

F. Measurements

Demographic and Background Information:

Demographic data to be obtained includes height (cm), weight (kg), age (yr), gender, (ASA) physical status, and self-declared ethnicity. Patients will be questioned for social history (tobacco) and medical history (pulmonary disease, kidney disease, diabetes mellitus, neurological disease, chronic pain conditions, illegal drug usage, alcohol abuse, myocardial infarction, previous surgery or stent placement and medications usage). Available preoperative laboratory tests and medication list will be recorded. Individual risk for nausea and vomiting will be determined using the Apfel score.

ViSi mobile (Sotera Wireless) patient monitoring system will be used to continuously record noninvasive blood pressure, patient activity, posture, 3-lead ECG, SpO_2, and respiratory rate. Data will be recorded at one-minute intervals and downloaded daily to a laptop.

ExSpiron Respiratory Volume Monitor (RVM) has been shown to provide accurate real-time, continuous, non-invasive measurements of tidal volume, minute ventilation and respiratory rate. This system will be used to record respiratory data and downloaded for analysis.

Data obtained from electronic medical records will include: operation time, surgery type, intraoperative opioid consumption, postoperative opioid consumption in PACU and in ward, breakthrough pain medication requirements, pain scores in PACU and ward, requirement of oxygen in PACU and ward, nausea and vomiting, requirement of antiemetics, pruritus, requirement of antihistaminic medications, requirement of naloxone, itching, ambulation time, flatus, ileus, bowel movements (first time, all bowel sounds at all quadrants), constipation, length of stay and any side effects or complications. Preoperative and postoperative laboratory data including but not limited to liver function and coagulations test results will also be collected from electronic medical records. Patient functionality will also be recorded including, bathing, toileting, walking and moving.

Brief Pain Inventory and the Short Form 12 health survey (SF 12) will be completed before surgery, and at the 90-day follow up. Brief Pain Inventory is a practical method of evaluating pain severity and impact on patient function. BPI includes four rating pain intensity, and seven covering the impact of pain. Intensity is recorded on an ordinal scale from zero (no pain) to ten (worst imaginable pain). Impact of the pain section these ratings are made on zero-to ten numeric scales running from no interference to complete interference. The Short Form 12 health survey is an abbreviated version of the SF-36 health survey, a well-established instrument to assess psychological and physical aspects of health related quality of life.

Patient satisfaction with their pain treatment will be questioned after 48 hours using 0-100 scales and we will also use Myles QoR scale to formally evaluate quality of recovery. Myles QoR scale is a validated scoring system allows quantification of patient's early postoperative health status, which is also a description of quality of recovery.

Patient satisfaction with the comfort of wearing the ViSi and ExSpiron devices will be questioned on the second post-operative day after the monitoring session is stopped.

Primary Aim

Duration of hypoxic events (SpO_2 < 90):

Patients will have nearly continuous pulseoxymeter monitoring and recording. Nurses and the study personal will be blinded to data on the monitor and standard of care will be provided. Data from the monitor will be downloaded daily for 48 hours postoperatively, incidence of hypoxia and the time spend hypoxic will be determined. We will be using ViSi mobile (Sotera Wireless) patient monitoring system a platform for comprehensive vital sign monitoring. This is a comfortable body-worn sensor that allows the patient to ambulate or move, providing accurate and continuous monitoring of all the vital signs including beat-to beat noninvasive blood pressure, patient activity, and posture. This system will measure 3 lead ECG, SpO2 and number of respirations continuously. The primary outcome will be area-under-the-curve for saturation over time with the threshold set at 90%.

Secondary Aim 1

Total opioid consumption, in morphine equivalents, will be the major measure of opioid use. However, we will also record the number of times fentanyl is given for breakthrough pain.

Secondary Aim 2

Our major outcome for pain will be time-weighted pain scores from discharge from the PACU until 48 hours after the end of surgery. PACU pain scores will also be compared separately. Sedation will be determined and recorded at roughly 4-hour by ward nurses per clinical routine.

Secondary Aim 3

Our major outcome for PONV will be the cumulative incidence of nausea and vomiting outcome during the initial postoperative 48 hours. However, we will also consider the number anti-emetic rescue treatments.

Secondary Aim 4

Our major outcome for sedation will be severity of sedation, as determined by the Richmond Agitation Sedation Scale, during the initial 48 postoperative hours. Sedation will be determined and recorded by ward nurses per clinical routine.

Secondary Aim 5

Our major measure of activity will be the time spend while sitting or upright, as determined by the ViSi mobile monitoring system, during the initial 48 postoperative hours.

Secondary Aim 6

Our major measure of fatigue will be a VRS score determined on the first postoperative morning.

Secondary Aim 7

A cost-benefit analysis will be conducted to determine the optimal strategy of IV acetaminophen compared to placebo. The analysis will compare the costs of the intervention compared to the monetary value of the benefits. The benefits will include opioid medication reduction, LOS reduction, nursing time reduction, hypoxia reduction, PONV reduction, and any health care resource utilization reduction attributable to reduced opioid use in the 3 months post surgery.

Secondary Aim 8

Continuous ExSpiron impedance data collection will occur during PACU and postoperative study period. Our major outcomes will be the tidal volume, minute volume and respiratory rate.

Secondary Aim 9

We will conduct a secondary analysis within the subset of patients who has their BIS values measured. We will compare the two randomized groups on total amount of anesthetic gas (MAC-hours) receive from induction to extubation, using multivariable linear regression adjusting for the time-weighted average BIS value and any imbalanced baseline variables within the subset. Intraoperative BIS values and amount of anesthetic gas will be obtained from the Cleveland Clinic Anesthesia Record Keeping System.

G. Data Analysis

Analyses will be intent to treat. The randomized groups will first be compared for balance on all potentially confounding baseline variables using standard descriptive statistics. Any imbalanced factors will be used for adjustment in all analyses comparing randomized groups on outcome.

To evaluate our primary hypothesis, we will compare patients randomized to acetaminophen to those randomized to placebo on the total duration of hypoxia (defined as time spent with SpO_2 < 90%). Various graphical and tabular summaries will be undertaken to characterize the hypoxic events in the two study populations (e.g., reporting

incidence of any hypoxic event, summaries of timing and duration of hypoxic events relative to surgery, etc.).

To formally test our primary hypothesis, we expect that the duration of hypoxia outcome will exhibit a skewed distribution, with many patients having durations of zero. Thus, standard tests and methods for normally-distributed outcomes may not be applicable. Further, separate analyses need to be considered depending on whether or not there is a presence of chance imbalance on baseline characteristics between the groups. If there are no such imbalanced factors, we will utilize the two-sample Wilcoxon rank sum test for our primary comparison. If there are imbalanced factors to be used for adjustment in our analysis, we will do so by developing either a multivariable Poisson regression model, a multivariable negative binomial (NB) regression model, or a multivariable zero-inflated negative binomial (ZINB) regression model depending on the specific distributional characteristics of duration of hypoxia in the samples (we will choose the model which exhibits the best goodness of fit). In any case, a significance level of 0.05 will be used to evaluate the primary hypothesis.

Secondary outcomes will each be compared at the 0.005 significance level, reflecting a Bonferroni correction for ten simultaneous comparisons in order to maintain overall Type I error rate at 0.05 for the set of secondary hypotheses. Opioid consumption, patient-mean pain scores, total time spent sitting, total time spent upright, and fatigue score will be analyzed using either t-tests of multivariable linear regression models (depending on whether or not there are any imbalanced factors). Prior to analysis, morphine equivalent doses will be transformed using the logarithm in order to stabilize the distributions and model percent differences in geometric means. For incidence of nausea and vomiting, we will use either chi-squared tests or multivariable logistic regression models.

Tidal volume, minute ventilation and respiratory rate will each be analyzed using respective mixed effects regression models. These outcomes will be expressed as differences from their baseline value to indicate levels of depression throughout the monitoring period. A power series correlation structure will be used to adjust analysis for the intra-subject correlation exhibited by multiple outcomes made within a patient; this structure assigns a higher degree of correlation/redundancy for measurements made more closely together in time than for measurements made more distant in time from one another. The hypothesis of difference in average level respiratory depression between the acetaminophen group and placebo group will be assessed by comparing regression coefficients associated with the group effect in these models. Tests for interactions with time (i.e., time-dependent effects of acetaminophen on depression outcomes) will be performed, and, if significant, results will be expressed as a function of monitoring time.

All analyses will be performed using R statistical software for 64-bit Microsoft Windows (The R Foundation for Statistical Computing, Vienna, Austria).

Economic Analysis

The impact of postoperative opioid related complications is significant from not only a clinical standpoint but from an economic standpoint. The additional cost attributable to opioid side effects has not been well defined and usually depends on estimations rather than solid data. Our study will provide a cost-benefit analysis where the costs and benefits in monetary terms of the outcomes of multiple benefits can be compared.

A cost-benefit analysis will be conducted to determine the optimal strategy for economic outcomes related to IV acetaminophen and surgery. A cost benefit analysis is based on welfare economics and allows us to determine whether the outcome/benefit is worth achieving given the opportunity cost to society of all the resources consumed to achieve this outcome (42). In cost benefit analysis, all costs and benefits are measured in monetary terms. For benefits that cannot be directly measured monetarily, they are valued using a human capital, revealed preferences, or stated willingness to pay (WTP) method (43). By using uniform unit of benefit, multiple benefits can be included the analysis as compared to a cost-effectiveness analysis where only one unit of effect or benefit can be compared. In a cost-benefit analysis, the incremental difference in costs and benefits between interventions being evaluated determines the optimal strategy of choice.

To undertake this form of analysis, a decision analytic model using Treeage Pro® will be developed. A decision analytic model is a systematic, quantitative approach to decision making and can aid in health-care resource allocation. The decision analytic model will compare two possible intervention arms: A- IV Acetaminophen and B-Placebo. All possible outcomes will be incorporated into the model. PONV reduction will be incorporated as a decision node. Opiod reduction, LOS reduction, nursing time reduction, hypoxia reduction, and 3-month health care utilization benefits will be incorporated at the terminal nodes. A simplified decision tree is presented in Figure 1. A hospital/payer perspective will be adopted and include all relevant costs and outcomes. Only costs and benefits relevant to the interventions in question will be included. All outcome probabilities used in the model will be determined from the clinical trial.

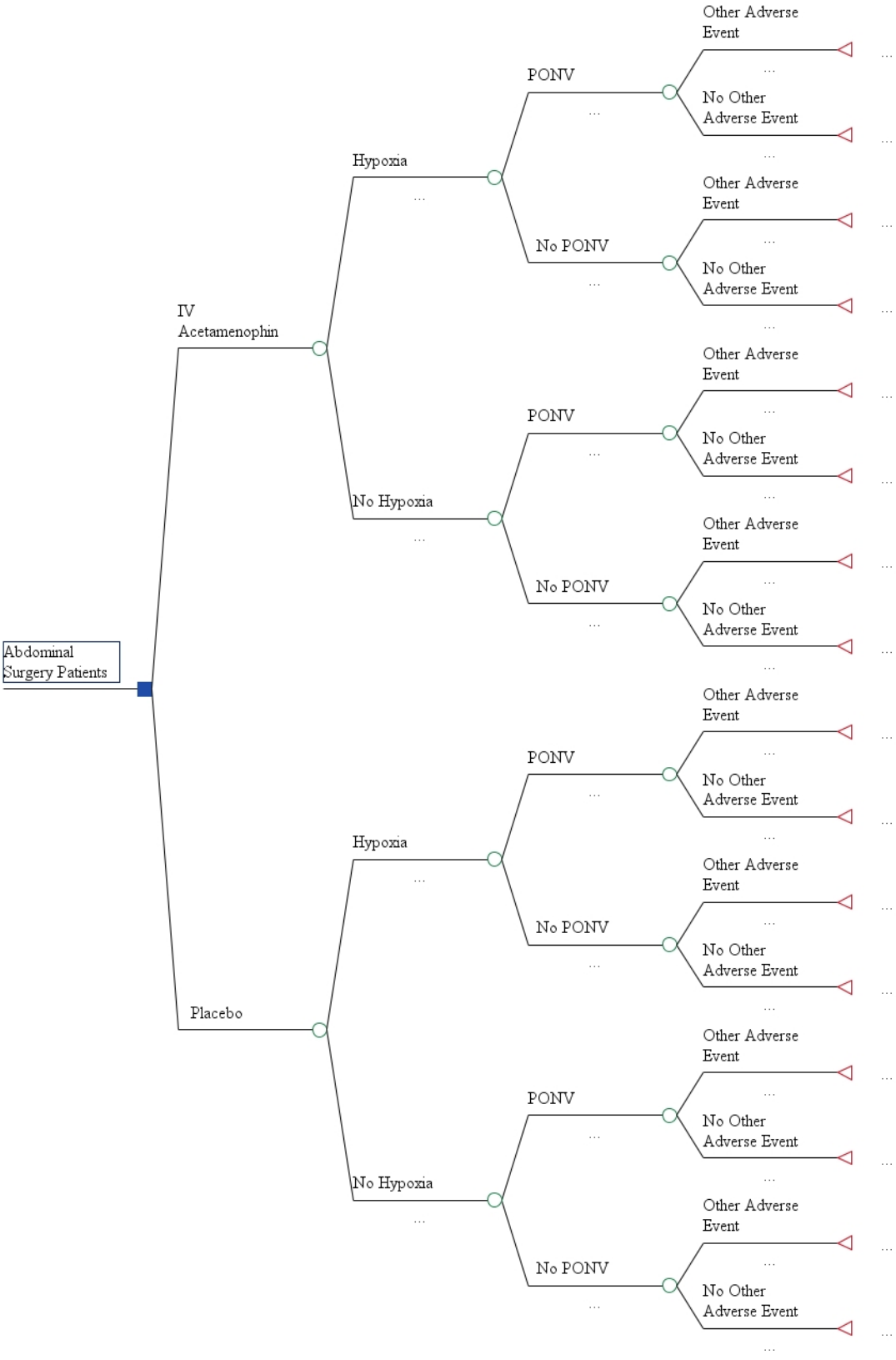
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Figure 1 – Skeleton Decision Tree – IV Acetaminophen vs. Placebo

Costs to be included will be the costs of the intervention drugs, the cost of adverse events, cost of any additional labor required, and cost of any healthcare resources required in the 3 months post surgery. These resources may include ER visits, physician visits or hospitalizations attributable to, and reduction of health care resource use in the 3 months post surgery. The opioid reduction will be valued by determining quantity and cost using the average wholesale drug acquisition costs. These costs will be sourced from the Elselvier Rx Verify database. The value of LOS will be valued based on Medicare/Medicaid reimbursement schedules. The value of avoiding PONV will be determined from a willingness to pay analysis (contingency valuation) as published at the time of analysis (40, 41). As with costs, all benefits will be adjusted to the same base year using the Medical Component of the Consumer Price Index and all future benefits will be discounted at a rate of 3%.

The determined costs and benefits for each arm of the decision tree will be incorporated. The analysis of the model will use the costs, benefits and probabilities of each arm of the decision tree. The analysis outcome will be a cost benefit ratio for each arm. The incremental cost-benefit ratio will be calculated for the interventions. Depending on the results, one intervention may be dominated in terms of cost and benefit or the optimal strategy may be dependent on willingness to pay for additional units of benefit.

The initial analysis would use direct clinical trial data. One criticism of clinical trial data, especially when it is used in an economic evaluation is that its outcomes can't always be generalized to other settings (42). Through the use of economic modeling, clinical trial outcomes can be modeled to real world conditions. Models can also extrapolate data beyond the clinical trial, link intermediate clinical endpoints to final outcomes, and simulate head to head comparisons of interventions where a trial does not exist. For this study, complex sensitivity analysis will be conducted to test the robustness of the results to variability and uncertainty in the models values and its effect on the choice of optimal strategy. The model will be populated with not just point estimates, but with the range of data values including distributions.

Variability and uncertainty in the model will be analyzed from 3 aspects; variability in the population, uncertainty in the structure of the model, and uncertainty of the variables used within the model. Variability of the population will be tested using a Monte Carlo Microsimulation. This analysis involves running one patient at a time through the model with the events based on the underlying probabilities and a random number generator within the model. This analysis simulates differences in populations and the distribution of potential outcomes including optimal intervention choice can be plotted. Uncertainty within the model will be analyzed using one-way sensitivity analysis. This analysis involves varying the value of one variable at a time within the predetermined range. From this analysis will be conducted where one value will be varied at a time. From this analysis, the variables who are the biggest drivers of changes in the model will be identified and summarized with a tornado diagram. To test the uncertainty of the variables used in the

model, probabilistic sensitivity analysis will be conducted. This form of analysis allows the uncertainty of all the variables in the model to be assessed at the same time. The values of variables are sampled from the distributions within the model. Using these results, the incremental cost benefit ratios will be determined with confidence intervals. Incremental net benefits will also be determined by determining a cost-effectiveness acceptability curve. This curve summarizes what proportion of time the optimal strategy will indeed be the optimal strategy as it depends on willingness to pay.

From all the analyses presented above, a transparent, easy to follow cost-benefit summary will be produced to aid persons in decision making positions. The summary will include the costs and benefits of each intervention, the incremental costs and benefits between the interventions, the cost benefit ratio of the interventions, and the incremental cost benefit ratio between the interventions. The uncertainty around the results will also be summarized to show that the optimal strategy is the choice strategy in 'what' percentage of time and for 'what' variable values.

H. Sample Size Considerations

VISION is a large prospective observational cohort study with the primary aim to evaluate major vascular events in patients undergoing noncardiac surgery. We analyzed preliminary data on postoperative SpO_2 from the all 833 patients who had >12 hours continuous monitoring with <20% missing data (Table 1). Each patient's SpO_2-versus-time data was first smoothed using kernel regression in order to remove excess variability (see Figure 2 for examples).

Total duration of hypoxia was then computed for each patient according to their smoothed SpO_2-versus-time profiles. The distribution of total duration of hypoxia is summarized in Table 1 below, under "Preliminary Observational Data":

	Preliminary Observational Data N (Percent)	**Assumed Percentage Under Acetaminophen**
No Hypoxia	461 (55.3%)	65%
Hypoxia <1 Hour	33 (4.0%)	10%
Hypoxia 1-2 Hours	59 (7.1%)	6%
Hypoxia 2-4 Hours	67 (8.0%)	5%
Hypoxia 4-12 Hours	118 (14.2%)	7%
Hypoxia >12 Hours	95 (11.4%)	7%

Table 1

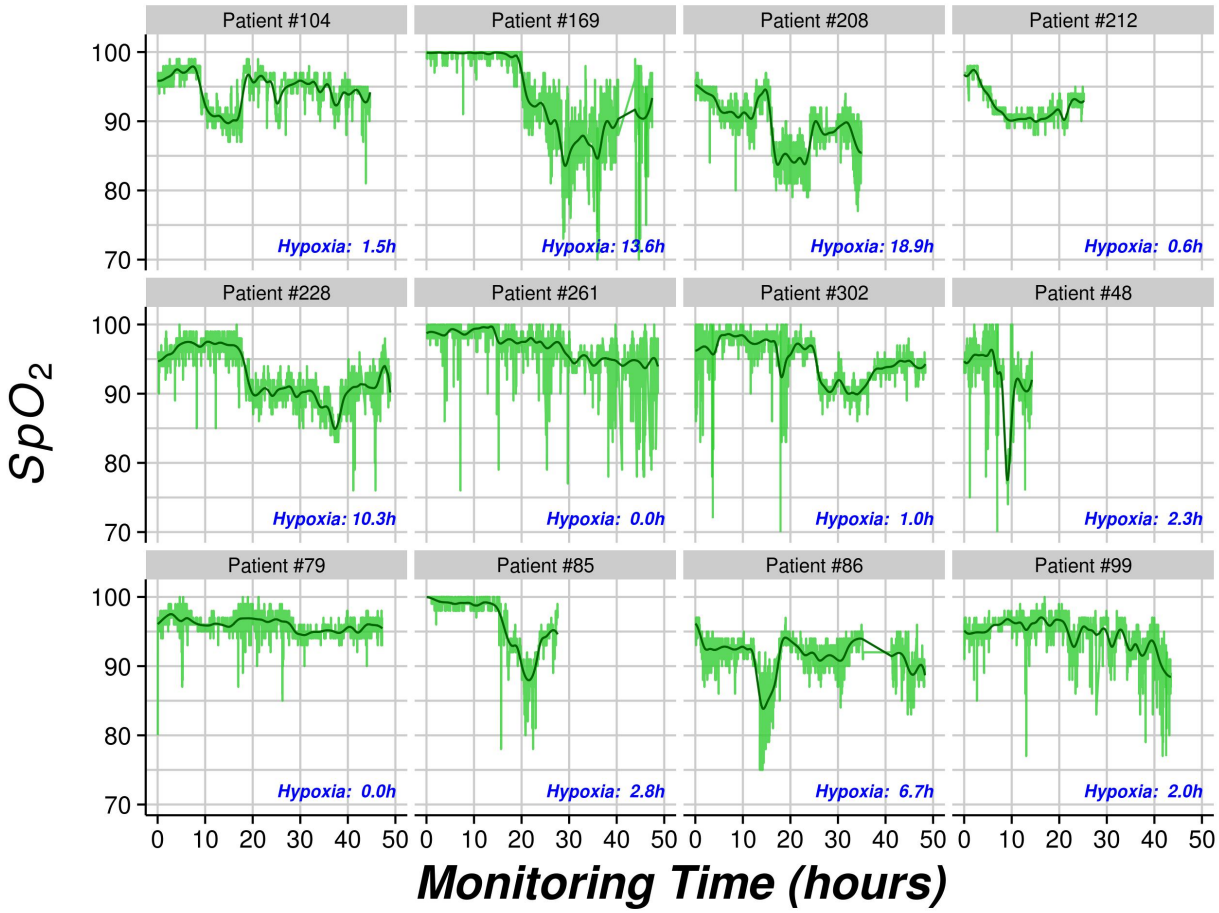

Figure 2: *Time series of SpO_2 (green lines) for a stratified random sample of patients (i.e., two from each hypoxia classes: no hypoxia, hypoxia <1h, hypoxia 1-2h, hypoxia 2-4h, hypoxia 4-12h, and hypoxia >12h). Curves representing kernel smooth estimates of each time series – by which the duration of hypoxia outcomes are defined – are overlayed (black lines).*

For sample size planning purposes, it suffices to use power calculations for the two-sample Wilcoxon rank sum test (i.e., the planned test in the absence of imbalanced potential confounding factors). Assuming that acetaminophen reduces hypoxia risk such that the distribution of total duration of hypoxia is that given in the right column of Table 1, a minimum of 528 patients would be required for the Wilcoxon test to have 90% power to identify a significant difference at the 0.05 level. Thus, without adjusting for interim analyses, we would enroll 528 patients in our study.

Interim Monitoring

Three interim analyses and one final analysis will be conducted. This allows for the possibility of stopping the trial early for efficacy or for futility (should the results indicate either outcome), at the potential expense of increasing the maximum possible study sample size (i.e., that which would be used if the trial is not stopped early).

Stopping boundaries are formally defined according to respective Type I (false positive) and Type II (false negative) error spending rates. As mentioned above, the total Type I error rate for the primary hypothesis will be controlled over the entire study period at 5%. The Type II error rate for the entire study will be controlled at 10%, corresponding to 90% power. We used gamma error spending functions with rate parameters of -4 for Type I error and -2 for Type II error (Figure 3).

Interim analyses will be conducted at equally spaced intervals: 25%, 50%, 75%, and 100% of maximum planned sample size, respectively. The critical p-values of our Wilcoxon rank sum test at each of these four analyses (defined by the curves in Figure 3) will be P<0.0016, P<0.0048, P<0.0147, and P<0.0440 for efficacy and P>0.9572, P>0.7186, P>0.2389, and P>0.0441 for futility (Figure 4). The cumulative probability of crossing a boundary at the 1st through 4th interim analyses, assuming that hypothesized treatment effect reflects the true population difference, will be 0.04, 0.31, 0.80 and 1.0, respectively.

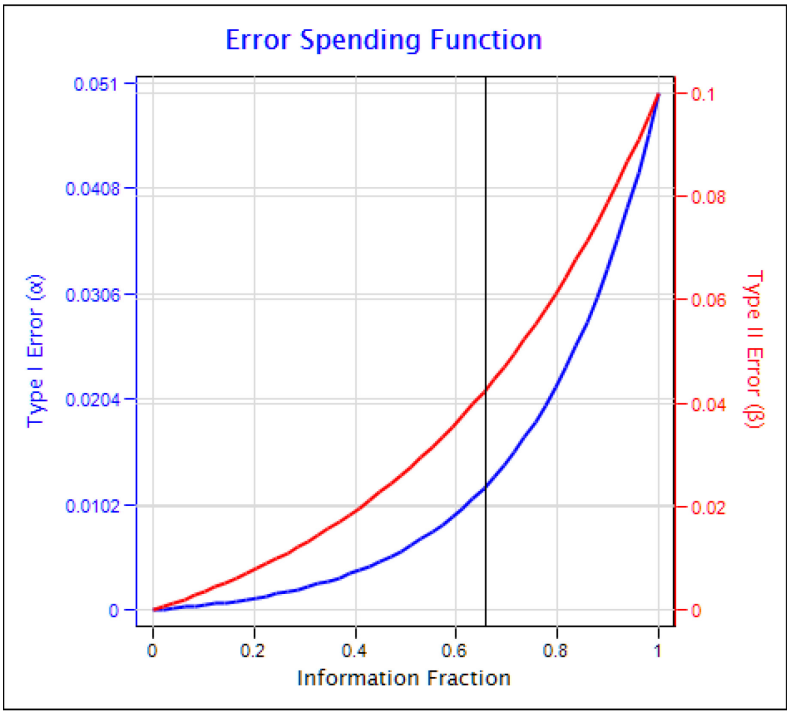

Figure 3 – Type I (alpha) and Type II (beta) error spending functions over the accrued *information fraction* – i.e., the proportion of the maximum total sample size accrued.

Adjusting for interim analyses, the maximum possible sample size will be N=580 patients, corresponding to interim analyses at N=145, N=290, N=435 and 580, respectively, as needed.

Though boundaries may be crossed, imbalanced covariables may yet remain (and thus the need to use the multivariable Poisson/negative binomial regression model to account for chance imbalances). Stopping criteria under these count regression models are difficult to define, as two effects result from such analyses (the odds ratio for zero versus positive hypoxia outcome as well as the ratio of means among patients with positive outcomes). We will report balance on covariables and results from the count regression models at each stage of the study to the Data Safety Monitoring Board. Figure 3).

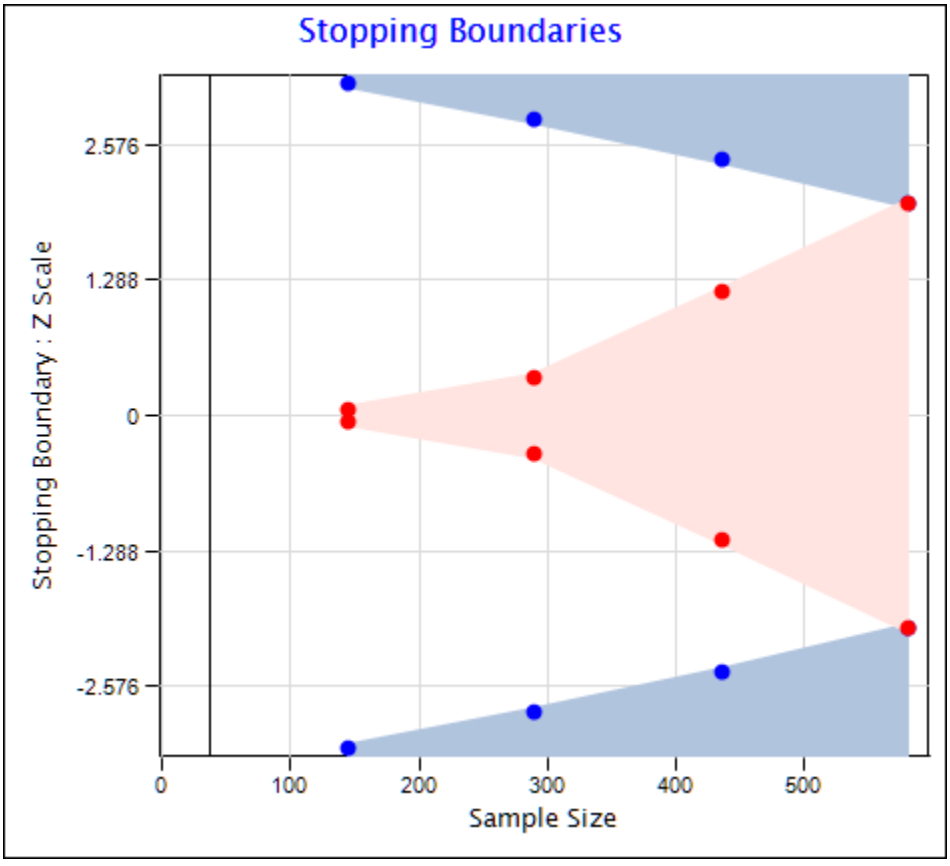

Figure 4 – Type I (alpha) and Type II (beta) error boundaries over the accrued sample size.

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