DETAILED PROTOCOL

Assessing efficacy of IV acetaminophen for perioperative pain control for oocyte retrieval: a randomized, double blind, placebo-controlled trial

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I. BACKGROUND AND SIGNIFICANCE

a. Historical background

Due to the current opioid crisis, non-opioid options for effective multimodal postoperative anesthesia have been explored in many recent studies. Intravenous acetaminophen has rapid onset and potent analgesic properties, but due to its high cost and relatively limited clinical data concerning its efficacy compared with other agents, physicians are hesitant to use intravenous acetaminophen in the perioperative period. Importantly, for minor outpatient procedures such as oocyte retrievals, use of IV acetaminophen offers the opportunity to greatly reduce perioperative narcotic intake in women of reproductive age.

b. Previous pre-/clinical studies supporting the proposed research

Postoperative pain
The majority of postoperative patients experience moderate to severe postsurgical pain, which can lead to complications such as impaired wound healing.[1,2] Although we rely heavily on opioids to alleviate much of postoperative pain, this analgesia is not without adverse effects. Opioids are associated with drowsiness, postoperative nausea and vomiting, ileus, respiratory depression, and bladder dysfunction, all of which can hamper post-operative recovery and discharge.[3] Thus, as we attempt across surgical specialties to reduce the use of opiates for outpatient procedures, IV acetaminophen is an important consideration for multimodal anesthesia for oocyte retrievals.[4]

Safety of IV acetaminophen
Although IV acetaminophen is more expensive than PO acetaminophen and less likely to be fully reimbursed by insurance companies, there is evidence that favors the intravenous formulation over the oral agent. The bioavailability of IV acetaminophen in cerebrospinal fluid compared with oral acetaminophen after the administration of 1 gram over 6 hours is 24.9 versus 14.2 μg•hr/mL.[5] IV acetaminophen produces more consistent plasma concentrations of acetaminophen over time than PO administration, leading to a longer duration of therapeutic drug plasma level.[1] The intravenous route also peaks much faster (15 minutes vs. 45 minutes).[1] Though the risk for overdose always exists, there is evidence that IV acetaminophen may be safer than the same dose of PO acetaminophen: IV administration creates a lower accumulation of acetaminophen's toxic metabolite (n-acetyl-p-benzoquinoneimine) than oral administration and produces a peak acetaminophen concentration in the liver estimated to be 50% less than the same oral dose.[6]

IV acetaminophen for postsurgical analgesia

A recent review of 14 randomized controlled trials examining the efficacy of IV acetaminophen for postoperative pain in a wide variety of surgeries found that patients receiving IV acetaminophen had improved analgesia in 12 of the studies examined.[7] Sinatra et al. showed that IV acetaminophen use (one gram every six hours) was associated with a decrease in morphine consumption by 46% ($p=0.0003$) on postoperative day one after total hip replacement or total knee replacement and increased time until rescue morphine (hip replacement, 3.9 hours and knee replacement, 2.1 hours) compared with placebo (0.8 hours).[8] Other studies in hysterectomy and laminectomy patients suggest that patients receiving IV acetaminophen may have a reduction in postoperative nausea and vomiting, although this has yet to be formally evaluated.[7] Furthermore, both preemptive (before surgical incision) and preventive (after surgical incision) use of IV acetaminophen appears to produce a decrease in pain scores 6 hours after surgery compared with placebo ($p<0.001$).[9] Therefore, the available evidence suggests that the addition of IV acetaminophen can bolster effective analgesia in patients while decreasing the amount of opioids required.[2,3,9,10]

c. Rationale behind the proposed research, and potential benefits to patients and/or society.

The use of IV acetaminophen is approved by the Food and Drug Administration for the management of mild to moderate pain, the management of moderate to severe pain with opioid analgesic adjuncts, and fever reduction in adults and children over the age of 2.[11] As discussed above, recent studies have shown several benefits of using IV acetaminophen perioperatively, including a reduction in opiate consumption, improved analgesia, and reduced postoperative nausea and vomiting.[3,10] While the cost effectiveness of using IV acetaminophen has not been extensively evaluated in surgical patients, a randomized controlled trial of bariatric surgery patients suggests that IV acetaminophen significantly decreases mean direct hospital costs and emergency department visits within 30 days of surgery.[12] However, more research is needed to better assess the efficacy of IV acetaminophen compared to PO acetaminophen in treating postoperative pain and to further evaluate the potential reduction in opioid use.

In our field, recent attention has focused on prescribing practices after oocyte retrievals as many opiate addictions begin with prescription medications.[13,14] However, there are no studies to our knowledge assessing multimodal options for optimal pain control in the perioperative period, which may also impact the perceived need for pain medication prescriptions. Additionally, since cost is one of the limiting factors for giving patients IV acetaminophen, studies like this one that compare IV acetaminophen to oral acetaminophen and assess the impact on time to PACU discharge in both inpatient and outpatient settings are warranted. Our primary goal is to assess the efficacy of pre-operative IV versus PO Acetaminophen compared to placebo (standard of care) for pain control after oocyte retrieval, with the hypothesis that IV acetaminophen will reduce pain scores, reduce overall narcotic burden, shorten time to discharge from PACU, increase time to rescue medication, and decrease opiate-associated side effects.

Investigating the use of non-opiate alternatives for perioperative anesthesia is a crucial aspect of reducing the overall use of opiates in outpatient procedures. IV acetaminophen has the potential

to be a versatile and worthwhile addition to achieving adequate postoperative analgesia in patients undergoing a wide variety of surgical procedures and in numerous hospital settings.

II. SPECIFIC AIMS

a. Specify objective and hypotheses to be tested in the project

Objective:
- To compare the efficacy of pre-operative IV acetaminophen versus PO acetaminophen, versus placebo (standard of care) for adjunctive pain control in the setting of oocyte retrieval in an *in vitro* fertilization clinic setting.

Hypothesis:
- Our hypothesis is that patients receiving IV acetaminophen pre-operatively will have improved postoperative pain scores, lower overall opiate consumption, and shortened time to discharge from PACU than those receiving PO acetaminophen or placebo.

III. RESEARCH DESIGN AND METHODS

This randomized, double blind, placebo-controlled study will be conducted over approximately 12 months at the MGH Fertility Center. Our goal recruitment is 174 patients to achieve statistical power for our primary outcomes.

a. Inclusion/exclusion criteria.

Inclusion Criteria:
[ ] Patient is 18 years or over, undergoing oocyte retrieval.
[ ] Patient is English-speaking.

Exclusion criteria:
[ ] Allergy to acetaminophen or opiates.
[ ] Any history of liver disease, history of alcohol depending, or renal impairment as reported in the electronic health record.
[ ] Any history chronic opiate use or chronic pain disorder as reported in the electronic health record.
[ ] Weight less than 50kg as reported in the medical record.

b. Source of subjects and recruitment methods.

Adult patients from the reproductive endocrinology practice at MGH undergoing oocyte retrieval. Patients will be recruited at the time of their IVF cycle.

IV. SUBJECT ENROLLMENT

a. Methods of enrollment, including procedures for patient registration and/ or randomization

All patients will be offered the chance to enroll in the study by a licensed MD at the time of their baseline ultrasound (IVF cycle start). The licensed physician will introduce the study and provide an information packet containing the study recruitment letter and informed consent at that time. The patient will have the opportunity to opt out of the study at any time. Study staff will confirm patients' study eligibility by telephone during the cycle and indicate their participation on their IVF cycle monitoring schedule if they are eligible. Consent will occur in person during the IVF cycle by a licensed MD (see below).

When the enrolled patient's egg retrieval is scheduled (two days in advance of procedure), study staff will order the research medications in EPIC and will notify the IVF team and research pharmacy via secure email of the study patient's procedure date/time to coordinate medication pick up.

A computer-generated blocked randomization schema with alternating block sizes (http://www.randomization.com) will be generated by the research pharmacy. The fellow will enter a randomization number into the study patient's EPIC medication order, and the pharmacist will associate this number to the patient's assigned study group. The research pharmacist will prepare the appropriate medications, and the IVF care team will be blinded to the medications.

b. Procedures for obtaining informed consent

A licensed MD will consent the patient during one of their morning ultrasound appointments prior to the egg retrieval. It should be noted at the time of consent that participation in the study will in no way impact their infertility treatment or cycle management, that they will receive standard of care anesthesia, and that all perioperative pain will be treated. Consented patients must agree to avoid taking pain medications (including acetaminophen or NSAIDs) during the 24hrs prior to their procedure, which will be confirmed prior to data collection on the day of procedure, as this would necessitate exclusion from study.

c. Study interventions and data collection

The study staff will transport the blinded medications from the research pharmacy to the IVF suite on the day of the procedure. Anesthesia will log medications in EPIC per research pharmacy protocols.

Group 1: In the pre-op suite, these patients will receive 1000mg IV acetaminophen and PO placebo, followed by standard protocol anesthesia and pain control as needed.

Group 2: In the pre-op suite, these patients will receive 1000mg PO acetaminophen and IV placebo, followed by standard protocol anesthesia and pain control as needed.

Group 3:

In the pre-op suite, these patients will receive PO and IV placebo, followed by standard protocol anesthesia and pain control as needed.

In all groups, pain control will be provided by anesthesia peri-operatively as needed. Pain medication such as opiates may be given post-operatively as needed for pain measured by VAS score. In order to be consistent in assessment of immediate post-operative pain, narcotic use, and

discharge timing per our primary outcomes, NSAIDs will be avoided in the recovery room for all study patients, regardless of embryo transfer timing, as they are routinely contraindicated in our practice for any patient undergoing a fresh embryo transfer. However, patients not undergoing fresh transfer may take NSAIDs at home post-operatively as needed per standard of care.

The PACU nurses will assess and document VAS numeric pain scores as they do routinely in EPIC as well as on the study data collection sheet for the study patients. Data collection sheets will be secured in a lock box until input into Redcap by study staff. Study staff will review the data collection and study protocols with the PACU nurses prior to the start of patient enrollment.

After same-day discharge from the PACU, patients will receive a call from a trained member of the study staff on POD2 to assess their recovery and pain medication use. The POD2 phone visit data collection form will be completed at this time. Ability to use NSAIDs in the non-transfer subgroup will be taken into account at the time of the statistical analysis.

The anesthesia and IVF providers will retain the discretion to exclude patients on the day of the procedure from the study if they took extra analgesics in the 24 hours prior to the procedure or experience any non-study related complications of anesthesia and/or surgery.

d. Current standard of care

Current standard of care for patients undergoing oocyte retrieval involves monitored MAC anesthesia with opiates for pain control.

e. Risks

Risks to the patients will be minimized because they will be undergoing anesthesia that is the current standard of care, and pain will be treated, as the patient requires. The patients' IVF cycle management and oocyte retrieval approach will not be altered in any way by participation in the study.

An adverse reaction to acetaminophen could occur. Hepatotoxicity is possible but unlikely in the setting of one dose of IV acetaminophen.

f. Equitable selection of patients

All patients presenting for oocyte retrieval≥ 18 years old who speak English and do not possess any other exclusion criteria may be eligible for inclusion. Our exclusion criteria are relatively few and do not impair our ability to make conclusions that may benefit these patients.

People who do not speak English will be excluded from this study due to the low volume of these patients in our clinic population and the inconsistent ability to arrange for appropriate interpreters during all study-associated interactions in the cycle.

V. BIOSTATISTICAL ANALYSIS

a. Specific data variables being collected for the study (e.g., data collection sheets).

Clinical data regarding pain levels, pain medication use, and time to discharge will be collected on a PACU data collection sheet and POD2 phone visit data collection sheet. The EPIC record will be used to record clinical and IVF cycle history, perioperative care, embryology findings, and pregnancy outcomes.

b. Study endpoints.

The primary study endpoints will include post-operative pain levels in PACU and after discharge through POD2, post-operative pain medication requirements and timing in PACU and through POD2, and time to discharge from PACU. Secondary endpoints include procedure length, post-operative nausea, embryology outcomes, and pregnancy outcomes.

c. Statistical methods.
The difference in pain scores will be assessed by using Fisher's Exact and chi-square tests as appropriate. A multivariable regression model will be performed to control for potentially confounding variables, such as maternal age, BMI, medical comorbidities, procedure duration, and oocytes retrieved.

d. Power analysis (e.g., how sample size determined, evaluable subjects, etc.)

We plan to enroll 58 patients in each of the three treatment groups (n = 174). Allowing for attrition of 5 patients per group (approximately 10%), we assume that we will be able to evaluate outcome data for 159 patients. Based on OR times from 13 patients, we estimate a mean recovery time of 88 minutes, with a standard deviation (SD) of 19 minutes. Using this SD, we anticipate 80% power to detect a difference in mean recovery time between either of the two treatment groups and the standard of care of 8 minutes or greater in absolute value, or approximately 10%, based on two-sample t-tests at the 0.025 two-tailed significance level, where this significance level reflects adjustment for the two comparisons with the control group.

From these 13 patients, we also estimated the SD of the VAS post-operative pain rating to be approximately 2.8. Using this SD, we anticipate 80% power to detect a difference in mean post-operative pain between either of the two treatment groups and the standard of care of 1.7 or greater in absolute value, based on two-sample t-tests as above. Alternatively, assuming that the population mean pain scores for the three groups are 1, 1.5 and 2.5, respectively, then we will have 80% power to detect that the three group means are different, based on a one-way ANOVA at the 0.05 two-tailed significance level.

VI. RISKS AND DISCOMFORTS (STRATIFY BY COMMON AND UNCOMMON)

Drug side effects and toxicities
Potential side effects of acetaminophen include nausea, headache, loss of appetite, rash, and itching. However, acetaminophen is generally very well tolerated. All other medications proposed for this study are currently standard of care for perioperative analgesia.

Serious:
Acetaminophen: anaphylaxis, hepatotoxicity

Risk to privacy:
The collection and processing of personal data from subjects enrolled in this study will be limited to data that are necessary to investigate the efficacy of the study treatment protocol. The treatment plans and medications will be blinded by the MGH Research Pharmacy, and the randomization key will be maintained securely per pharmacy protocols. Study members whose responsibilities require access to personal data agree to keep the identity of the study subjects confidential. The subject's information will be kept confidential according to HIPAA guidelines.

Psychosocial (non-medical) risks
Because the treatment plan involves standard care for egg retrievals with immediate management of pain with medications as needed, we estimate no psychosocial risks.

VII. POTENTIAL BENEFITS

a. Potential benefits to participating individuals.
- Improved analgesia postoperatively
- Decreased overall consumption of opiates postoperatively which may reduce opiate related complications such as postoperative nausea and vomiting
- Decreased time to discharge from the PACU

b. Potential benefits to society (e.g., increased understanding of disease process, etc.)
Investigating the use of non-opiate alternatives for perioperative anesthesia is a crucial aspect of reducing the overall use of opiates in the outpatient setting and preventing new opiate addiction. IV acetaminophen has the potential to be a versatile and worthwhile addition to achieving adequate postoperative analgesia in patients undergoing a wide variety of outpatient surgical procedures. This research will help establish whether PO and IV acetaminophen are cost-effective adjuncts for multimodal analgesia during oocyte retrievals.

VIII. MONITORING AND QUALITY ASSURANCE

a. Independent monitoring of source data
Data will be collected by study staff from the Department of Reproductive Endocrinology and Infertility. Eligible patients will be logged in a secure data form on a Partner's password-protected computer accessible only to study staff. Data collection sheets will be stored securely in a lock box on Yawkey 10 during study recruitment and then entered into RedCap, a secure online database program, with de-identified patient ID numbers assigned. Only the PI and research team will have access to the online and hard copy database, and identifying information will not be released. After the first subject has been enrolled, the data collection binder will be reviewed monthly by a member of the study staff and the PI at a research meeting in a de-identified manner. The PI will be responsible for determining whether the research should be altered or stopped.

b. Safety monitoring (e.g. Data Safety Monitoring Board, etc.)
The PI will evaluate all acute safety data. If 3 subjects experience a grade 2 or greater Adverse Event (AE) that is possibly related to study procedures, the study will be paused to fully evaluate

the safety of continuing enrollment. The PI will be responsible for reviewing the data and determining whether the research should be altered, paused, or stopped. Any adverse events and/ or decision to stop enrollment will be reported to the IRB.

c. Outcomes monitoring

The research assistant and IVF fellows will collect and monitor the data collection forms and Redcap database monthly for accuracy and completeness. The PI will also conduct periodic review of the case report forms and source documentation. The study staff will meet after 50% desired enrollment to review data on enrolled subjects, CRFs, and source documentation.

d. Adverse event reporting guidelines.

Throughout the duration of the study, the PI will perform ongoing evaluation of subject safety data in order to identify AEs and trends as soon as possible. Any unanticipated problems, involving risks to subjects or others including AEs, will be reported to the IRB in accordance with PHRC unanticipated problems reporting guidelines.

IX. References

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