

A Randomized Controlled Trial of Oral Acetaminophen for
Analgesic Control After Transvaginal Oocyte Retrieval

Study Protocol & Statistical Analysis Plan

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1 INTRODUCTION

1.1 Background

The current standard of pain control during oocyte retrieval for in vitro fertilization (IVF) involves fentanyl, propofol, as well as oxycodone [1]. However, there exists little data of alternatives to narcotic medications for analgesic purposes in oocyte retrieval procedures. Potential for non-steroidal anti-inflammatory drugs (NSAIDs), specifically ketorolac, to significantly improve pain scores in women undergoing oocyte retrieval has been shown previously [2]. In that study, ketorolac was administered immediately after oocyte retrieval procedures in addition to standard sedation. It was also shown that the use of these medications did not significantly alter pregnancy rate, live birth rate, or miscarriage rate in these patients [2]. Few other studies have delved into the question of anesthetics for oocyte retrievals other than a retrospective study that showed no significant difference in pregnancy rates or implantation with the use of acetaminophen and diclofenac vs. acetaminophen alone if given postoperatively [3]. However, pain was not measured in this study for either group.

Acetaminophen and NSAIDs have been studied as an adjunctive treatment in a single prospective study with no significant differences in outcomes other than cumulative pain scores and reduction in use of rescue analgesia with tramadol [4]. Additionally, few alternatives other than narcotic medications have been studied; such adjuncts as EMLA cream and acupuncture have not shown a significant reduction in analgesic effect [5,6]. The paucity of data on analgesics used for IVF oocyte retrievals illustrates that more research is necessary to determine if there are safe and effective non-narcotic medications that can be used for this purpose.

1. Kwan I, et al, *Pain relief for women undergoing oocyte retrieval for assisted reproduction*. Cochrane Database Syst Rev, 2013. 1: p. CD004829.
2. Mesen TB, et al, *The effect of ketorolac on pregnancy rates when used immediately after oocyte retrieval*. Fertil Steril 2013. 100(3): 725-/.
3. Akande V, Garas A, and Cahill D, *The effect of diclofenac and paracetamol on pregnancy and implantation rates in infertile women undergoing IVF treatment*. J Obstet Gynaecol 2006. 26(8): 785-7.
4. Mohamad AH, et al, *Parecoxib and paracetamol for pain relief following minor day-stay gynaecological surgery*. Anaesth Intensive Care 2014. 42(1): 43-50.
5. Piroli A, et al, *Comparison of different anaesthetic methodologies for sedation during in vitro fertilization procedures: effects on patient physiology and oocyte competence*. Gynecol Endocrinol, 2012. 28(10): 796-9.
6. Gejervall AL, et al, *Electro-acupuncture versus conventional analgesia: a comparison of pain levels during oocyte aspiration and patients' experience of well-being after surgery*. Hum Reprod 2005. 20(3): 728-35.

1.2 Preclinical Data

None

1.3 Clinical Data to Date

N/A

2 STUDY OBJECTIVES

The objective of this randomized double-blinded placebo-controlled trial is to determine whether preoperative acetaminophen administration improves post-operative pain control following transvaginal cyst puncture for oocyte retrieval. We hypothesize that patients administered an oral dose of acetaminophen one hour before the procedure will have significantly lower cumulative pain scores at both 60 minutes post-procedure and 24 hours post-procedure as compared to patients randomly assigned to placebo.

3 STUDY DESIGN

3.1 GENERAL DESIGN

Randomized double-blinded placebo-controlled trial

3.2 PRIMARY STUDY ENDPOINTS

Primary outcome measures are as follows:

1. Median of cumulative pain scores up to 60 minutes post-procedure
2. Median of cumulative pain scores up to 24 hours post-procedure

4 SUBJECT SELECTION AND WITHDRAWAL

4.1 INCLUSION CRITERIA

Females ages 21-45 undergoing planned TVCP for oocyte retrieval for IVF; English-speaking

4.2 EXCLUSION CRITERIA

Opioid use within 24 hours prior to procedure; acetaminophen use within 24 hours prior to procedure; allergy to acetaminophen

4.3 SUBJECT RECRUITMENT AND SCREENING

Potential subjects were recruited and screened for eligibility on the morning of the procedure by study personnel (staff and physicians involved in the study).

4.4 EARLY WITHDRAWAL OF SUBJECTS

4.4.1 WHEN AND HOW TO WITHDRAW SUBJECTS

Subjects who consented to participate were informed that they could voluntarily withdraw consent for participation in the study at any time. Subjects were also informed that they could be removed from the study if it was determined that participation would be harmful to the patient's health or if the patient did not follow the study rules and requirements.

4.4.2 DATA COLLECTION AND FOLLOW-UP FOR WITHDRAWN SUBJECTS

Median cumulative pain scores at 60 minutes post-procedure and at 24 hours post-procedure were compared between groups in an intent-to-treat analysis.

5 STUDY DRUG

This study involves administration of either a single 1000-mg oral dose of acetaminophen (administered in the form of two 500-mg tablets) or a drug placebo (administered in the form of two tablets, identical in appearance to the study drug). Administration of the study drug or placebo occurs at 60 minutes prior to the TVCP oocyte retrieval procedure.

6 STUDY PROCEDURES

As each patient arrives to the IVF procedure suite on their scheduled procedure date, study personnel will recruit and obtain informed consent from willing participants for the study. Also, patients will be questioned to determine whether there are any exclusion criteria that would preclude their participation in the study. Demographic data including body mass index, alcohol and tobacco use, history of prior oocyte retrieval, history of prior pelvic surgery, and history of chronic pelvic pain or endometriosis. The serum estradiol level at the time of ovulation trigger was abstracted from each participant's medical record.

Those patients who consent to participate will then have a numbered envelope from the Research Pharmacy Department assigned to their data collection form. The anesthesiologist, who is the only person not blinded to the intervention, will then open the envelope to reveal the patient's group assignment. After study personnel have obtained a baseline pain score from the patient using a visual analog scale (VAS) corresponding to numbers 1 through 10. The anesthesiologist will subsequently administer either acetaminophen or placebo 60 minutes prior to the procedure.

During the procedure, participants are given the usual medications administered during all TVCP procedures at this institution, which consist of propofol, fentanyl, and midazolam.

After the procedure is completed, patients will be asked for a pain score using the VAS every 15 minutes for 60 minutes as per routine care in the recovery suite. Additionally, study personnel will document all other procedure and recovery data listed on the data collection form. All participants were discharged home with a prescription for 8 tablets of hydrocodone/acetaminophen (5 mg / 325 mg), as per clinic protocol for all patients undergoing TVCP procedure.

On post-procedure day one, 24 hours post-procedure, participants will be contacted by phone to obtain a pain score on a scale of 1 to 10.

7 STATISTICAL PLAN

7.1 SAMPLE SIZE DETERMINATION

Based on data from prior studies evaluating pain control after minor gynecologic surgery, a power analysis determined that 50 subjects in each arm are needed to detect a 2-point difference in median cumulative pain score at 24 hours post-procedure, with 80% power and an alpha error 0.05.

7.2 STATISTICAL METHODS

Baseline characteristics will be compared between groups with student's t-test, Mann-Whitney U, chi-squared, or Fisher's exact as appropriate. Median cumulative pain scores at 24 hours post-procedure will be compared between groups in an intent-to-treat analysis using Mann Whitney U-test. Use of additional medications within 60 minutes post-procedure or in the first 24 hours post-procedure will be compared using a chi-squared test.

8 SAFETY AND ADVERSE EVENTS

8.1 DEFINITIONS

Adverse Events

An adverse event is defined as "any untoward or unfavorable medical occurrence in a participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research" (clinicaltrials.gov).

The following categories of adverse event data will be reported as applicable: "All-Cause Mortality," "Serious," and "Other (Not Including Serious)" adverse events.

1. All-Cause Mortality: The occurrence of death due to any cause.
2. Serious Adverse Events: Adverse events that result in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
3. Other (Not Including Serious) Adverse Events: Adverse events that are not Serious Adverse Events.

Possible risks of acetaminophen include allergic reactions (rash, urticaria, and/or anaphylaxis) and, rarely, liver dysfunction. The latter is associated with doses greater than 4000 mg. This study will involve administration of only 1000 mg in the treatment group. Patients with recent acetaminophen use will be excluded. Additionally, participants will be counseled to avoid post-procedure acetaminophen use.

8.2 RECORDING OF ADVERSE EVENTS

Each participant will be followed from baseline (administration of study or placebo drug) to 24 hours post-procedure, and any adverse events will be recorded by study personnel and the principal investigator.

As the study involves only the potential pre-procedure administration of oral acetaminophen (or non-active placebo), there is minimal risk for harm or discomfort to participants. The study group will receive two 500-mg tablets, for a total of 1000 mg of acetaminophen, a dose well below the threshold for toxicity.

8.3 REPORTING OF SERIOUS ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

Any serious adverse events or other unanticipated problems will be reported immediately to the Institutional Review Board.

8.4 MEDICAL MONITORING

The study drug or placebo will be administered pre-procedure while in the preoperative area where the participants are already being monitored with routine vital signs prior to the procedure. They are then observed and monitored during the actual procedure (the average duration of which is 30 minutes) by the anesthesiologist providing conscious sedation as per routine. Additionally, one outcome measure requires a 60-minute post-procedure assessment. Thus, in total, each participant will be directly monitored on the day of the procedure for at least 2.5 hours following drug administration.

Participants will be given instructions at discharge to report any problems to the on-call physician. Specifically, participants will be instructed to seek medical assistance immediately if they experience any symptoms suggestive of liver damage, including dark urine, persistent nausea and/or vomiting, stomach/abdominal pain, extreme tiredness, or yellowing of the eyes or skin.

Finally, the participant will be contacted by phone 24 hours post-procedure for final assessment of pain score and will be asked about any side effects or unanticipated problems.

9 DATA HANDLING AND RECORD KEEPING

9.1 CONFIDENTIALITY, 9.2 SOURCE DOCUMENTS, 9.3 RECORDS RETENTION

A study code will be assigned to each enrolled subject. The link between samples and the enrollee will be stored in an encrypted database on a secure, password-protected server. Access to the server and database will be granted only to those personnel with IRB approval for this study. There will be data recorded on paper that will only be handled by study personnel. All paper data collection forms will be stored in the locked office of the principal investigator.

10 STUDY MONITORING, AUDITING, AND INSPECTING

10.1 STUDY MONITORING PLAN

The principal investigator will review the individual data forms daily to monitor for any adverse events or deviations from study protocol. Any such incident will be reported to the Institutional Review Board immediately.

11 ETHICAL CONSIDERATIONS

Currently there are no oral pain medications given to patients prior to oocyte retrieval. Participants will not receive any alterations in the current medication standard of care but if randomized to the study group will receive an additional preoperative pain medication, acetaminophen. Control subjects will receive placebo which should not cause harm. There are no anticipated delays, withholding, or washouts for standard of care treatment as part of this study. If patients have used acetaminophen-containing products within the 24 hours prior to the oocyte retrieval procedure, they will be excluded from the study.

12 STUDY FINANCES

12.1 FUNDING SOURCE

This study is not funded by any grants or outside funding. The minimal cost of acetaminophen and placebo will be covered by the general research fund of the UAB Division of Reproductive Endocrinology and Infertility.

12.2 CONFLICT OF INTEREST

There are no conflicts of interest among study personnel.

12.3 SUBJECT STIPENDS OR PAYMENTS

Subjects will not be compensated for their participation in this study.