A randomized, controlled trial of IV acetaminophen versus IV morphine to manage pain in pregnancy: Can opioid use be reduced in pregnant women?

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A randomized, controlled trial of IV acetaminophen versus IV morphine to manage pain in pregnancy: Can opioid use be reduced in pregnant women?

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Pain during pregnancy

Pain control is considered an important measure of quality in healthcare. Women encounter pain at various times during their pregnancy.[1] The pain may range from mild discomfort associated with the physiologic changes of pregnancy to moderate pain from labor contractions, and ultimately to severe pain associated with surgery from cesarean section. Myometrial pain associated with uterine contractions are typically a visceral pain associated with nociceptor stimuli.[2] Although the intensity of pain changes with pre-labor contractions and at various stages of labor, pregnant women have reported that their highest intensity of pain occurs in the first stage of labor at less than 5 cm dilation. In addition, maternal medical conditions such sickle cell crises and pyelonephritis or even a simple headache may cause pain that is not relieved by simple oral analgesics. In these scenarios, various opioids are often administered parenterally for systemic analgesia.

Parenteral opiods in pregnancy

In pregnancy, parenteral opioid administration, particularly in labor, results in minimal reduction in maternal pain scores and are associated with adverse side effects.[1] These effects from opioid can range from nausea, vomiting and pruritus but also be associated with dangerous events such as maternal respiratory depression and aspiration.[3- 4] All opioids cross the placenta and reside in the neonatal system for up to three to six days.[5] Opioids are associated with alterations in the fetal heart rate pattern including variability, accelerations and decelerations. [6-7] Moreover, in high doses opioids are associated with increased risk of depressed neonates requiring resuscitation at delivery.[1] Due to both maternal and fetal effects, it is preferred to refrain from opioid agents if alternative options are available.

Intravenous acetaminophen

Acetaminophen is a common medication used to treat pain. When administered intravenously, it has been shown to be an effective in controlling pain and reducing the need for narcotics in postoperative patients. [8-13] Until recently, intravenous acetaminophen was only available in its prodrug form, paracetamol, which is metabolized to acetaminophen post-injection. It has been in use for over 25 years and has been shown to be very effective in pain control [14] Intravenous (IV) acetaminophen is currently approved by the FDA for use to treat fever, mild to moderate pain, and moderate to severe pain when used with adjunctive opioid analgesics. Pain relief is reached within 15 minutes of IV acetaminophen [15]. High plasma concentrations

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appear to help drive IV acetaminophen across the blood brain barrier to work in the central nervous system by likely inhibition of central prostaglandin synthesis. While the area under the curve for both oral and intravenous acetaminophen is similar, clinical and anecdotal evidence appears to weigh heavily towards a greater analgesic effect for intravenous administration [15]. Most importantly, IV acetaminophen is associated with a reduction in opiod consumption in surgical patients. [16-17]

IV Acetaminophen in pregnancy

In pregnancy, IV acetaminophen has also been shown to be effective in controlling pain. Prior randomized controlled trials have been conducted, but none within the United States. [14, 18-21,] These smaller trials ranged in size from 45 to 80 women in each trial. When IV acetaminophen was compared to placebo in women with cesarean section, visual analog scores (VAS) of pain were significantly reduced in the following 24 hours. [14, 20] Women in the placebo group required a higher frequency of rescue courses of medication and reported lower patient satisfactions scores. When IV acetaminophen was compared to IV meperidine in women following cesarean section, there were similar VAS scores, but reduced frequency of rescue analgesia and total analgesia consumed.[19] In comparing women receiving IV acetaminophen versus IV pethidine (meperidine) in the first stage of labor, IV acetaminophen significantly reduced pain scores. However, maternal side effects were reported in 64% of women who received pethidine. [22]

Rationale for this clinical trial

The goal of analgesia in pregnancy is to reduce pain while minimizing both maternal and fetal adverse effects. Current opioids used in pregnancy provide minimal pain relief and are associated with adverse effects. IV acetaminophen has been shown to significantly improve pain control following cesarean section and in the first stage of labor. Moreover, IV acetaminophen reduces the need and consumption of opioids following surgery. If IV acetaminophen can be as effective in controlling pain associated with maternal medical conditions and uterine contractions with labor, then the use of parenteral opiods in pregnant women and its exposure to the fetus could be reduced. This could provide new opportunities in the medical management of pain in pregnancy. Thus we propose a comparative effectiveness trial of IV acetaminophen compared to IV morphine.

Hypothesis:

We hypothesize that IV acetaminophen is as effective as IV morphine in reducing pain in pregnant women. In doing so, IV acetaminophen can reduce the amount of narcotics needed in women with pain.

Objectives:

To determine if IV acetaminophen can:

1. Decrease pain in pregnant women
2. Reduce the amount of opioid use in pregnant women who encounter pain

3. Reduce maternal and fetal adverse effects compared to opioids

Study Design:
For this comparative effective trial, we propose a randomized, controlled trial of IV acetaminophen vs. IV morphine in pregnant women. Prior studies have confirmed that IV acetaminophen is effective in controlling pain compared to placebo.[14,20] Thus, administering just a placebo for pain control is not justified at this time.

We will include 3 different groups of pregnant populations who encounter pain for different reasons.
Group 1: Pregnant women with uterine contractions, but not in labor
Group 2: Pregnant women with uterine contractions in the first stage of labor
Group 3: Pregnant women with a medical condition associated with pain.

Inclusion criteria:
Group 1. We will include pregnant women greater than 34 weeks of pregnancy who present with uterine contractions, but are not in labor and who are warranting treatment with intravenous medication for pain control as part of their routine treatment. This will be defined as the presence of uterine contractions documented on the tocodynanometer. However, the cervix remains less than 2 cm dilated and has not changed after 1 hour after re-examining her cervix.[23]

Group 2. We will include pregnant women greater than 37 weeks of pregnancy who present with uterine contractions and are in the first stage of labor and who are warranting treatment with intravenous medication for pain control as part of their routine treatment. This will be defined as the presence of uterine contractions documented on the tocodynanometer and cervical dilation greater than 2 cm, but less than 4 cm. [23]

Group 3. We will include pregnant women greater than 16 weeks of pregnancy who present with pain due to a maternal medical condition including sickle cell crisis, pyelonephritis, pancreatitis, cholecystitis, nephrolithiasis or headache and who are warranting treatment with intravenous medication for pain control as part of their routine treatment.

Exclusion criteria:
We will exclude women less than 18 years of age, less than 16 weeks gestation, with weight less than 50 kg, and contraindications to acetaminophen including reported elevated liver function tests, hepatic injury, hepatic disorder, active liver disease, alcoholism, chronic malnutrition, known coagulapathy, hemorrhage, creatinine > 1.0, or known allergy or hypersensitivity to acetaminophen. We will also exclude women who have received any opioids within the last 24 hours.

Recruitment:

All participants will be admitted for hospital care either for observation, to the antepartum unit or to labor and delivery. Eligible women will be identified after it is deemed necessary by the caring physician to provide medical treatment for pain control according to each of the 3 groups. Those who meet study criteria will be approached about the study in the admission area/OB triage at the time of admission. Written, informed consent will be obtained by a member of our research team, either a physician or research assistant.

Randomization:
Randomization will be performed based on a computer generated list that will be created by a non-clinical member of the research team. Randomization will be stratified by site and by group/patient type. A permuted block randomization with a random fashion will be used to prevent imbalances between groups. The medication based on the computer generated list will be typed out on a piece of paper with the medication regimen written according to the below regimens. This piece of paper will be placed in an opaque envelope and numbered according to the computer generated list. The opaque envelopes will be kept on the obstetrical unit and be managed by the research nurses and team.

Methods:
Women will receive the first dose of either IV acetaminophen or IV morphine after it is determined necessary that the patient will require medications for pain by the caring physician according to clinical management. Data will also be collected regarding maternal demographics, pregnancy characteristics, medications administered, visual analog scales, and maternal/fetal adverse effects.

Medication regimen:
Women randomized to IV acetaminophen will receive 1000 mg IV, repeated every 6 hours as needed up to a maximum of 24 hours [total 4 doses].

Women randomized to IV morphine will receive morphine 2 mg IV, repeat every 4 hours as needed up to a maximum of 24 hours [total 6 doses].

The regimens above were chosen based on the regimens used in prior studies. Morphine was chosen as the comparative opioid since prior studies have demonstrated that morphine provides better pain control, has more patient satisfaction and less adverse effects. [3,5]

Rescue regimen:
If it is determined that either the IV acetaminophen or IV morphine is not adequate in controlling the patient's pain, then a rescue course of opioids [higher dose morphine, meperidine or hydromorphone] may be administered to capture the pain according to the managing physicians. Analgesics that contain acetaminophen will not be administered as a rescue regimen to prevent the potential for acetaminophen toxicity.

If a rescue regimen is required, IV acetaminophen will resume for all 4 doses with its continued intent to treat pain.

Primary Outcome:
The primary outcome variable will be the summed difference in pain intensity in those women in Group 2 in the first stage of labor. Pain intensity will be based on a 100 mm visual analog scale. The subject will be asked to mark with a pen on the scale to rate their pain. If they are unable to mark the scale with a pen, this will be noted.

The pain intensity via the VAS will determined at 6 time points:
[1] prior to administration of the medication
[2] 15 minutes after administration
[3] 1 hours after administration
[4] 2 hours after administration
[5] 6 hours after administration. This will be obtained within 30 minutes after the second dose is given.
[6] 24 hours after administration if the patient is still hospitalized. This will be obtained within 30 minutes after 24 hour dose is given.

The summed difference in pain intensity will be defined as the difference in pain scale from each point 2-6 minus point 1.

Secondary outcomes:
Secondary outcomes will include the following:

1. Pain relief based on a 5 point verbal scale at 15 minutes, 1, 2, 6 and 24 hours
2. The time to first rescue medication
3. The quantity of rescue medication over 24 hours or hospital stay
4. Total amount of either acetaminophen, morphine or other analgesics over 24 hours
5. Patient's global satisfaction at 24 hours. This will be patient reported.
6. Reports of maternal adverse effects such as nausea, vomiting, pruritus, headache, pyrexia, insomnia, sedation
7. Effects on fetal heart rate tracing including acceleration, decelerations, change in baseline and variability. This will occur about 30 minutes after the medication is given with a range of ± 30 minutes.

No human specimens will be obtained for this study.

Sample size:
The sample size calculation is based on the mean difference in the VAS at 2 hours in women who received IV acetaminophen (mean=75.7) compared to IV pethidine (mean=72.7) in women with pain during the first stage of labor. There are no trials of IV acetaminophen versus IV morphine. Based on the above means, an alpha of 0.05 and a power of 0.80, a sample size of 44 women in each arm would be needed for a total of 88

women. To account for a 20% attrition rate from withdrawal, etc., 110 women for each pregnancy population will be enrolled with 55 in each medication group. Thus, for the 3 pregnancy populations [pre-labor contractions, first stage of labor and maternal medical conditions], we will enroll a total of 330 women.

Data analysis

Analysis will be performed on the basis of intent to treat. Chi-square tests will be used to compare categorical data between the two treatment groups. Student's t-test will be used to compare numerical data. Logistic regression analysis will include patient group as a stratifying variable.

Procedures to Maintain Confidentiality

All information and data will be kept on paper research charts that will be stored in a locked file cabinet within a locked research office of our research team/research coordinator. In addition, an electronic database of information and data will be stored on the computer of our research coordinator that is password protected, and in a locked office of the research coordinator. We will record subject information only by study code number.

Potential Benefits and Risks

In general, women will be a part of a study that may potentially affect how we manage pain control in pregnancy. As a specific benefit, half of the patients will be given IV acetaminophen, a drug associated with reduced opioid requirements and opioid-related side effects in non-pregnant women and post-surgical patients.

Acetaminophen is a classified as a Category C medication. There are no studies focusing on congenital malformations from IV acetaminophen in pregnancy. However, epidemiologic data on oral acetaminophen use in pregnancy show no increased risk of major congenital anomalies. A large population-based prospective cohort study of 26, 424 women with exposure to oral acetaminophen during the first trimester indicated no increased risk for congenital malformations.[24] Another population based, case control study from the National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to oral acetaminophen during the first trimester had no increased risk of birth defects compared to 4500 children in the control group. [24] Since the administration of IV acetaminophen will occur greater than 16 weeks, the risks are predicted to be very low.

There are no studies focusing on IV acetaminophen and breastfeeding. Acetaminophen is secreted in human breast milk after oral administration. Based on 15 nursing mothers, the infant daily dose of acetaminophen is approximately 1-2 % of the maternal dose, which is considered minimal. [24]

Hepatic toxicity and renal toxicity are rare adverse effects of acetaminophen. Thus, subjects with known liver or kidney conditions will be ineligible for and excluded from this study. [24]

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