AN EVALUATION OF HYDROCODONE/ACETAMINOPHEN FOR PAIN CONTROL IN FIRST TRIMESTER SURGICAL ABORTION

By

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List of Abbreviations

BMI……..…Body mass index

CI……..…Confidence interval

EVA……..…Electric vacuum aspiration

GA……..……...…Gestational age

HC/APAP…….……Hydrocodone/acetaminophen

IV……..…Intravenous

MVA……Manual vacuum aspiration

NAF……..…National Abortion Federation

NSAID……..……Non-steroidal anti-inflammatory analgesic

PCB……..…Paracervical block

PPCW……..…….Planned Parenthood Columbia Willamette

RCT……..…Randomized clinical trial

VAS…….……Visual analog scale

WHO…….……..…..World Health Organization

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ABSTRACT

Background: The majority of patients undergoing first trimester surgical abortion in the United States receive oral ibuprofen and a paracervical block for pain control. Hydrocodone/acetaminophen (HC/APAP) is increasingly added to this regimen, and is recommended by the World Health Organization. The efficacy of oral opioid agonists for decreasing pain during surgical abortions has not been established.

Objective: To study the effect of oral HC/APAP on patient pain perception during first trimester surgical abortion.

Methods: A randomized, double-blinded, placebo-controlled trial of 120 women receiving two tablets of 5/325 mg HC/APAP or identical placebo administered prior to surgical abortion up to 10 6/7 weeks gestation. The primary outcome was pain with uterine aspiration reported on a 100 mm visual analogue scale. Secondary outcomes were pain at additional time points, satisfaction, side effects, adverse events, and need for additional medications. Linear regression analysis was performed to determine predictors of pain and satisfaction.

Results: 121 subjects were enrolled. There were no differences in mean pain scores between patients receiving HC/APAP versus placebo at any procedural time point. There were no differences in satisfaction or need for additional pain medications. Subjects who received HC/APAP had more postoperative nausea than those receiving placebo, when controlling for baseline nausea. A trend towards greater postoperative sleepiness in the active drug group was observed. No medication-related adverse events were noted. In regression analysis, preoperative anxiety, expected pain, and race were significantly associated with procedural and postoperative pain. Pain during dilation and aspiration were the strongest predictors of patient satisfaction.

Conclusion: Hydrocodone/acetaminophen does not decrease first trimester abortion pain among patients receiving ibuprofen, lorazepam, and a paracervical block. However, this medication may increase postoperative nausea and sleepiness.

CHAPTER 1 – INTRODUCTION

Elective abortion is one of the most common outpatient surgical procedures, with an estimated 45.6 million performed annually worldwide.[1] In the United States, approximately 20% of all pregnancies, and nearly half of unintended pregnancies, end in abortion.[2] In 2008, 1.2 million abortions were performed in the U.S.[3] Despite a variety of analgesic approaches, many patients find surgical abortion extremely uncomfortable; 78-97% report at least moderate procedural pain.[4-6] Finding an effective pain management strategy is an important clinical concern.

The majority of patients undergoing a surgical first trimester abortion in the United States receive oral ibuprofen and local anesthesia via a paracervical block (PCB).[7] While this regimen provides inadequate pain control for many patients, there are several reasons why patients and physicians choose local anesthesia over intravenous (IV) sedation or general anesthesia. IV sedation, generally consisting of an opioid such as fentanyl and a benzodiazepine (typically midazolam), requires additional monitoring and clinic staff, and is often more expensive for patients paying out of pocket. General anesthesia, most commonly induced with propofol, requires an even higher level of monitoring, by a nurse anesthetist or anesthesiologist, and greater availability of emergency medical equipment.[8] Abortion-related mortality is rare (0.1 to 0.6 per 100,000 procedures depending on gestational age), but complications of anesthesia account for 16% of deaths.[9]

Many invasive procedures can be performed under local anesthesia with minimal or no discomfort for patients. Local or regional nerve blocks are very effective for many areas of the body. However, local anesthesia does not entirely anesthetize the uterus and therefore does not provide consistent pain relief for surgical abortions. The body of the uterus is innervated by sympathetic fibers from the T10 to L1 nerve roots, whereas the cervix is innervated by parasympathetic fibers originating from S2 to S4.[10] Nerves to the uterus are distributed with uterine and cervical blood vessels. Despite use of the PCB, in which an anesthetic such as lidocaine is injected at several points around the cervix,

significant cramping typically occurs during abortions and other procedures that require instrumentation of the uterus and cervix. Surgical abortions are just one example; other office gynecologic procedures performed under local anesthesia include dilation and curettage for miscarriage management or diagnostic purposes, hysteroscopy, transcervical sterilization, hysterosalpingography, sonohysterography, endometrial ablation, and procedures for cervical dysplasia.

In addition to clinic logistical issues and concerns about cost and risks, another reason why abortions are more often performed under local anesthesia is the short procedure time. Surgical abortions are typically completed in under 10 minutes.[11] After insertion of a vaginal speculum, PCB is placed, followed by dilation of the cervical canal and aspiration of the uterus with a suction cannula. For most women, dilation and aspiration are the most painful portions of the procedure.[12-14] In one recent study, dilation required less than one minute and aspiration approximately two minutes on average.[12] Patients and providers may be willing to accept a high level of procedural pain because IV sedation and general anesthesia greatly increase the total visit time due to preoperative assessment, induction, and recovery.

Opioid Analgesics in Abortion Care

The risks and benefits of various pain management regimens for first trimester surgical abortion have been evaluated in both observational studies and randomized clinical trials (RCTs). Suboptimal pain control remains a problem in abortion care, but there is clearly motivation among patients and providers to avoid IV medications. For this reason, oral opioids are often utilized in this setting. However, few studies have evaluated these medications for pain control during surgical abortions. A recent Cochrane review highlighted the absence of data to support the use of oral narcotics such as hydrocodone/acetaminophen (HC/APAP) in abortion procedures.[5] While this medication is rarely used as the sole analgesic for abortions, HC/APAP is increasingly added to the regimen of ibuprofen and PCB (personal communication with Planned Parenthood Columbia Willamette [PPCW]) and recommended by

the WHO as a pain control option.[7,15] No RCT has evaluated the efficacy of HC/APAP for pain control during first trimester surgical abortion.

One RCT studied an oral centrally-acting analgesic (and weak opioid agonist), tramadol 50 mg, which was compared to ibuprofen 800 mg. Both were administered one hour preoperatively. There was no difference in immediate post-procedure pain between women receiving oral tramadol or ibuprofen. Ibuprofen was more effective than tramadol at reducing pain 30 minutes following surgical abortion.[16] In another RCT, oral oxycodone 10 mg and lorazepam 1 mg was compared to an IV regimen with fentanyl 100 mcg and midazolam 2 mg.[17] The patients in the IV group had significantly lower intraoperative pain scores on a 100 mm scale (61.2 versus 36.3, mean difference 24.9, 95% CI 15.9 to 33.9). The authors of this study noted that pain scores of subjects in the oral oxycodone arm were comparable to published results for local anesthesia and non-steroidal anti-inflammatory analgesics (NSAIDs), suggesting that the oral opioid is no better than local anesthesia alone.

Other opioids have been studied as premedication for general anesthesia in three RCTs. IV nalbuphine 0.25 mg/kg achieved better one hour postoperative pain control than fentanyl 1.5 mcg/kg IV (Peto OR 0.21 95% CI 0.05 to 0.86, N 40).[18] Nausea and recovery (reaction time) did not differ between nalbuphine and fentanyl. Oral controlled-released dihydrocodone 60 mg did not alter postoperative pain or the incidence of nausea compared to placebo.[19] Paracetamol with codeine suppository 800/60 mg compared to placebo did not affect pain at 30 and 60 minutes postoperatively or prior to discharge, but more patients were sleepy 30 minutes postoperatively after paracetamol with codeine (Peto OR 3.17 95% CI 1.39 to 7.23).[20]

Several studies have evaluated the efficacy of IV opioids for patients undergoing procedures with a PCB. In one large RCT, IV fentanyl (50 or 100 mcg) reduced pain by 1.0 point on an 11-point pain scale compared to placebo.[21] Another study found that patients receiving conscious sedation with IV

fentanyl 25 mcg and midazolam 2 mg had similar pain scores as patients receiving placebo, however their overall satisfaction with the procedure was greater.[22]

Oral opioids have not been well studied in other gynecologic settings. A 2011 systematic review and meta-analysis of pain management for office gynecologic procedures (hysteroscopy, hysterosalpingography, sonohysterography, and endometrial ablation) identified only one placebo-controlled RCT evaluating an opioid medication.[23] This study of sublingual buprenorphine for hysteroscopy concluded that this medication did not decrease pain, but substantially increased side effects including nausea, vomiting, and drowsiness.[24]

Non-opioid Oral Analgesics in Abortion Care

NSAIDs such as ibuprofen decrease uterine activity and pain by inhibiting cyclooxygenase and thereby reducing circulating prostaglandins. Several NSAIDs have been examined in RCTs and found to decrease patient-reported pain. Ibuprofen 600 mg, given 30 minutes preoperatively, improved pain control with aspiration and postoperatively compared to placebo.[25] Oral naproxen sodium 550 mg given 1 to 2 hours preoperatively significantly decreased intraoperative and postoperative pain.[26] However, a recent RCT evaluating ketorolac given prior to surgical abortions under general anesthesia found no difference in postoperative pain.[27]

Benzodiazepines, such as lorazepam, are anxiolytic medications that have been shown to be safe during first trimester surgical abortion.[6,28] However, there are no data suggesting this type of medication decreases procedural pain. In women who self-selected their type of anesthesia, sublingual lorazepam did not decrease pain compared with local anesthesia alone and was associated with more dissatisfaction with pain control.[6] A second trial with oral lorazepam, given one hour preoperatively, did not show decreased pain or anxiety.[28] Despite this lack of benefit, in a large survey of members of the National Abortion Federation (NAF), 30% of providers reported offering it at a dose of 1 to 2 mg.[7] Most patients at PPCW choose it when offered (personal communication with PPCW).

Predictors of Pain during Abortion

Use of anesthesia or analgesic medications are not the only determinants of pain perception during surgical abortion. Several studies have examined other factors that affect a patient's experience of pain. A landmark 1979 study of over 2,200 patients who underwent first trimester abortions under local anesthesia (PCB and diazepam) found that younger patients, and those with fewer prior pregnancies reported more pain.[14] Patients with a high degree of fearfulness prior to the procedure reported more pain. A more recent study showed that pain experienced during menses, or dysmenorrhea, was associated with increased postoperative pain following surgical abortion.[29]

Gestational age has been shown to influence pain experience. Post hoc analysis of a prospective RCT assessing the benefit of intrauterine lidocaine demonstrated increased abortion-related pain at a gestational age of 8 weeks 0 days or more compared to 7 weeks 6 days or less.[13,30] This is in contrast to the results of an observational study.[31]

Procedure type and other factors have been evaluated for their affect on pain experience during abortion. The 1979 study of abortion pain noted that increased provider experience and shorter operative time were significant predictors of pain.[14] First trimester surgical abortion practice varies but manual vacuum aspiration (MVA) and electrical vacuum aspiration (EVA) are both commonly used. NAF's most recent survey shows that 50% of providers use MVA, with 30% of those surveyed using MVA for procedures up to 7 weeks.[7] Randomized studies of electrical or manual aspiration for first trimester abortion have shown no difference in pain perception.[11,32]

Rationale for the Current Study

Further research is needed to study the effects of oral opioids before their use is routinely incorporated into abortion care. No previous study has examined the effect of HC/APAP on intraoperative or postoperative pain relief for pregnancy termination under local anesthesia.

Hydrocodone is a semisynthetic codeine derivative that is commonly used in combination with acetaminophen. Analgesia is produced primary through interaction with endogenous opioid mu-receptors. Acetaminophen is an aniline analgesic which acts as a cyclooxygenase inhibitor. Both medications are metabolized by the liver. The time to peak concentration after ingestion is 1.3 hours.[33] Allergic reactions to either medication are rare, but common side effects include pruritis, nausea, vomiting, constipation, drowsiness, dizziness, and dysphoria.[34] Severe dose-related effects include respiratory depression (due to the hydrocodone), and liver failure (due to the acetaminophen). Rare adverse effects include agranulocytosis and thrombocytopenia.

Results of an RCT examining HC/APAP versus placebo will provide evidence as to whether HC/APAP is truly of analgesic value when used along with a standard regimen of ibuprofen, lorazepam, and a PCB, and may have a substantial impact on current abortion practices. If a clinically significant reduction in pain is not found among women randomized to HC/APAP compared to placebo, its use in women undergoing first trimester abortion should be discontinued. This could enable lower procedure costs and prevent associated side effects and allergic reactions.

In addition, the data will be used to determine predictors of pain during first trimester surgical abortion, which may help optimize anesthesia regimens for this common procedure. Previous studies examining pain during abortion procedures have not examined potential predictors such as body mass index (BMI), type of abortion provider (attending physician versus fellow or midlevel provider), or prior use of pain medications. Furthermore, factors that affect overall patient satisfaction and satisfaction with pain control have also not been determined.

Objectives

The primary objective of this study was to determine whether HC/APAP, given in addition to a standard regimen of ibuprofen, lorazepam, and PCB, affects patient pain perception at the time of uterine

aspiration, as measured by distance (mm) from the left of the 100 mm visual analog scale (VAS), compared to placebo with standard regimen.

Secondary objectives were to assess whether HC/APAP affects pain at different time points during the abortion procedure (anticipated, baseline prior to premedication, after premedication, after speculum insertion, with placement of the PCB, with cervical dilation, and 30 min postoperatively), and whether it affects patient satisfaction with pain control and the overall abortion procedure. We also aimed to assess side effects including nausea, pruritis, and sleepiness, and adverse events associated with HC/APAP, and whether HC/APAP is associated with a need for additional intraoperative or postoperative pain medications. Finally, we planned to assess possible predictors for anxiety, pain, and satisfaction associated with surgical abortions.

CHAPTER 2 – METHODS

This double-blinded randomized placebo-controlled trial was conducted at PPCW in Portland, Oregon. Study procedures were initiated on February 22, 2011 after approval by the institutional review boards at Oregon Health & Science University (OHSU) and Planned Parenthood Federation of America. Complete enrollment occurred on October 15, 2011. The study aimed to assess the incremental efficacy of oral HC/APAP (2 tablets of 5/325 mg) given 45 to 90 minutes prior to the procedure along with a standard medication regimen of ibuprofen, lorazepam, and PCB, in decreasing pain related to first trimester surgical abortion in patients less than 11 weeks gestation compared to placebo plus the standard medication regimen. Randomization was stratified by gestational age (GA) (less than 8 weeks 0 days, and 8 weeks 0 days to 10 weeks 6 days).

Selection of Subjects

Eligible women were recruited by research personnel at PPCW until the required sample size was obtained. Potential study subjects were approached after the decision to undergo a surgical abortion was made and GA was determined by ultrasound. Patients were informed that they would receive the same care whether or not they chose to participate in the study, and that they could remove themselves from the study at any time.

Subjects in this RCT were English or Spanish-speaking women aged 18 years or older, at less than 11 weeks gestation by ultrasound dating, voluntarily requesting surgical pregnancy termination at PPCW. The upper GA limit was selected because misoprostol is utilized for cervical ripening starting at 11 weeks, per clinic protocol. Patients must have had an ultrasound demonstrating intrauterine gestational sac. All subjects were required to be eligible for suction curettage, in good general health, and willing and able to give informed consent and agree to the terms of the study.

Women were excluded if they had symptomatic early pregnancy failure, received premedication with misoprostol, used any opioid within the last 7 days or requested an opioid medication or IV sedation

during the procedure, or if they had contraindications to any of the medications used in the study protocol. Patients were also excluded if they refused ibuprofen or lorazepam, or if they had evidence of pelvic inflammatory disease, or known hepatic disease.

Study Procedures

After establishing that all inclusion criteria were met, patients received detailed information about the study and, if interest continued, signed an OHSU IRB-approved written consent available in English and Spanish. A recruitment log tracked patients who were excluded at any point throughout recruitment of the study, or who declined entry. Their age, GA, and reason for exclusion or refusal, and choice of anesthesia were documented.

After enrollment, subjects completed a detailed questionnaire inquiring about demographic information, previous use of HC/APAP and other opioids, health and pregnancy history, baseline pain, anxiety, nausea, and expected pain.

Randomization and Allocation Concealment: After written consent was obtained and the initial questionnaire was completed, subjects were randomized to treatment group using a predetermined computer-generated blocked randomization (block size of 6) and were allocated using sequentially numbered, opaque, sealed envelopes. Patients were concurrently assigned a study number. The Research Pharmacy at OHSU generated the randomization sequence and prepared the envelopes containing placebo or active study drug. The randomization scheme was provided to the primary investigator after enrollment and data entry were completed.

The study coordinator presented the nurse administering the preoperative medications with the allocation sealed envelope containing either HC/APAP or placebo. All patients received premedication with 800 mg oral ibuprofen and 2 mg oral lorazepam, along with either two tablets of HC/APAP or two tablets of placebo. The placebo and the HC/APAP were prepared by the OHSU Research Pharmacy. Each HC/APAP tablet was placed inside of a separate capsule. The placebo, methylcellulose powder, was

placed into identical capsules to ensure blinding. The participant, the patient advocate who was present for the procedure, the physician performing the procedure, and the study coordinator assessing outcomes were blinded to participant's allocation status. Premedication occurred between 45 and 90 minutes prior to the procedure.

The procedures were performed in accordance with standard clinical procedure. Research personnel collected patient pain scores on the VAS immediately after each step. After placement of the speculum, patients received a standard PCB, based on the most commonly used technique:[7] A total of 20 ml 1% buffered lidocaine, with 2 ml injected into the anterior cervical lip prior to tenaculum placement, and the remaining 18 ml injected paracervically to 3 cm deep at 2, 4, 8 and 10 o'clock. The cervix was then dilated to the number of mm equivalent to or one mm less than the patient's gestational age in weeks (i.e. to 8 mm at 8 weeks 0 days to 8 weeks 6 days gestation), and a corresponding size suction cannula was used. Up to a gestational age of 7 weeks 6 days, manual vacuum aspiration was generally used, and beyond this gestational age electric vacuum aspiration was selected. In order to minimize variability in procedures, all procedures were performed by an experienced provider (attending physician, nurse practitioner, nurse midwife, or fellow).

Research personnel collect post-procedure information from subjects 30 minutes after speculum removal, including vital signs (heart rate and blood pressure), pain, side effects (nausea, sleepiness, and pruritis) and satisfaction. Providers were also given a questionnaire to report any unusual or adverse events.

The primary outcome was patient perception of pain with uterine aspiration reported on a 100-mm VAS. Secondary outcomes included reported pain at time points before, during, and after the procedure, side effects, anxiety/nervousness, as well as subject satisfaction with pain control and overall procedure.

Number of Subjects and Statistical Power

Based on previous data, a 13 to 20 mm, or 30%, difference in pain on a 100 mm VAS has been considered clinically meaningful.[35-37] The mean standard deviation using the VAS to evaluate pain during first trimester abortion was 26.[5] To achieve 80% power, at a significance level of 5% (two-sided alpha = 0.05), a total of 54 subjects (27 in each arm) were required to detect a 20 mm difference or greater on a 100 mm VAS for each gestational age strata (a total of 108 patients for both strata). Combining the two gestational age strata would allow detection of a 15 mm difference in pain. Adding 10% more patients to compensate for possible withdrawal of study participants resulted in a total of 120 subjects.

Statistical Analyses

Data were analyzed with Stata (Version 11.2; StataCorp LP, College Station, TX). Graphics were created with Stata and Prism (Version 5; GraphPad Software, La Jolla, CA). All variables were analyzed using an intention-to-treat approach. The two gestational age groups were analyzed separately to evaluate effects within each group, as well as together for an overall effect.

The sociodemographic profiles of the two treatment groups were summarized using descriptive statistics. For means of continuous sociodemographic variables, t-tests were utilized. Pearson's chi-square and Fisher's exact test were used for categorical data. The Mann-Whitney U test was used to compare the ordinal data for level of menstrual symptoms between groups. Similarly, procedural characteristics of the two study groups including procedure time and postoperative vital signs were compared using t-tests. Fisher's exact test was used to compare adverse events and provider type between groups due to small numbers in several categories.

For most outcomes measured on the VAS, the groups were compared using t-tests. However, baseline pain, postoperative nausea, and postoperative itching were not normally distributed; these outcomes were highly positively skewed, with most patients reporting values near 0 mm. For these three variables, group medians were compared using the Mann-Whitney U test.

Multivariate regression analysis was also performed to determine whether study group (HC/APAP or placebo) was significantly associated with procedural pain and satisfaction when controlling for expected pain. This analysis was performed because patients undergoing abortions who expect to have significant pain are more likely to ask for and receive medications such as HC/APAP. Expected pain scores on the VAS were also dichotomized in order to determine whether there was a subgroup with high expected pain that may benefit from this medication. Subjects with VAS scores for expected pain less than 50 mm were considered to have low expected pain; those with scores of 50 mm or higher were considered to have high expected pain.

Univariate linear regression was performed to explore predictors of intraoperative pain at different steps of the procedure and 30 minutes postoperatively. Gestational age, patient age, race, parity, and prior surgical abortion variables were dichotomized for the univariate analysis. BMI, provider type, and level of menstrual symptoms were analyzed as categorical independent variables. Preoperative VAS scores for anxiety (nervousness), expected pain, baseline pain and nausea were evaluated as continuous independent variables in the regression analysis.

Univariate linear regression analysis was also performed to determine predictors of postoperative satisfaction with pain control. In addition to the independent variables used for the analyses of pain outcomes, intraoperative pain scores were examined as possible predictors.

Multivariate linear regression was then performed to examine pain during aspiration (the most painful part of the procedure), pain 30 minutes postoperatively, and satisfaction with pain control using the significant ($p<0.05$) predictors identified in the univariate linear regression analysis. Clinically relevant variables including study group and and gestational age (in weeks) were also added to the models, though these variables were not statistically significant in the univariate analysis. As expected, there was significant colinearity between nervousness about pain, nervousness about the procedure, and expected pain. For this reason, only one of these was selected as an independent variable in each of the

multivariable models for pain (aspiration and postoperative). Model diagnostics including plots of residuals versus fitted values and Q-Q plots were performed.

The quadratic terms for nervousness about pain, nervousness about the procedure, pain during dilation, and pain during aspiration were also evaluated in the multivariate analysis to explore potential nonlinear relationships with the outcomes. Quadratic variables found to be significant were then examined as categorical variables. Pain scores were categorized using established methodology:[38,39] 30 mm or less was considered "mild", 31 to 69 mm was considered "moderate", and 70 mm or greater was considered "severe".

CHAPTER 3 – RESULTS

Participant flow is shown in Figure 1. A total of 911 patients were assessed for eligibility in order to enroll 121 patients. The most common reason for exclusion was gestational age. Enrollment of the early GA stratum was completed first; 109 early GA patients were excluded while recruitment of the late GA stratum continued. Other frequent reasons for exclusion were request for IV sedation or oral opioids, and requesting ibuprofen only for the procedure. Patients who did not have someone to drive them home after the procedure were not eligible for lorazepam or opioids and were provided ibuprofen only.

Two participants randomized to the placebo group did not complete the study. One subject in the late GA stratum vomited immediately after ingesting the study medication and declined further participation in the study after completing the initial questionnaire and baseline VAS questions. A subject at 10 weeks gestation experienced a uterine perforation necessitating transfer to a hospital for laparoscopy, and did not complete any study procedures after the VAS for pain with cervical dilation. The existing data for these two subjects was included in the analysis. One additional patient beyond the planned 60 was recruited in the late gestational age group.

Demographic characteristics of subjects according to study group and GA stratum are shown in Table 1. Subjects enrolled in the study were in their mid-twenties, on average, and most identified as Caucasian. Approximately half of participants were nulliparous. Average GA was 7.2 weeks for the placebo group, and 7.4 weeks for the HC/APAP group (p=0.58). Within the early GA stratum, subjects randomized to the HC/APAP group had a higher mean BMI (27.1 versus 22.9, p=0.01), and a greater proportion had at least one prior surgical abortion (46.7% versus 20.0%, p=0.03). However, there were no significant differences between subjects receiving placebo and HC/APAP when the GA strata were combined. Most participants described their level of menstrual symptoms as easy, or mild cramping. A greater number of participants randomized to the HC/APAP group reported pain with menses requiring over-the-counter medication, however this difference was not statistically significant (p=0.23).

Procedural characteristics for the study groups are shown in Table 2. Two obstetrics and gynecology attendings, one family practice attending, three mid-level providers, and three family planning fellows performed procedures for study subjects. There were no significant differences in provider type, procedure time, or post-procedure vital signs among subjects receiving placebo or HC/APAP. There was no difference in adverse events. One subject in the HC/APAP underwent reaspiration for hematometra shortly after the procedure. Three subjects experienced vomiting while in the recovery room; two had received HC/APAP and one received placebo.

VAS scores are summarized in Table 3, stratified by GA, and with both strata combined. Baseline pain and nausea, pain prior to speculum insertion, and postoperative nausea and itching were not normally distributed. Each had the majority of values near zero and was positively skewed.

As shown in Table 3, there were no significant differences in preoperative, intraoperative, or postoperative VAS scores between subjects receiving placebo or active drug when stratifying by GA group. Results were similar when combining GA strata. Notably, there were no differences in mean pain scores at any time point during the abortion procedure. On average, subjects experienced the greatest amount of pain during aspiration (63.2 mm for the placebo group, 65.7 mm for the HC/APAP group, $p=0.59$). Mean VAS scores throughout the abortion procedure for subjects receiving placebo versus HC/APAP are shown for the early and late GA strata in Figures 2a and 2b, respectively.

There were no statistically significant differences in postoperative side effects including nausea, sleepiness, and itching among study groups. In the late GA stratum, there was a trend towards increased nausea among subjects who received HC/APAP ($p=0.05$). Baseline nausea was significantly greater in the placebo group. Figure 3a and 3b demonstrate distributional dot plots of pre- and postoperative nausea VAS scores among study participants. Among the late GA stratum (Figure 3b), it is clear that a greater number of subjects in the placebo group experienced nausea before the procedure; postoperatively this trend was reversed and a greater number of subjects in the HC/APAP group had nausea postoperatively.

Figure 4 illustrates the distributional dot plots of VAS scores for postoperative sleepiness. As shown in Table 3, mean postoperative sleepiness was not statistically significantly different among subjects receiving HC/APAP or placebo, for both GA strata. Sleepiness scores on the VAS were high for all subjects, and there was a trend towards increased sleepiness in the active drug group (54.1 in the placebo group, 63.2 in the HC/APAP group, p=0.06). The high degree of sleepiness among all participants was likely secondary to the lorazepam.

Subject satisfaction with pain control and with the overall procedure was high for both study groups. For both the early and late GA strata, the two satisfaction VAS scores were higher in the HC/APAP group, but the differences were not statistically significant in either GA stratum or in the combined analysis. Mean satisfaction with pain control was 67.3 in the placebo group and 74.8 in the HC/APAP group (p=0.10). Distributional dot plots for satisfaction with pain control are shown in Figure 5, and for satisfaction with the overall procedure in Figure 6.

Because there were no statistically significant differences in VAS scores comparing the placebo and HC/APAP groups, these groups were combined to explore potential differences between the early and late GA strata (Table 4). Average GA for the early group was 6.3 weeks, and for the late group was 9.2 weeks. There were no significant differences in preoperative, intraoperative, or postoperative VAS scores comparing the two strata. On average, the late GA subjects did not have a greater degree of nervousness or expected pain, and they did not experience significantly more pain during the procedure.

Linear Regression Analysis

In the univariate linear regression analysis of pain during aspiration (Tables 5a and 5b), only Hispanic race, nervousness about the procedure and pain, and expected pain were found to be significantly associated with this outcome. On average, Hispanic subjects experienced 17.3 mm greater pain with aspiration on the VAS than non-Hispanic subjects (95% CI 3.4-31.2 mm, p=0.02). For each 10 mm increase in nervousness about the procedure on the VAS, subjects on average had a 2.4 mm increase

in pain during aspiration (95% CI 0.6-4.2 mm, p=0.01). Nervousness about pain and expected pain had a similar relationship with aspiration pain; a 10 mm increase in each of these predictors led to a 2.3 mm increase in aspiration pain (95% CI 0.6-4.0 mm, p=0.01 for nervousness about pain, 95% CI 0.1-4.5 mm, p=0.04 for expected pain). The relationship between nervousness about pain and pain during aspiration is illustrated in Figure 7.

In the univariate analysis of postoperative pain (Tables 6a and 6b), it was determined that non-Caucasian race was associated with significantly decreased pain. On average, non-Caucasian subjects reported 12.4 mm less pain on the VAS at 30 minutes postoperatively (95% CI 2.7-22.1 mm, p=0.01). As with pain during aspiration, subjects of Hispanic race experienced significantly greater postoperative pain: 22.1 mm (95% CI 10.1-34.2 mm, p<0.001). Nervousness about pain, nervousness about the procedure, and expected pain were also found to be significant predictors. According to this analysis, a 10 mm increase in nervousness about pain was associated with a 1.6 mm increase in postoperative pain (95% CI 0.04-3.1 mm, p=0.04); each 10 mm increase in nervousness about the procedure was associated with a 2.6 mm increase in postoperative pain (95% CI 1.0-4.2 mm, p=0.002), and a 10 mm increase in expected pain was associated with a 2.3 mm increase in postoperative pain (95% CI 0.4-4.3 mm, p=0.02).

Variables that were significantly associated with pain during aspiration and postoperative pain were not significant in the univariate analysis of satisfaction with pain control (Tables 7a and 7b). For this outcome, none of the demographic variables or preoperative VAS scores was a significant predictor. Pain during the different procedural time points (speculum insertion, PCB placement, dilation, and aspiration), postoperative pain, and subject belief about study group (placebo or HC/APAP) were significantly associated with decreased satisfaction with pain control. Subjects who believed they received HC/APAP had on average 13.1 mm higher satisfaction on the VAS (95% CI 4.0-22.2 mm, p=0.01). An increase in dilation pain of 10 mm was associated with a 3.8 mm decrease in satisfaction with pain control (95% CI 2.3-5.2 mm, p<0.001). An increase in aspiration pain of 10 mm was associated with a 4.4 mm decrease in

satisfaction (95% CI 2.9-5.8 mm, p<0.001). Scatter plots of pain during dilation and aspiration with satisfaction with pain control are shown in Figures 8 and 9.

In multivariate analysis, study group (HC/APAP or placebo) was not found to be a significant predictor of pain at any procedural time point even when controlling for expected pain as a continuous or dichotomous variable. Similarly, it was not significantly associated with pain outcomes when controlling for BMI and prior surgical abortion, the two demographic variables that were significantly different between study groups in the early GA stratum.

Multivariate analysis was also performed to explore the relationship between study group and postoperative nausea. Median postoperative nausea was not significantly different between groups, however baseline nausea was greater among the placebo group. In regression analysis controlling for baseline nausea, study group was significantly associated with postoperative nausea. In this analysis, the HC/APAP group experienced 9.74 mm greater postoperative nausea (95% CI 0.74 – 18.73, p=0.03) than the placebo group.

Multivariate models predicting pain and satisfaction

Multivariable linear regression models are shown in Tables 8a-c. In the multivariate model for pain with aspiration (Table 8a), nervousness about the procedure and expected pain were no longer significant predictors when nervousness about pain was already in the model. Hispanic race and nervousness about pain were both significantly associated with aspiration pain after controlling for GA and study group. This model was found to explain approximately 10% of the variation in pain during aspiration in this study (R-squared 0.103).

The scatter plot of nervousness about pain and aspiration pain (Figure 7) suggested the possibility of a nonlinear relationship. However, the quadratic variable for nervousness about pain was not a significant predictor of aspiration pain in a model already containing the linear term, and it was not significant when added to a multivariate model with GA, study group, and Hispanic race.

For postoperative pain, nervousness about the procedure was a stronger predictor than nervousness about pain and expected pain, and was maintained in the multivariate model. The quadratic term for nervousness about the procedure was tested, but was not significant when the linear variable was in the model, and did not improve the prediction of postoperative pain in the multivariate model. Controlling for GA and study group, Caucasian race, Hispanic race, and nervousness about the procedure were each significantly associated with increased postoperative pain (Table 8b). Together, these independent variables explained over 18% of the variation in postoperative pain (R-squared 0.189).

In the multivariate analysis for satisfaction with pain control, only pain during dilation and aspiration were found to be significant predictors, when controlling for GA and study group (Table 8c). Pain during other procedural time points and belief about study group assignment did not significantly contribute to the prediction of satisfaction once dilation and aspiration pain were already in the model. The regression coefficients for these variables did change approximately 50% in the multivariate model, demonstrating that study group and GA are confounders of the relationship between procedural pain and satisfaction. In this model, for each 10 mm increase in pain during dilation, satisfaction decreased 2.3 mm (95% CI 0.5-4.0 mm, p=0.02). For each 10 mm increase in pain during aspiration, satisfaction decreased 3.0 mm (95% CI 1.1-4.9, p=0.002). R-squared for this model was 0.274. On average, subjects in the HC/APAP group had 7.89 mm higher satisfaction with pain control on the VAS than subjects in the placebo group in this model (95% CI 0.01 – 15.77, p=0.05).

The scatter plots in Figure 8 and 9 demonstrated a potentially nonlinear relationship between dilation and aspiration pain and satisfaction with pain control. However, adding the quadratic (pain-squared) term for dilation pain did not increase the prediction of satisfaction in the multivariate model. Conversely, the quadratic variable for aspiration pain was found to be statistically significant in multivariate analysis of satisfaction (p=0.02). Using the quadratic term and linear terms for aspiration pain in the multivariate model with GA, study group, and dilation pain increased the R-squared to 0.297. To improve clinical interpretation of this quadratic term, aspiration pain was categorized as described in

the Methods. However, using this categorical variable instead of the linear term in the model decreased the R-squared to 0.259. The linear, continuous term was retained in the final model of satisfaction with pain control.

Model diagnostics using scatter plots of residuals versus fitted values are shown in Figures 10, 11, and 12 for linear predictions of pain during aspiration, postoperative pain, and satisfaction with pain control, respectively. Figure 11, for postoperative pain, suggests increasing variance as the predicted values increase. Conversely, Figure 12, for satisfaction with pain control, demonstrates decreasing variance as the predicted values increase. Both figures may indicate heteroscedasticity. Q-Q plots for residuals in each of the models are shown in Figures 13-15. All models appear normally distributed. No outliers were identified in the Q-Q plots or in the analysis using Cook's Distance.

CHAPTER 4 – DISCUSSION

This study investigated whether or not HC/APAP is beneficial when given to women prior to surgical abortions. While only 4.4% of abortion providers in North America reporting routinely using HC/APAP in 2002, this number has increased with the rise of prescription and illicit opioid use, and at PPCW 80% of patients choose this for premedication when offered (personal communication with PPCW 2010). Additionally, the WHO recommends opioids such as HC/APAP as an analgesic choice prior to surgical abortion.

HC/APAP did not contribute to improved pain control during surgical abortions in this study. There were no significant differences between mean pain scores for the two study groups at any procedural time point or 30 minutes postoperatively. This was found in both the analysis of the individual GA strata and in the combined analysis. Controlling for the two demographic variables that were significantly different between study groups in the early GA stratum, prior surgical abortions and BMI, did not affect this result.

The greatest difference in mean pain scores between the two study groups occurred during speculum insertion, in which the mean difference was just 4.5 mm. For the primary outcome, pain during aspiration, the mean difference was 2.6 mm, with slightly higher pain in the active HC/APAP group. The 95% confidence interval for this mean difference, and for the differences at each procedural time point, were within ±15 mm, indicating a less than a 5% chance that the true difference is outside this range. We have defined clinical significance as requiring a difference of at least 15 mm on the VAS. We therefore conclude that HC/APAP is clinically equivalent to placebo for pain control during surgical abortion.

In the analysis of the combined GA strata, median baseline nausea was significantly greater in the placebo group. Postoperatively, median nausea decreased for the placebo group. The opposite trend was observed in the HC/APAP group, in which higher median pain was observed postoperatively. Nausea trends throughout the abortion procedure have not been previously studied, so it is unclear whether it is

expected that pregnancy-related nausea would decrease immediately after an abortion. Nausea is, however, a known side effect of opioid medications, and it is unsurprising that study drug was significantly associated with postoperative nausea when controlling for baseline nausea.

Levels of patient-reported sleepiness after the procedure were high, and not significantly different between study groups. This suggests that the lorazepam given to all study subjects had the greatest sedating effect. Interestingly, the combination of HC/APAP and lorazepam did not cause higher levels of sleepiness. HC/APAP does not appear to be effective for pain, or to be associated with serious adverse effects.

The regression analysis in the study aimed to determine what factors were the strongest predictors of procedural pain and patient satisfaction in abortion care. Only Hispanic race, nervousness about pain and the procedure, and expected pain were significantly associated with procedural pain. Other factors found to be predictors in previous studies, such as patient age, GA, parity, procedure time, and provider experience, were not significant in our analysis. This suggests that an intervention to decrease patient anxiety and expectation for pain may have an impact on procedural pain. These factors clearly have a greater effect on pain than HC/APAP. However, in the multivariate analysis of aspiration pain, the optimal model only predicted 10% of the variation in pain. Unmeasured factors, such as individual patient anatomy and sensitivity to painful stimuli, are likely much more important factors in procedural pain.

As expected, procedural pain scores during dilation and aspiration were the strongest predictors of patient satisfaction. The multivariate model predicted over a quarter of the variation in satisfaction scores. Interestingly, study group was nearly significant in this model, with a p-value of 0.05. Subjects who received HC/APAP were more satisfied with their pain control regimen than those who received placebo, despite no difference in procedural pain scores. This was the only analysis in which HC/APAP appeared to have an effect on any outcome in the study. The modest improvement in patient satisfaction, in the absence of any effect on procedural pain, is interesting given that patients were not able to

accurately determine their assignment to the placebo or HC/APAP group. This difference does not indicate that HC/APAP is effective or that it should be used as a pain medication for abortion.

The major strength of this study is that it is a placebo-controlled RCT, which avoids bias and confounding in evaluating the effect of HC/APAP on study outcomes. Furthermore, it was powered to detect a clinically significant 15 mm difference between study groups. While a larger study powered to detect a smaller difference may find a statistically significant effect of HC/APAP on pain scores, such a small difference would not warrant the addition of this medication to the standard pain regimen for abortion.

All participants received oral ibuprofen 800 mg and oral lorazepam 2 mg for analgesia and anxiolysis per current standard protocol at PPCW. In addition, all subjects received a standard PCB. It is possible that HC/APAP, if given alone, would decrease pain during abortion. However, NSAIDs and PCB are established pain interventions that are used by the vast majority of abortion providers. It would be unethical and clinically unnecessary to carry out a study of abortion pain without these interventions. Rather, the addition of HC/APAP was hypothesized to decrease patient perception of pain when added to the standard regimen because hydrocodone and acetaminophen target different pain pathways. A multimodal approach to pain management, with different medications targeting different pathways, has been shown to be effective in other surgical settings.[40,41] In the case of cervical and uterine pain, however, direct conduction blockade with a PCB, and prevention of prostaglandin production in the periphery with ibuprofen are much more effective than the centrally acting HC/APAP.

Another limitation is that study subjects were less than 11 weeks gestation, limiting generalizability to subjects in the later first trimester. However, given that no significant difference was observed between study groups at any procedural time point, and there were no trends of decreased pain among subjects at any gestational age in the HC/APAP group, it is very unlikely that subjects between 11 and 14 weeks gestation would benefit from this medication.

Our study, the first RCT to examine this question, failed to demonstrate that HC/APAP decreases pain during first trimester abortion. This finding has the potential to influence pain management in future abortion practice. For the greater than one million women who have abortions in the U.S. each year, and the 45.6 million worldwide, this study provides guidance for their physicians in selecting a pain management strategy. Particularly in low resource settings, IV sedation and general anesthesia are not widely available, and provision of these potent medications significantly increases procedural risks. For women having surgical abortion under local anesthesia, NSAIDs remain the only oral medications that have been shown to be efficacious for reducing pain.

Our findings have implications beyond surgical abortion. Other gynecologic procedures involving the cervix and uterus are performed in the office under local anesthesia, and it is not known whether oral opioids are beneficial in this setting. However, our study provides evidence suggesting that HC/APAP would not be expected to decrease pain due to cervical dilation and uterine instrumentation performed as part of any gynecologic procedure.

It is unknown why HC/APAP does not improve procedural pain during abortions. This medication is generally used in postoperative settings and for chronic pain. It is possible that the opioid dose in our study is too low to affect acute procedural pain. However, 10 mg of hydrocodone is a standard oral dose, and higher doses would be more likely to cause excess sedation and complications. Although the biological mechanism is unknown, opioids in general may be less effective than other modalities for uterine and cervical pain. Women experience significant pain during surgical abortion, and few oral medications have been shown to be effective. Other pain management strategies must be studied in order to improve patient care in this setting.

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Figure 1: Study flowchart

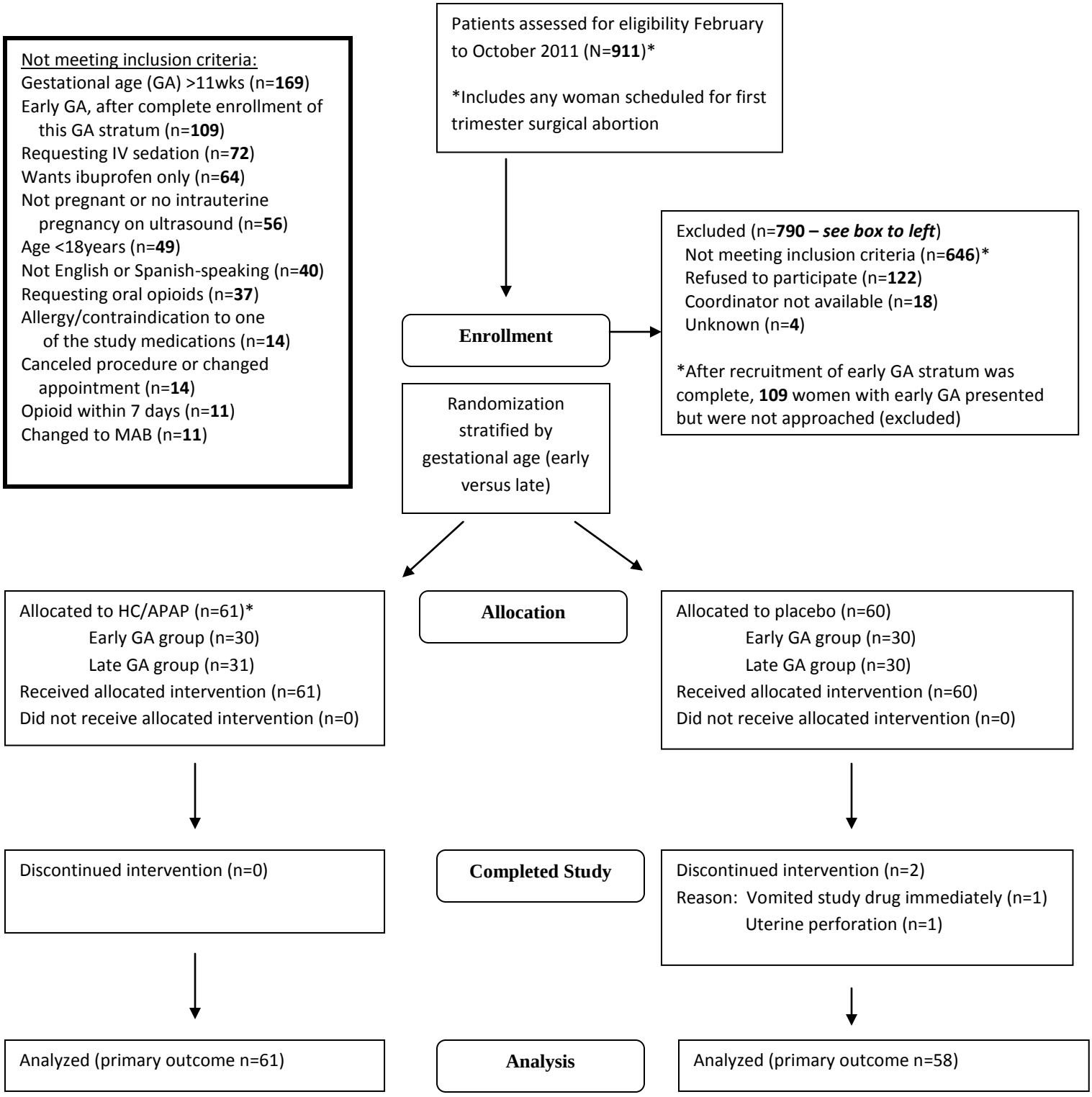

Figure 2a.

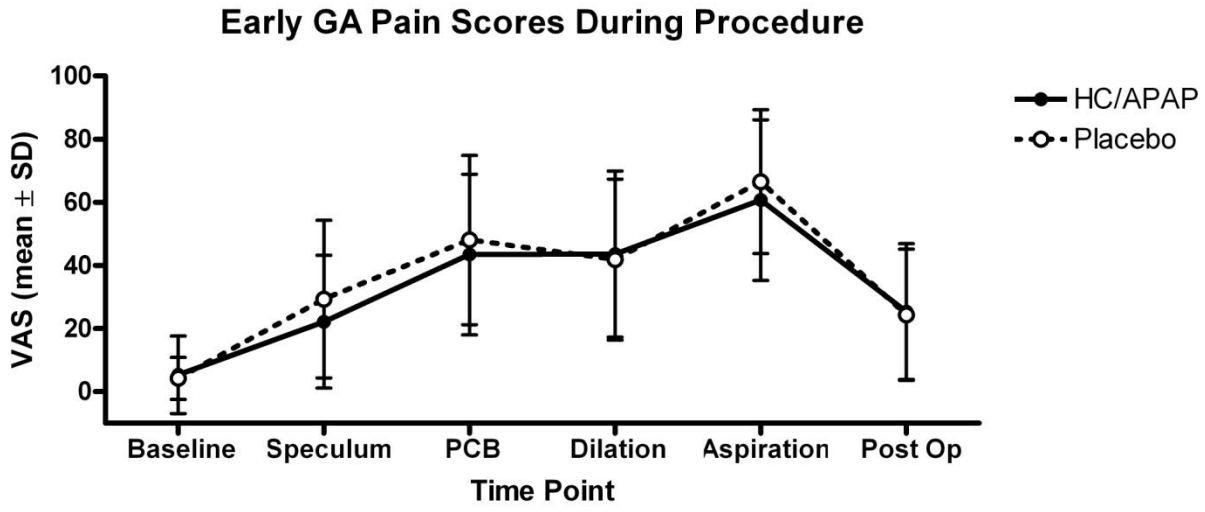

Figure 2b.

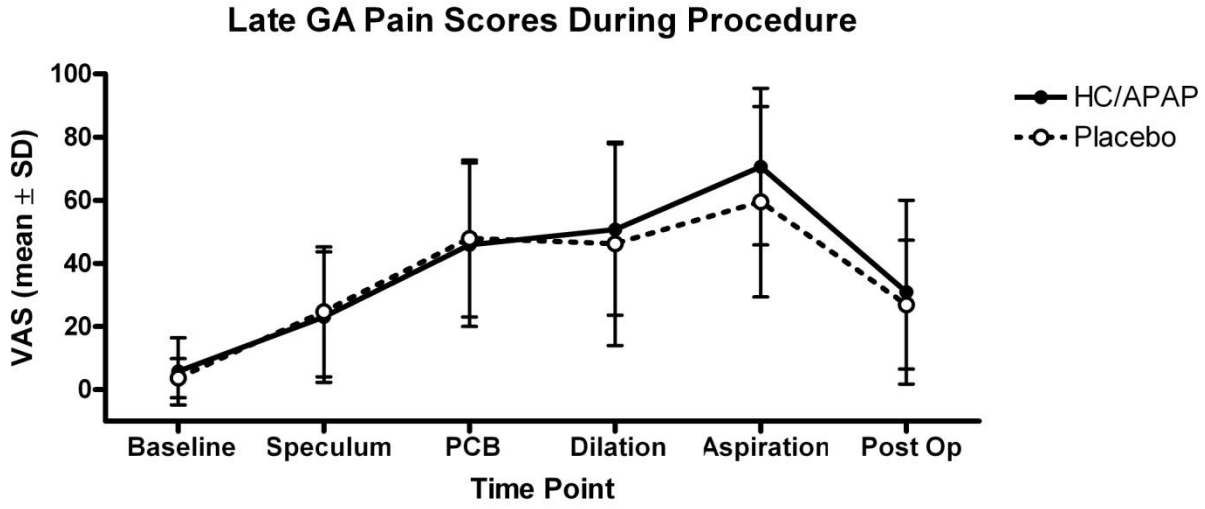

Figure 3a. Distributional dot plot of pre and post-op nausea for early GA stratum

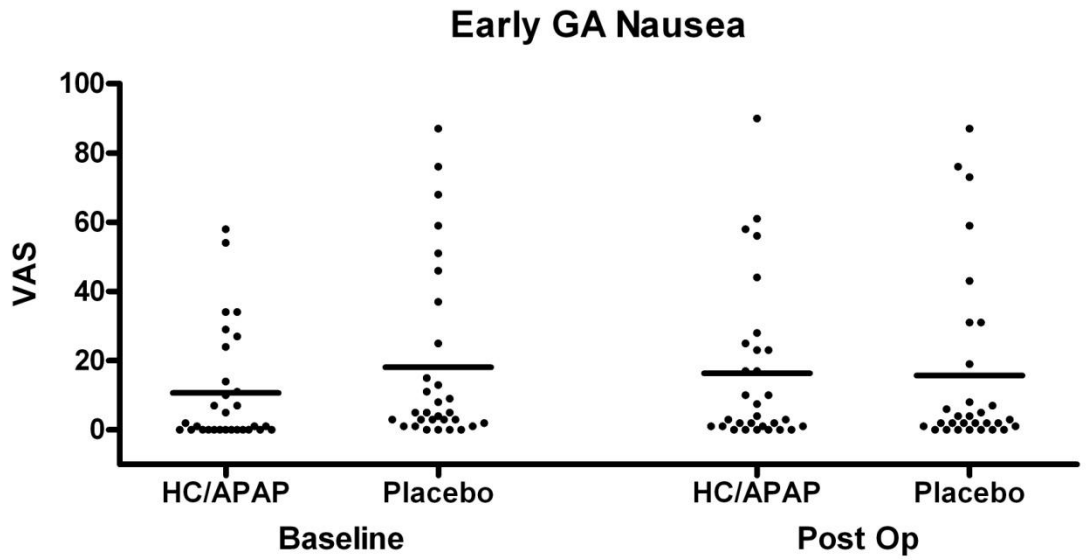

Figure 3b. Distributional dot plot of pre and post-op nausea for late GA stratum

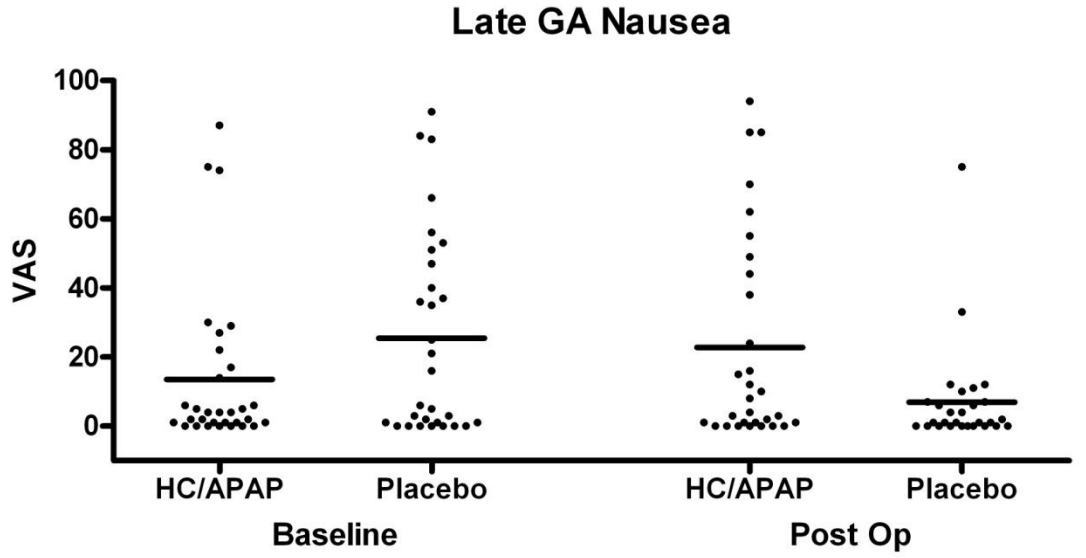

Figure 4. Distributional dot plot of postoperative sleepiness for early and late GA strata

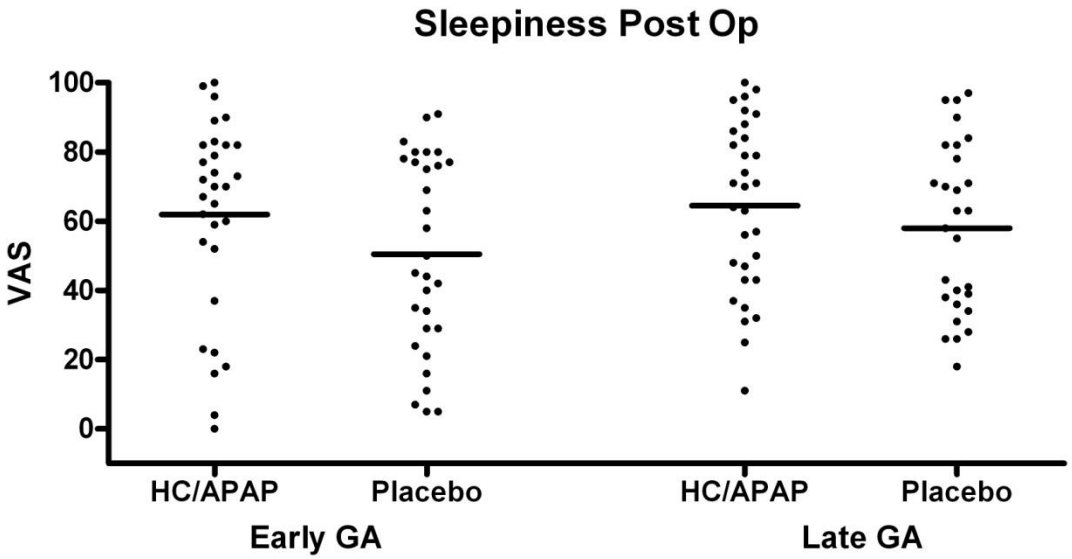

Figure 5. Distributional dot plot of satisfaction with pain control for early and late GA strata

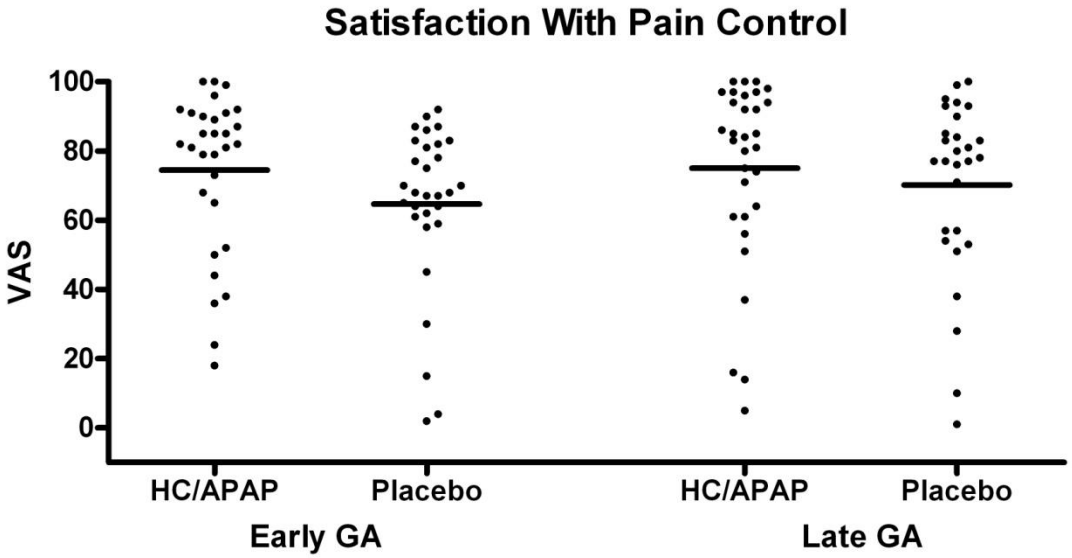

Figure 6. Distributional dot plot of satisfaction with overall procedure for early and late GA strata

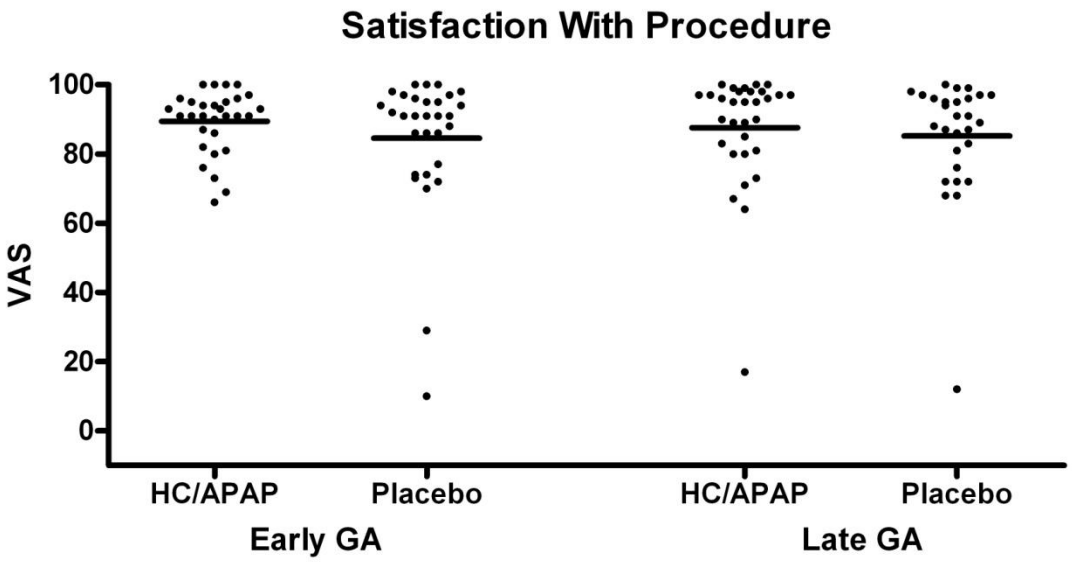

Figure 7. Scatter plot of VAS scores for preoperative nervousness about pain and aspiration pain

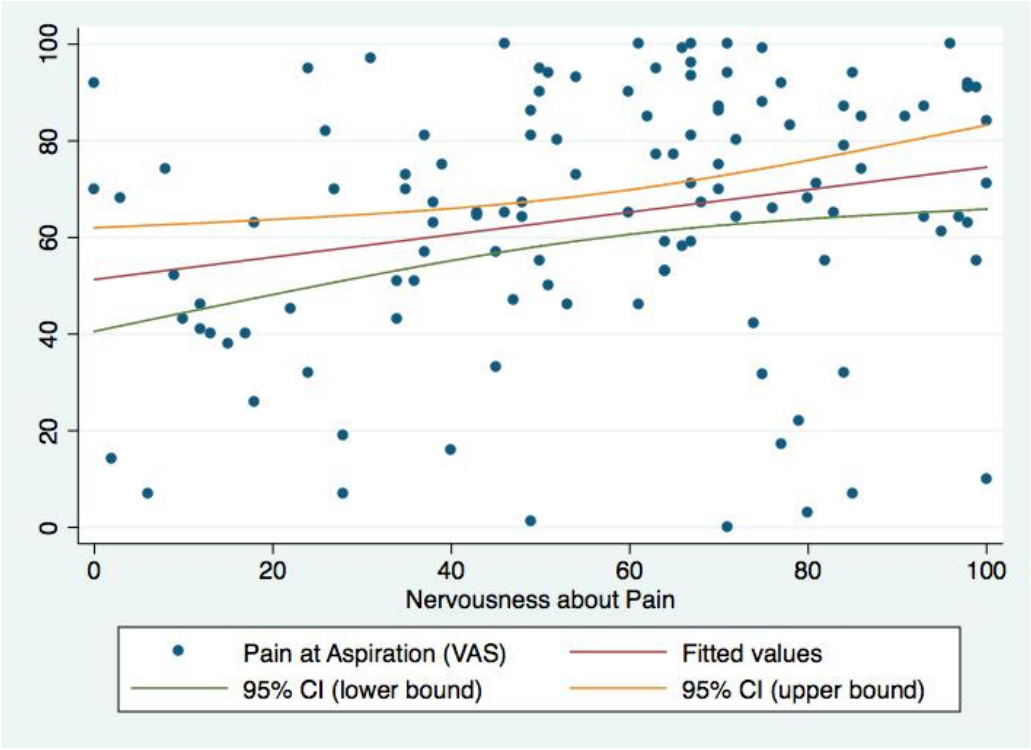

Figure 8. Scatter plot of VAS scores for pain with dilation and satisfaction with pain control

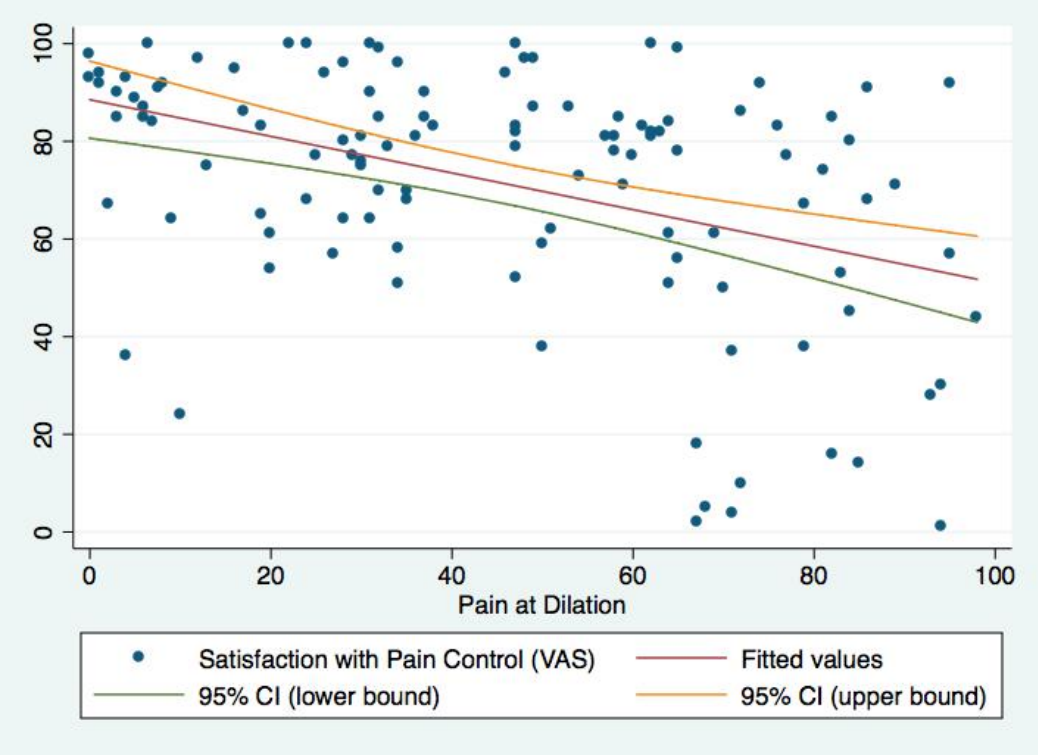

Figure 9. Scatter plot of VAS scores for pain with aspiration and satisfaction with pain control

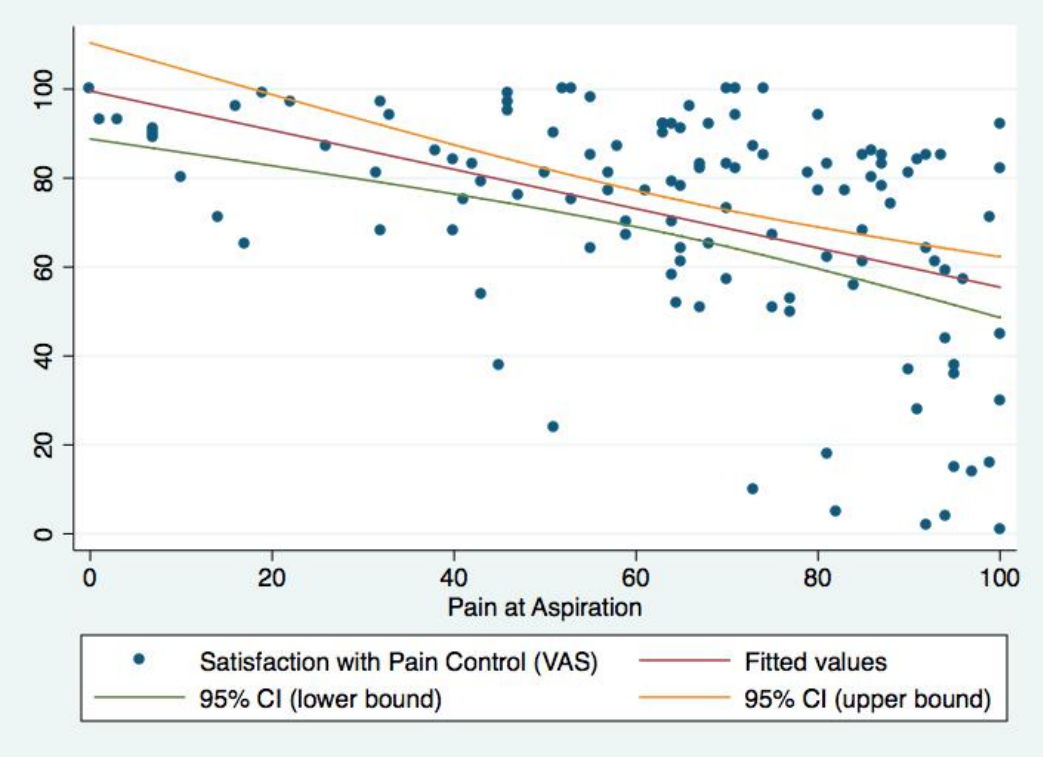

Figure 10. Residuals versus fitted values: Pain during aspiration

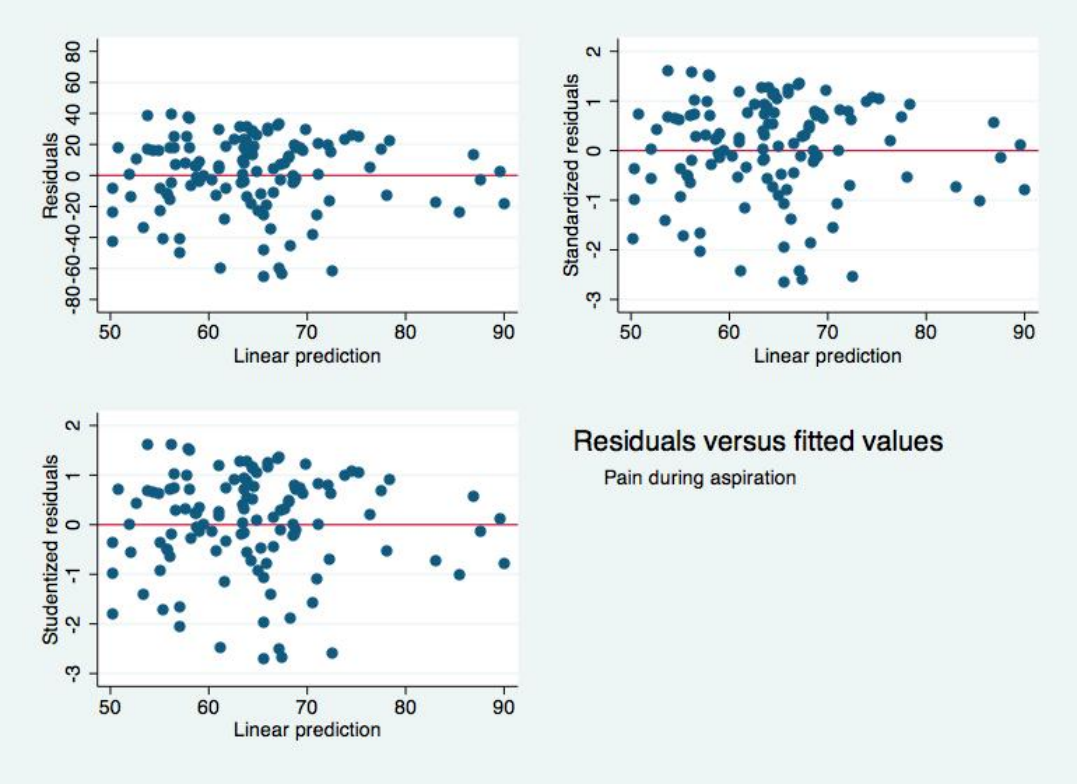

Figure 11. Residuals versus fitted values: Postoperative pain

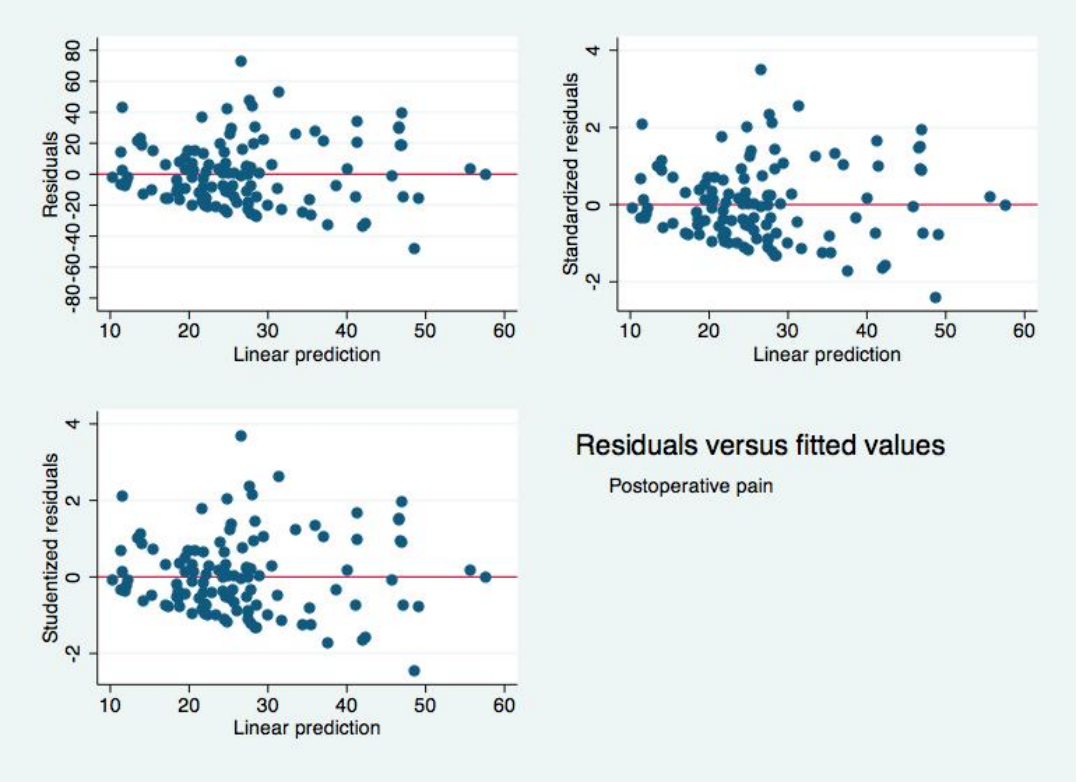

Figure 12. Residuals versus fitted values: Satisfaction with pain control

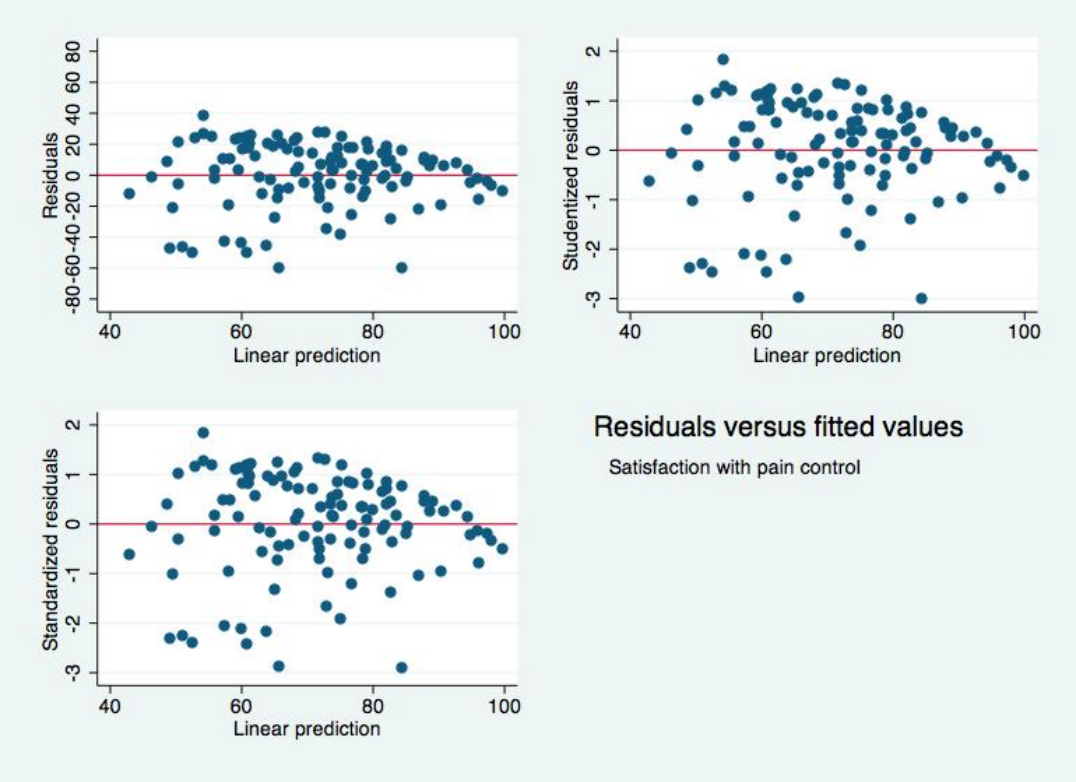

Figure 13. Q-Q Plots: Pain during aspiration

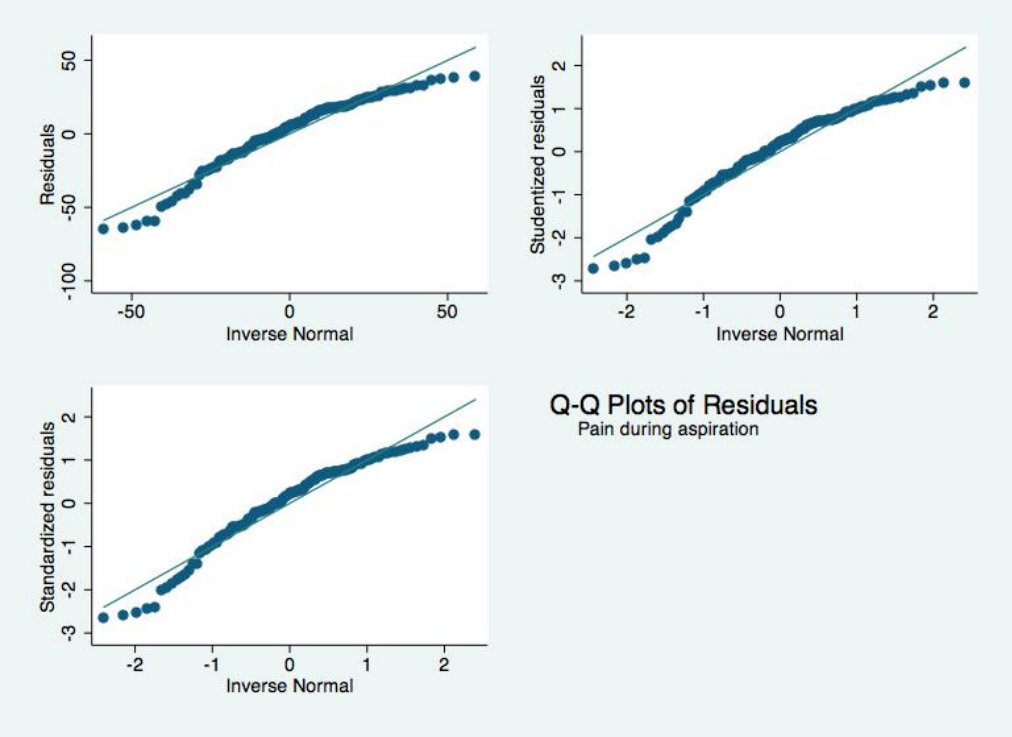

Figure 14. Q-Q Plots: Postoperative pain

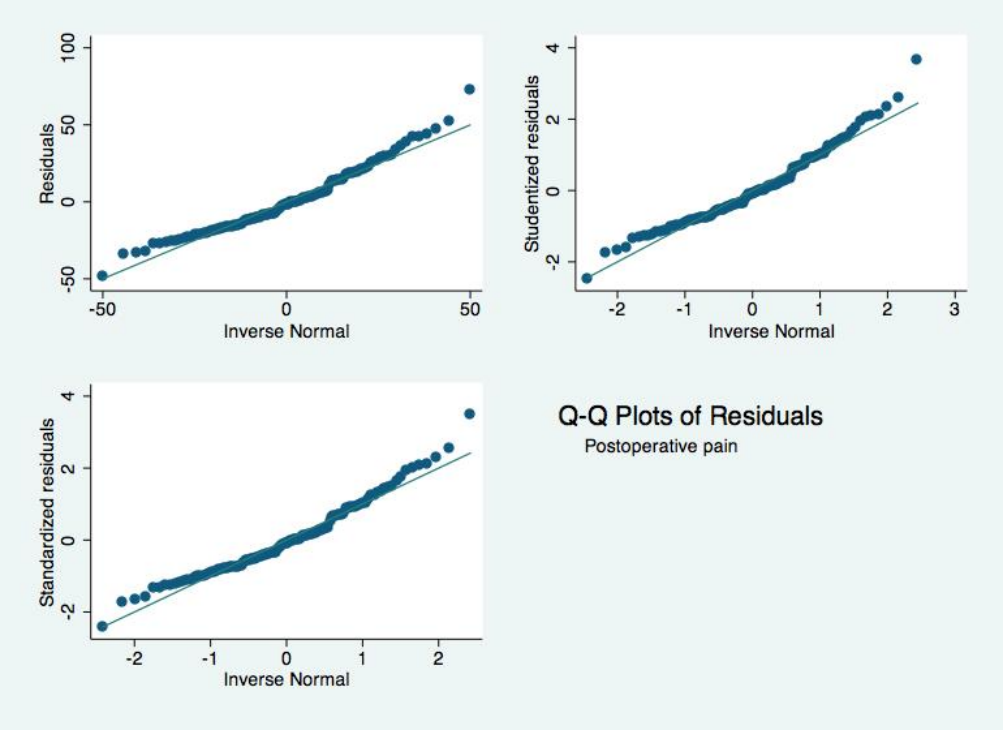

Figure 15. Q-Q Plots: Satisfaction with pain control

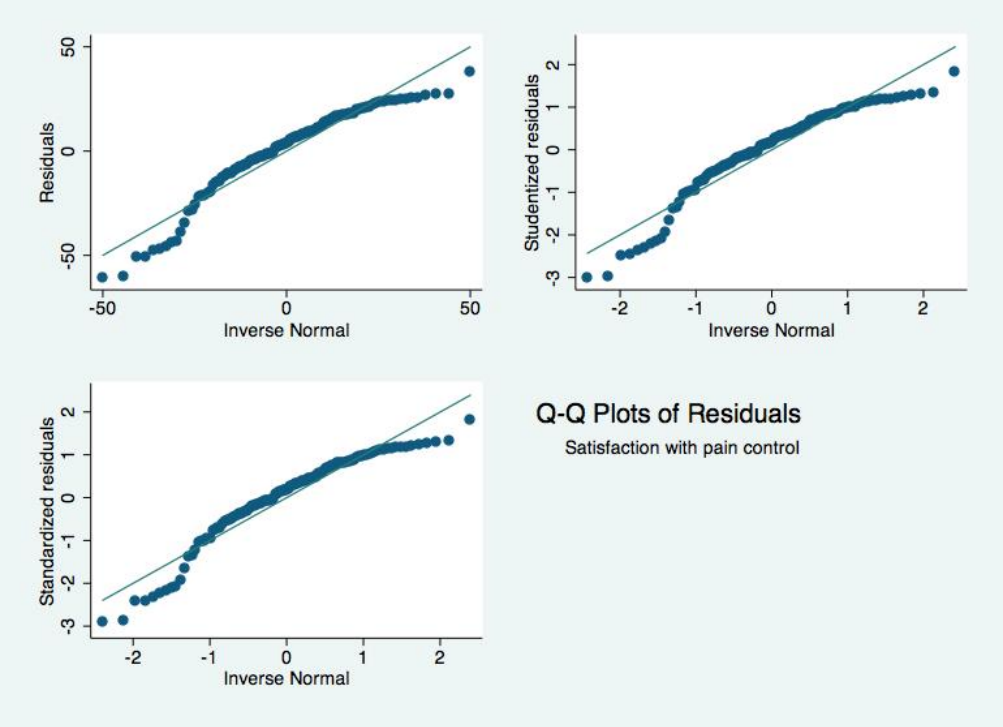

Table 1. Demographic characteristics

	Early GA Stratum			Late GA Stratum			Combined GA Strata		
	Placebo (n=30)	**HC/APAP (n=30)**	***P***	**Placebo+ (n=30)**	**HC/APAP+ (n=31)**	***P***	**Placebo (n=60)**	**HC/APAP (n=61)**	***P***
Patient age* (years)	24.0 ± 4.1	26.5 ± 6.4	0.08	25.3 ± 4.9	25.6 ± 6.3	0.83	24.7 ± 4.5	26.1 ± 6.3	0.17
Gest. age* (weeks)	6.2 ± 1.0	6.3 ± 0.9	0.80	9.1 ± 0.9	9.3 ± 0·8	0.34	7.2 ± 1.7	7.4 ± 1.8	0.58
Race#									
Caucasian	29 (96.7)	24 (80.0)	0.22	22 (73.3)	21 (67.7)	0.55	51 (85.0)	45 (73.8)	0.19
African American	0 (0)	0 (0)		2 (6.7)	4 (12.9)		2 (3.3)	4 (6.6)	
Asian	0 (0)	0 (0)		2 (6.7)	0 (0)		2 (3.3)	0 (0)	
Native Hawaiian/ Pacific Islander	0 (0)	2 (6.7)		0 (0)	1 (3.2)		0 (0)	3 (4.9)	
American Indian/ Alaskan Native	0 (0)	1 (3.3)		1 (3.3)	2 (6.5)		1 (1.7)	3 (4.9)	
More than one race	1 (3.3)	3 (10.0)		3 (10.0)	3 (9.7)		4 (6.7)	6 (9.8)	
Hispanic+	3 (11.1)	3 (13.0)	1.0	3 (13.6)	6 (31.6)	0.47	6 (10.0)	9 (14.8)	0.58
Parity#			0.27			0·49			0.21
Nulliparous	22 (73.3)	18 (60.0)		20 (66.7)	18 (58.1)		42 (70.0)	36 (59.0)	
Parous	8 (26.7)	12 (40.0)		10 (33.3)	13 (41.9)		18 (30.0)	25 (41.0)	
Previous vaginal deliveries# (yes/no)	6 (20.0)	12 (40.0)	0.09	10 (33.3)	12 (38.7)	0.66	16 (26.7)	24 (39.3)	0.14
Previous surgical abortions# (yes/no)	6 (20.0)	14 (46.7)	**0.03**	12 (40·0)	7 (22.6)	0.14	18 (30.0)	21 (34.4)	0.60
Level of menstrual symptoms#^			0.33			0.54			0.23
Easy	6 (20.0)	4 (13.3)		5 (17.9)	6 (19.4)		11 (19.0)	10 (16.4)	
Mild cramping	12 (40·0)	7 (23.3)		13 (46.4)	10 (32.3)		25 (43.1)	17 (27.9)	
OTC med	11 (36.7)	18 (60.0)		8 (28.6)	12 (38.7)		19 (32.8)	30 (49.2)	
Prescription med	0 (0)	0 (0)		1 (3.6)	0 (0)		1 (1.7)	0 (0)	
Unable attend work	1 (3.3)	1 (3.3)		1 (3.6)	3 (9.7)		2 (3.4)	4 (6.6)	
BMI*	22.9 ± 5.6	27.1 ± 5.6	**0.01**	26.8 ± 6.5	25.8 ± 6.7	0.51	24.9 ± 6.4	26.5 ± 5.7	0.16
Pain med. use in last 60 days (yes/no)#	21 (70.0)	19 (63.3)	0.30	19 (63.3)	15 (48.4)	0.24	40 (66.7)	34 (55.7)	0.22

Values are mean ± standard deviation or n (%)
* Independent t test
# Pearson Chi-squared test
+ Fisher's Exact test
^ Dysmenorrhea data missing for two subjects in late GA strata, placebo group

Table 2. Procedural characteristics

	Early GA stratum			Late GA stratum			Combined GA strata		
	Placebo (n=30)	**HC/APAP (n=30)**	***P***	**Placebo (n=30)**	**HC/APAP (n=31)**	***P***	**Placebo (n=60)**	**HC/APAP (n=61)**	***P***
Provider#			0.79			0.91			0.71
Ob/Gyn att. (n=2)	8 (26.7)	5 (16.7)		4 (13.3)	4 (12.9)		12 (20.0)	9 (14.8)	
Fam Prac att. (n=1)	10 (33.3)	10 (33.3)		8 (26.7)	8 (25.8)		18 (30.0)	18 (29.5)	
Mid-level (n=3)	4 (13.3)	6 (20.0)		7 (23.3)	10 (32.3)		11 (18.3)	16 (26.2)	
Fellow (n=3)	8 (26.7)	9 (30.0)		11 (36.7)	9 (29.0)		19 (31.7)	18 (29.5)	
Proc. time (min)*	8.2 ± 1.4	9.8 ± 4.3	0.05	9.5 ± 3.1	10.0 ± 2.8	0.53	8.8 ± 2.4	9.9 ± 3.6	0.06
Postop vital signs*									
Heart rate	79.5 ± 9.6	74.4 ± 10.1	0.05	74.8 ± 10.4	75.3 ± 10.7	0.86	77.2 ± 10.2	74.8 ± 10.3	0.20
Systolic BP	109.7 ± 8.5	110.9 ± 15.4	0.71	112.5 ± 14.3	107.4 ± 8.5	0.10	111.1 ± 11.7	109.1 ± 12.3	0.37
Diastolic BP	67.2 ± 6.7	70.3 ± 9.7	0.16	69.0 ± 8.2	67.6 ± 7.9	0.52	68.1 ± 7.5	68.9 ± 8.9	0.57
Adverse event#			1.00			1.00			1.00
Uterine perforation	0 (0)	0 (0)		1 (3.3)	0 (0)		1 (1.7)	0 (0)	
Reaspiration	0 (0)	1 (3.33)		0 (0)	0 (0)		0 (0)	1 (1.6)	
Vomiting	1 (3.33)	1 (3.33)		0 (0)	1 (3.2)		1 (1.7)	2 (3.3)	
Additional postop pain medications	0 (0)	0 (0)		0 (0)	0(0)		0 (0)	0 (0)	

Values are mean ± standard deviation or n (%). Percent totals may not add up to 100 due to rounding

Fisher's exact test

* Independent t test

Speculum placement to speculum removal (in some cases includes immediate postoperative IUD insertion)

Table 3. Summary of VAS Scores

	Early GA Stratum			Late GA Stratum			Combined GA Strata		
	Placebo (n=30)	**HC/APAP (n=30)**	***P***	**Placebo+ (n=30)**	**HC/APAP+ (n=31)**	***P***	**Placebo (n=60)**	**HC/APAP (n=61)**	***P***
Preoperative VAS scores (prior to premedication)									
Nervous about procedure	56.4 ± 24.2	47.9 ± 25.5	0.19	56.8 ± 24.7	55.8 ± 27.8	0.88	56.6 ± 24.2	51.9 ± 26.7	0.31
Nervous about pain	55.1 ± 25.6	51.2 ± 24.5	0.55	57.3 ± 24.9	64.5 ± 31.1	0.32	56.2 ± 25.1	58.0 ± 28.6	0.72
Expected pain	54.2 ± 19.1	54.9 ± 23.9	0.90	53.7 ± 17.9	56.7 ± 23.2	0.58	53.9 ± 18.4	55.8 ± 23.4	0.63
Baseline pain*	0.5 (0 – 27)	1 (0 – 25)	0.68	1.5 (0 – 76)	1 (0 – 54)	0.74	1 (0 – 76)	1 (0 – 54)	0.98
Baseline nausea*	5 (0 – 87)	1 (0 – 58)	0.06	11 (0 – 91)	4 (0 – 87)	0.21	**5 (0 – 91)**	**2 (0 – 87)**	**0.03**
Intraoperative VAS pain scores									
Prior to speculum*	1 (0 – 31)	1.5 (0 – 66)	0.95	1 (0 – 28)	2 (0 – 51)	0.54	1 (0 – 31)	2 (0 – 66)	0.68
Speculum insertion	29.3 ± 25.0	22.2 ± 21.0	0.24	24.6 ± 20.6	23.0 ± 20.6	0.76	27.0 ± 22.9	22.6 ± 20.7	0.27
Paracervical block	48.0 ± 26.8	43.5 ± 25.4	0.50	47.9 ± 24.9	45.9 ± 25.9	0.76	48.0 ± 25.6	44.7 ± 25.5	0.48
Dilation	41.9 ± 25.5	43.6 ± 26.3	0.80	46.2 ± 32.2	50.7 ± 27.1	0.56	44.0 ± 28.9	47.3 ± 26.8	0.53
Aspiration	66.5 ± 22.8	60.7 ± 25.5	0.35	59.5 ± 30.2	70.6 ± 24.8	0.13	63.2 ± 26.6	65.7 ± 25.4	0.59
30 Minutes Postoperative VAS scores									
Pain	24.4 ± 20.7	25.4 ± 21.5	0.86	26.9 ± 20.4	30.9 ± 29.1	0.55	25.6 20.4	28.2 ± 25.6	0.55
Nausea*	1.5 (0 – 87)	2.5 (0 – 90)	0.73	1 (0 – 75)	6 (0 – 94)	0.05	2 (0 – 87)	4 (0 – 94)	0.10
Sleepiness	50.5 ± 28.1	61.9 ± 28.4	0.12	58.0 ± 24.4	64.5 ± 24.6	0.31	54.1 ± 26.4	63.2 ± 26.3	0.06
Itching*	0 (0 – 15)	1 (0 – 35)	0.53	1 (0 – 45)	0 (0 – 58)	0.34	0.5 (0 – 45)	0 (0 – 58)	0.77
Satisfaction with pain control	64.7 ± 23.8	74.5 ± 23.1	0.11	70.2 ±25.8	75.0 ± 26.5	0.48	67.3 ± 24.7	74.8 ± 24.7	0.10
Satisfaction with overall procedure	84.5 ± 20.0	89.4 ± 9.1	0.23	85.2 ± 17.6	87.6 ± 16.7	0.59	84.9 ± 18.7	88.5 ± 13.4	0.23

+Some data points missing for one subject in placebo group and one subject in HC/APAP group, data analyzed with intention to treat approach

*Reported as median (range), Mann-Whitney U Test for non-normally distributed data; otherwise mean ± standard deviation, Independent t test

Table 4. Summary of VAS Scores Comparing Early and Late GA Strata

	Early GA Strata (n=60)	Late GA Strata (n=61)	*P*
Preoperative VAS scores (prior to premedication)			
Nervous about procedure	52.2 ± 25.0	56.3 ± 26.1	0.37
Nervous about pain	53.2 ± 25.0	61.0 ± 28.5	0.11
Expected pain	54.5 ± 21.5	55.2 ± 20.7	0.86
Baseline pain*	1 (0 – 27)	1 (0 – 76)	0.30
Baseline nausea*#	3.5 (0 – 87)	4 (0 – 91)	0.46
Intraoperative VAS scores			
Pain prior to speculum*	1 (0 – 66)	1.5 (0 – 51)	0.57
Pain with speculum insertion	25.7 ± 23.2	23.8 ± 20.5	0.63
Pain with paracervical block	45.7 ± 26.0	46.9 ± 25.2	0.81
Pain with dilation	42.7 ± 25.7	48.5 ± 29.5	0.26
Pain with aspiration	63.6 ± 24.1	65.4 ± 27.8	0.71
30 Minutes Postoperative VAS scores			
Pain	24.9 ± 20.9	29.0 ± 25.2	0.33
Nausea*	3 (0 – 90)	3 (0 – 94)	0.49
Sleepiness	56.2 ± 28.6	61.4 ± 24.5	0.29
Itching*	0.5 (0 – 35)	0 (0 – 58)	0.80
Satisfaction with pain control	69.6 ± 23.7	72.7 ± 26.1	0.49
Satisfaction with overall procedure	87.0 ± 15.6	86.5 ± 17.0	0.87

*Reported as median (range), Mann-Whitney U Test for non-normally distributed data; otherwise mean ± standard deviation, Independent t test

Table 5. Pain during aspiration: Univariate linear regression analysis

5a. Differences in mean VAS scores for pain during aspiration by dichotomous or categorical subject and procedural characteristics

Characteristic	**Δ VAS (mm)**	**95% CI**	**P value**
Age			
Less than 25 years	Ref.		
25 years or older	-0.7	(-10.2, 8.8)	0.88
Gestational age			
Early (Less than 8 weeks)	Ref		
Late (8 weeks to 10 weeks 6 days)	-1.8	(-11.2, 7.7)	0.71
Caucasian			
Yes	Ref.		
No	-2.6	(-13.7, 8.5)	0.65
Hispanic			
No	Ref.		
Yes	**17.3**	**(3.4 , 31.2)**	**0.02**
Parity			
Nulliparous	Ref.		
Parous	0.3	(-9.5, 10.2)	0.95
Prior vaginal delivery			
None	Ref.		
1 or more	-1.6	(-11.6, 8.4)	0.75
Prior surgical abortion			
None	Ref.		
1 or more	1.7	(-8.5, 11.8)	0.74
Level of menstrual symptoms			0.58
Easy	Ref.		
Mild cramping	7.4	(-6.5, 21.4)	
Over-the-counter medication	1.4	(-12.2, 15.0)	
Prescription medication use	-18.5	(-71.7, 34.6)	
Unable to attend work	-5.2	(-29.2, 18.8)	
Has used any narcotic medication before			
No	Ref.		
Yes	-6.4	(-18.8, 5.9)	0.31
BMI			0.30
Underweight (less than 18.5)	Ref.		
Normal (18.5 – 24.9)	-13.3	(-37.3, 10.6)	
Overweight (25 – 29.9)	-10.1	(-34.6, 14.3)	
Obese (30 or more)	-20.4	(-45.5, 4.7)	
Provider			0.18
Ob/Gyn attending	Ref.		
Family Practice attending	-0.8	(-14.8, 13.3)	
Mid-level provider	-13.1	(-28.0, 1.9)	
Family Planning fellow	-8.9	(-22.8, 5.0)	
Study group			
Placebo	Ref.		
HC/APAP	2.6	(-6.9, 12.0)	0.59

5b. Regression coefficients for pain during aspiration by subject preoperative VAS scores

Characteristic	**B_1**	**95% CI**	**P value**
Nervous about procedure	**0.24**	**(0.06, 0.42)**	**0.01**
Nervous about pain	**0.23**	**(0.06, 0.40)**	**0.01**
Expected pain	**0.23**	**(0.01, 0.45)**	**0.04**
Baseline pain	0.10	(-0.29, 0.50)	0.60
Baseline nausea	-0.07	(-0.27, 0.12)	0.45

Bold indicates variables selected for multivariate analysis

Table 6. Postoperative Pain: Univariate linear regression analysis

6a. Differences in mean VAS scores for postoperative pain by dichotomous or categorical subject and procedural characteristics

Characteristic	**Δ VAS (mm)**	**95% CI**	**P value**
Age			
Less than 25 years	Ref.		
25 years or older	-5.4	(-13.8, 3.1)	0.21
Gestational age			
Early (Less than 8 weeks)	Ref		
Late (8 weeks to 10 weeks 6 days)	4.2	(-4.3, 12.6)	0.33
Caucasian			
Yes	Ref.		
No	**-12.4**	**(-22.1, -2.7)**	**0.01**
Hispanic			
No	Ref.		
Yes	**22.1**	**(10.1, 34.2)**	**<0.001**
Parity			
Nulliparous	Ref.		
Parous	-1.1	(-9.9, 7.7)	0.81
Prior vaginal delivery			
None	Ref.		
1 or more	-1.5	(-10.4, 7.5)	0.75
Prior surgical abortion			
None	Ref.		
1 or more	-4.3	(-13.3, 4.7)	0.35
Level of menstrual symptoms			0.97
Easy	Ref.		
Mild cramping	3.5	(-8.9, 16.0)	
Over-the-counter medication	2.5	(-9.7, 14.6)	
Prescription medication use	2.6	(-45.0, 50.1)	
Unable to attend work	-2.4	(-23.9, 19.1)	
Has used any narcotic medication before			
No	Ref.		
Yes	-2.6	(-13.6, 8.5)	0.65
BMI			0.87
Underweight (less than 18.5)	Ref.		
Normal (18.5 – 24.9)	-2.7	(-24.4, 18.9)	
Overweight (25 – 29.9)	0.9	(-21.2, 23.1)	
Obese (30 or more)	-3.3	(-26.0, 19.4)	
Provider			0.16
Ob/Gyn attending	Ref.		
Family Practice attending	6.8	(-5.7, 19.4)	
Mid-level provider	-0.4	(-13.7, 13.0)	
Family Planning fellow	11.2	(-1.2, 23.6)	
Study group			
Placebo	Ref.		
HC/APAP	2.6	(-5.8, 11.0)	0.55

6b. Regression coefficients for postoperative pain by subject preoperative VAS scores and procedural time

Characteristic	**B_1**	**95% CI**	**P value**
Nervous about procedure	**0.26**	**(0.10, 0.42)**	**0.002**
Nervous about pain	**0.16**	**(0.004, 0.31)**	**0.04**
Expected pain	**0.23**	**(0.04, 0.43)**	**0.02**
Baseline pain	0.18	(-0.17, 0.53)	0.31
Baseline nausea	0.07	(-0.10, 0.24)	0.43
Procedure time	-0.32	(-1.68, 1.04)	0.64

Bold indicates variables selected for multivariate analysis

Table 7. Satisfaction with Pain Control: Univariate linear regression analysis

7a. Differences in mean VAS scores for satisfaction with pain control by dichotomous or categorical subject and procedural characteristics

Characteristic	**Δ VAS (mm)**	**95% CI**	**P value**
Age			
Less than 25 years	Ref.		
25 years or older	-0.8	(-10.0, 8.3)	0.86
Gestational age			
Early (Less than 8 weeks)	Ref		
Late (8 weeks to 10 weeks 6 days)	3.2	(-5.9, 12.2)	0.49
Caucasian			
Yes	Ref.		
No	-7.1	(-17.7, 3.5)	0.19
Hispanic			
No	Ref.		
Yes	-6.2	(-19.8, 7.4)	0.37
Parity			
Nulliparous	Ref.		
Parous	7.3	(-2.1, 16.6)	0.13
Prior vaginal delivery			
None	Ref.		
1 or more	7.0	(-2.6, 16.5)	0.15
Prior surgical abortion			
None	Ref.		
1 or more	-6.0	(-15.7, 3.7)	0.22
Level of menstrual symptoms			0.35
Easy	Ref.		
Mild cramping	1.4	(-11.8, 14.7)	
Over-the-counter medication	10.1	(-2.8, 23.1)	
Prescription medication use	-12.1	(-62.8, 38.5)	
Unable to attend work	10.2	(-12.7, 33.1)	
Has used any narcotic medication before			
No	Ref.		
Yes	-2.0	(-13.9, 9.9)	0.74
BMI			0.30
Underweight (less than 18.5)	Ref.		
Normal (18.5 – 24.9)	0.5	(-22.5, 23.4)	
Overweight (25 – 29.9)	1.1	(-22.4, 24.5)	
Obese (30 or more)	11.4	(-12.6, 35.5)	
Provider			0.73
Ob/Gyn attending	Ref.		
Family Practice attending	5.2		
Mid-level provider	4.5		
Family Planning fellow	-0.5		
Study group			
Placebo	Ref.		
HC/APAP	7.4	(-1.5, 16.4)	0.10
Belief about study group			
Placebo	Ref.		
HC/APAP	**13.1**	**(4.0, 22.2)**	**0.01**

7b. Regression coefficients for satisfaction with pain control by subject VAS scores and procedural time

Characteristic	B_1	95% CI	P value
Preoperative VAS scores			
Nervous about procedure	-0.10	(-0.28, 0.08)	0.27
Nervous about pain	-0.003	(-0.17, 0.17)	0.98
Expected pain	-0.09	(-0.31, 0.12)	0.40
Baseline pain	0.09	(-0.29, 0.46)	0.65
Baseline nausea	-0.009	(-0.19, 0.18)	0.92
Procedure Time	0.04	(-1.43, 1.50)	0.96
Intraoperative VAS scores			
Pain prior to speculum	-0.24	(-0.72, 0.25)	0.34
Pain with speculum insertion	**-0.27**	**(-0.47, -0.06)**	**0.01**
Pain with paracervical block	**-0.23**	**(-0.40, -0.06)**	**0.01**
Pain with dilation	**-0.38**	**(-0.52, -0.23)**	**<0.001**
Pain with aspiration	**-0.44**	**(-0.58, -0.29)**	**<0.001**
Postoperative VAS scores			
Pain	**-0.28**	**(-0.47, -0.09)**	**0.005**
Nausea	0.02	(-0.17, 0.20)	0.87
Sleepiness	0.06	(-0.11, 0.23)	0.66
Itching	-0.04	(-0.56, 0.48)	0.88

Bold indicates variables selected for multivariate analysis

Table 8. Multivariate linear regression analysis*^

8a. Pain during aspiration: Multivariate linear regression analysis

Aspiration Pain = β_0 + β_1 (GA weeks) + β_2 (Study group) + β_3 (Hispanic) + β_4 (Nervous about pain)

Characteristic	B_x	95% CI	P value
Study group			
Placebo	Ref.		
HC/APAP	1.13	(-8.00, 10.25)	0.81
Gestational age (weeks)	1.18	(-1.49, 3.85)	0.38
Hispanic			
No	Ref.		
Yes	15.14	(0.03, 28.94)	0.03
Nervous about pain	0.20	(0.03, 0.37)	0.02

8b. Postoperative pain: Multivariate linear regression analysis

Postoperative Pain = β_0 + β_1 (GA weeks) + β_2 (Study group) + β_3 (Race) + β_4 (Hispanic) + β_5 (Nervous about procedure)

Characteristic	B_x	95% CI	P value
Study group			
Placebo	Ref.		
HC/APAP	1.30	(-6.65, 9.24)	0.75
Gestational age (weeks)	0.12	(-2.16, 2.40)	0.92
Caucasian			
Yes	Ref.		
No	-10.18	(-19.60, -0.76)	0.03
Hispanic			
No	Ref.		
Yes	16.52	(4.42, 28.62)	0.01
Nervous about procedure	0.21	(0.06, 0.37)	0.01

8c. Satisfaction with pain control: Multivariate linear regression analysis

Satisfaction with Pain Control = β_0 + β_1 (GA weeks) + β_2 (Study group) + β_3 (Pain with Dilation) + β_4 (Pain with Aspiration)

Characteristic	**B_x**	**95% CI**	**P value**
Study group			
Placebo	Ref.		
HC/APAP	7.89	(0.01, 15.77)	0.05
Gestational age (weeks)	1.22	(-1.10, 3.54)	0.30
Pain with dilation	-0.23	(-0.40, -0.05)	0.02
Pain with aspiration	-0.30	(-0.49, -0.11)	0.002

***Gestational age added to the models as a continuous variable**

^Final models developed with forward stepwise variable selection procedure, with GA and study group locked