AN EVALUATION OF ORAL MIDAZOLAM FOR ANXIETY AND PAIN IN FIRST-TRIMESTER SURGICAL ABORTION: A RANDOMIZED CONTROLLED TRIAL

By

Lisa L. Bayer, M.D.

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CERTIFICATE OF APPROVAL

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This is to certify that the Master's thesis of

Lisa L. Bayer, MD

has been approved

_____
Alison Edelman, MD MPH, Chair

_____
Jeffrey Jensen, MD MPH

_____
William Lambert, PhD

_____
Rochelle Fu, PhD

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LIST OF ABBREVIATIONS

ANCOVA – Analysis of covariance

BMI – Body mass index

CI – Confidence interval

EVA – Electronic vacuum aspirator

GA – Gestational age

GEE – Generalized Estimating Equations

IUD – Intrauterine device

IV – Intravenous

MVA – Manual vacuum aspirator

NAF – National Abortion Federation

NSAID – Non-steroidal anti-inflammatory analgesic

OHSU – Oregon Health & Science University

PI – Principal investigator

PCB – Paracervical block

PPCW – Planned Parenthood Columbia/Willamette

RCT – Randomized clinical trial

SD – Standard Deviation

STAI – State Trait Anxiety Inventory

US – United States

VAS – Visual analog scale

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ABSTRACT

Background: Despite the common use of anxiolytics, previous studies have not demonstrated a clear benefit of oral lorazepam or diazepam on abortion-related pain or anxiety. The utilization of a more potent and higher dose benzodiazepine has the potential to be a more effective premedication. Oral midazolam is an appealing option as it has a fast onset, wide safety margin, short duration of action, and a reliable dose-dependent amnesic effect. We hypothesized that the anxiolysis and amnesia produced by oral midazolam would result in decreased perception of pain and anxiety during the abortion experience.

Objectives: To estimate the effect of oral midazolam on patient pain and anxiety perception during first-trimester surgical abortion.

Methods: We conducted a randomized, double-blind, placebo-controlled trial. Patients between 6 0/7 and 10 6/7 weeks gestation received oral midazolam 10 mg or placebo 30-60 minutes before surgical abortion. All subjects received ibuprofen and a paracervical block. We powered the study (beta=80%) to detect a 15 mm difference in our two *a priori* primary outcomes of pain and anxiety at time of uterine aspiration (100 mm visual analog scale) at a significance level of 0.025. Secondary outcomes were pain and anxiety at additional time points, memory, satisfaction, side effects, and adverse events. For our primary analysis, a two-sample *t* test was used to compare mean visual analog scale scores for pain and anxiety with uterine aspiration. To account for within subject correlation, a general linear model was also used to test changes in pain and anxiety scores throughout different procedural time points.

Results: There were no significant differences in demographics or baseline pain or anxiety between the groups (n=124). Compared to those randomized to placebo, subjects who received midazolam had significantly less anxiety pre-operatively and postoperatively, which reached a clinically important difference after entry into the procedure room (51.4 mm placebo vs 34.5 mm midazolam, $P<0.001$). However, there was no difference in pain (74.3 mm placebo, 70.1 mm midazolam, $P=0.28$) or anxiety (68.2 mm, 60.9 mm, $P=0.14$) during uterine aspiration or at other procedural time points. A significantly greater number of subjects in the midazolam group reported partial amnesia (50.8% vs 26.2%, p=0.005). Subjects who received midazolam were more likely to report postoperative sleepiness ($P<0.001$) while those who received placebo reported more postoperative nausea ($P=0.004$). There was no difference in overall satisfaction ($P=0.88$).

Conclusions: Although oral midazolam reduces pre-procedural anxiety, it does not reduce pain or anxiety with uterine aspiration during first-trimester surgical abortions.

CHAPTER 1 – INTRODUCTION

Surgical abortion is one of the most common outpatient procedures performed in the United States (US). In 2008, an estimated 1.21 million abortions were performed in the US with approximately 90% occurring at 13 weeks' gestation or less [1, 2]. The majority of abortions in the US occur in the outpatient setting, where general anesthesia is infrequently used [1, 3]. In turn, the most commonly used regimens to help relieve procedural related pain with first trimester surgical abortion include local anesthesia with intravenous (IV) sedation (33%) or local anesthesia with or without oral premedication (46%) [3]. When oral premedications are used, the most commonly cited include nonsteroidal anti-inflammatory drugs (NSAIDs; 57%) and anxiolytics (35%).

Despite the use of various analgesic techniques during first-trimester abortions, most women experience at least a moderate level of procedural pain [4-7]. Perception of pain at the time of an abortion is complex and involves physical and psychosocial elements [8, 9]. Importantly, studies have shown that women who are more anxious report significantly more pain during abortion procedures [4, 10, 11]. Other predictors of pain during surgical abortion include young patient age, baseline depression, "moral conflicts," high anticipated pain, a retroverted uterus, history of dysmenorrhea, and increasing gestational age [4, 6, 11, 12].

The type of pain control chosen for an abortion procedure is highly individual, often based on patient preference [13]. Additionally, there are other factors that come into play, including counseling bias, practitioner choice, side effects, cost, recovery time, and facility infrastructure [13]. Outside of general anesthesia, it remains unclear what the best

regimen for pain management is for women undergoing abortions. NSAIDs and local anesthesia with a paracervical block (PCB) have been found to be effective in reducing pain [14-16]. Oral premedication using a combination of an opioid and benzodiazepine have not been effective in reducing pain as demonstrated by two randomized controlled trials (RCTs) [17, 18]. Alternatively, IV sedation with an opioid and benzodiazepine has been found to be effective in reducing pain, but requires additional resources such as patient monitoring, nursing staff, and procedural costs [5, 18]. In addition, some women fear the use of needles and prefer oral medication.

Benzodiazepines in Abortion Care

Oral benzodiazepines have been studied as a premedication for first-trimester surgical abortion under local anesthesia in two prospective studies and one RCT. Oral benzodiazepines make an ideal premedication due to anxiolytic, muscle relaxant, sedative, and anterograde amnesic properties [19-21]. In a 1979 prospective observational study of 1,792 women undergoing standardized first-trimester surgical abortion under local anesthesia, the 75% of women who chose to receive 5 mg of oral diazepam preoperatively (varied time interval <15 minutes to >90 minutes prior to procedure) reported significantly more pain than those who were not premedicated [6]. This finding persisted after controlling for pre-procedure fear, timing of drug administration, age, education, and gestational age. Of note, the more fearful patients were significantly more likely to take diazepam (P<0.001). In 2006, a prospective observational study measured pain scores during first-trimester surgical abortions (using 11-point verbal rating scale) of

330 women who chose between no additional premedication, sublingual lorazepam (0.5 to 1mg) or IV sedation for first-trimester surgical abortions [5]. All women received ibuprofen and local anesthesia. Significantly higher pain scores were reported among those that chose lorazepam (6.78), ibuprofen only (6.22) or low-dose IV sedation (6.18) compared to moderate-dose IV sedation (4.93; $P<0.001$). In addition, women who chose sublingual lorazepam had the highest percentage of unsatisfactory pain control (23.8%), while those who chose ibuprofen only had the lowest percentage (5.8%; OR: 1.93, 95% CI: 1.13, 3.26). Both of these studies were non-randomized and it is possible that the women choosing to receive benzodiazepines were expecting a larger anxiolytic effect and received too little to make a difference in pain scores [5].

In 2002, a randomized, double-blind, placebo-controlled study of 104 women compared local anesthesia and 1mg of oral lorazepam to local anesthesia alone and found no difference in pain or anxiety scores (using 11-point numeric scale) during first-trimester surgical abortion procedures (pain: 4.1 vs. 4.0, $P=0.70$; anxiety: 4.9 vs. 5.2, $P=0.32$) [22]. For women who did not wish to be randomized in this study, an observational group was also included that compared women who chose to take lorazepam (varied dose from 0.5 to 2mg dependent on the women's weight and anxiety level) to women who did not take lorazepam. The women who chose to take lorazepam were significantly more anxious before taking the medication (5.5 vs. 3.8, $P<0.001$). In addition, there was a small, non-clinically significant drop in anxiety level (from 5.5 to 4.7) for the women who took lorazepam while those women who were not premedicated had an increase in anxiety scores (from 3.8 to 4.9) during the procedure. There was no difference in pain scores between the groups (5.8 vs. 5.4, $P=0.18$). These results show a

trend toward lorazepam improving anxiety scores and making patients more comfortable. However, this population was self-selected and may not necessarily representative of the general population by declining to participate in the RCT.

Rationale for Current Study

The utilization of a more potent and higher dose benzodiazepine as a premedication for first-trimester abortions has the potential to be effective in decreasing abortion-related anxiety and pain. Oral midazolam is an appealing option as it has a fast onset, wide safety margin, and short duration of action when compared to other benzodiazepines [20]. Midazolam belongs to a newer class of benzodiazepines called "imidazobenzodiazepines." As such, there is a receptor antagonist, flumazenil, available for reversing midazolam [23]. In addition, unlike oral lorazepam or diazepam, midazolam possesses a reliable dose-dependent amnesic effect that is seen with both oral and intravenous (IV) routes of administration [21, 24-26]. The combination of anxiolysis and amnesia produced by oral midazolam may result in decreased perception of pain or increased satisfaction with the abortion experience.

Oral midazolam has been studied and found to be safe and effective in reducing perioperative pain and/or anxiety for adults undergoing outpatient dermatologic surgery [27], flexible sigmoidoscopy [28], diagnostic upper endoscopy [29], and dental surgery [30]. Oral midazolam has also been found to be safe and effective as a premedication prior to general anesthesia or IV conscious sedation [31-39]. While no major adverse events were reported in these studies, oral midazolam has known side effects including

nausea, paradoxical reactions, or excessive sedation (with potential to cause oxygen desaturation or delayed discharge) and can cause allergic reactions. Oral midazolam has not been reported as a premedication for first-trimester surgical abortion with local anesthesia. Further research is needed to study the effects of more potent benzodiazepines, like oral midazolam, before it is incorporated into abortion care.

A more effective oral option for pain and anxiety control during first-trimester surgical abortion is needed. Results of this RCT will provide evidence as to whether oral midazolam is of anxiolytic, analgesic or amnesic value, which will impact current abortion practices. Data derived from this study will also be used to determine factors associated with satisfaction with pain and anxiety control.

Objectives

Our primary objective is to determine whether oral midazolam, when given in addition to a standard regimen of ibuprofen and PCB, affects patient anxiety and pain perception at the time of uterine aspiration, as measured by a 100 mm Visual Analog Scale (VAS), compared to placebo with standard regimen.

Our secondary objectives include assessing whether oral midazolam affects anxiety and pain at different time points during the abortion procedure or patient satisfaction with pain or anxiety control and overall abortion experience. We also aimed to assess side effects (amnesia, nausea and sleepiness) and adverse events, and sought to determine predictors of satisfaction with anxiety and pain control.

CHAPTER 2 – METHODS

This randomized, double-blind, placebo-controlled trial was conducted at Planned Parenthood Columbia/Willamette (PPCW) in Portland, Oregon. Study procedures were initiated on May 15, 2013 after approval by the institutional review boards at Oregon Health & Science University (OHSU) and Planned Parenthood Federation of America. Enrollment was completed on December 21, 2013. We assessed the efficacy of oral midazolam 10mg given 30 to 60 minutes prior to the procedure (approximate time until peak effect [40]), along with a standard medication regimen of ibuprofen and PCB, in decreasing anxiety and pain compared to placebo plus the standard medication regimen in women undergoing first-trimester surgical abortion between 6 0/7 and 10 6/7 weeks gestation.

Eligibility and enrollment

Eligible women at PPCW were recruited until the required sample size was obtained. Potential study subjects were approached for enrollment only after the decision to undergo a surgical abortion was made. Patients were informed that they would receive the same care whether or not they chose to participate in the study, and that they could withdraw from the study at any time. In order to increase generalizability, eligible participants did not have access to oral benzodiazepines for premedication outside of the current study.

Participants in this RCT were 18 years or older requesting an elective surgical termination of pregnancy at PPCW between 6 0/7 and 10 6/7 weeks gestation by ultrasonographic dating. The rationale for this upper gestational age limit is that misoprostol is routinely utilized for cervical ripening starting at 11 weeks, and pretreatment with misoprostol may alter procedural or pre-procedural pain, which could impact anxiety [41-44]. The rationale for using a minimum gestation of 6 0/7 weeks is that these patients commonly need serial laboratory or ultrasound follow-up, which could confound pre- and post-procedure anxiety as well as satisfaction with the abortion experience.

All participants were English or Spanish speaking, in general good health, eligible for suction aspiration, and able and willing to give informed consent and agree to the study terms. In addition, participants were required to have assistance home and not drive for the remainder of the day. Patients were excluded if they had an early pregnancy failure, were premedicated with misoprostol, weighted less than 100 pounds, had any contraindications to the study medications (ibuprofen, lidocaine, sodium bicarbonate, midazolam, cherry flavoring), had used heroin or methadone within the last three months, requested narcotic or IV sedation, or had used narcotic pain, alcohol, or benzodiazepine medication within the past 24 hours. Patients were also excluded if they had evidence of untreated acute cervicitis or pelvic inflammatory disease.

All eligible patients were recruited for study participation. Interested patients received detailed information about the study. Those patients who wished to participate signed an OHSU IRB-approved written consent. Each potential subject was then screened to confirm eligibility. A recruitment log was maintained to track patients who were

excluded at any point throughout recruitment of the study, or who decline entry. Their age, gestational age, race/ethnicity, and reason for exclusion or refusal were documented.

Study Procedures

After enrollment, participants completed a baseline questionnaire to collect sociodemographic data, pregnancy and menstrual history, health history (including depression and anxiety history), pain and anxiety assessments, memory testing, level of sedation, desired level of memory of the abortion procedure, vital signs, and baseline sleepiness and nausea. Research personnel then presented the health care provider with an allocation sealed envelope containing the study medication. Participants were medicated with either 5mL of oral midazolam 2mg/mL syrup (total of 10mg midazolam) or 5mL of oral cherry syrup placebo. To ensure blinding, the study syrups were placed in identical oral dosing syringes with tamper evident caps. The participant, clinic staff, abortion provider, and research assistant were all blinded to the participant's allocation status. Premedication occurred 30 to 60 minutes prior to the procedure. Participants were not fasting preoperatively. All participants had previously been premedicated with 800mg oral ibuprofen prior to study enrollment.

The abortion procedures were performed in accordance with standard clinical procedure. Research personnel collected pain and anxiety scores on the VAS immediately after each step. All participants received a PCB using 20mL buffered 1% lidocaine based on a technique shown to be effective [14]. In the current study, there was no wait time between PCB administration and cervical dilation. The cervical dilation and cannula size

in millimeters (mm) generally corresponded to the gestational age in weeks; a 6 mm cannula was the smallest size used. All procedures were performed using either a manual (usually less than 8 weeks) or electric (usually 8 weeks or more) vacuum aspirator. Randomized studies have shown no difference in pain perception between the two techniques [45, 46]. Procedures were performed by experienced abortion providers (four attending physicians, two family planning fellows, and one certified nurse midwife).

Appropriate resuscitative equipment and qualified personnel (Advanced Cardiovascular Life Support trained) were available during all procedures to respond in the event of respiratory depression or other adverse events. In addition, a continuous pulse oximeter was used during the abortion procedure to further monitor for respiratory depression (defined as oxygen saturation of less than 90%).

Participant and procedural descriptors were abstracted from the medical record, including age, height, weight, vital signs, gestational age, uterine position, cannula size, and type of vacuum aspirator. Research personnel recorded the number and type of attendants in the procedure room for the abortion. Abortion providers completed a questionnaire to report on the ease of the procedure, adverse event, and maximum sedation of the participant. They also guessed the treatment assignment of the participants to see if the sedating effects of midazolam were easily observed. Approximately 30 minutes after the conclusion of the procedure, research personnel collected a postoperative assessment of participants, including pain, anxiety, memory, side effects, vital signs, and satisfaction. The final question participants were asked was to guess their assigned treatment group and to report if they would recommend the treatment to a friend. Participants were discharged after having met standard clinic discharge criteria.

Lastly, participants were asked to complete a single one-page questionnaire 1-3 days post-operatively and mail back it to the principal investigator (PI) using a pre-addressed and stamped envelope. Participants were reminded to return the survey by two different methods of their choice (phone, text message, or email). Participants were contacted for up to 3 days post-operatively or until they reported mailing in the survey, whichever came first. For all subjects, study participation was complete at 3 days postoperatively.

Randomization and Allocation Concealment

Participants were randomized to a treatment group in a 1:1 allocation ratio using a predetermined computer-generated blocked randomization in a block size of four. The Research Pharmacy at OHSU generated the randomization sequence and prepared the study medication in sequentially numbered, opaque, sealed envelopes. The randomization scheme was provided to the PI after the completion of enrollment and data entry.

Data collection

Pain was assessed using a visual analog scale (VAS, anchors 0 mm = no pain and 100 mm = worst imaginable pain) at five time points: (1) baseline, prior to randomization; (2) procedure room entry; (3) just after cervical dilation; (4) just after uterine aspiration (primary outcome); and (5) 30 minutes postoperatively. The VAS is one of the most commonly used and validated measures of pain in clinical trials [47] and has been used in many prior abortion studies [14, 16, 17, 48-54].

Anxiety was assessed using two scales: the State-Trait Anxiety Inventory (STAI) during the preoperative assessment and a VAS at multiple time points. The STAI is validated assessment of anxiety that has been used in clinical research [55, 56]. It is a self-administered questionnaire written at a sixth-grade reading level that assesses state (situational) anxiety and trait (baseline) anxiety using two scales. Each scale consists of 20 questions with the total score ranging from 20 to 80 points, with a higher score corresponding to more anxiety. A cut-off score for high anxiety was derived from normative data for working females in the age range of 19-39 years by Spielberger, et al [56]. The mean state anxiety score for this normative group was 36.17 (SD 10.96), with high state anxiety being defined as 1 SD above the mean at 47. The mean trait anxiety score for this normative group was 35.55 (SD 9.76), with high trait anxiety being defined as 1 SD above the mean at 46. Anxiety was also assessed using a VAS (anchors 0 mm = no anxiety and 100 mm = worst imaginable anxiety) at five time points: (1) baseline, prior to randomization; (2) procedure room entry; (3) after positioning on exam table, prior to starting pelvic exam; (4) just after uterine aspiration (primary outcome); and (5) 30 minutes postoperatively. The VAS offers a more practical, alternative means for assessing anxiety, and previous studies (not in abortion) have shown a significant and positive correlation between the VAS for anxiety and STAI state anxiety scale (r = 0.58 – 0.82) [33, 57-61].

Memory was assessed using tests of visual recognition and recall using picture images. The twelve images were matched based on the level of familiarity, visual complexity, and object agreement [62]. Three images (PRE1-PRE3) were shown to the participants prior to receiving the study medication. Participants were asked to identify

each image at time of visual presentation and to memorize the cards. After the images were taken away, participants were asked to recall the three images. Participants were then shown three new images (POST4-POST6) 30-60 minutes after premedication, upon entering the procedure room. Participants were asked to identify each image at time of visual presentation and to memorize the cards. Thirty minutes postoperatively, subjects were asked to verbally recall any of the six previously seen images (PRE1-PRE3, POST4-POST6). In addition, participants were asked to recognize the six previously seen images (PRE1-PRE3, POST4-POST6) mixed with six distracter cards (SHAM7-SHAM12) to identify spurious recollections.

Additional memory assessments were performed thirty minutes postoperatively, including a VAS (anchors 0 mm = remember nothing and 100 mm = remember everything). An amnesia score was also assigned based on participant recall of events using a 4-point scale (0 = unable to recall any proportion of the procedure; 1 = able to recall and describe some portions of the procedure, but overall has minimal recall of the procedure; 2 = able to recall and describe most of the procedure, but admits to inability to recall some portion of the procedure; 3 = able to recall and describe the entire procedure). Lastly, participants were asked if they had any unpleasant memories of the procedure and a description of the unpleasant memory. Unpleasant memories were then coded based on the central theme.

Nausea and sleepiness were assessed at baseline and 30 minutes postoperatively using a 100 mm VAS (anchors 0 mm = no nausea/not at all sleepy and 100 mm = worst nausea in my life/extremely sleepy). Other side effects were recorded as reported by the participant. Satisfaction was measured using a 100 mm VAS (anchors 0 mm = not at all

satisfied and 100 mm = very satisfied).

Sedation was monitored at various time points by research personnel or providers using the Ramsay sedation scale, which is a reliable sedation measure (1 = patient anxious, agitated, or restless; 2 = patient cooperative, oriented, and tranquil; 3 = patient asleep, responds to commands only; 4 = patient asleep, responds to gentle shaking, light glabellar tap, or loud auditory stimulus; 5 = patient asleep, responds to noxious stimuli such as firm nail bed pressure; 6 = patient asleep, has no response to firm nail bed pressure or other noxious stimuli) [63, 64].

Sample size

Previous data indicate that a 13 to 20 mm difference on a 100 mm VAS for pain is considered a clinically meaningful reduction [65-67]. In this study, a clinically important difference was defined as 15 mm on the 100 mm VAS scale for pain.

There is limited data available for the clinically meaningful reduction on a 100 mm VAS for anxiety. In a study evaluating VAS for anxiety in patients with Generalized Anxiety Disorder initiating treatment, the minimum important difference was estimated between 10 and 15 mm on a 100 mm scale [68]. We assumed that a 15 mm difference on a 100 mm VAS for anxiety would be clinically meaningful.

We estimated our sample size to achieve 80% power to detect a 15 mm reduction in VAS for both pain and anxiety (standard deviation of 26 mm), using a significance level of 0.025 (adjusted for the two primary outcomes). Accounting for 5% subject withdrawal, resulted in a minimum total sample of 124 subjects.

Statistical Methods

Study data was managed using REDCap (Research Electronic Data Capture) electronic data capture tool hosted at Oregon Health & Science University. Data were exported from REDCap for statistical analysis using Stata (Version 12.1, StatCorp LP, College Station, Tx). Graphics were created with Stata and Prism (Version 6, GraphPad Software, La Jolla, Ca). All variables were analyzed using an intention-to-treat approach.

Descriptive statistics of baseline characteristics of the two study groups were compared using Pearson chi-squared or Fisher's exact test for nominal data, Mann-Whitney U test for ordinal data, and two-sample *t* test for continuous data. Procedural characteristics, post-operative characteristics and memory testing were analyzed in a similar fashion. VAS scores were analyzed as continuous variables and treatment group comparisons were performed using two-sample *t* tests. However, because many of the VAS scores were not normally distributed, medians and ranges are also reported and comparisons between treatment groups were additionally performed using Mann-Whitney U test. Pain scores were also analyzed as ordinal using established methodology, with 30 mm or less labeled mild pain, 31 to 69 mm labeled moderate pain, and 70 mm labeled severe pain [66, 69]. In addition, an ANCOVA model was used to compare postoperative nausea and sleepiness between the treatment groups after adjusting for baseline differences. Lastly, a paired *t* test was used to compare satisfaction scores 30 minutes postoperatively to those scores 1-3 days postoperatively.

For the primary analysis, a two-sample *t* test was used to compare mean VAS scores for pain and anxiety with uterine aspiration. To account for the within subject correlation, a general linear model was created using generalized estimating equations (GEE) with an "unstructured" variance-covariance structure and robust estimator for standard errors. A GEE model was chosen because the main interest was to investigate group differences (population-average) in mean pain and anxiety scores. The "unstructured" variance-covariance structure was chosen because it best models the within-subject correlation. The interaction term between procedural time point and treatment group was tested to determine if there was a difference in change of the mean pain or anxiety scores at various time points between the treatment groups.

Univariate linear regression was performed to explore predictors of postoperative satisfaction with pain and anxiety control. Race, education level, parity, prior vaginal delivery, prior surgical abortion, menstrual symptoms, provider type, and extent of amnesia were dichotomized for the univariate analysis. BMI, ethnicity, anxiety history, depression history, presence of a companion, treatment group, and presence of unpleasant memories were analyzed as categorical independent variables. Gestational age, subject's age, STAI level (state and trait), VAS anxiety scores at different time points, VAS pain scores at different time points, procedure time, expected pain and anxiety VAS scores, and postoperative nausea and sleepiness VAS scores were analyzed as continuous independent variables.

Multivariate linear regression was then performed to examine predictors of satisfaction with pain and anxiety using the significant predictors ($P<0.1$) identified in the univariate analysis. Clinically relevant variables including gestational age and study

group were added into the model. Interaction terms between gestational age and treatment group, STAI state anxiety level and treatment group, and amnesia score and treatment group were tested. Significant collinearity was found between presence of unpleasant memories and pain with uterine aspiration, which was expected as participants reported pain as being the most common unpleasant memory. Therefore, only pain with uterine aspiration was selected as an independent variable in the model. Collinearity was also found between aspirator type and gestational age, thus gestational age was selected as the independent variable in the model. Forward, backward and stepwise model selection procedures were performed using the predictor variables and three interaction terms. Model diagnostics were performed including residual analysis, Q-Q plots, Shapiro-Wilk test, Variance Inflation Factor (VIF) analysis, Cook's distance and Leverages.

Lastly, we measured the correlation of our two measures of anxiety (STAI state and baseline anxiety VAS score) using the Pearson product-moment correlation. We also measured the correlation between our subjective memory tests (VAS and amnesia score) and the picture image testing using the Spearman's rank correlation. For our two primary comparisons, $P<0.025$ was used to define statistical significance. For all other comparisons, a $P< 0.05$ was considered statistically significant.

CHAPTER 3 – RESULTS

A total of 870 women were screened for study eligibility between May and December 2013. Of these, 746 women were excluded and 124 were enrolled. Participant flow is depicted in Figure 1. The main reasons for study exclusion were gestational age or declining to participate. One participant in the placebo group did not complete the study after she changed her mind to have an abortion. This woman had previously changed her mind about having an abortion one month prior and reported a high level of baseline anxiety with a STAI state anxiety score of 69. The data for this participant was included in the analysis.

When comparing those who declined to participate (n=157) with study participants, there was no difference in age (declined: 26.8 years versus enrolled: 25.7 years, *P*=0.11), race (declined: 78% white versus enrolled: 69%, *P*=0.09), ethnicity (declined: 10.3% Hispanic versus enrolled: 13.7%, *P*=0.40) or gestational age (declined: 7.8 weeks versus enrolled: 8.1 weeks, *P*=0.10).

Baseline characteristics

Baseline characteristics are presented in Table 1 and were similar between the groups. The majority of participants were white and in their mid-20s. Over half of participants were nulliparous, with a third reporting a prior surgical abortion and a prior vaginal delivery. The mean gestational age in the placebo group was 8.2 weeks and 7.9 weeks in the midazolam group. According to the STAI and using normative data, most

participants had a high level of state anxiety (65.3%), while trait anxiety was less common (21.0%). There was a significant correlation between baseline VAS anxiety score and baseline STAI state anxiety score (r = 0.52, 95% CI 0.38, 0.64, P<0.0001; see Figure 2a). Of note, while the STAI state anxiety scores followed a normal distribution, the VAS scores for baseline anxiety were negatively skewed (see Figure 2b). Thus, although the two anxiety measures are significantly correlated, using a VAS might inflate the anxiety score.

Procedural characteristics

Procedural characteristics are shown in Table 2. More procedures in the midazolam group were performed by an obstetrician/gynecologist than the certified nurse midwife (72.6% versus 53.2%, P=0.03). There were no significant differences between treatment groups in procedure time, presence of a companion, aspirator type, timing from premedications (ibuprofen and study drug) to start of procedure, use of ondansetron (anti-nausea) premedication, provider rated ease of procedure, uterine position, or placement of a post-abortal intrauterine device (IUD). In addition, there were no differences in procedural or postoperative characteristics by provider type (data not shown). Most women experienced a severe level of pain (65%; VAS $\geq$ 70 mm) at the time of uterine aspiration.

Adverse events were rare, not medication-related, and did not vary by provider type. One participant in each the placebo and the midazolam group underwent reaspiration for hematometra shortly after the procedure. One participant in the placebo

group underwent reaspiration after visual inspection of the uterine aspirate revealed an incomplete procedure. One participant in the midazolam group experienced a cervical laceration from the tenaculum, requiring a single suture for hemostasis. Lastly, one participant in the midazolam group experienced hemorrhage in the setting of a large fibroid uterus that was responsive to suction aspiration and uterotonic medications.

VAS scores are summarized in Table 3. There was no significant difference in preoperative VAS scores (prior to receiving allocated treatment). Most participants desired to have little memory of the procedure as 83% (104/124) of participants marked a VAS score of 50 mm or less while only 6.5% (8/124) of participants marked a VAS score of 80 mm or greater (see Figure 3).

The mean VAS score for the primary outcome, pain during uterine aspiration, was 70.1 mm in the midazolam group, which was not significantly different from the mean score of 74.3 mm in the placebo group based on the two-sample *t* test (P=0.28, see Figure 4). A profile plot for VAS pain scores throughout the abortion procedure is shown in Figure 5, and the mean VAS pain scores are shown in Figure 6. Pain during aspiration was also analyzed ordinally and there was no difference between the groups in the experience of moderate or severe pain (placebo: moderate 26.2%, severe 70.5% versus midazolam: moderate 32.3%, severe 59.7%). Based on the GEE model, there was no significant difference in change of mean pain score between participants in treatment groups at any time point throughout the procedure (see Table 4). Overall, the pattern of change in mean VAS pain scores was the same for midazolam and placebo (P=0.32).

The mean VAS score for the second primary outcome, anxiety during uterine aspiration, was 60.9 mm in the midazolam group and 68.2 mm in the placebo group

(P=0.14, see Figure 7). A profile plot for VAS anxiety scores throughout the abortion procedure is shown in Figure 8, while mean VAS anxiety scores are shown in Figure 9. Anxiety and pain during aspiration were significantly correlated (r = 0.60, P<0.0001). Based on the GEE model, the overall pattern of change in mean VAS anxiety scores was significantly different between the treatment groups (P<0.0001; see Table 5). There was a significant difference in anxiety scores between treatment groups at room entry (Estimate: -19.24 mm, P<0.0001), start of procedure (Estimate: -13.42 mm, P=0.003), and postoperative (Estimate = -10.81mm, P=0.01); there was no difference in anxiety scores during uterine aspiration (Estimate -9.57 mm, P=0.08). This difference was clinically important (≥ 15 mm) at room entry where the VAS anxiety score was 35.5 mm for the midazolam group and 51.4 mm for the placebo group.

Postoperative characteristics (30 minutes post)

There were statistically significant differences between the treatment groups in postoperative side effects including nausea, sleepiness, and dizziness (see Table 6). Median nausea VAS score was 9.5 mm for the placebo group and 3.5 mm for the midazolam group (P=0.02). Using regression analysis to control for baseline differences confirmed this significant difference in postoperative nausea (P=0.004). Mean sleepiness VAS scores were significantly greater for the midazolam group compared to the placebo group (midazolam: 56.6 mm versus placebo: 40.1 mm, P=0.001). This was confirmed using regression analysis controlling for baseline group differences (P<0.0001). Dizziness was reported significantly more frequently in the midazolam group

(midazolam: 49.2% versus placebo: 29.5%, P=0.03). There was no difference in preoperative or postoperative use of the antiemetic, ondansetron (preoperative use: P=0.28; postoperative use: P=1.0). Hiccupping was reported more frequently in the midazolam group, but did not reach statistical significance (11.5% versus 1.6%, P=0.06). Requesting additional pain medication postoperatively was rare in both groups. Vital signs and sedation score did not differ between the groups at any time point before, during or after the procedure (see Table 7). There were no episodes of hypoxia nor was a reversal agent needed.

Subjective measures of memory were significantly lower in the midazolam group, including median VAS memory score (82 mm versus 97 mm, P<0.0001) and amnesia score (partial to complete amnesia: 50.8% midazolam group versus 26.2% placebo group, P=0.005). Using picture images, there was no evidence of retrograde amnesia, as there was no difference in ability to recall or recognize the images shown prior to study drug administration (see Figure 10a and 10b). In contrast, significantly fewer participants in the midazolam were able to recall and recognize the picture images shown after study drug administration. We also measured the correlation between these subjective and objective measures of memory and found a significant correlation between both of the subjective measures of memory and the ability to recall the picture images shown after study drug administration (VAS memory and recall of picture images: rho = 0.40, P<0.0001; amnesia score and recall of picture images: rho = 0.32, P=0.0003). However, there was no correlation between the either of the subjective measures of memory and the ability to recognize the picture images shown after study drug administration, likely due to the high rates of image recognition among all participants.

Participants were better than providers in correctly identifying their treatment group. Thirty minutes postoperatively, there were significantly more participants in the midazolam group who would recommend the study medication to a friend (80.3% versus 61.0%, P=0.02). Overall satisfaction with the abortion procedure did not differ between the study groups (placebo: 77.8 mm versus midazolam: 78.4 mm, P=0.88; see Figure 11). Satisfaction with pain control was low for both groups (placebo: 43.2 mm versus midazolam: 50.0 mm, P=0.20). Satisfaction with anxiety control was significantly higher in the midazolam group (68.9 mm versus 56.1 mm, P=0.01).

Postoperative characteristics (1-3 days post)

Response rates from the follow-up mail in survey were similar between the treatment groups (placebo: 66.1% versus midazolam 71.0%, P=0.56; see Table 6). There was no statistical difference in baseline, procedural or postoperative characteristics between participants who did (n=85) and did not (n=39) complete the follow-up survey (data not shown), except that postoperative nausea was significantly lower in those that completed the survey even after controlling for baseline differences (P=0.002). The proportion of participants reporting an unpleasant memory did not change during the follow-up time (30 minutes postop: 75/122, 61.5%; 1-3 days postop: 55/85, 64.7%; P=0.10). Median memory VAS scores were significantly lower in the midazolam group (P<0.0001) as was the ability to recall the picture images shown after study drug administration (see Figure 10c). Satisfaction with anxiety control was significantly higher in the midazolam group during follow-up (Placebo: 50.2 mm versus midazolam: 64.7

mm, P=0.03). Overall satisfaction and satisfaction with pain control did not differ between the treatment groups during follow-up (overall: P=0.11; pain control: P=0.08). Overall satisfaction scores decreased significantly for the placebo group but not for the midazolam group during follow-up (placebo: P=0.0009 versus midazolam: P=0.78). Satisfaction with pain control and anxiety control decreased for both treatment groups during follow-up, but not significantly (pain control: P=0.20; anxiety control: P=0.16). Lastly, there was no statistical difference in the recommendation of the study medication to a friend during follow-up (placebo: 60.0% versus midazolam 72.7%, $P=0$.25). A total of 13 subjects changed their recommendation at time of follow-up, most commonly from "yes" to "uncertain" (5 placebo and 3 midazolam).

Linear Regression Analysis: Satisfaction with pain and anxiety control

Since overall satisfaction with the abortion procedure was relatively high and less varied than satisfaction with pain and anxiety control, a regression analysis was performed to look at predictors of satisfaction with pain and anxiety control. In addition, there was significant correlation between overall satisfaction and satisfaction with anxiety control (r = 0.49, P<0.0001) and satisfaction with pain control (r = 0.42, P=<0.0001). In the univariate linear regression analysis of satisfaction with pain control (see Tables 8a and 8b), later gestational age, parity, prior vaginal delivery, prior surgical abortion, high baseline anxiety, anxious about procedure, presence of a companion, unpleasant memories, anxiety and pain during the procedure and anxiety and pain postoperatively were associated (P<0.1) with lower satisfaction. Subject who believed they received

midazolam and those reporting partial amnesia were associated with having higher satisfaction with pain control. Pain during uterine aspiration explained about 25% of the variability in satisfaction with pain control, the highest of any single predictor (R-squared = 0.253). For each 10 mm increase in pain during aspiration, satisfaction decreased 6.8 mm (95% CI -8.9 mm, -4.7 mm; $P<0.0001$).

In the univariate linear regression analysis of satisfaction with anxiety control (see Tables 9a and 9b), later gestation age, prior surgical abortion, high baseline anxiety, use of an electric vacuum aspirator, presence of a companion, unpleasant memories, anxious about procedure, pain and anxiety during the procedure, pain and anxiety postoperatively, nausea postoperatively and a higher memory VAS score postoperatively were all associated ($p<0.1$) with lower satisfaction with anxiety control. Subjects who either received midazolam or who believed they received midazolam, those reporting partial amnesia and those with postoperative sleepiness were associated with having higher satisfaction with anxiety control. Anxiety postoperatively explained 20% of the variability in satisfaction with pain control, the highest of any single predictor (R-squared = 0.198). For each 10 mm increase in anxiety postoperatively, satisfaction decreased 6.5 mm (95% CI -8.9 mm, -4.2 mm; $P<0.0001$).

Multivariable Analysis: Satisfaction with pain and anxiety control

Multivariable linear regression models are presented in Tables 10 and 11. The final model of regression on satisfaction with pain control included study group, pain during aspiration, the presence of a companion, amnesia, gestational age, and the

interaction term between gestational age and treatment group (see Figure 12). Satisfaction with pain control was lower for those participants with higher pain during aspiration, those who had a companion present for the procedure and those who received midazolam at more than 7 4/7 weeks gestation age. Satisfaction with pain control was higher for those reporting amnesia and for those who received midazolam at less than 7 4/7 weeks gestation age. For example, at 6 weeks gestation, satisfaction with pain control is predicted as 10.3 mm higher for a woman who received midazolam compared to placebo. However, at 10 6/7 weeks gestation, satisfaction with pain control for a woman who received midazolam will be 19.6 mm lower than placebo. Taken together, these predictors accounted for 39% of the variability in satisfaction with pain control (R-squared = 0.390).

For satisfaction with anxiety control, study group, subject belief about study group, anxiety during aspiration, anxiety postoperatively, the presence of a companion, and the interaction term between gestational age and treatment group were found to be significant predictors (see Figure 13). Satisfaction with anxiety control was lower for those participants with higher anxiety during aspiration, anxiety postoperatively, those who had a companion present for the procedure, and those who received midazolam at greater than 8 weeks gestational age. Satisfaction with anxiety control was higher in those who believed they received midazolam as well as those who received midazolam at less than 8 weeks gestational age. For example, at 6 weeks gestation, satisfaction with anxiety control is predicted as 15.0 mm higher for a woman who received midazolam compared to placebo. However, at 10 6/7 weeks gestation, satisfaction with anxiety control for a woman who received midazolam will be 21.3 mm lower than placebo. This model was

found to explain 43% of variation in satisfaction with anxiety control (R-squared = 0.429).

Model diagnostics were performed on the final models to assure that the assumptions of linear regression were not violated. The regression assumptions of homoscedasticity and linearity were assessed using residual analysis and scatter plots (see Figures 14 and 16). Normality was confirmed using Q-Q plots and Shapiro-Wilk test (see Figures 15 and 11). All participants were assumed to provide independent data. VIF analysis was also performed in order to confirm the absence of multicollinearity. Besides treatment group and the interaction term, the VIF for the remaining variables were low (range: 1.04 to 1.85). For satisfaction with pain control, seven data points had high leverage and three were identified using Cook's distance. For satisfaction with anxiety control, eight data points had high leverage and three were identified using Cook's distance. No data points were excluded from the analysis.

CHAPTER 4 – DISCUSSION

We investigated whether 10mg of oral midazolam is beneficial as a premedication to reduce abortion-related pain and anxiety. For our two primary outcomes, we found that oral midazolam did not decrease pain or anxiety during uterine aspiration for first-trimester surgical abortion. The mean difference in pain during uterine aspiration was 3.2 mm, with slightly higher pain in the placebo group. The mean difference in anxiety during aspiration was 7.3 mm, with slightly higher anxiety in the placebo group. This difference is smaller than the 15 mm difference we considered, *a priori*, to be clinically meaningful. Oral midazolam did not significantly decrease pain at any procedural time point before, during or after the abortion when compared to placebo.

Oral midazolam significantly decreased anxiety preoperatively when compared to placebo. This difference was most pronounced upon procedure room entry, 30 to 60 minutes after premedication, where the difference in mean anxiety was 16.9 mm lower in the midazolam group. Differences in mean anxiety were also lower in the midazolam group after positioning on the exam table (11.2 mm) and postoperatively (8.5 mm); however, these differences were not considered clinically important. This reduction in preoperative anxiety is likely to benefit patients and providers alike. Preparing a calm patient versus a highly anxious patient for a surgical procedure is likely to be easier for providers and staff. Unfortunately, we did not measure this outcome explicitly. In addition, it is possible that a placebo effect was observed, as mean anxiety scores for both groups decreased after study drug administration (from baseline to procedure room entry). Without a placebo effect, differences in mean anxiety scores could be even more

pronounced than demonstrated in this study. Not surprisingly, there was significant correlation between overall satisfaction and satisfaction with anxiety control ($r = 0.49$, $P<0.0001$) and satisfaction with pain control ($r = 0.42$, $P<0.0001$).

Midazolam does have known side effects, which were observed in this study. The midazolam group demonstrated significantly lower postoperative nausea scores and higher postoperative sleepiness scores. Dizziness was reported significantly more in the midazolam group. As anticipated, subjective and objective memory testing scores were lower in the midazolam group. Importantly, there were no episodes of hypoxia or serious drug-related events in this study.

The anterograde amnesia induced by midazolam is likely of benefit to some women undergoing first trimester surgical abortion. In this study, the majority of women desired to remember less than half of the abortion experience according to a memory VAS scale. However, only 11 women achieved this level of anterograde amnesia when measured 30 minutes postoperatively (10 in the midazolam group and 1 in the placebo group). Interestingly, that number increased to 16 women when measured 1-3 days postoperatively (15 in the midazolam group and 1 in the placebo group). Thus, it appears at the current dosing, oral midazolam did not achieve the desired amnesic effect for most women. However, caution must be applied as using a higher dose of oral midazolam (15mg) as a premedication is associated with delayed discharge [36, 37, 70, 71].

Despite these potential advantages of midazolam, there was no difference in overall satisfaction with the abortion experience between the two groups. In univariate analysis, satisfaction with anxiety control was significantly higher in the midazolam group, but in the multivariate analysis this benefit was only seen at lower gestational ages

(less than 8 weeks). For satisfaction with pain control, midazolam was only significant with multivariable analysis, likely due to the large within-group variation and the presence of the interaction term between treatment group and gestational age. Interestingly, satisfaction with pain control was much lower than expected for both groups (midazolam: 50.0 mm versus placebo: 43.2 mm). These low scores for satisfaction with pain control were similar to those of women in another RCT based at the same clinic site who received a sham paracervical block (49 mm) for pain control during first-trimester surgical abortion [14]. It is unclear why the satisfaction scores were so low, but may be due to the study design that created a context where women felt that they lacked control over their pain management, as there was a 50% chance of receiving a placebo premedication. Women's preferences for pain control during first-trimester surgical abortions are highly individual [13]. In this study, women did not have access to oral benzodiazepines outside of the study. Although IV sedation was an option, this lack of control may have decreased satisfaction with our participants. In addition, the dissatisfaction with pain control could be due to high expectations for the study drug after explaining the possible effects listed in the consent form.

We used regression analysis to determine predictors of patient satisfaction with pain control and anxiety control. We found a significant interaction between gestational age and treatment group. In effect, higher satisfaction with pain and anxiety was only seen with midazolam at lower gestational ages. In addition, participant belief that they received midazolam was also predictive of patient satisfaction with anxiety control, demonstrating a placebo effect in anxiety control. Interestingly, a subjective measure of amnesia was predictive of satisfaction with pain control while the objective measure

(recall of picture images) was not predictive. Thus, patient perception of amnesia appears to be more important to women than objective measures of memory.

The presence of a companion was predictive of lower satisfaction scores for pain and anxiety control. This is in contrast to a prior study, which found a positive correlation between bringing someone to the clinic and overall satisfaction [72]. It can be hypothesized that the companion might not have supported the woman during the procedure the same way that a trained counselor or advocate could have. We did not explore the relationship between the companion and the participant in further detail to see if coercion or intimate partner violence was present.

It is important to note that 45/123 (36.6%) of the abortion procedures in this study were performed by a certified nurse midwife. There were no differences in adverse events, procedural characteristics, or satisfaction scores for participants under the care of the certified nurse midwife when compared to obstetrician/gynecologists. While this study is underpowered to draw conclusions regarding safety of advanced practice clinicians in providing abortions, we can see that participants had a similar abortion experience under the care of a certified nurse midwife. Increasing the use of advanced practice clinicians can help alleviate the abortion provider shortage in the US.

The major strength of this study is its design and execution as a placebo-controlled, double-blind RCT, which reduces bias and confounding. In addition, oral benzodiazepines were only available to eligible women through the participation in the study to decrease selection bias. Several limitations are recognized. Our study population reflects abortion patients in an outpatient setting who desired an oral premedication in addition to ibuprofen. In effect, participants in this study had a high baseline anxiety.

However, this is exactly the target population who would request and receive oral midazolam in our clinic's routine practice. Thus, our results should be generalizable to other outpatient abortion clinics, but may not be generalizable to all other settings. In addition, the study did not include gestational ages less than 6 weeks or greater than 11 weeks. It is likely that the effect of midazolam at lower gestational ages would be similar to that observed in this study as the procedures are the same. In contrast, procedures at later gestational ages can involve additional waiting and side effects with the use of cervical preparation with misoprostol. Another limitation is the low follow-up rate at 1-3 days postoperatively. Despite the use of multiple reminders, only 69% of women returned the survey, somewhat limiting our confidence in conclusions at this time point. Based on our results, it appears that a women's perception of her abortion experience may evolve over time. Longer-term follow-up of women after the abortion are needed to characterize this better. An additional limitation was our use of the VAS for anxiety. The VAS was used in our study for ease of administration because we were measuring anxiety at multiple time points. Although we found a significant correlation between baseline VAS anxiety score and baseline STAI state anxiety score ($r = 0.52$), the correlation was not as strong as previously reported ($r = 0.58 – 0.82$) [33, 57-61]. In effect, use of the VAS likely inflated the anxiety scores in our study. Use of a different validated instrument to measure anxiety should be considered for future abortion-related research. Lastly, we used a standard dose of midazolam for all participants and excluded women weighing less than 100 pounds. Use of a tailored dosing based on patient weight and anxiety level may be beneficial to achieving an optimal sedation level.

This study clearly defines the role of oral midazolam for first-trimester surgical abortions. Similar to the one other RCT investigating oral lorazepam, we did not find that oral midazolam reduced pain perception during first-trimester surgical abortion [22]. This fact must be explicitly stated when using oral midazolam in this setting. Alternatively, oral midazolam is effective in reducing preprocedural anxiety. In addition, women must be aware of the possible side effects of midazolam, including possible anterograde amnesia. While this is a desirable side effect for many women, some women may prefer to remember everything. In contrast to oral or sublingual lorazepam, oral midazolam does offer several benefits, including faster onset and shorter half-life, with return to baseline typically seen within two hours [20].

Results of this study have public health implications surrounding pain management in abortion care. Since most abortions are performed in the first-trimester in the outpatient setting, maximizing pain control with oral premedication is a priority. The use of oral premedication over IV sedation or general anesthesia not only reduces healthcare costs, but also decreases anesthesia-related complications [73]. In addition, oral premedication can easily be used in low resource settings to improve the care of women.

Congruent with previous reports we failed to demonstrate that an oral premedication reduces pain during first-trimester surgical abortion [5, 6, 17, 18, 22]. The major drawback of an oral premedication, whether a benzodiazepine or opioid, is that it is more difficult to titrate according to patient response. Unlike IV sedation, achieving optimal effect with oral medications is challenging due to the more varied onset of effect, observed response, and duration of effect. NSAIDs and PCB remain as the only

pharmacologic options other than IV sedation to significantly reduce first-trimester abortion related pain. However, oral midazolam is safe and effective in reducing preprocedural anxiety, and can be considered as a premedication to decrease anxiety and improve the patient experience.

REFERENCES

[1] Jones RK, Kooistra K. Abortion incidence and access to services in the United States, 2008. Perspect Sex Reprod Health 2011;43:41-50.

[2] Pazol K, Zane S, Parker WY, et al. Abortion surveillance - United States, 2007. MMWR Surveill Summ 2011;60:1-42.

[3] O'Connell K, Jones HE, Simon M, Saporta V, Paul M, Lichtenberg ES. First-trimester surgical abortion practices: a survey of National Abortion Federation members. Contraception 2009;79:385-92.

[4] Belanger E, Melzack R, Lauzon P. Pain of first-trimester abortion: a study of psychosocial and medical predictors. Pain 1989;36:339-50.

[5] Allen RH, Kumar D, Fitzmaurice G, Lifford KL, Goldberg AB. Pain management of first-trimester surgical abortion: effects of selection of local anesthesia with and without lorazepam or intravenous sedation. Contraception 2006;74:407-13.

[6] Smith GM, Stubblefield PG, Chirchirillo L, McCarthy MJ. Pain of first-trimester abortion: its quantification and relations with other variables. Am J Obstet Gynecol 1979;133:489-98.

[7] Rawling MJ, Wiebe ER. Pain control in abortion clinics. Int J Gynaecol Obstet 1998;60:293-5.

[8] Stubblefield PG. Control of pain for women undergoing abortion. Suppl Int J Gynecol Obstet 1989;3:131-40.

[9] Meckstroth KR, Mishra K. Analgesia/pain management in first trimester surgical abortion. Clin Obstet Gynecol 2009;52:160-70.

[10] Rawling MJ, Wiebe ER. A randomized controlled trial of fentanyl for abortion pain. Am J Obstet Gynecol 2001;185:103-7.

[11] Pud D, Amit A. Anxiety as a predictor of pain magnitude following termination of first-trimester pregnancy. Pain Med 2005;6:143-8.

[12] Borgatta L, Nickinovich D. Pain during early abortion. J Reprod Med 1997;42:287-93.

[13] Allen RH, Fortin J, Bartz D, Goldberg AB, Clark MA. Women's preferences for pain control during first-trimester surgical abortion: a qualitative study. Contraception 2012;85:413-8.

[14] Renner RM, Nichols MD, Jensen JT, Li H, Edelman AB. Paracervical block for pain control in first-trimester surgical abortion: a randomized controlled trial. Obstet Gynecol 2012;119:1030-7.

[15] Wiebe ER, Rawling M. Pain control in abortion. Int J Gynaecol Obstet 1995;50:41-6.

[16] Suprapto K, Reed S. Naproxen sodium for pain relief in first-trimester abortion. Am J Obstet Gynecol 1984;150:1000-1.

[17] Micks EA, Edelman AB, Renner RM, et al. Hydrocodone-acetaminophen for pain control in first-trimester surgical abortion: a randomized controlled trial. Obstet Gynecol 2012;120:1060-9.

[18] Allen RH, Fitzmaurice G, Lifford KL, Lasic M, Goldberg AB. Oral compared with intravenous sedation for first-trimester surgical abortion: a randomized controlled trial. Obstet Gynecol 2009;113:276-83.

[19] Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. Anesthesiology 1985;62:310-24.
[20] Greenblatt DJ, Divoll M, Abernethy DR, Ochs HR, Shader RI. Clinical pharmacokinetics of the newer benzodiazepines. Clin Pharmacokinet 1983;8:233-52.
[21] O'Boyle CA. Benzodiazepine-induced amnesia and anaesthetic practice: a review. Psychopharmacol Ser 1988;6:146-65.
[22] Wiebe E, Podhradsky L, Dijak V. The effect of lorazepam on pain and anxiety in abortion. Contraception 2003;67:219-21.
[23] Glass PS, Jhaveri RM, Ginsberg B, Ossey K. Evaluation of flumazenil for reversing the effects of midazolam-induced conscious sedation or general anesthesia. South Med J 1993;86:1238-47.
[24] O'Boyle CA, Harris D, Barry H, McCreary C, Bewley A, Fox E. Comparison of midazolam by mouth and diazepam i.v. in outpatient oral surgery. Br J Anaesth 1987;59:746-54.
[25] Dundee JW, Wilson DB. Amnesic action of midazolam. Anaesthesia 1980;35:459-61.
[26] Twersky RS, Hartung J, Berger BJ, McClain J, Beaton C. Midazolam enhances anterograde but not retrograde amnesia in pediatric patients. Anesthesiology 1993;78:51-5.
[27] Ravitskiy L, Phillips PK, Roenigk RK, et al. The use of oral midazolam for perioperative anxiolysis of healthy patients undergoing Mohs surgery: conclusions from randomized controlled and prospective studies. J Am Acad Dermatol 2011;64:310-22.
[28] Kuganeswaran E, Clarkston WK, Cuddy PG, et al. A double-blind placebo controlled trial of oral midazolam as premedication before flexible sigmoidoscopy. Am J Gastroenterol 1999;94:3215-9.
[29] Mui LM, Teoh AY, Ng EK, et al. Premedication with orally administered midazolam in adults undergoing diagnostic upper endoscopy: a double-blind placebo-controlled randomized trial. Gastrointest Endosc 2005;61:195-200.
[30] Rodrigo MR, Cheung LK. Oral midazolam sedation in third molar surgery. Int J Oral Maxillofac Surg 1987;16:333-7.
[31] Pippingskold K, Lehtinen AM, Laatikainen T, Hanninen H, Korttila K. The effect of orally administered diazepam and midazolam on plasma beta-endorphin, ACTH and preoperative anxiety. Acta Anaesthesiol Scand 1991;35:175-80.
[32] Kikuchi K, Konishi A, Watanabe Y. [Efficacy of oral midazolam as premedication in adult]. Masui 1994;43:1824-7.
[33] Abdul-Latif MS, Putland AJ, McCluskey A, Meadows DP, Remington SA. Oral midazolam premedication for day case breast surgery, a randomised prospective double-blind placebo-controlled study. Anaesthesia 2001;56:990-4.
[34] Short TG, Galletly DC. Double-blind comparison of midazolam and temazepam as oral premedicants for outpatient anaesthesia. Anaesth Intensive Care 1989;17:151-6.
[35] Ahmed N, Khan FA. Evaluation of oral midazolam as pre-medication in day care surgery in adult Pakistani patients. J Pak Med Assoc 1995;45:239-41.

[36] Nightingale JJ, Norman J. A comparison of midazolam and temazepam for premedication of day case patients. Anaesthesia 1988;43:111-3.
[37] Hargreaves J. Benzodiazepine premedication in minor day-case surgery: comparison of oral midazolam and temazepam with placebo. Br J Anaesth 1988;61:611-6.
[38] Luyk NH, Whitley BD. Efficacy of oral midazolam prior to intravenous sedation for the removal of third molars. Int J Oral Maxillofac Surg 1991;20:264-7.
[39] Khan EI, Kamal RS, Ullah H. Anxiolytic effect of midazolam premedication assessed by clinical and platelet aggregation profiles. J Ayub Med Coll Abbottabad 2010;22:4-7.
[40] Kanto JH. Midazolam: the first water-soluble benzodiazepine. Pharmacology, pharmacokinetics and efficacy in insomnia and anesthesia. Pharmacotherapy 1985;5:138-55.
[41] Platz-Christensen JJ, Nielsen S, Hamberger L. Is misoprostol the drug of choice for induced cervical ripening in early pregnancy termination? Acta Obstet Gynecol Scand 1995;74:809-12.
[42] Cakir L, Dilbaz B, Caliskan E, Dede FS, Dilbaz S, Haberal A. Comparison of oral and vaginal misoprostol for cervical ripening before manual vacuum aspiration of first trimester pregnancy under local anesthesia: a randomized placebo-controlled study. Contraception 2005;71:337-42.
[43] de Jonge ET, Jewkes R, Levin J, Rees H. Randomised controlled trial of the efficacy of misoprostol used as a cervical ripening agent prior to termination of pregnancy in the first trimester. S Afr Med J 2000;90:256-62.
[44] Hall G, Ekblom A, Persson E, Irestedt L. Effects of prostaglandin treatment and paracervical blockade on postoperative pain in patients undergoing first trimester abortion in general anesthesia. Acta Obstet Gynecol Scand 1997;76:868-72.
[45] Edelman A, Nichols MD, Jensen J. Comparison of pain and time of procedures with two first-trimester abortion techniques performed by residents and faculty. Am J Obstet Gynecol 2001;184:1564-7.
[46] Singh RH, Ghanem KG, Burke AE, Nichols MD, Rogers K, Blumenthal PD. Predictors and perception of pain in women undergoing first trimester surgical abortion. Contraception 2008;78:155-61.
[47] Jensen MP, Karoly P. Self-report scales and procedures for assessing pain in adults. In: Turk DC, Melzack R, eds. Handbook of pain assessment. New York: Guilford Press, 2001.
[48] Dahl V, Fjellanger F, Raeder JC. No effect of preoperative paracetamol and codeine suppositories for pain after termination of pregnancies in general anaesthesia. Eur J Pain 2000;4:211-5.
[49] Edelman A, Nichols MD, Leclair C, Astley S, Shy K, Jensen JT. Intrauterine lidocaine infusion for pain management in first-trimester abortions. Obstet Gynecol 2004;103:1267-72.
[50] Edelman A, Nichols MD, Leclair C, Jensen JT. Four percent intrauterine lidocaine infusion for pain management in first-trimester abortions. Obstet Gynecol 2006;107:269-75.

[51] Kan AS, Ng EH, Ho PC. The role and comparison of two techniques of paracervical block for pain relief during suction evacuation for first-trimester pregnancy termination. Contraception 2004;70:159-63.
[52] Kan AS, Caves N, Wong SY, Ng EH, Ho PC. A double-blind, randomized controlled trial on the use of a 50:50 mixture of nitrous oxide/oxygen in pain relief during suction evacuation for the first trimester pregnancy termination. Hum Reprod 2006;21:2606-11.
[53] Li CF, Wong CY, Chan CP, Ho PC. A study of co-treatment of nonsteroidal anti-inflammatory drugs (NSAIDs) with misoprostol for cervical priming before suction termination of first trimester pregnancy. Contraception 2003;67:101-5.
[54] Liu W, Loo CC, Chiu JW, Tan HM, Ren HZ, Lim Y. Analgesic efficacy of pre-operative etoricoxib for termination of pregnancy in an ambulatory centre. Singapore Med J 2005;46:397-400.
[55] Spielberger CD. State-trait anxiety inventory : a comprehensive bibliography. Palo Alto, CA: Consulting Psychologists Press, 1989.
[56] Spielberger CD, Gorsuch R, Lushene R, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Pyschologists Press, 1983.
[57] Davey HM, Barratt AL, Butow PN, Deeks JJ. A one-item question with a Likert or Visual Analog Scale adequately measured current anxiety. J Clin Epidemiol 2007;60:356-60.
[58] Boker A, Brownell L, Donen N. The Amsterdam preoperative anxiety and information scale provides a simple and reliable measure of preoperative anxiety. Can J Anaesth 2002;49:792-8.
[59] Vogelsang J. The Visual Analog Scale: an accurate and sensitive method for self-reporting preoperative anxiety. J Post Anesth Nurs 1988;3:235-9.
[60] Millar K, Jelicic M, Bonke B, Asbury AJ. Assessment of preoperative anxiety: comparison of measures in patients awaiting surgery for breast cancer. Br J Anaesth 1995;74:180-3.
[61] Elkins G, Staniunas R, Rajab MH, Marcus J, Snyder T. Use of a numeric visual analog anxiety scale among patients undergoing colorectal surgery. Clin Nurs Res 2004;13:237-44.
[62] Brodeur MB, Dionne-Dostie E, Montreuil T, Lepage M. The Bank of Standardized Stimuli (BOSS), a new set of 480 normative photos of objects to be used as visual stimuli in cognitive research. PLoS One 2010;5:e10773.
[63] Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J 1974;2:656-9.
[64] De Jonghe B, Cook D, Appere-De-Vecchi C, Guyatt G, Meade M, Outin H. Using and understanding sedation scoring systems: a systematic review. Intensive Care Med 2000;26:275-85.
[65] Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain 2003;4:407-14.
[66] Rowbotham MC. What is a "clinically meaningful" reduction in pain? Pain 2001;94:131-2.

[67] Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. Ann Emerg Med 1996;27:485-9.
[68] Williams VS, Morlock RJ, Feltner D. Psychometric evaluation of a visual analog scale for the assessment of anxiety. Health Qual Life Outcomes 2010;8:57.
[69] Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emerg Med J 2001;18:205-7.
[70] Forrest P, Galletly DC, Yee P. Placebo controlled comparison of midazolam, triazolam and diazepam as oral premedicants for outpatient anaesthesia. Anaesth Intensive Care 1987;15:296-304.
[71] Raybould D, Bradshaw EG. Premedication for day case surgery. A study of oral midazolam. Anaesthesia 1987;42:591-5.
[72] Guilbert E, Roter D. Assessment of satisfaction with induced abortion procedure. J Psychol 1997;131:157-66.
[73] Nichols MD, Halvorson-Boyd G, Goldstein R, Gevirtz C, Healow D. Pain management. In: Paul M, Lichtenberg ES, Borgatta L, Grimes DA, Stubblefield PG, eds. Management of unintended and abnormal pregnancy : comprehensive abortion care. West Sussex, England: Wiley-Blackwell, 2009.

Figure 1. Study flowchart

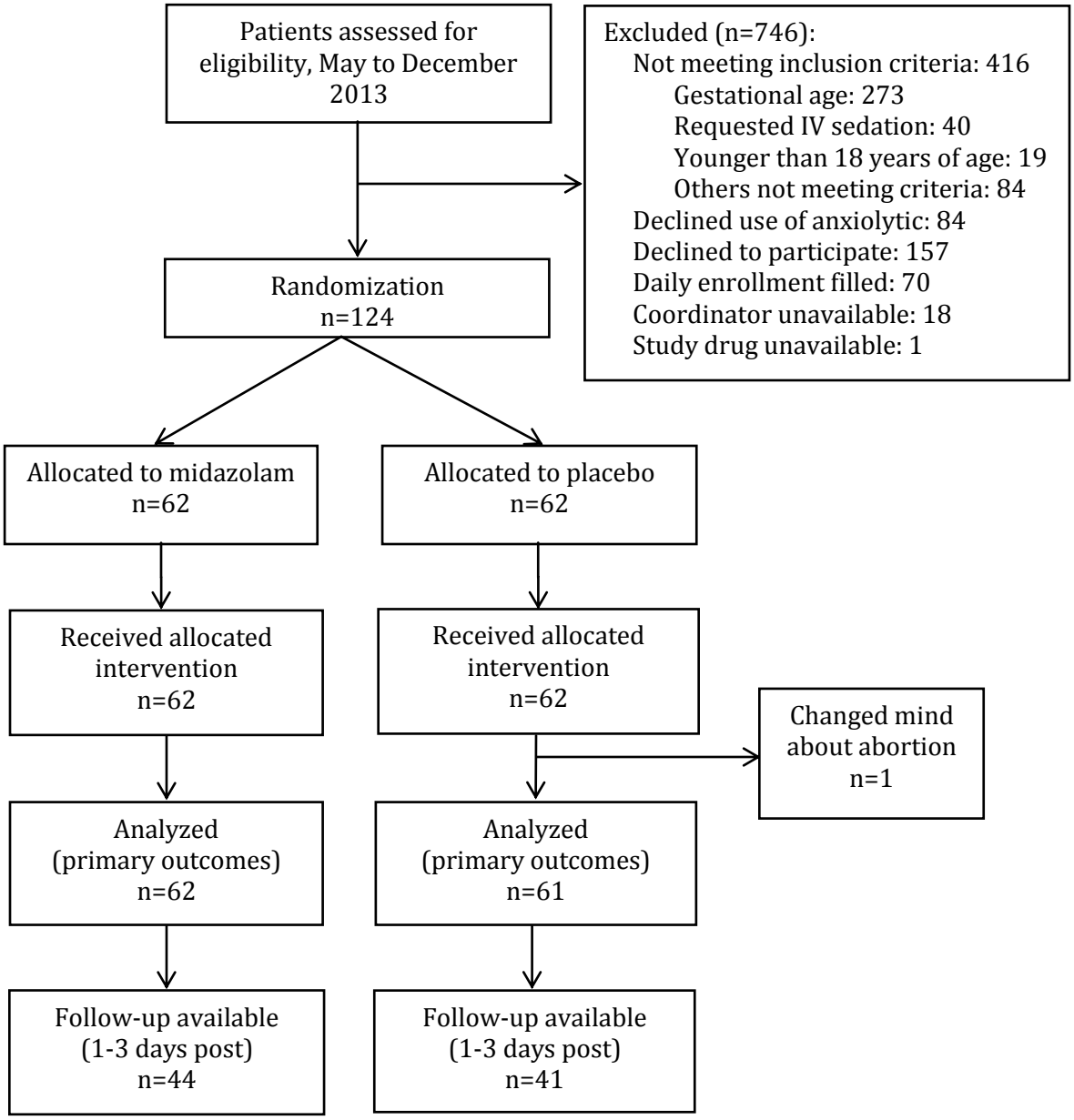


Figure 2a. Scatter plot of Baseline STAI State Anxiety score and Visual Analog Scale Baseline Anxiety score

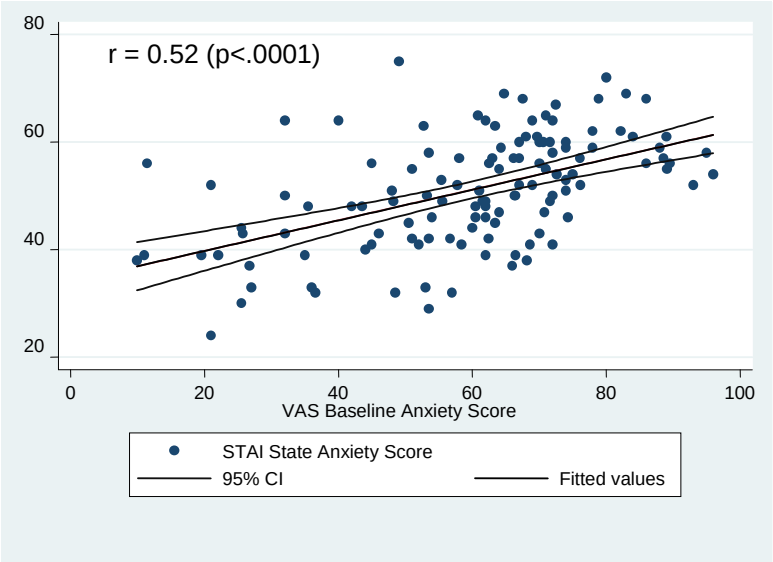
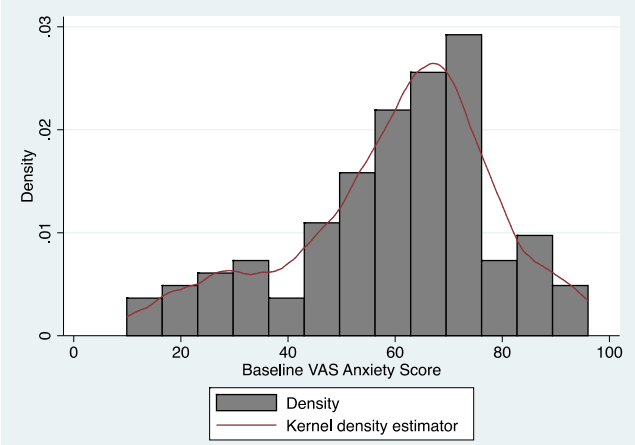


Figure 2b. Histogram of Baseline STAI State Anxiety score and Visual Analog Scale Baseline Anxiety score



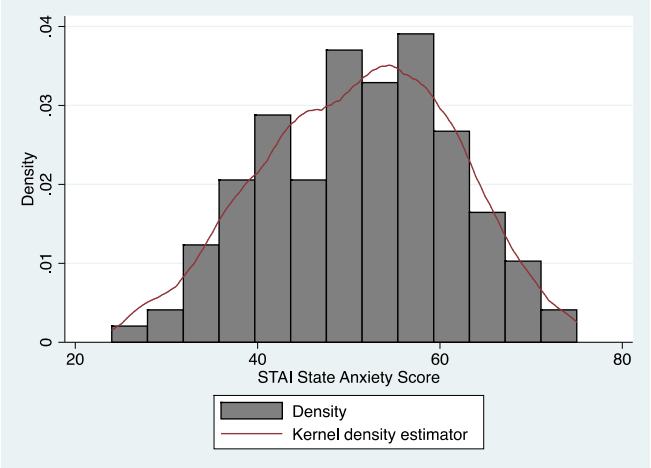


Figure 3. Histogram of desired Memory Visual Analog Scale score

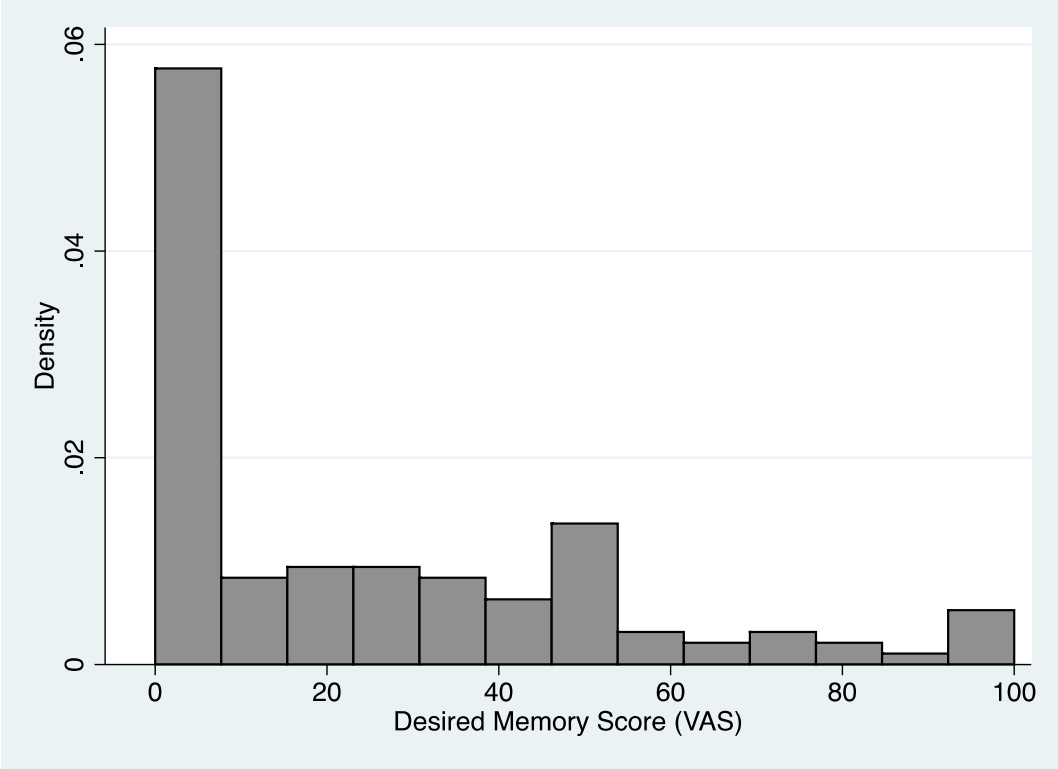


Figure 4. Distribution dot plot of Visual Analog Scale Pain scores during aspiration

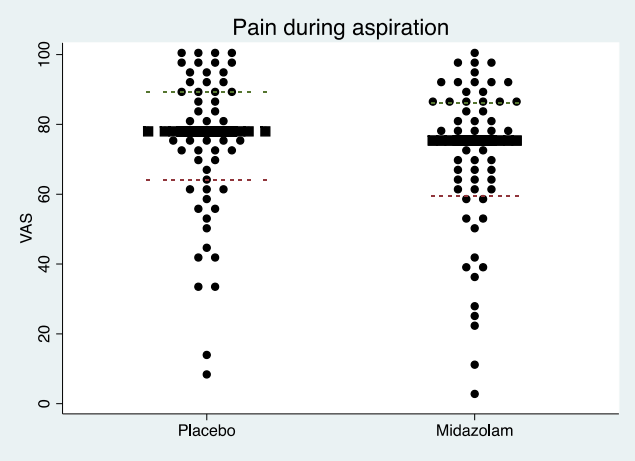


Figure 5. Profile plot of Visual Analog Scale Pain scores for placebo (top) and midazolam (bottom)

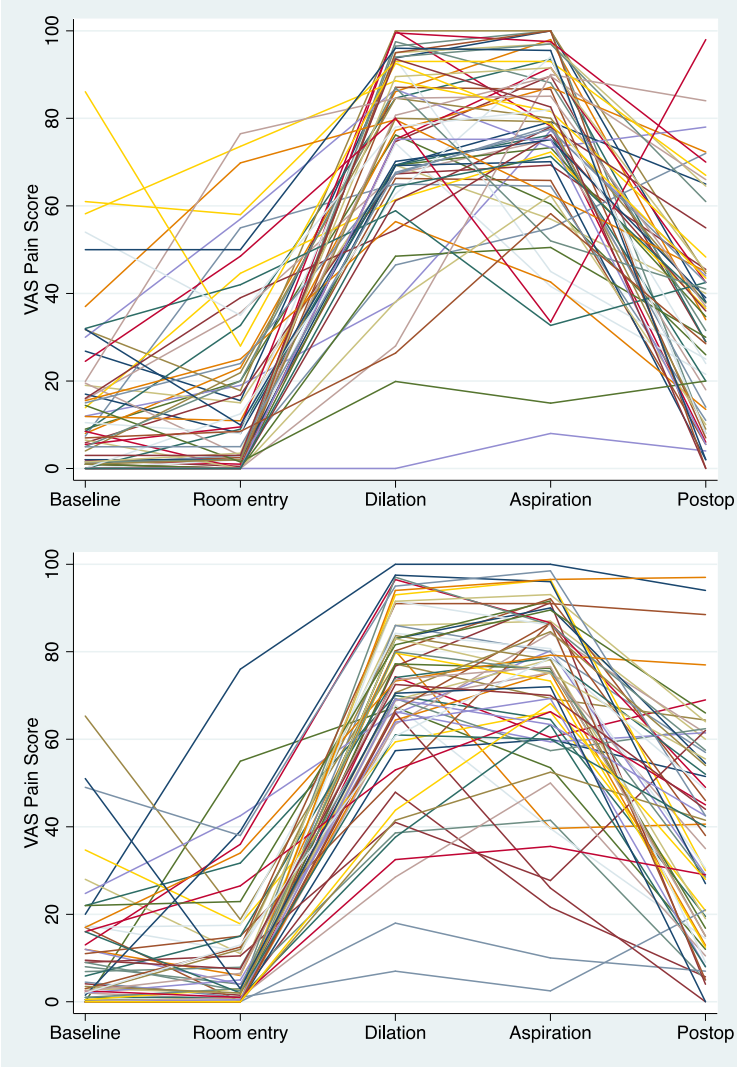


Figure 6. Mean Visual Analog Scale Pain scores during the abortion procedure

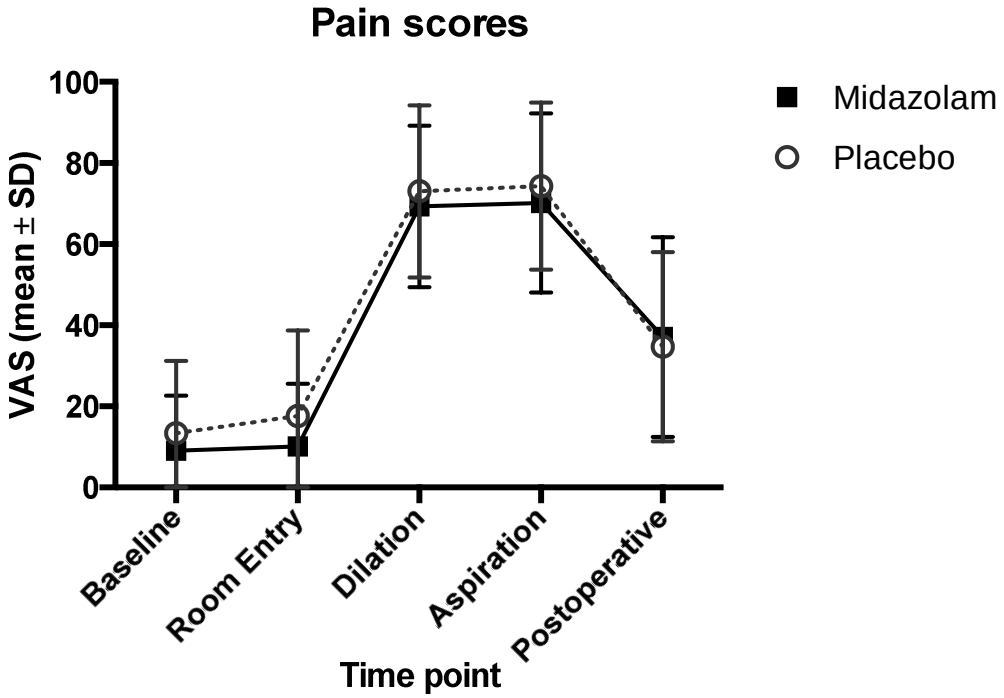


Figure 7. Distribution dot plot of Visual Analog Scale Anxiety scores during aspiration

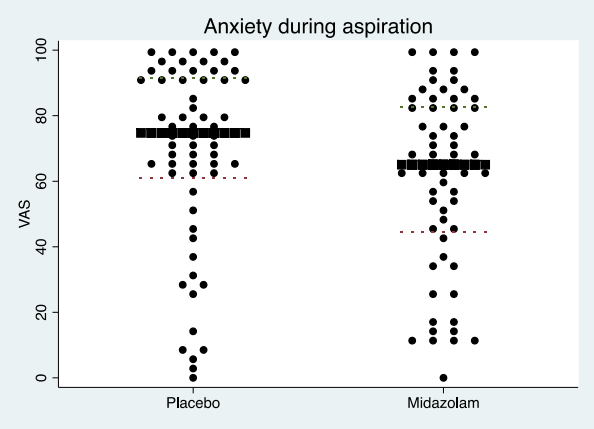


Figure 8. Profile plot of Visual Analog Scale Anxiety scores for placebo (top) and midazolam (bottom)

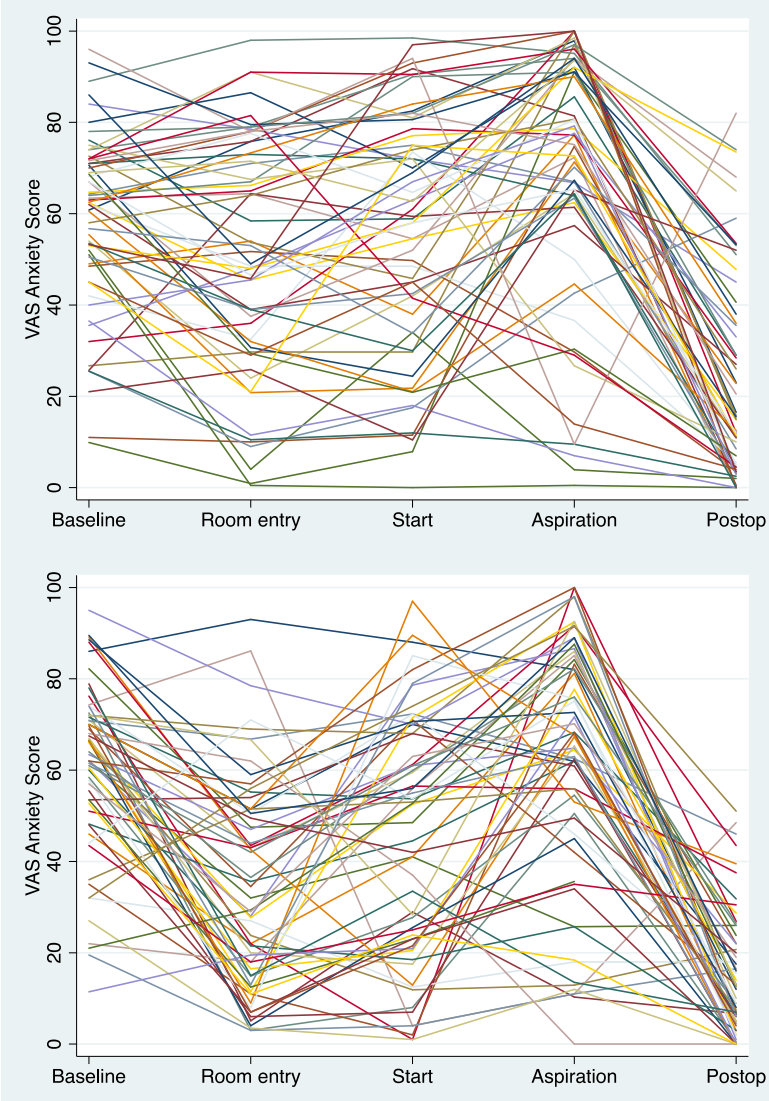


Figure 9. Mean Visual Analog Scale Anxiety scores during the abortion procedure

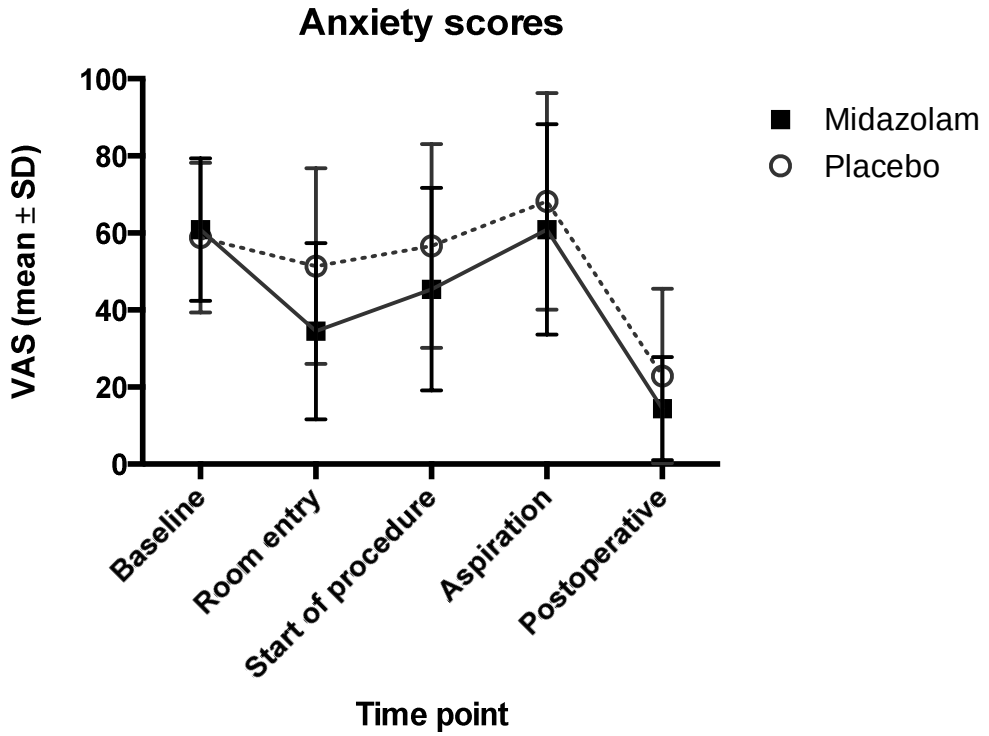
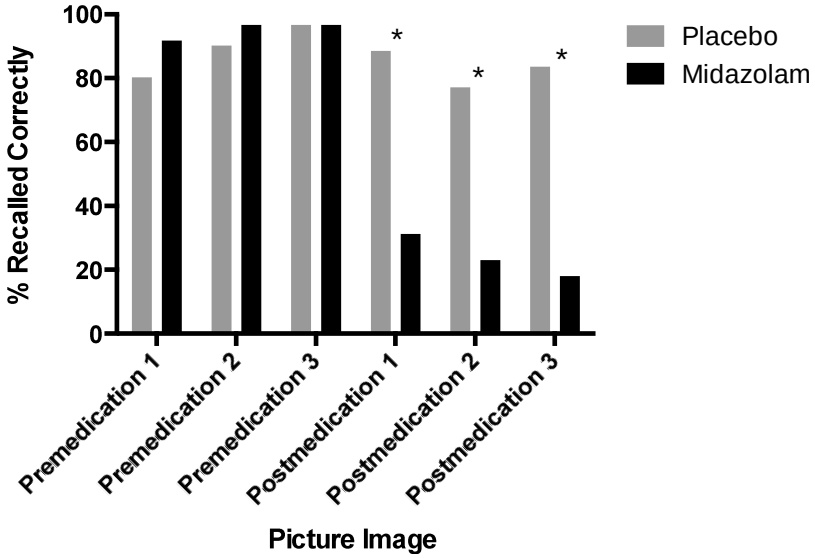
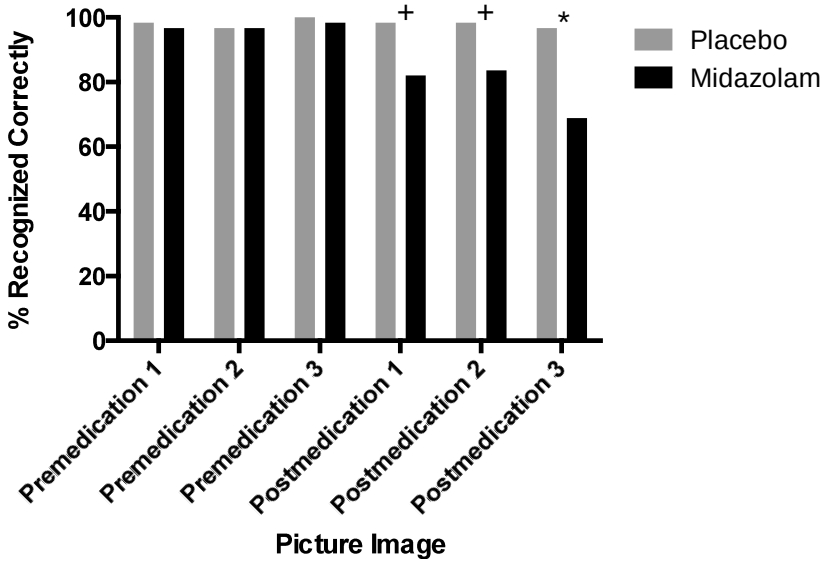


Figure 10a. Verbal recall of picture image 30 minutes postoperatively



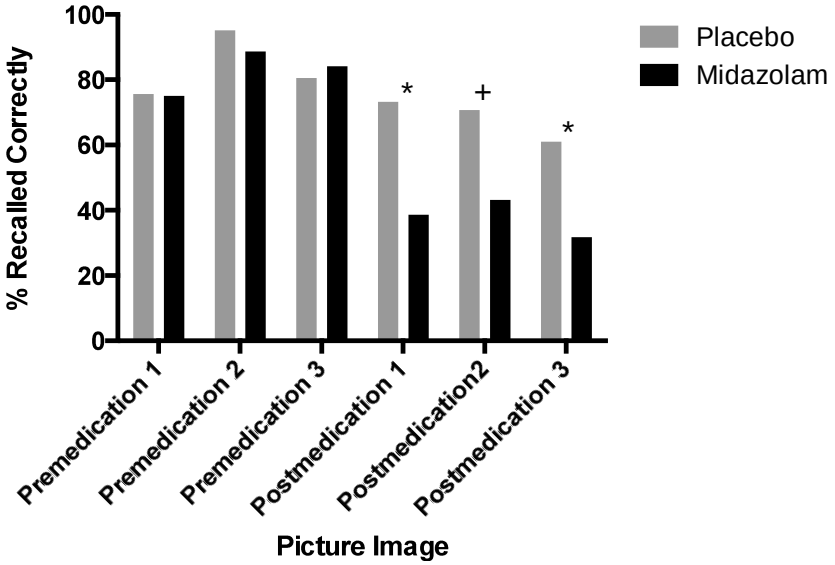
Pearson Chi-squared test
* p<0.0001

Figure 10b. Verbal recognition of picture image 30 minutes postoperatively



Fisher's exact test
+ p<0.01
* p<0.0001

Figure 10c. Written recall of picture image 1-3 days postoperatively



Perason Chi-squared test
+ p<0.01
* p<0.0001

Figure 11. Distribution dot plot of Visual Analog Scale Satisfaction scores for the total procedural, anxiety control, and pain control

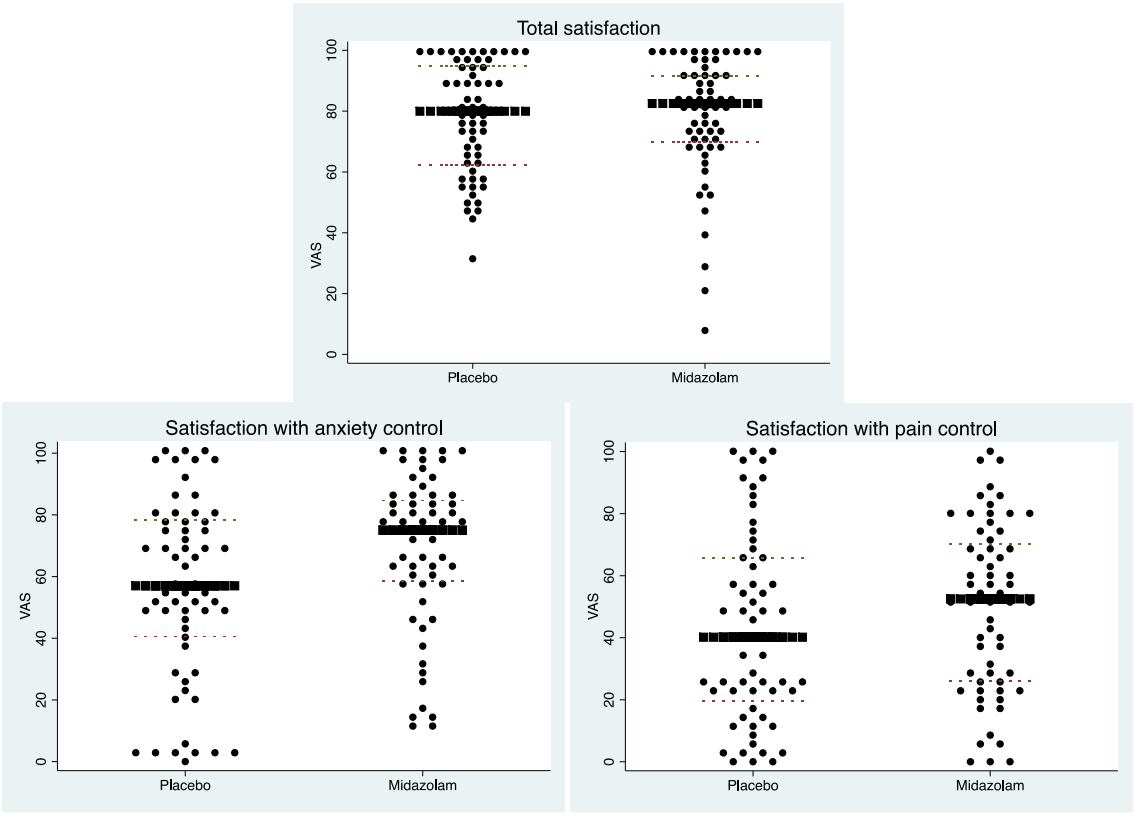


Figure 12. Scatter plot of satisfaction with pain control and gestational age by treatment group

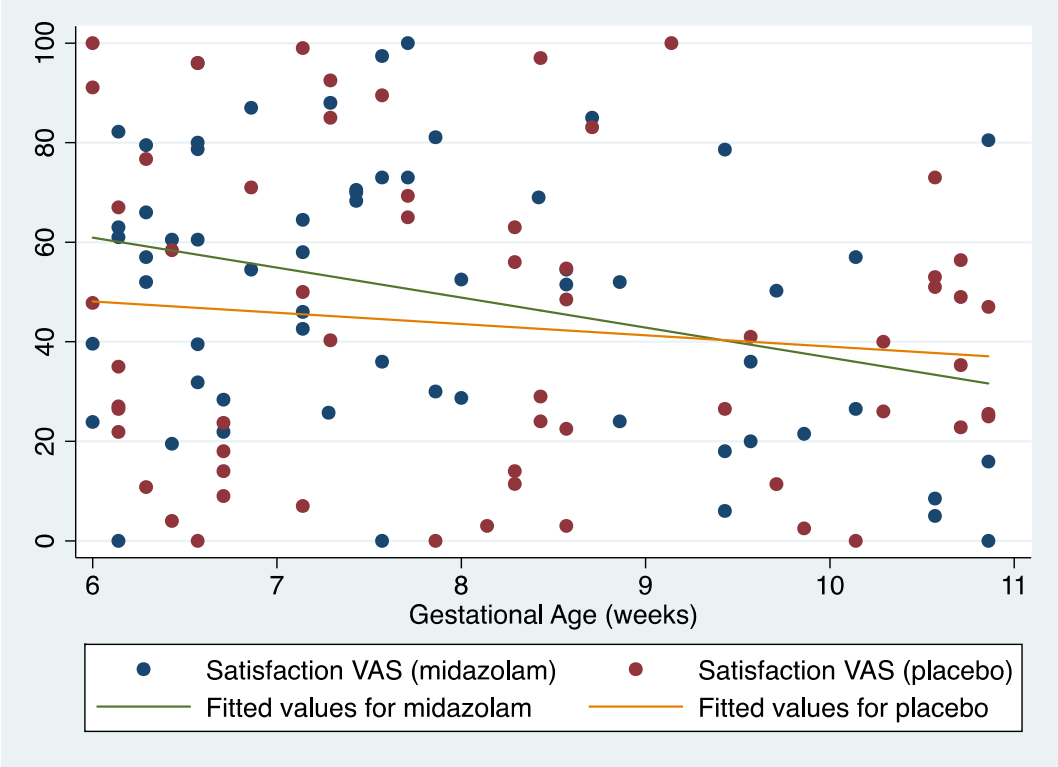


Figure 13. Scatter plot of satisfaction with anxiety control and gestational age by treatment group

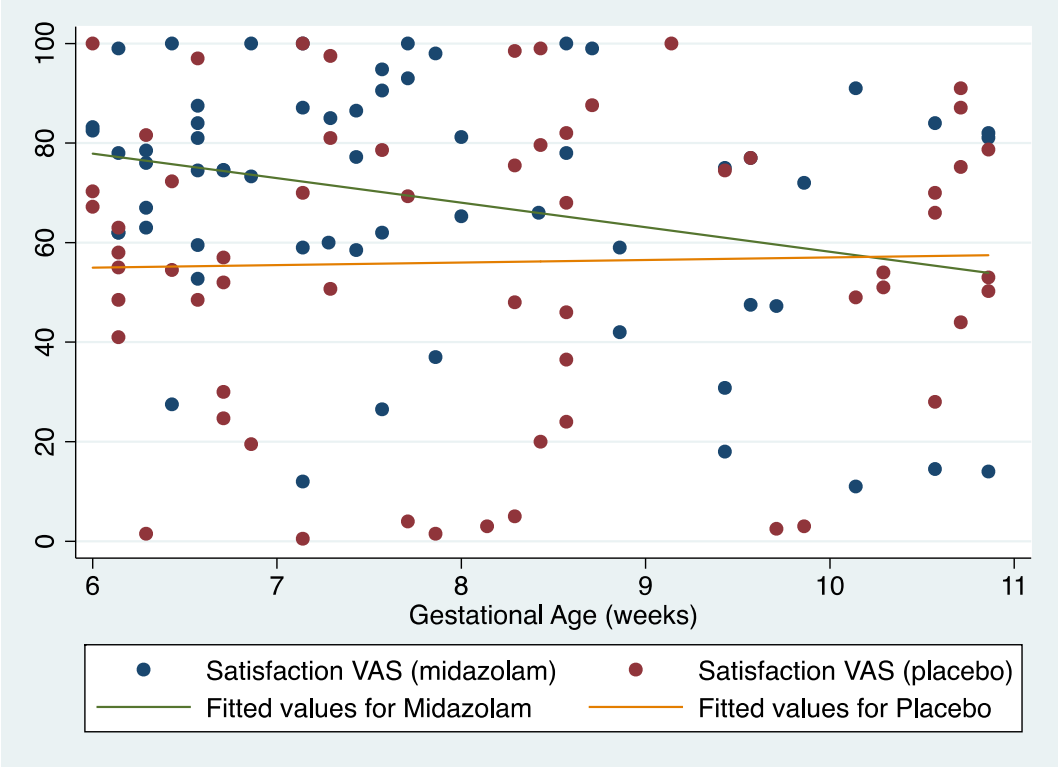


Figure 14. Residuals versus fitted values: satisfaction with pain control

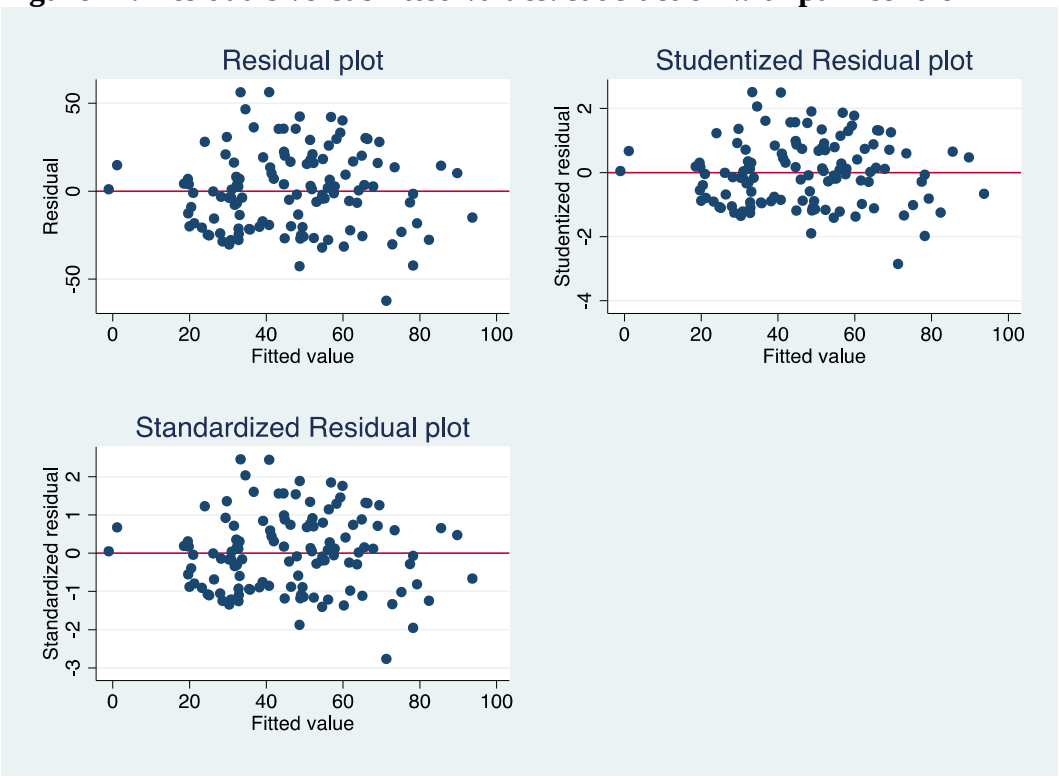


Figure 15. Q-Q Plots: satisfaction with pain control

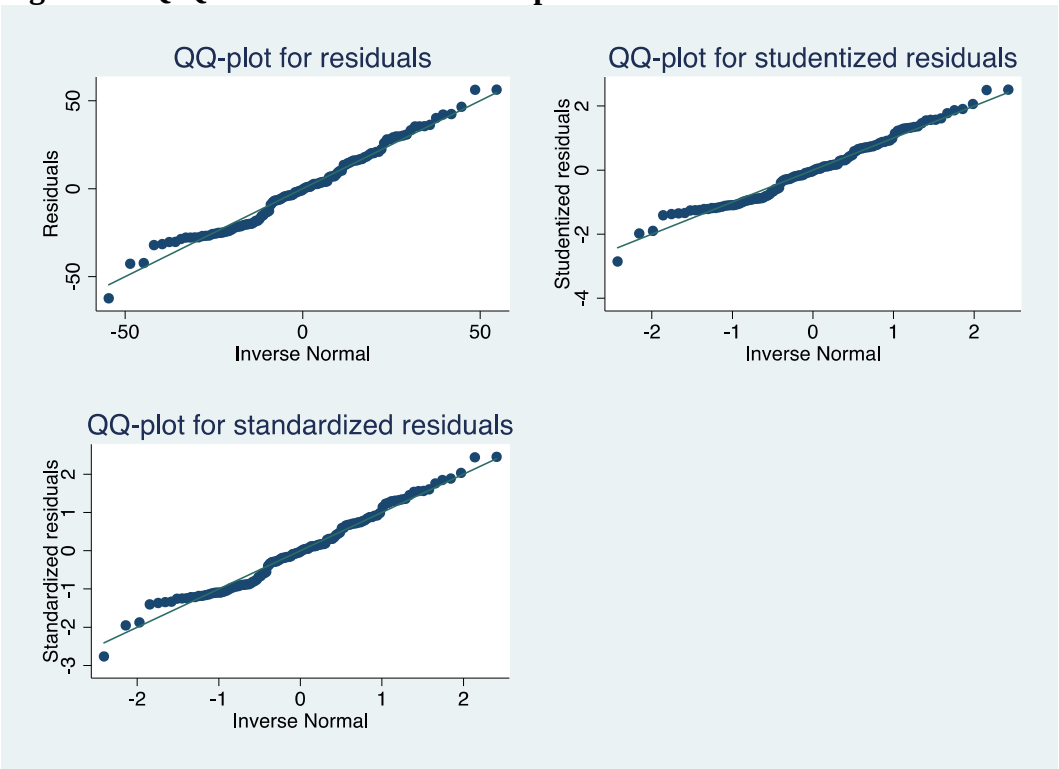


Figure 16. Residuals versus fitted values: satisfaction with anxiety control

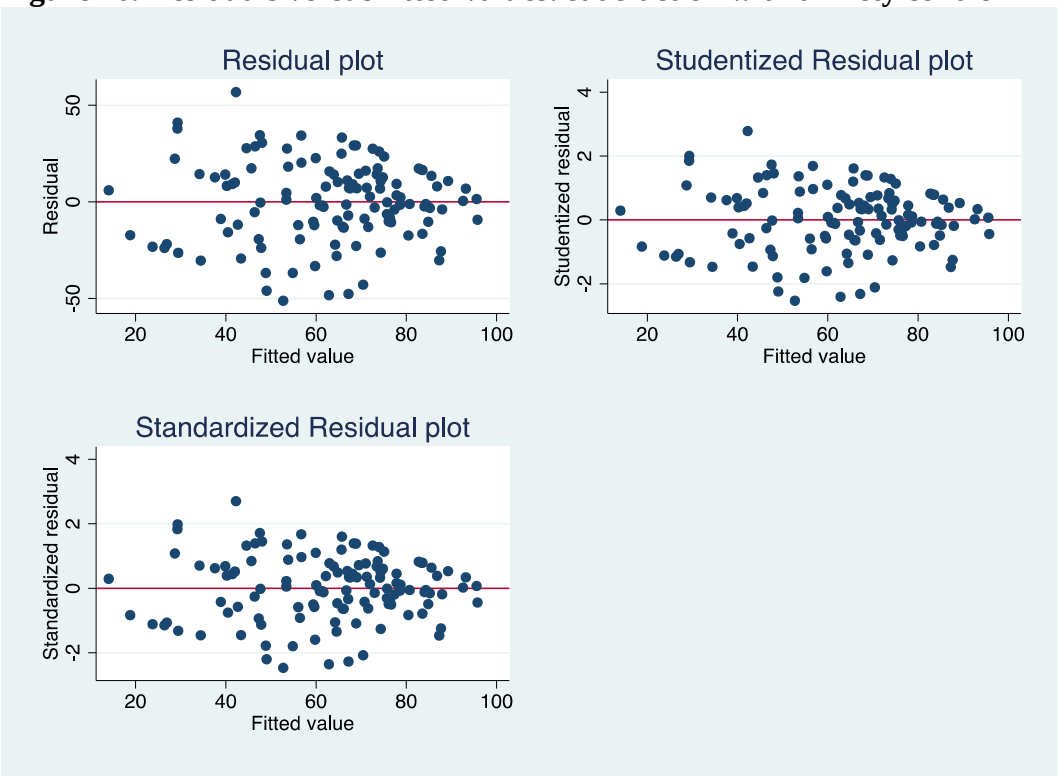


Figure 17. Q-Q Plots: satisfaction with anxiety control

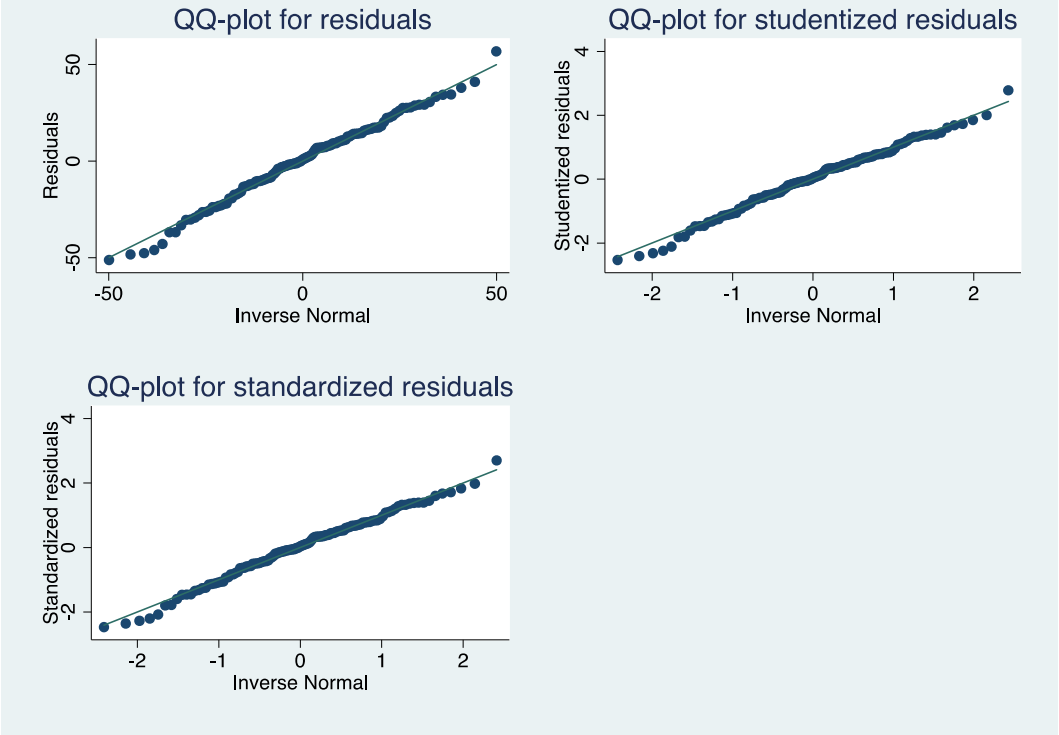


Table 1. Baseline characteristics

	Placebo (n=62)	**Midazolam (n=62)**	***P***
Patient age (years)*	25.8±5.3	25.5±5.8	0.80
Gestational age (weeks)*	8.2±1.6	7.9±1.5	0.21
Race+			0.44
White	44 (71.0)	42 (67.7)	
African American	3 (4.8)	6 (9.7)	
Asian	4 (6.5)	1 (1.6)	
More than one race or other	11 (17.7)	13 (21.1)	
Ethnicity#			0.79
Hispanic	9 (14.5)	8 (12.9)	
Parity#			0.28
Nulliparous	38 (61.3)	32 (51.6)	
Parous	24 (38.7)	30 (48.4)	
Previous vaginal deliveries (yes/no)#	20 (32.3)	22 (35.5)	0.70
Previous surgical abortion (yes/no)#	21 (33.9)	23 (37.1)	0.70
Level of menstrual symptoms#			0.07
Easy or mild cramping	30 (48.4)	40 (64.5)	
Requiring medication or unable to attend work	32 (51.6)	22 (35.5)	
Body mass index (kg/m^2)*	25.9±6.0	25.9±5.5	0.94
Self reported depression (yes/no)#	19 (30.6)	14 (22.6)	0.31
Self reported anxiety (yes/no)#	14 (22.6)	14 (22.6)	1.0
State Trait Anxiety Inventory (STAI)*			
State anxiety level	50.8±11.0	51.3±9.7	0.80
Trait anxiety level	40.1±10.8	38.6±9.7	0.40
High state anxiety (STAI state level >47)#	37 (59.7)	44 (71.0)	0.19
High trait anxiety (STAI trait level >46)#	15 (24.2)	11 (17.7)	0.38
Taken benzodiazepine before (yes/no)#	18 (29.0)	24 (39.3)	0.23
Education+~			0.88
High school	22 (36.1)	21 (36.8)	
University	38 (62.3)	34 (59.7)	
Post-graduate	1 (1.6)	2 (3.5)	

Values are mean ± standard deviation or n (%)
* Independent *t* test
# Pearson Chi-squared test
+ Fisher's Exact test
^ Mann-Whitney U test
~ Education data missing for five subjects in the midazolam group, one in placebo

Table 2. Procedural characteristics

	Placebo (n=62)	**Midazolam (n=62)**	***P***
Provider#			0.03
Obstetrician/Gynecologist	33 (53.2)	45 (72.6)	
Certified Nurse Midwife	29 (46.8)	17 (27.4)	
Procedure time (minutes)^	5.9 (3.4-10.8)	5.9 (2.8-20.9)	0.82
Use of manual vacuum aspirator#	30 (49.2)	41 (66.1)	0.06
Companion present (yes/no)#	31 (50)	25 (41)	0.32
Relationship of companion (n=31/25)+			0.61
Friend	6 (19.4)	5 (20)	
Partner/Husband	24 (77.4)	17 (68)	
Parent	1 (3.2)	2 (8)	
Sibling	0 (0)	1 (4)	
Adjunctive comfort measures+			
Music	1 (1.6)	5 (8.1)	0.21
Heating pad	59 (95.2)	59 (95.2)	1.0
Time from study drug administration to start of procedure (minutes)*	44.5±9.1	47.6±10.4	0.09
Time from ibuprofen administration to start of procedure (minutes)*	115.9±30.6	122.0±27.4	0.24
Ondansetron premedication#	31 (50)	25 (40.3)	0.28
Provider ease of procedure^	10.9 (0-61)	10 (0-81)	0.46
Post-abortal IUD (yes/no)#	11 (17.7)	14 (22.6)	0.50
Uterine position#			0.34
Anteverted	47 (79.7)	47 (77.1)	
Midposition	2 (3.4)	6 (9.8)	
Retroverted	10 (17.0)	8 (13.1)	
Pain during uterine aspiration^			0.17
Mild (VAS ≤30 mm)	2 (3.3)	5 (8.1)	
Moderate (VAS 31-69 mm)	16 (26.2)	20 (32.3)	
Severe (VAS ≥70 mm)	43 (70.5)	37 (59.7)	
Adverse events+			1.0
Uterine perforation	0 (0)	0 (0)	
Reaspiration	2 (3.2)	1 (1.6)	
Cervical laceration	0 (0)	1 (1.6)	
Hemorrhage	0 (0)	1 (1.6)	

Values are n (%), mean ± standard deviation, or median (range) for non-normally distributed data
* Independent *t* test
+ Fisher's Exact test
# Pearson Chi-squared test
^ Mann-Whitney U Test

Table 3. Summary of Visual Analog Scale scores

	Placebo (n=62)	Midazolam (n=62)	*P*
Preoperative VAS scores (prior to premedication)			
Baseline anxiety	58.8±19.4 62.5 (9.9-96.0)	60.9±18.5 65 (11.4-95.0)	0.53* 0.56^
Anxious about procedure	66.5±19.9 70.5 (5.9-96.0)	66.3±20.5 69.2 (7.0-99.5)	0.94* 0.87^
Expected anxiety during procedure	77.5±20.6 83.8 (16.8-100)	74.2±20.1 80.3 (20.8-100)	0.37* 0.29^
Baseline pain	13.4±17.8 7 (0-86.0)	9.0±13.6 2.5 (0-65.0)	0.13* 0.11^
Expected pain during procedure	67.2±19.7 68.8 (12.9-100)	69.2±17.8 68.7 (19.5-100)	0.54* 0.57^
Baseline nausea	30.8±27.0 24.3 (0-91.0)	34.7±27.5 34.2 (0-100)	0.42* 0.40^
Baseline sleepiness	35.0±25.8 31.9 (0-91.0)	32.2±28.5 22.7 (0-100)	0.57* 0.46^
Desired memory of procedure	27.0±27.9 17.7 (0-95.0)	22.0±26.6 8.3 (0-100)	0.31* 0.19^
Intraoperative VAS anxiety scores+ (n=61/62)			
Room entry	51.4±25.4 51.7 (0.5-98.0)	34.5±22.9 30.7 (3.0-93.0)	0.0002* 0.0003^
Positioning	56.6±26.4 59.4 (0-98.5)	45.4±26.3 52.6 (1.0-97.0)	0.02* 0.02^
Aspiration	68.2±28.1 74.8 (0.5-100)	60.9±27.3 65.1 (0-100)	0.14* 0.08^
Intraoperative VAS pain scores+ (n=61/62)			
Room entry	17.5±21.1 9 (0-77.0)	10.1±15.4 3 (0-76.0)	0.03* 0.06^
Dilation	73.0±21.2 75.2 (0-100)	69.3±19.9 70.6 (7.0-100)	0.32* 0.19^
Aspiration	74.3±20.6 78 (8.0-100)	70.1±22.1 75.4 (2.5-100)	0.28* 0.25^
30 minutes postoperative VAS scores+ (n=61/61)			
Anxiety	22.9±22.6 14.9 (0-82.0)	14.4±13.5 12 (0-51.0)	0.01* 0.10^
Pain	34.7±23.3 36 (0-98.0)	37.1±24.6 38 (0-97.0)	0.58* 0.57^
Nausea	19.1±22.1 9.5 (0-80.0)	14.4±14.7 3.5 (0-71.0)	0.007* 0.02^
Sleepiness	40.1±29.3 39.5 (0-100)	56.6±24.6 60.7 (0-100)	0.001* 0.001^
Memory score	91.6±11.7 97 (43.0-100)	73.4±27.4 82 (7.0-100)	<0.0001* <0.0001^
Satisfaction with anxiety control	56.1±29.6 57.0 (0.5-100)	68.9±24.7 75 (11.0-100)	0.01* 0.01^

Satisfaction with pain control	43.2±30.7 40.2 (0-100)	50.0±27.3 52.5 (0-100)	0.20* 0.16^
Overall satisfaction	77.8±18.3 80.0 (32.0-100)	78.4±20.1 82.5 (8.3-100)	0.88* 0.65^
1-3 day postoperative VAS scores+ (n=41/44)			
Memory score	91.5±12.8 97.5 (34.7-100)	61.3±25.8 62.3 (8.9-100)	<0.0001* <0.0001^
Satisfaction with anxiety control	50.2±31.7 54.0 (1.0-100)	64.7±28.2 67.5 (1.0-100)	0.03* 0.03^
Satisfaction with pain control	36.6±30.8 31.0 (0.5-100)	48.2±30.1 47.4 (0-100)	0.08* 0.07^
Overall satisfaction	65.7±26.4 72.8 (1.5-100)	74.9±25.5 79.8 (0.5-100)	0.11* 0.05^

+ Some data points missing, data analyzed with intention to treat approach
Reported mean ± standard deviation and median (range)
* Independent *t* test
^ Mann-Whitney U Test

Table 4. GEE Model for Pain

Covariate		95% CI	*P*
Treatment group (Midazolam = 1)	-4.33	-9.88,1.23	0.13
Time 1 (room entry)	4.13	0.02, 8.25	0.05
Time 2 (dilation)	59.59	53.61, 65.57	<0.0001
Time 3 (aspiration)	60.90	54.34, 67.46	<0.0001
Time 4 (postoperative)	21.30	14.87, 27.72	<0.0001
Interaction terms:			
Treat x Time 1 (room entry)	-3.04	-8.74, 2.67	0.30
Treat x Time 2 (start of procedure)	0.63	-4.50, 8.75	0.88
Treat x Time 3 (aspiration)	0.12	-8.85, 9.09	0.98
Treat x Time 4 (postoperative)	6.24	-2.31, 16.00	0.14

Table 5. GEE Model for Anxiety

Covariate		95% CI	*P*
Treatment group (Midazolam = 1)	2.15	-4.49, 8.79	0.53
Time 1 (room entry)	-7.22	-11.65, -2.79	0.001
Time 2 (start of procedure)	-2.06	-7.39, 3.26	0.45
Time 3 (aspiration)	9.50	1.70, 17.30	0.02
Time 4 (postoperative)	-35.81	-42.19, -29.42	<0.0001
Interaction terms:			
Treat x Time 1 (room entry)	-19.24	-26.55, -11.92	<0.0001
Treat x Time 2 (start of procedure)	-13.42	-22.12, -4.69	0.003
Treat x Time 3 (aspiration)	-9.57	-20.42, 1.27	0.08
Treat x Time 4 (postoperative)	-10.81	-19.28, -2.34	0.01

Table 6. Postoperative characteristics

	Placebo (n=62)	Midazolam (n=62)	*P*
30 minutes postoperatively			
Side effect (n=60/61)			
Dizziness*	18 (29.5)	30 (49.2)	0.03
Hiccupping+	1 (1.6)	7 (11.5)	0.06
Vomiting+	1 (1.6)	1 (1.6)	1.0
Additional postoperative medications (n=61/61)+			0.76
Ondansetron	2 (3.3)	3 (4.9)	
Hydrocodone/acetaminophen	1 (1.6)	2 (3.3)	
Amnesia score (n=61/61)#			0.005
Partial to complete amnesia (score 0, 1, 2)	16 (26.2)	31 (50.8)	
No amnesia	45 (73.8)	30 (49.2)	
Unpleasant memories (yes/no; n=61/61)#	40 (65.6)	35 (57.4)	0.35
Detail of unpleasant memory (n=40/35)+			0.38
Noise of suction	2 (5)	2 (5.7)	
Pain	30 (75)	28 (80)	
Emotional (sad, scared)	0 (0)	1 (2.9)	
Unspecified	8 (20)	4 (11.2)	
Provider correct identification of study group (n=62/61)#	43 (69.4)	36 (59.0)	0.23
Subject correct identification of study group (n=60/61)#	43 (71.7)	48 (78.7)	0.37
Recommend to a friend (n=60/61)*			0.02
Yes	37 (61.7)	49 (80.3)	
No or uncertain	23 (38.3)	12 (19.7)	
1-3 days postoperatively (n=41/44)			
Follow-up survey complete (yes/no)#	41 (66.1)	44 (71.0)	0.56
Postoperative day follow-up survey completed (n=38/43)*	2.4±2.4 (range 0 to 15)	2.3±1.7 (range 0 to 9)	0.85
Unpleasant memories (1-3 days postop; yes/no)#	30 (73.2)	25 (56.8)	0.12
Detail of unpleasant memory (1-3 days postop)+			0.38
Noise of suction	1 (2.4)	3 (6.8)	
Pain	23 (56.1)	20 (45.5)	
Emotional (sad, scared)	3 (7.3)	1 (2.3)	
Unspecified	3 (7.3)	1 (2.3)	
Recommend to a friend (n=40/44)#			0.22
Yes	24 (60.0)	32 (72.7)	
No or uncertain	16 (40.0)	12 (27.3)	

Values are n (%) or mean ± standard deviation
* Independent *t* test
+ Fisher's Exact test
# Pearson Chi-squared test
^ Mann-Whitney U Test

Table 7. Vital signs and sedation

	Placebo (n=62)	**Midazolam (n=62)**	***P***
Baseline vital signs*			
Heart rate	75.4±10.4	77.2±12.2	0.36
O2 saturation (%)	97.7±0.9	97.7±0.8	0.91
Systolic BP	110.5±9.5	112.2±12.1	0.41
Diastolic BP	72.7±7.8	72.4±9.1	0.84
Baseline sedation (Ramsay Sedation Scale)^			0.63
1	9 (14.5)	11 (17.7)	
2	53 (85.5)	51 (82.3)	
>/=3	0 (0)	0 (0)	
Immediate pre-op vital signs*			
Heart rate	78.2±12.0	78.8±12.9	0.80
O2 saturation (%)	97.7±1.3	97.7±1.5	0.92
Immediate post-op vital signs			
Heart rate^	80 (53-126)	78.5 (50-137)	0.72
O2 saturation (%)*	98.3±1.2	98.1±1.0	0.54
Systolic BP*	111.2±11.9	113.0±9.6	0.36
Diastolic BP*	71.8±10.6	69.9±8.2	0.28
Maximum procedural sedation (Ramsay Sedation Scale)^			0.75
1	12 (19.4)	10 (16.1)	
2	50 (89.7)	51 (82.3)	
3	0 (0)	1 (1.6)	
>/=4	0 (0)	0 (0)	
30 min postoperative vital signs*			
Heart rate	70.1±12.4	72±11.8	0.22
O2 saturation (%)	97.9±1.3	97.8±1.4	0.83
Systolic BP	115.1±9.9	115.3±11.0	0.92
Diastolic BP	74.1±10.3	72.6±11.8	0.44
30 min postoperative sedation (Ramsay Sedation Scale; N=60/59)^			0.75
1	5 (8.3)	4 (6.8)	
2	55 (91.7)	55 (93.2)	
>/=3	0 (0)	0 (0)	

Values are n (%), mean ± standard deviation, or median (range) for non-normally distributed data
* Independent *t* test
^ Mann-Whitney U Test

Table 8. Satisfaction with Pain Control: Univariate Linear Regression Analysis

8a. 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*
Gestational age			
Early (6 to 8 weeks)	Reference		
Late (8 weeks to 10 weeks 6 days)	-14.56	-24.82, -4.3	0.006
Race			
White/Caucasian	Reference		
Other	-1.94	-13.26, 9.38	0.74
Hispanic			
No	Reference		
Yes	-10.03	-25.05, 4.99	0.19
Parity			
Nulliparous	Reference		
Parous	-10.02	-20.51, 0.47	0.06
Prior vaginal delivery			
No	Reference		
Yes	-11.50	-22.41, -0.60	0.04
Prior surgical abortion			
No	Reference		
Yes	-9.99	-20.82, 0.85	0.07
Level of menstrual symptoms			
Easy or mild cramping	Reference		
Requiring medication or unable to attend work	-2.66	-13.22, 7.91	0.62
Self reported depression			
No	Reference		
Yes	-0.45	-12.36, 11.47	0.94
Self reported anxiety			
No	Reference		
Yes	0.12	-12.50, 12.75	0.99
High trait anxiety (STAI trait level >46)			
No	Reference		
Yes	-4.56	-17.52, 8.39	0.49
High state anxiety (STAI state level >47)			
No	Reference		
Yes	-13.47	-24.24, -2.70	0.02
Prior use of benzodiazepine			
No	Reference		
Yes	-0.48	-11.72, 10.77	0.93
Education			
High school	Reference		
University or Post-graduate	2.42	-8.61, 13.45	0.67
Provider			
Obstetrician/Gynecologist	Reference		
Certified Nurse Midwife	2.35	-8.57, 13.27	0.67
Aspirator type			
Manual vacuum aspirator	Reference		

Electric vacuum aspirator	-17.52	-27.71, -7.33	0.001
Postabortal IUD			
No	Reference		
Yes	-8.87	-21.96, 4.21	0.18
Companion present			
No	Reference		
Yes	-14.96	-25.24, -4.68	0.005
Study group			
Placebo	Reference		
Midazolam	6.79	-3.65, 17.23	0.20
Subject belief about study group			
Placebo	Reference		
Midazolam	12.01	1.76, 22.26	0.02
Unpleasant memories			
No	Reference		
Yes	-28.07	-27.63, -18.52	<0.0001
Recall of postmedication picture images			
2-3 out of 3 images	Reference		
0-1 out of 3 images	1.59	-8.97, 12.14	0.77
Amnesia score			
No amnesia	Reference		
Partial to complete amnesia (score 0, 1, 2)	18.72	8.44, 20.00	<0.0001
CI, confidence interval			

8b. Regression coefficients for satisfaction with pain control by subject and procedural characteristics

Characteristic	**Beta Coefficient**	**95% CI**	***P***
Age (y)	-0.29	-1.23, 0.66	0.55
Gestational age (wk)	-4.15	-7.46, -0.83	0.02
Body mass index (kg/m^2)	-0.65	-1.56, 0.27	0.16
Weight (pounds)	-0.08	-0.23, 0.07	0.28
STAI - State anxiety level	-0.64	-1.14, -0.14	0.01
STAI - Trait anxiety level	-0.25	-0.77, 0.27	0.34
Preoperative VAS scores			
Anxious about procedure	-0.27	-0.53, -0.01	0.04
Expected anxiety during procedure	-0.18	-0.43, 0.08	0.18
Baseline anxiety	-0.22	-0.49, 0.06	0.12
Expected pain during procedure	-0.04	-0.32, 0.24	0.77
Baseline pain	-0.19	-0.51, 0.14	0.27
Procedure time (minutes)	-1.25	-3.58, 1.08	0.29
Provider ease of procedure (VAS)	-0.23	-0.55, 0.08	0.15
Intraoperative VAS scores			
Anxiety at room entry	-0.32	-0.52, -0.12	0.002
Anxiety with positioning	-0.32	-0.50, -0.13	0.001
Anxiety during aspiration	-0.37	0.55, -0.19	<0.0001
Pain at room entry	-0.23	-0.50, 0.05	0.11
Pain during dilation	-0.60	-0.83, -0.36	<0.0001
Pain during aspiration	-0.68	-0.89, -0.47	<0.0001

30 min postoperative VAS scores			
Anxiety	-0.43	-0.69, -0.16	0.002
Pain	-0.40	-0.61, -0.19	<0.0001
Memory score	-0.15	-0.38, 0.08	0.19
Nausea	-0.15	-0.42, 0.12	0.27
Sleepiness	0.13	-0.06, 0.31	0.17
CI, confidence interval; VAS, visual analogue scale			

Table 9. Satisfaction with Anxiety Control: Univariate Linear Regression Analysis

9a. Differences in mean VAS scores for satisfaction with anxiety control by dichotomous or categorical subject and procedural characteristics

Characteristic	**Δ VAS (mm)**	**95% CI**	***P***
Gestational age			
Early (6 to 8 weeks)	Reference		
Late (8 weeks to 10 weeks 6 days)	-7.05	-17.10, 2.99	0.17
Race			
White/Caucasian	Reference		
Other	3.76	7.08, 14.59	0.49
Hispanic			
No	Reference		
Yes	-7.91	-22.36, 6.53	0.28
Gravidity			
Nulligravid	Reference		
Gravid	-4.57	-14.96, 5.82	0.39
Parity			
Nulliparous	Reference		
Parous	-4.78	-14.91, 5.35	0.35
Prior vaginal delivery			
No	Reference		
Yes	-7.62	-18.17, 2.94	0.16
Prior surgical abortion			
No	Reference		
Yes	-12.99	-23.25, -2.70	0.01
Level of menstrual symptoms			
Easy or mild cramping	Reference		
Requiring medication or unable to attend work	-5.71	-15.79, 4.36	0.26
Self reported depression			
No	Reference		
Yes	3.75	-7.66, 15.16	0.52
Self reported anxiety			
No	Reference		
Yes	4.86	-7.22, 16.94	0.43
High trait anxiety (STAI trait level >46)			
No	Reference		
Yes	0.88	-11.58, 13.33	0.89
High state anxiety (STAI state level >47)			
No	Reference		
Yes	-12.20	-22.49, -1.91	0.02
Prior use of benzodiazepine			
No	Reference		
Yes	-0.43	-11.13, 10.27	0.94
Education			
High school	Reference		
University or Post-graduate	-3.97	-14.56, 6.61	0.46
Provider			

Obstetrician/Gynecologist	Reference		
Certified Nurse Midwife	-4.72	-15.16, 5.71	0.37
Aspirator type			
Manual vacuum aspirator	Reference		
Electric vacuum aspirator	-8.54	-18.62, 1.54	0.10
Postabortal IUD			
No	Reference		
Yes	1.06	-11.59, 13.71	0.87
Companion present			
No	Reference		
Yes	-14.36	-24.04, -4.68	0.004
Study group			
Placebo	Reference		
Midazolam	12.81	3.03, 22.60	0.01
Subject belief about study group			
Placebo	Reference		
Midazolam	20.23	10.83, 29.63	<0.0001
Unpleasant memories			
No	Reference		
Yes	-10.19	-20.36, -0.03	0.05
Recall of postmedication picture images			
2-3 out of 3 images	Reference		
0-1 out of 3 images	6.98	-3.05, 17.00	0.17
Amnesia score			
No amnesia	Reference		
Partial to complete amnesia (score 0, 1, 2)	14.88	4.90, 24.85	0.004
CI, confidence interval			

9b. Regression coefficients for satisfaction with anxiety control by subject and procedural characteristics

Characteristic	**Beta Coefficient**	**95% CI**	***P***
Age (y)	-0.76	-1.66, 0.13	0.10
Gestational age (wk)	-2.37	-5.61, 0.86	0.15
Body mass index (kg/m^2)	-0.10	-0.99, 0.78	0.82
Weight (pounds)	-0.02	-0.17, 0.12	0.75
STAI - State anxiety level	-0.51	-0.10, -0.03	0.04
STAI - Trait anxiety level	0.05	-0.45, 0.54	0.85
Preoperative VAS Scores			
Anxious about procedure	-0.24	-0.49, 0.01	0.06
Expected anxiety during procedure	-0.19	-0.44, 0.05	0.12
Baseline anxiety	-0.26	-0.52, 0.00	0.05
Expected pain during procedure	-0.16	-0.42, 0.11	0.25
Baseline pain	-0.25	-0.56, 0.07	0.12
Procedure time (minutes)	0.11	-2.16, 2.37	0.93
Provider ease of procedure (VAS)	-0.19	-0.49, 0.12	0.22
Intraoperative VAS Scores			
Anxiety at room entry	-0.42	-0.60, -0.24	<0.001
Anxiety with positioning	-0.38	-0.55, -0.20	<0.001

Anxiety during aspiration	-0.36	-0.53, -0.19	<0.001
Pain at room entry	-0.25	-0.51, 0.02	0.07
Pain during dilation	-0.41	-0.64, -0.17	0.001
Pain during aspiration	-0.45	-0.67, -0.23	<0.0001
30 min postoperative VAS scores			
Anxiety	-0.65	-0.89, -0.42	<0.0001
Pain	-0.33	-0.53, -0.12	0.002
Memory score	-0.29	-0.51, -0.08	0.01
Nausea	-0.31	-0.57, -0.06	0.02
Sleepiness	0.23	0.06, 0.41	0.009
CI, confidence interval; VAS, visual analogue scale			

Table 10. Multivariable linear regression: satisfaction with pain control

Characteristic		**95% CI**	***P***
Study group			0.04
Placebo	Reference		
Midazolam	47.15	1.82, 92.49	
Gestational Age (weeks)	-0.31	-4.04, 3.43	0.87
Interaction term (Gestational Age * Treat)	-6.14	-11.76, -0.53	0.03
6 weeks gestational age:			
Placebo	Reference		
Midazolam	10.31		
9 weeks gestational age:			
Placebo	Reference		
Midazolam	-8.15		
10 6/7 weeks gestational age:			
Placebo	Reference		
Midazolam	-19.56		
Pain during aspiration (VAS)	-0.63	-0.83, 0.43	<0.0001
Amnesia score			0.01
No amnesia	Reference		
Partial to complete amnesia (score 0, 1, 2)	11.93	2.61, 21.25	
Companion Present			0.03
No	Reference		
Yes	-9.70	-18.36, -1.04	
CI, confidence interval; VAS, visual analogue scale			

Table 11. Multivariable linear regression: satisfaction with anxiety control

Characteristic		**95% CI**	***P***
Study group			0.006
Placebo	Reference		
Midazolam	59.90	17.37, 102.43	
Gestational age (weeks)	1.35	-2.10, 4.81	0.44
Interaction term (Gestational Age * Treat):	-7.48	-12.69, -2.27	0.005
6 weeks gestational age:			
Placebo	Reference		
Midazolam	15.04		
9 weeks gestational age:			
Placebo	Reference		
Midazolam	-7.42		
10 6/7 weeks gestational age:			
Placebo	Reference		
Midazolam	-21.31		
Anxiety postoperatively (VAS)	-0.50	-0.72, -0.29	<0.0001
Anxiety during aspiration (VAS)	-0.29	-0.43, -0.14	<0.0001
Subject belief about study group			
Placebo	Reference		
Midazolam	11.78	2.38, 21.18	0.01
Companion Present			
No	Reference		
Yes	-9.17	-17.10, -1.25	0.02
CI, confidence interval; VAS, visual analogue scale			