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Contents: Abortion: Original Research

Nitrous Oxide Compared With Intravenous Sedation for Second-Trimester Abortion

A Randomized Controlled Trial

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OBJECTIVE:

To assess whether inhaled nitrous oxide is noninferior to intravenous (IV) sedation for pain control during outpatient surgical abortion between 12 and 16 weeks of gestation.

METHODS:

We enrolled women undergoing surgical abortion at 12–16 weeks of gestation into a multisite, double-blind clinical trial. Participants were randomized to sedation with nitrous oxide (70% nitrous/30% oxygen) or IV fentanyl (100 micrograms) and midazolam (2 mg). Paracervical block was administered to both groups. The primary outcome measure was immediate postabortion recall of maximum pain on a 100-mm visual analog scale.

RESULTS:

Between August 2016 and March 2017, we assessed 170 women for eligibility and enrolled 39, 19 in the nitrous group and 20 in the IV sedation group. Seven participants in the nitrous group (36.8%) required conversion to IV sedation for

inadequate pain control. No participants in the IV sedation group required additional medication. The proportion of women requiring additional pain control in the nitrous group exceeded our predefined stopping rule. Intention-to-treat analysis demonstrated that immediate postabortion visual analog scale pain scores were lower by 20.1 mm (95% CI 1.6–38.6) in women randomized to IV sedation than in women randomized to nitrous.

CONCLUSION:

Intravenous sedation is a better choice than inhaled nitrous oxide for pain control in second-trimester abortion.

CLINICAL TRIAL REGISTRATION:

ClinicalTrials.gov, NCT02755090.

Pain management is an important component of patient-centered abortion care. Of the estimated 926,200 abortions that occur annually in the United States, 96% occur in an office setting with limited analgesia options.[1] Second-trimester abortion is painful and commonly performed with use of intravenous (IV) sedation with midazolam and fentanyl.[2] Women receiving IV sedation are advised not to drive after their procedure,[3] a potentially burdensome requirement for those traveling long distances and who need or desire to maintain privacy. Furthermore, many women who have second-trimester abortions are mothers and may need to manage child care on the day of an abortion.[4] The ideal anesthetic for second-trimester abortion would effectively control procedural pain, maintain patient safety, be easily administered, and have rapid onset and clearance.

Nitrous oxide sedation offers analgesia, anxiolysis, and amnesia; has immediate onset of action; and dissipates rapidly.[5–7] Its safety and efficacy have been established for dentistry, emergency department procedures, and vaginal delivery.[8,9] Few studies have examined nitrous oxide for sedation in outpatient gynecologic procedures. Prior research has not demonstrated pain reduction compared with air in first-trimester abortion when using nitrous oxide as an adjuvant treatment at lower concentrations (50% nitrous/50% oxygen).[10,11] However, one prior study evaluated nitrous oxide at an increased titration schedule (70% nitrous/30% oxygen) compared with oral sedation for first-trimester surgical abortion and found similar mean pain scores. Secondary outcomes included satisfaction with anesthesia; both groups demonstrated high satisfaction scores.[12] Nitrous oxide is superior to oral sedation for transcervical sterilization procedures.[13]

In this multisite, double-blind, randomized clinical trial, we investigated whether nitrous oxide was noninferior to IV sedation for pain management in surgical abortion between 12 and 16 weeks of gestation. Our primary outcome was the difference between groups in maximum pain immediately postabortion as measured on a visual analog scale (VAS). We hypothesized that VAS pain scores of participants receiving nitrous oxide would be noninferior to those of participants receiving IV sedation.

MATERIALS AND METHODS

From August 2016 to March 2017, eligible women were recruited from the University of New Mexico and the University of Colorado reproductive health clinics. Both clinics are university-based practices with a focus on complex contraception and abortion care and are sites of training for obstetrics and gynecology family planning fellows.

Eligible women were older than age 18 years, between 12 and 16 weeks of gestation by ultrasound dating, had requested and consented to a uterine aspiration procedure, were English- or Spanish-speaking, and had postoperative transportation. Exclusion criteria were clinical contraindications to outpatient abortion such as invasive placentation or significant medical comorbidities or contraindications to nitrous oxide such as active upper respiratory tract infection, chronic obstructive pulmonary disease, pernicious anemia, and current treatment with bleomycin chemotherapy. Additional exclusion criteria were chronic narcotic use, prior adverse reactions to any of the study drugs, or intrauterine

fetal demise, because women with fetal demise may experience pain differently than women undergoing uterine aspiration for other indications. We created a block randomization scheme stratified by gestational age in weeks with a block size of six using Microsoft Excel's RAND function.

After women decided on outpatient abortion and gave written informed consent for the procedure, research staff approached and offered study participation to eligible women. Participants provided informed consent for the trial. Participants scored their baseline pain before their procedure ("baseline pain") as well as the maximum amount of pain they expected to experience during the procedure ("expected pain"). Cervical preparation occurred at the treating physician's discretion and included intracervical dilators, misoprostol, or both. Participants may have received pain medications or a paracervical block with cervical preparation at the discretion of the physician. Participants received 600 mg ibuprofen, an IV, and a scented face mask worn for the duration of the procedure. Participants were randomly assigned to IV sedation or nitrous oxide just before the abortion procedure. The anesthesia provider opened the appropriate opaque envelope to determine the allocation, which was hidden from the patient and physician. Participants were positioned for the procedure and the unblinded anesthesia provider administered the allocated study medications at least 2 minutes before starting the procedure. The IV sedation group received 100 micrograms of fentanyl and 2 mg midazolam IV and 100% oxygen through a face mask; the nitrous group received IV saline and inhaled nitrous oxide, titrated to 70% nitrous oxide/30% oxygen through a face mask. All participants received a standardized paracervical block of 20 mL of buffered lidocaine with 1–2 mL injected at the tenaculum site and 18 mL divided between the 4 and 8 o'clock positions at the cervicovaginal junction.[14] If, in the opinion of the participant and confirmed by the physician, a participant needed further pain medication during the procedure, those in the IV sedation group received additional IV sedation medications (50 micrograms of fentanyl or 1 mg midazolam) and those in the nitrous oxide group received 100 micrograms of fentanyl and 2 mg midazolam IV after discontinuation of the nitrous oxide. In the event of oversedation, as defined by meeting criteria for deep sedation or greater,[15] all members of the team were unblinded and appropriate resuscitative measures initiated.

The abortion technique followed the clinical standard of care and was not altered for the study. Immediately after the procedure and while still receiving the allocated medication, participants rated their maximum pain on the VAS. The VAS is a 100-mm linear scale with anchors at 0 mm reflecting "no pain" and 100 mm reflecting "pain as bad as it could be." Participants were monitored until they achieved an Aldrete score of 8 or greater, indicating recovery from sedation.[16] At 30 minutes postprocedure, participants completed another VAS, recalling maximum pain during the abortion procedure. To maintain blinding, all procedural data were entered into a REDCap database[17] by study coordinators; medication information was entered separately by the anesthesia provider (Colorado) or research pharmacy (New Mexico).

We calculated sample size based on a prior study showing a median pain score of 70 mm.[18] Using a one-sided, two-group test of noninferiority, we determined that a sample size of 76 participants with 38 per treatment group could detect a noninferiority margin of 15 mm with 90% power and type 1 error of 5%.

We convened a data safety monitoring board of three external reviewers. Prior clinical data from the University of Colorado demonstrated that 24±7% (95% CI) of patients undergoing early second-trimester abortion who used IV sedation for pain management required additional IV medication for inadequate pain control. Inadequate pain control was determined by the need for more pain medications as articulated by the participant, in conjunction with the judgment of the physician, as would be the case in usual clinical care. Based on this percentage, we decided that the data safety monitoring board would halt the study and conduct a full data and safety review if more than 35% of women in either group required additional pain medication. If this stopping rule were met, we planned an analysis of participants recruited to that point based on the assumption that pain scores would be significantly different compared with women who did not require additional pain medication.

We computed descriptive statistics and tests of normality for participant characteristics; we used Wilcoxon rank-sum tests to compare nonnormally distributed continuous data and Pearson χ^2 tests for categorical variables. Both intention-to-treat and per-protocol analyses were performed, with per-protocol analyses reported only if findings were

different from intention-to-treat.[19,20] Participants requiring additional pain medication were then considered as a separate group and median pain scores were analyzed by one-way Kruskal-Wallis test. Sample size calculation was performed and data were analyzed using STATA/SE 14.1. The institutional review boards at the University of New Mexico Health Sciences Center and the University of Colorado School of Medicine approved the study.

RESULTS

Of 170 participants assessed for eligibility, 39 were enrolled, 19 in the nitrous group and 20 in the IV sedation group (Fig. 1). One participant in the nitrous group did not receive her allocated intervention as a result of equipment failure. Seven women required additional pain medication as determined by the patient and the physician and underwent conversion to IV sedation, per protocol. These seven women represented a diversity of recruitment sites and physicians performing their procedures: four women were recruited from Colorado and both fellows and attendings were represented among the physician types. All seven women requiring additional pain medication were in the nitrous group; no women in the IV sedation group required additional pain medication. This proportion (36.8%) exceeded our prespecified stopping rule of 35%. Enrollment was halted by the data safety monitoring board and data were analyzed.

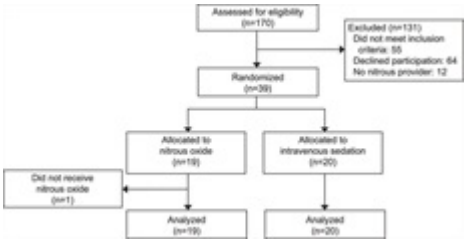

Fig. 1.:
Study flow diagram.*Thaxton. Nitrous Oxide vs IV Sedation for Second-Trimester Abortion. Obstet Gynecol 2018.*

Baseline participant demographic and procedural characteristics were similar between the two study groups (Tables 1 and 2). The median age of the cohort was 26 years (range 18–42 years), and just more than half of women were parous. Participants were diverse in ethnicity, consistent with the population of the two study sites, and were recruited evenly from both locations. All procedures were performed by an attending physician (either obstetrics and gynecology or family medicine) or a family planning fellow. Most procedures required cervical preparation with misoprostol, osmotic dilators, or both and most were completed on the same day as the cervical preparation (Table 2).

Characteristic	Nitrous Oxide (n=19)	IV Sedation (n=20)
Age (y)	27 (19–40)	26 (18–42)
History of		
Vaginal delivery	10 (52.6)	11 (55.0)
Cesarean delivery	6 (31.6)	2 (10.0)
Abortion	7 (36.8)	5 (25.0)
Miscarriage	5 (26.3)	8 (40.0)
Stillbirth	1 (5.3)	0 (0.0)
Nulliparous	3 (26.3)	8 (40.0)
Hispanic ethnicity	10 (52.6)	9 (45.0)
Race		
White	8 (47.4)	8 (40.0)
Black	4 (21.1)	0 (0.0)
Native American or Alaska Native	1 (5.3)	3 (15.0)
Other including mixed	6 (26.3)	9 (45.0)
Education		
High school or equivalent	8 (42.1)	8 (40.0)
More than high school	8 (42.1)	9 (45.0)
Bachelor's or graduate degree	3 (15.8)	2 (15.0)
Gestational age (wk)		
12	8 (42.1)	8 (40.0)
13	3 (15.8)	4 (20.0)
14	5 (26.3)	5 (25.0)
15	3 (15.8)	3 (15.0)

IV, intravenous.
Data are median (range) or n (%).

Table 1.:
Baseline Participant Characteristics

Characteristic	Nitrous Oxide (n=19)	IV Sedation (n=20)
Health care provider		
Obstetrician–gynecologist attending	7 (36.8)	10 (50.0)
Family practice attending	1 (5.3)	1 (5.0)
Family planning fellow	11 (57.9)	9 (45.0)
Location		
New Mexico	11 (57.9)	12 (60.0)
Colorado	8 (42.1)	8 (40.0)
Cervical preparation		
Misoprostol	15 (78.9)	13 (65.0)
Osmotic dilators	5 (26.3)	8 (40.0)
1-d preparation	16 (84.2)	14 (80.0)

IV, intravenous.
Data are median (range) or n (%).

Table 2.:
Procedure Information

In intention-to-treat analysis, immediate VAS pain scores were significantly lower among women randomized to IV sedation by 20.1 mm (95% CI 1.6–38.6) (Fig. 2). Although our a priori sample size was not met, this difference in pain scores represents inferiority of nitrous sedation.[19] In per-protocol analysis, this effect was no longer significant. To evaluate pain scores of women converted from nitrous to IV sedation, the groups were divided into three categories: IV sedation, nitrous sedation, and initial nitrous converted to IV sedation. Immediate postabortion median and first and third quartile VAS pain scores were 29 mm (range 16–49), 30 mm (range 15–78), and 67 mm (range 60–75), respectively (P<.05) (Fig. 3).

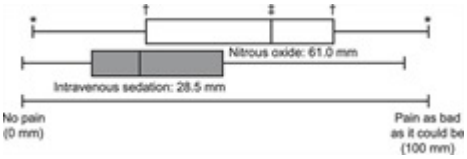

Fig. 2.:
Median maximum procedural pain as measured on the visual analog scale by intention-to-treat groups (P=.03). *Minimum and maximum; †interquartile range; ‡median.*Thaxton. Nitrous Oxide vs IV Sedation for Second-Trimester Abortion. Obstet Gynecol 2018.*

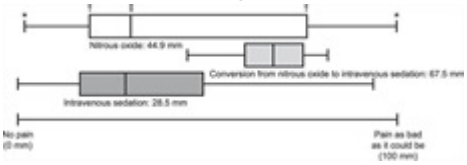

Fig. 3.:
Median maximum procedural pain as measured on the visual analog scale by groups (P=.004). *Minimum and maximum; †interquartile range; ‡median.*Thaxton. Nitrous Oxide vs IV Sedation for Second-Trimester Abortion. Obstet Gynecol 2018.*

Similar to immediate postabortion VAS pain scores, the median VAS scores for recall of maximum abortion pain (assessed just before discharge from the clinic) were lower among women randomized to IV sedation: 66 mm (range 38–88) in the nitrous group and 17 mm (range 6–40) in the IV sedation group (P=.001) (Table 3). Duration of the procedure was longer among women randomized to nitrous: 14 minutes (range 7–22) in the nitrous group and 11 minutes (range 5–21) in the IV sedation group (P=.01). Longer procedural duration was the result of conversion from nitrous to IV sedation. Participants reported few side effects; one noted nausea and five required adjuvant medications for hemostasis with no difference between groups. No women in either group became oversedated.

Pain Time Point	Nitrous Oxide (n=19)	IV Sedation (n=20)	P
Baseline (before procedure)	3 (0–50)	2 (0–75)	.77
Expected (anticipated pain with procedure)	49 (10–99)	54 (1–99)	.63
Maximum experienced (immediate recall)	61 (2–100)	28 (0–94)	.03
Maximum experienced* (recall before leaving the clinic)	66 (3–100)	17 (0–92)	.001

IV, intravenous.
Data are median (range) unless otherwise specified.
* n=18 in nitrous oxide group.

Table 3.:
Visual Analog Scale Pain Scores (Millimeters on 100-mm Scale)

DISCUSSION

The main finding of our study was that inhaled nitrous oxide was inferior to IV sedation for pain control in surgical abortion at 12–16 weeks of gestation. We investigated nitrous oxide as an analgesic agent for early second-trimester abortion because of potential patient benefits. Advantages of nitrous oxide include its low cost and nonburdensome training of clinic staff. Additionally, nitrous oxide sedation has a rapid onset, is quickly reversible with administration of 100% oxygen, and delivery of the gas is noninvasive.[6,7] When evaluating the quality of the abortion care experience, women value both pain control and privacy[21]; an effective rapidly reversible medication would provide both. Clinic provision of multiple efficacious options for anesthesia allows women to identify the anesthetic that best fits their needs. Although nitrous oxide was not found to be a viable alternative to IV sedation, more research is needed to identify sedation options that meet these patient values. Additionally, it is unclear whether nitrous may confer benefit over no sedation in cases in which women declined or were not candidates for IV or oral sedation.

Strengths of this study included its randomized, controlled, double-blind design with multisite recruitment in clinical settings with experienced health care providers. We used validated metrics to evaluate pain. Limitations of the study included use of nitrous oxide in the high-altitude cities of Albuquerque and Denver where the analgesic effect may be slightly reduced.[22] Additionally, median pain scores were much lower in our study than in the prior study used as the basis of our sample size calculation.[18] Many potential participants declined enrollment and our study results may not be generalizable to all women undergoing pregnancy termination, particularly those with fetal anomaly indications who were the least likely to enroll. Given our finding of inferiority of nitrous oxide for pain control, however, it is unlikely that women with fetal indications for abortion would have experienced better pain control than women who were more likely to enroll in the study, those with maternal indications for abortion. Although paracervical block administration was standardized, there was no formal assessment of the paracervical block performed; it is possible that differences in administration between health care providers could account for some of the differences in pain experienced. Differences in the properties of nitrous and IV medications must be considered in the interpretation of study results: the half-life of midazolam, a medication with strong amnestic effect, is between 2 and 4 hours, and fentanyl is approximately 3.5 hours,[23] whereas nitrous oxide is rapidly cleared from the body after administration of 100% oxygen.[6]

Nitrous oxide is inferior to IV sedation for 12- to 16-week surgical abortion. The need for alternative anesthetic options persists, especially for women who travel alone or choose to maintain privacy. In women who might otherwise not be candidates for sedation, nitrous oxide may have benefit over paracervical block and ibuprofen alone. Future research should investigate nitrous oxide or other short-acting sedation options compared with no sedation.

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