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Nitrous Oxide for Pain Management during In-office Hysteroscopic Sterilization

Emily N. Schneider

Emily N. Schneider, MD
Candidate

Biomedical Sciences Graduate Program (BSGP)
Department

This thesis is approved, and it is acceptable in quality and form for publication:

Approved by the Thesis Committee:

Rameet Singh, MD, MPH, Chairperson

Eve Espey, MD, MPH

Shiraz Mishra, MBBS, PhD

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Emily N. Schneider

B.S. Chemical Engineering
University of Colorado Boulder, 2002

Doctor of Medicine
University of Colorado Denver School of Medicine, 2009

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Emily N. Schneider

B.S., Chemical Engineering, University of Colorado, 2002

M.D., University of Colorado, 2009

M.S., Biomedical Sciences, University of New Mexico, 2015

ABSTRACT

Objectives: To determine if inhaled nitrous oxide with oxygen (NOS) is superior to oral sedation for pain management during in-office hysteroscopic sterilization.

Methods: This double blinded randomized controlled trial enrolled women undergoing in-office hysteroscopic sterilization. The intervention group received NOS titrated to a maximum 70%:30% NO:O2 mixture and placebo pills 30 minutes prior to the procedure. The control group received inhaled O2 during the procedure and 5/325mg hydrocodone/acetaminophen and 1mg lorazepam 30 minutes prior to the procedure. The primary outcome was maximum procedural pain, assessed on a 100mm Visual Analogue Scale (VAS) 3 minutes post

procedure. A sample size of 30 women per treatment arm was required to detect a clinically significant pain difference of 20mm on the VAS.

Results: 72 women, 36 per study arm, were randomized in order to account for unsuccessful bilateral coil placement and drop out after randomization. Two women in the study group and 6 in the control group were excluded due to unsuccessful bilateral coil placement. Mean age of participants was 34.1 ± 5.7 years and mean BMI was 30.1 ± 6.6 kg/m^2. Mean maximum procedural pain scores were 22.8 ± 27.6 mm and 54.5 ± 32.7 mm for study and control groups, respectively ($p < 0.001$). Most study participants (97%) stated NOS should be offered for gynecologic office procedures and 86% would pay extra for NOS if it were not a covered benefit.

Conclusions: NOS significantly decreased pain with in-office hysteroscopic sterilization compared to PO sedation. Given its safety and favorable side effect profile, routine availability of NOS should be considered for in-office hysteroscopic sterilization.

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Introduction

Sterilization is a leading form of contraception in the United States (1). Compared with other means of achieving sterilization, hysteroscopic sterilization can be performed in the office setting. Advantages of in-office procedures include lower costs (2-4), faster recovery and less morbidity due to avoidance of an abdominal incision, general anesthesia (5), and rare but serious complications associated with laparoscopy and mini laparotomy (6).

Outpatient hysteroscopic transcervical sterilization can be a painful procedure (7, 8), challenging physicians to provide better pain management (9). Previous studies of pain interventions for this procedure in the office include intrauterine lidocaine infusion, intravenous sedation, and paracervical block (10-12). These interventions did not reduce maximum pain women experience during the procedure, but these studies demonstrated the most painful part of the in-office procedure was deployment of the coils. A paracervical block was shown to decrease pain with insertion of the hysteroscope through the cervix, but did not affect pain during placement of the coils.

Inhaled nitrous oxide administered with oxygen (NOS) has proven effective for short painful procedures involving dental (13, 14), pediatric (15, 16), and urologic procedures (17), and in the emergency room (18-21). NOS has analgesic, anxiolytic and amnestic properties, and is vasodilatory to smooth muscle (22,

23). Advantages of NOS include rapid onset and reversal of the inhaled gas (24) with minimal side effects and few contraindications (25). Further, NOS is extremely safe, and can be administered after training by various medical personnel (26, 27).

The primary objective of this study was to determine if NOS reduced pain of in-office hysteroscopic sterilization more than oral sedation.

Methods

We conducted a double-blinded randomized controlled trial comparing NOS to oral sedation during in-office hysteroscopic sterilization at the University of New Mexico Center for Reproductive Health clinic from February 2014 through March 2015. Participants signed written informed consent for both the permanent sterilization procedure and study participation; each participant received a $75 gift card to a local retailer. The University of New Mexico Human Research Review Committee approved this study. The study was registered with ClinicalTrials.gov NCT02312739.

Women seeking in-office hysteroscopic sterilization were approached for study participation. English or Spanish speaking women were eligible if they were at least 21 years of age, were using hormonal endometrial preparation prior to the procedure or scheduled the procedure on menstrual cycle days 5 – 12, had a negative urine pregnancy test, and agreed to an alternative contraceptive method for 3 months post procedure if sexually active until their confirmatory hysterosalpingogram. Participants were excluded if they took narcotics prior to their clinic appointment, had allergies to study medications, or had contraindications to NOS including active respiratory infection, chronic obstructive pulmonary disease, intoxication or active use of street drugs, or inability to breathe through the nose.

The intervention arm (NOS group) received NOS during the procedure and two placebo pills at least 30 minutes prior to the procedure. The control group (PO group) received inhaled oxygen during the procedure, and one 5/325 mg oral tablet of hydrocodone/acetaminophen and a single 1 mg oral tablet of lorazepam at least 30 minutes prior to the procedure. PO sedation was chosen as the comparative group as oral narcotics/anxiolytics was the clinical standard for pain management for hysteroscopic sterilization at the UNM Center for Reproductive Health at the time of the study. All participants received 30 mg of intramuscular ketorolac at least 30 minutes prior to the procedure.

A research coordinator not involved with recruitment of study participants used a computer program to generate a block randomization scheme. Sequence generation with random blocks of 6 with 1:1 allocation to the two treatment groups was concealed in sequentially numbered opaque envelopes that were opened only by the nurse actually administering pain management: either NOS with placebo pills or inhaled oxygen with hydrocodone/acetaminophen and lorazepam oral pills. NOS or oxygen was administered via a scented nasal mask to blind patients to the intervention. The physician performing the sterilization procedure was blinded from observing the patient's sedation type by a curtain shielding the participant's upper body and the nurse administering the inhaled gas. NOS was titrated to a maximum concentration of 70% nitrous oxide and 30% oxygen based on desired analgesic effects per a predetermined sedation scale as part of the clinic's nitrous oxide administration protocol. All participants

received a minimum of three minutes of 100% oxygen at the end of the procedure, regardless of randomization allocation.

Women completed a demographic questionnaire and received instructions on completing the 0-100 mm visual analogue scale (VAS) after consent into the study. Baseline pain score was recorded using a 100 mm VAS (anchors 0 = *no pain* and 100 = *worst pain imaginable*) (28). Baseline anxiety level was assessed using a short form Spielberger State-Trait Anxiety Inventory (STAI) (29-31). Participants rated five statements (*I feel calm, I am tense, I feel upset, I am relaxed, I am worried*) on a 1-4 scale. Women were given study medications for ingestion at least 30 minutes prior to the procedure. During the procedure, the same pain 100 mm VAS was administered after placement of the paracervical block and placement of the second coil. Three to five minutes following completion of the procedure, participants evaluated their maximum pain during the procedure on the same 100 mm VAS and post procedure anxiety was reassessed with the same STAI. Pain was also measured at second coil insertion as prior studies show that it is the most painful portion of the procedure. Our primary outcome measure was recall of maximum procedural pain 3-5 minutes post-procedure; this accounted for the amnestic properties of NOS. Prior to discharge from the clinic, participants rated their pain level using the same 100 mm VAS, and completed a satisfaction questionnaire on overall pain management using a 5-point Likert scale (*Very unsatisfied, Unsatisfied, Neutral, Satisfied, Very satisfied*). Physicians assessed ease of coil insertion and

hysteroscopic procedure difficulty immediately after the procedure on a 0-100 mm VAS (anchors 0 = *no difficulty*, 100 = *very difficult*).

Procedure start time was defined as speculum insertion. The tenaculum site was injected with 2 mL of 1% buffered lidocaine. A standardized paracervical block was administered to all women with 9 mL of buffered 1% lidocaine placed at 4 o'clock and 9 mL placed at 8 o'clock. In accordance with the prior in-office studies, which demonstrated no benefit of a waiting period after paracervical block, the procedure was initiated immediately after the injections (10-12). Cervical dilation was performed at the provider's discretion. A 5 mm operative hysteroscope was passed through the cervix and into the uterine cavity using normal saline for uterine distension. Procedure completion was marked at removal of the speculum.

Descriptive statistics were generated to determine normal distribution of the data. A two-sided student's t test was used to determine differences in normally distributed continuous variables. Categorical data were compared with Pearson χ^2 or Fisher's exact test as appropriate. Nonparametric Wilcoxon sum rank test was used for non-normally distributed data comparison. All data were analysed with SAS software (version 9.4; SAS Institute, Inc., Cary, NC).

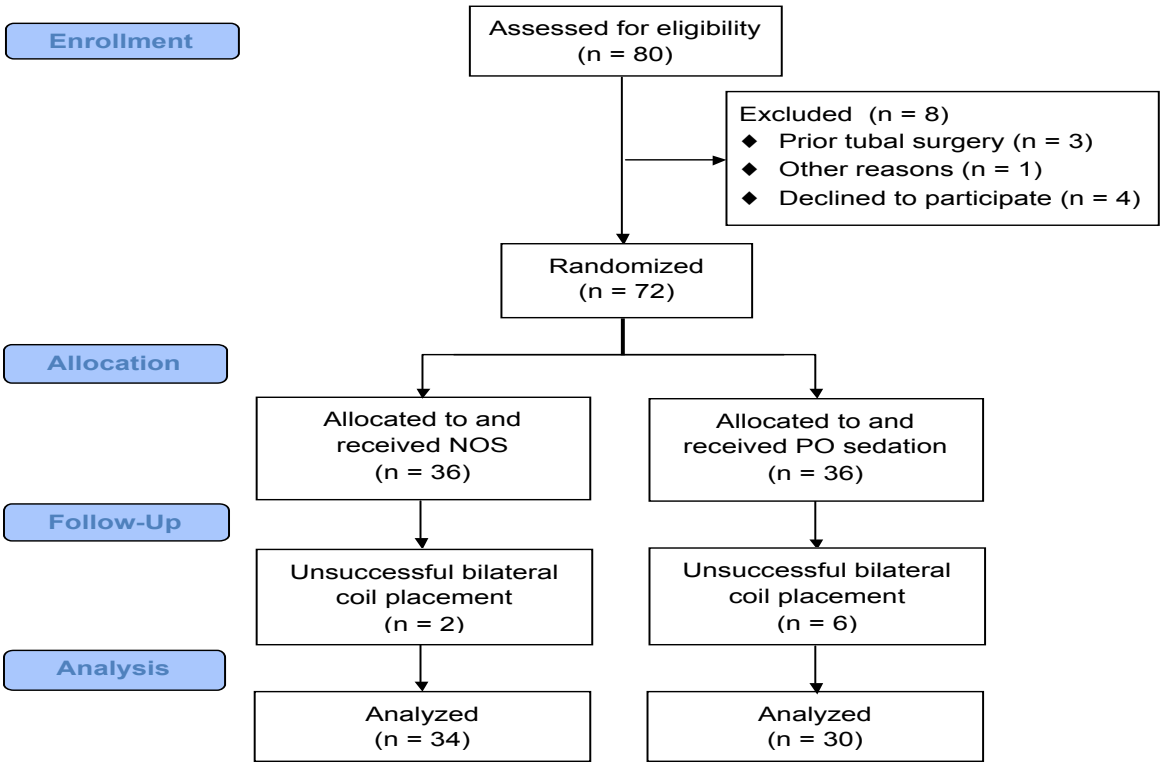
Sample size was determined by using mean procedural pain scores derived from the literature. Mean pain for the most painful part of hysteroscopic sterilization,

reported as second coil insertion, was rated as 43.6 ± 27.3 mm on a 0-100 mm VAS in women who received PO sedation (10). The smallest clinically meaningful difference in mean pain scores is 20 mm on a 0-100 mm VAS (28, 32). Our calculations using two-sided t test for two independent means demonstrated a requirement of at least 30 per study arm to detect a 20 mm difference with 80% power and α of 0.05, assuming the same variance between the two groups as a conservative estimation. We recruited 36 per study arm for a total of 72 women to allow for a 5% drop out rate after randomization and to account for further attrition due to unsuccessful bilateral coil placement. A recent review of our institutional success rates for first time bilateral device placement was 89% (33). Women who underwent unsuccessful bilateral coil placement were excluded from the analysis.

Results

During the study period 72 of 80 eligible women were enrolled, 36 per study arm. Eligibility was assessed and reported per CONSORT guidelines (FIGURE 1). A total of 8 participants (11.1%) were excluded due to unsuccessful bilateral coil placement leaving 34 women in the NOS group and 30 women in the PO group for analysis. Unsuccessful bilateral placement occurred as follows: in the NOS group, uterine perforation occurred with hysteroscope insertion in one and device malfunction precluded placement in another; in the PO group, poor visualization of the tubal openings occurred in four and inserter device malfunction with tubal spasm occurred in two.

FIGURE 1: Flow diagram for study participants.



Baseline characteristics were similar between the groups (TABLE 1). Women mostly relied on depot medroxyprogesterone acetate (43.8%) and combined oral contraceptive pills (21.9%) for endometrial preparation prior to the procedure. Experience level of provider, procedural difficulty rated by provider, or need for cervical dilation were similar between the groups (TABLE 2). The groups were also similar in time from study medication to procedure start, as well as time from paracervical block administration to hysteroscope insertion. Mean time to second coil placement and total procedure time was 4.5 minutes longer in the PO group (p=0.03 and p=0.04).

Table 1. Study participant characteristics and demographics. Data are mean ± standard deviation or number (%).

Characteristic	NOS (n=34)	PO (n=30)	P value
Age (years)	33.6 ± 4.9	34.6 ± 6.6	0.49
BMI (kg/m^2)	29.5 ± 6.6	30.7 ± 6.8	0.51
Ethnicity			0.58
Hispanic or Latino	26 (76.5)	21 (70.0)	
Not Hispanic or Latino	8 (23.5)	9 (30.0)	
Race			0.38
White	9 (26.5)	13 (43.3)	
Hispanic/Mexican/Spanish	16 (47.1)	14 (46.7)	
Native American/Alaska Native	3 (8.8)	0 (0)	
Unknown	5 (14.7)	3 (10.0)	
Marital status			0.79
Single living alone or with partner	16 (47.1)	16 (53.4)	
Married	16 (47.1)	11 (36.7)	
Divorced/Separated/Widowed	2 (5.9)	3 (10.0)	

Table 1 (cont.). Data are mean ± standard deviation or number (%).

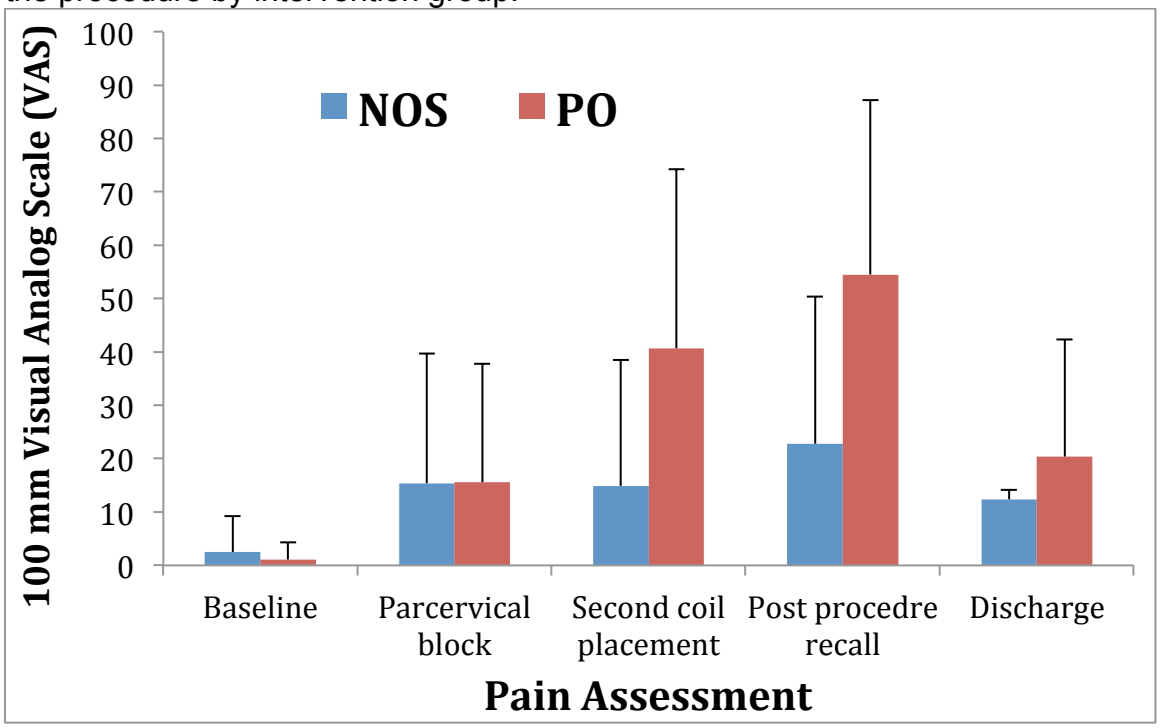
Education			0.60
Grade school	6 (17.7)	3 (10.0)	
Some high school	8 (23.5)	13 (43.3)	
High school graduate	10 (29.4)	8 (26.7)	
Community college/College graduate	8 (23.5)	4 (13.3)	
Postgraduate	2 (5.9)	2 (6.7)	
Employment status			0.82
Part time	6 (17.7)	3 (10.0)	
Full time	11 (32.4)	10 (33.3)	
Homemaker	11 (32.4)	10 (33.3)	
Unemployed	6 (17.7)	7 (23.3)	
Household income			0.73
< $20,000	19 (55.9)	19 (63.3)	
$20,000 - $60,000	14 (41.2)	9 (30.0)	
> $60,000	1 (2.9)	2 (6.7)	
Insurance type			0.48
Private	3 (8.8)	5 (16.7)	
Medicaid	13 (38.2)	8 (26.7)	
Uninsured	18 (52.9)	17 (56.7)	
Pregnancy outcomes			
Vaginal deliveries	2.8 ± 1.3	2.6 ± 1.8	0.68
Cesarean sections	0.1 ± 0.3	0.3 ± 0.8	0.34
Abortions	0.3 ± 0.1	0.4 ± 0.1	0.42
Miscarriages	0.3 ± 0.5	0.1 ± 0.4	0.16
History of sexually transmitted infection	11 (32.3)	8 (26.7)	0.62
History of cervical excisional procedure	1 (2.9)	0 (0)	0.53
Requires pain medications for menses	11 (32.3)	5 (16.7)	0.15
Current contraceptive use			
Combined oral pills	6 (17.6)	8 (26.7)	0.55
Progesterone only pills	0 (0.0)	2 (6.7)	0.22
Depot medroxyprogesterone acetate	16 (47.1)	12 (40.0)	0.62
Levonorgestrel intrauterine device	2 (5.9)	4 (13.3)	0.41
Copper intrauterine device	0 (0.0)	2 (6.7)	0.22
Sub-dermal implant	5 (14.7)	1 (3.3)	0.20
Male condoms	5 (14.7)	2 (6.7)	0.43

Table 2. Procedure characteristics. Data are mean ± standard deviation or number (%).

Characteristic	NOS (n=34)	PO (n=30)	P value
Cervical dilation performed			0.16
Yes	8 (23.5)	12 (40.0)	
No	26 (76.5)	18 (60.0)	
Provider Level			0.53
Attending	9 (26.5)	5 (16.7)	
Fellow	18 (52.9)	16 (53.3)	
Resident	7 (20.6)	9 (30.0)	
Total procedure time (min)	14.4 ± 6.5	18.9 ± 10.4	0.04
Time between paracervical block placement to hysteroscope insertion (min)	2.1 ± 1.1	2.5 ± 1.8	0.27
Time from procedure start to second device insertion (min)	12.6 ± 5.5	17.1 ± 9.6	0.03
Provider perceived level of difficulty			
Placement of first coil	18.1 ± 23.7	23.8 ± 28.8	0.40
Placement of second coil	19.6 ± 25.5	26.8 ± 27.0	0.27
Hysteroscopic difficulty	19.8 ± 20.7	22.7 ± 24.8	0.61

Maximum procedural pain was significantly lower for the NOS than the PO group, 22.8 ± 27.6 mm and 54.5 ± 32.7 mm, respectively ($p < 0.001$) (FIGURE 2). Pain at second coil insertion was also significantly lower for the NOS group than the PO group, 14.9 ± 23.6 mm and 40.7 ± 33.5 mm, respectively ($p < 0.001$). There was no difference in baseline pain, pain at paracervical block, or pain at clinic discharge between the groups. The mean pain score at second coil insertion and maximum procedural pain score were not different for either group ($p = 0.34$).

FIGURE 2: Pain scores for study participants at various time points during the procedure by intervention group.



The mean anxiety score pre and post procedure was similar between the NOS and PO groups, with zero being low anxiety and twenty being the highest anxiety state (TABLE 3). The mean difference between post and pre anxiety scores was also similar between NOS and PO, -1.2 ± 3.4 and 0.1 ± 3.4, respectively (p=0.14).

TABLE 3: Anxiety scores for study participants before and after the procedure.

STAI Anxiety Score	NOS (n=34)	PO (n=30)	P value
Pre-procedure	9.4 ± 2.9	8.4 ± 2.7	0.18
Post-procedure	8.2 ± 2.8	8.5 ± 2.9	0.65
Change Post – Pre Procedure	- 1.2 ± 3.4	0.1 ± 3.4	0.14

Most women in this study reported they were satisfied (very satisfied or satisfied) with their procedural pain management (81.3%) and would recommend this study to a friend (92.3%) regardless of study group. Sixty two (96.9%) of participants responded that NOS should be offered for pain management for in-office gynecologic procedures and fifty five (85.9%) responded they would pay extra for NOS as a pain management option if it was not a covered insurance benefit. 28 women in the NOS group (82.4%) correctly identified that they received NOS, whereas only 16 in the PO group (53.3%) mistakenly thought they received NOS (p=0.03) (TABLE 4).

TABLE 4: Satisfaction questionnaire completed by study participants.

Satisfaction	NOS (n=34)	PO (n=30)	P value
Pain control during procedure			0.50
Very unsatisfied/Unsatisfied/Neutral	15	23	
Satisfied/Very Satisfied	85	77	
Recommend this NOS study to a friend			0.37
Strongly disagree/Disagree/Neutral	3	13	
Agree/Strongly agree	97	87	
NOS should be used as a pain reliever in GYN clinic	97	97	1.0
Would pay for NOS if not covered benefit	82	90	0.25
Thought they received NOS	82	53	0.03

Discussion

Our study found that NOS was more effective than PO sedation in reducing pain of in-office hysteroscopic sterilization. Additionally, women expressed satisfaction with NOS and a majority in both groups felt NOS should be offered as a pain management option for in-office gynecologic procedures.

Previously studied comparisons include paracervical block with 1% lidocaine to saline, intravenous sedation using fentanyl and midazolam to oral naproxen sodium and oral oxycodone, 4% intrauterine lidocaine versus saline in women receiving oral ibuprofen and lorazepam with a 1% lidocaine paracervical block. There were no differences in pain scores between groups in each study. Each study demonstrated the most painful portion of the procedure was placement of the coils. Our study shows a reduction in pain at second coil placement using NOS with a 1% lidocaine paracervical block. Pain scores at paracervical block placement were similar between groups in this study. Given the procedural pain reduction with NOS, the paracervical block may not be a necessary intervention during hysteroscope insertion.

NOS has few side effects or contraindications. Its rapid onset and reversal obviates procedural delays and post-procedure monitoring. The unlikely complication of over-sedation is easily treated with administration of 100%

oxygen. Women are able to leave the clinic without residual sedation effects so they do not require others to provide transportation to and from the appointment.

An interesting finding in this study was the difference in unsuccessful bilateral coil placement between the two groups. Although excluded from the analysis, six women in the PO group had unsuccessful placement compared to two in the NOS group. Review of procedural documentation indicated that poor visualization was the most common cause for incomplete procedures. We theorize that fewer unsuccessful placements in the NO group could be due to uterine relaxation with increased uterine distention as a side effect of the NOS, causing improved visualization of the tubal ostia.

Major strengths of this study are the double blinded randomized controlled design and adequate sample size. Additionally, NOS was titrated individually for women in the treatment group. The ability to titrate medications is preferred to a single standard dosage to provide the minimal amount of drug necessary for the desired effect. Additionally, titration allows for dose increase during more painful portions of the procedure.

Use of NOS may allow more women to choose an in-office over an operating room procedure, minimizing overall cost of the procedure. Given the results of this study, future studies should examine the effectiveness of NOS for women seeking other in-office procedures, such as endometrial ablation or colposcopy.

After modest initial start up costs to install the NOS delivery system, minimal maintenance is required. Various medical personnel with appropriate training can safely administer NOS.

The dose of NOS in our study was titrated to levels considered to be “moderate sedation.” The American Society of Anesthesiologists (ASA) and the American Dental Association (ADA) define mild versus moderate sedation with NOS differently. According to the ASA, sedation is considered “minimal” when the NO:O2 mixture does not exceed 50%:50% concentration. As the maximum level of NO:O2 is 70%:30%, any NO level between 50 and 70 is considered “moderate” (34). The ADA, however, considers patient response to a medication as defining mild versus higher levels of sedation without a caveat of the absolute concentration of NOS (35). The Center for Reproductive Health clinic and the dental clinic at the University of New Mexico have the ability to administer NOS in concentrations higher than 50% mixed with oxygen as administration protocols are based on patient responses to determine their sedation level, not absolute NOS concentration. Continuous monitoring of the patient’s response is required during the procedure with NOS sedation; IV access or NPO status prior to the procedure are not necessary. This limits the generalizability of our study findings to clinics that approve sedation protocols based on the ASA guidelines. Almost 81% of this study population reached a moderate sedation level of NOS concentration greater than 50% according to the ASA but this entire cohort did not complete the procedure at moderate sedation levels as they were titrated

down to mild sedation dosing by completion of the procedure based on the patient's response.

We used PO sedation, which is considered mild sedation, as our control group for this study. With a majority of our women in the intervention group receiving moderate sedation dosing of NOS per ASA guidelines, we are comparing different levels of sedation. Our clinic standard for this in-office procedure is to offer patients an oral narcotic with anxiolytic in addition to IM ketorolac and a paracervical block. Our goal of this study was to investigate the use of a novel pain management option that would provide improved analgesic effect during the procedure with minimal risk and post procedure intervention, such as IV sedation.

Our study findings, even with the limitations of moderate sedation dosing of NOS and oral sedation as our comparator group, have significant impact on the ability to successfully reduce pain for women undergoing a painful in-office procedure. Outpatient gynecologic practices are expanding the repertoire of procedures that can be offered in the office setting creating the need to provide adequate analgesia. Our study findings demonstrate NOS is effective for pain management during in-office hysteroscopic sterilization and adds a safe, easily administered option to currently available strategies.

References

1. Jones J, Mosher W, Daniels K. Current contraceptive use in the United States, 2006-2010, and changes in patterns of use since 1995. Natl Health Stat Report. 2012(60):1-25.

2. Kraemer DF, Yen PY, Nichols M. An economic comparison of female sterilization of hysteroscopic tubal occlusion with laparoscopic bilateral tubal ligation. Contraception. 2009;80(3):254-60.

3. Hopkins MR, Creedon DJ, Wagie AE, Williams AR, Famuyide AO. Retrospective cost analysis comparing Essure hysteroscopic sterilization and laparoscopic bilateral tubal coagulation. Journal of minimally invasive gynecology. 2007;14(1):97-102.

4. Nichols M, Carter JF, Fylstra DL, Childers M. A comparative study of hysteroscopic sterilization performed in-office versus a hospital operating room. Journal of minimally invasive gynecology. 2006;13(5):447-50.

5. Levie MD, Chudnoff SG. Prospective analysis of office-based hysteroscopic sterilization. Journal of minimally invasive gynecology. 2006;13(2):98-101.

6. Ogburn T, Espey E. Transcervical sterilization: past, present, and future. Obstetrics and gynecology clinics of North America. 2007;34(1):57-72, viii.

7. Levie M, Weiss G, Kaiser B, Daif J, Chudnoff SG. Analysis of pain and satisfaction with office-based hysteroscopic sterilization. Fertility and sterility. 2010;94(4):1189-94.

8. Arjona JE, Mino M, Cordon J, Povedano B, Pelegrin B, Castelo-Branco C. Satisfaction and tolerance with office hysteroscopic tubal sterilization. Fertility and sterility. 2008;90(4):1182-6.

9. Jensen MP, Martin SA, Cheung R. The meaning of pain relief in a clinical trial. The journal of pain : official journal of the American Pain Society. 2005;6(6):400-6.

10. Thiel JA, Lukwinski A, Kamencic H, Lim H. Oral analgesia vs intravenous conscious sedation during Essure Micro-Insert sterilization procedure: randomized, double-blind, controlled trial. Journal of minimally invasive gynecology. 2011;18(1):108-11.

11. Chudnoff S, Einstein M, Levie M. Paracervical block efficacy in office hysteroscopic sterilization: a randomized controlled trial. Obstetrics and gynecology. 2010;115(1):26-34.

12. Isley MM, Jensen JT, Nichols MD, Lehman A, Bednarek P, Edelman A. Intrauterine lidocaine infusion for pain management during outpatient transcervical tubal sterilization: a randomized controlled trial. Contraception. 2012;85(3):275-81.

13. Al-Zahrani AM, Wyne AH, Sheta SA. Comparison of oral midazolam with a combination of oral midazolam and nitrous oxide-oxygen inhalation in the effectiveness of dental sedation for young children. Journal of the Indian Society of Pedodontics and Preventive Dentistry. 2009;27(1):9-16.

14. Wood M. The safety and efficacy of intranasal midazolam sedation combined with inhalation sedation with nitrous oxide and oxygen in paediatric dental patients as an alternative to general anaesthesia. SAAD digest. 2010;26:12-22.

15. Burnweit C, Diana-Zerpa JA, Nahmad MH, Lankau CA, Weinberger M, Malvezzi L, et al. Nitrous oxide analgesia for minor pediatric surgical procedures: an effective alternative to conscious sedation? Journal of pediatric surgery. 2004;39(3):495-9; discussion -9.

16. Tobias JD. Applications of nitrous oxide for procedural sedation in the pediatric population. Pediatric emergency care. 2013;29(2):245-65.

17. Young A, Ismail M, Papatsoris AG, Barua JM, Calleary JG, Masood J. Entonox(R) inhalation to reduce pain in common diagnostic and therapeutic outpatient urological procedures: a review of the evidence. Annals of the Royal College of Surgeons of England. 2012;94(1):8-11.

18. Faddy SC, Garlick SR. A systematic review of the safety of analgesia with 50% nitrous oxide: can lay responders use analgesic gases in the prehospital setting? Emergency medicine journal : EMJ. 2005;22(12):901-8.

19. McKinnon KD. Prehospital analgesia with nitrous oxide/oxygen. Canadian Medical Association journal. 1981;125(8):836-40.

20. Descamps MJ, Gwilym S, Weldon D, Holloway V. Prospective audit of emergency department transit times associated with entonox analgesia for reduction of the acute, traumatic dislocated shoulder. Accident and emergency nursing. 2007;15(4):223-7.

21. Baskett PJ. Use of Entonox in the ambulance service. British medical journal. 1970;2(5700):41-3.

22. Zacny JP, Hurst RJ, Graham L, Janiszewski DJ. Preoperative dental anxiety and mood changes during nitrous oxide inhalation. Journal of the American Dental Association (1939). 2002;133(1):82-8.

23. Becker DE, Rosenberg M. Nitrous oxide and the inhalation anesthetics. Anesthesia progress. 2008;55(4):124-30; quiz 31-2.

24. Sherwood ER, Williams CG, Prough DS. Townsend: Sabiston Textbook of Surgery: Elsevier; 2012.

25. O'Sullivan I, Benger J. Nitrous oxide in emergency medicine. Emergency medicine journal : EMJ. 2003;20(3):214-7.

26. Collado V, Nicolas E, Faulks D, Hennequin M. A review of the safety of 50% nitrous oxide/oxygen in conscious sedation. Expert opinion on drug safety. 2007;6(5):559-71.

27. Clark MS, Campbell SA, Clark AM. Technique for the administration of nitrous oxide/oxygen sedation to ensure psychotropic analgesic nitrous oxide (PAN) effects. The International journal of neuroscience. 2006;116(7):871-7.

28. DeLoach LJ, Higgins MS, Caplan AB, Stiff JL. The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. Anesthesia and analgesia. 1998;86(1):102-6.

29. Spielberger C. GR, Lushene N. Manual for the State-Trait Anxiety Inventory. 1970;Palo Alto Consulting Psychologist's Press.

30. Rossi V, Pourtois G. Transient state-dependent fluctuations in anxiety measured using STAI, POMS, PANAS or VAS: a comparative review. Anxiety Stress Coping. 2012;25(6):603-45.

31. Kruyen PM, Emons WH, Sijtsma K. Shortening the S-STAI: consequences for research and clinical practice. J Psychosom Res. 2013;75(2):167-72.

32. Rowbotham MC. What is a "clinically meaningful" reduction in pain? Pain. 2001;94(2):131-2.

33. Woods S, Wintermute, R., Ogburn T., Espey, E., Singh R., Pereda B.,. Essure procedure: a case series in an academic setting. Contraception. 2013;88(3):471.

34. Anesthesiologists ASo. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology. 2002;96(4):1004-17.

35. Guidelines for the Use of Sedation and General Anesthesia by Dentists. 2012. Accessed June 10, 2015 at www.ada.org.