ELSEVIER

Contraception xx (2016) xxx–xxx

Contraception

Original research article

Nitrous oxide for pain management during in-office hysteroscopic sterilization: a randomized controlled trial☆

Emily N. Schneider[a,1], Regan Riley[a], Eve Espey[a], Shiraz I. Mishra[b], Rameet H. Singh[a,*]

[a]University of New Mexico, Department of Obstetrics and Gynecology, 1 University of New Mexico, MSC10 5580, Albuquerque, NM 87131, USA
[b]University of New Mexico, Department of Pediatrics, 1 University of New Mexico, MSC 10 5590, Albuquerque, NM, USA

Received 27 May 2016; revised 31 August 2016; accepted 4 September 2016

Abstract

Objectives: To evaluate whether inhaled nitrous oxide with oxygen (N_2O/O_2) is associated with less pain compared to oral sedation for pain management during in-office hysteroscopic sterilization.

Study design: This double blinded randomized controlled trial enrolled women undergoing in-office hysteroscopic sterilization. All participants received pre-procedure intramuscular ketorolac and a standardized paracervical block. The intervention group also received N_2O/O_2 via a nasal mask titrated to a maximum 70%:30% mixture by a nurse during the procedure and placebo pills pre-procedure and the active control group received inhaled O_2 during the procedure and 5/325 mg hydrocodone/acetaminophen and 1 mg lorazepam pre-procedure. The primary outcome was maximum procedure pain on a 100 mm Visual Analog Scale (VAS with anchors at 0 = no pain and 100 = worst imaginable pain) assessed 3–5 min post procedure. Thirty women per treatment arm were required to detect a clinically significant pain difference of 20 mm.

Results: Seventy-two women, 36 per study arm, were randomized. Mean age of participants was 34.1±5.7 years and mean BMI was 30.1±6.6 kg/m^2. Mean maximum procedure pain scores were 22.8±27.6 mm and 54.5±32.7 mm for intervention and control groups, respectively ($p<.001$). Most study participants (97%) stated N_2O/O_2 should be offered for gynecologic office procedures and 86% would pay for it if not a covered benefit.

Conclusions: N_2O/O_2 decreased pain with in-office hysteroscopic sterilization compared to oral sedation and is an effective pain management option for this procedure.

Implications: Given its safety and favorable side effect profile, N_2O/O_2 can be used for pain management for in-office hysteroscopic sterilization and adds a safe, easily administered option to currently available strategies.

Keywords: Nitrous oxide; Pain; Hysteroscopic sterilization; Sedation

1. 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 and may be associated with lower costs [2–4], faster recovery and less morbidity due to avoidance of an abdominal incision, general anesthesia [5], and the rare but serious complications associated with laparoscopy and mini laparotomy [6].

Outpatient hysteroscopic transcervical sterilization can be painful, particularly with longer procedure times or in women with previous cesarean deliveries [7,8], challenging physicians to provide better pain management [9]. Previous studies of pain interventions include intrauterine lidocaine infusion, intravenous sedation, and paracervical block [10–12]. These interventions did not reduce pain, but studies identified deployment of the coils as the most painful part of the in-office procedure. Paracervical block decreased pain with insertion of the hysteroscope through the cervix, but did not affect pain during coil placement.

Inhaled nitrous oxide administered with oxygen (N_2O/O_2) has proven effective for short painful procedures involving

☆ Clinical Trial Registration: ClinicalTrials.gov, www.clinicaltrials.gov, NCT02312739.

* Corresponding author. Tel.: +1 505 925 0687.
E-mail addresses: schneidsem@gmail.com (E.N. Schneider), reriley@salud.unm.edu (R. Riley), eespey@salud.unm.edu (E. Espey), SMishra@salud.unm.edu (S.I. Mishra), rhsingh@salud.unm.edu (R.H. Singh).
[1] Present Address: CU Rocky Mountain OB-GYN, Rose Medical Center, POB II, 4500 E 9th Ave, #200, Denver, Colorado 80,220, USA.

http://dx.doi.org/10.1016/j.contraception.2016.09.006
0010-7824/

dental [13,14], pediatric [15,16], and urologic procedures [17], and in the emergency room [18–21]. N_2O/O_2 has analgesic, anxiolytic and amnestic properties, and vasodilates smooth muscle [22,23]. Advantages of N_2O/O_2 include rapid onset and reversal [24] with minimal side effects and few contraindications [25]. Early signs of over sedation with N_2O/O_2 include nausea, dizziness, drowsiness, light-headedness, and diaphoresis. N_2O/O_2 is safe, can be administered by various trained medical personnel, but it requires an upfront clinic infrastructure investment [26,27]. The primary objective of this study was to evaluate if N_2O/O_2 analgesia was associated with less pain during and after in-office hysteroscopic sterilization compared to oral sedation.

2. Material and methods

We conducted a double-blinded randomized controlled trial comparing N_2O/O_2 to oral sedation during in-office hysteroscopic sterilization at the University of New Mexico Center for Reproductive Health 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 the study. The study was registered with ClinicalTrials.gov NCT02312739. Our primary outcome measure was recall of maximum procedure pain 3–5 min post-procedure. Secondary outcomes measures were anxiety, patient satisfaction, and provider perception of ease of coil insertion.

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 or were scheduled 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 a confirmatory hysterosalpingogram. Participants were excluded if they took narcotics prior to the clinic appointment, had allergies to study medications, or had contraindications to N_2O/O_2 including active respiratory infection, chronic obstructive pulmonary disease, intoxication or active use of street drugs, or inability to breathe through the nose. The hysteroscopic procedure was completed by a Family Planning attending or fellow, or an OB/GYN resident with supervision.

All participants received 30 mg of intramuscular ketorolac at least 30 min prior to the procedure and a standardized paracervical block with 9 mL of buffered 1% lidocaine placed at 4 o'clock and 9 mL placed at 8 o'clock. Women in the intervention arm (N_2O/O_2 group) received inhaled N_2O/O_2 during the procedure and two placebo pills (methylcellulose gel) at least 30 min prior to the procedure. Women in the control group (PO group) received inhaled oxygen (O_2) during the procedure, and one 5/325 mg oral tablet of hydrocodone/acetaminophen and a 1 mg oral tablet of lorazepam at least 30 min prior to the procedure. All pills were concealed in identical gel caps. PO sedation was chosen as the comparison group as oral narcotics/anxiolytics was the clinical standard for pain management for hysteroscopic sterilization at the UNM Center for Reproductive Health.

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 six 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 the gas: either inhaled N_2O/O_2 with placebo pills or inhaled oxygen with hydrocodone/acetaminophen and lorazepam oral pills. N_2O/O_2 or O_2 was administered via a scented nasal mask to blind patients to the intervention. An Accutron36100 N_2O/O_2 portable machine attached to a RAMVAC Badger scavenging system was used to administer the gases. 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. N_2O/O_2 was titrated to a maximum concentration of 70% N_2O and 30% O_2 based on desired analgesic effects per a predetermined sedation scale as part of the clinic's nitrous oxide administration protocol (patient appeared comfortable and relaxed, acknowledged reduced fear and anxiety, was aware of surroundings, responded to directions and conversation, eyes became less active and glazed look appeared). All participants received a minimum of 3 min of 100% O_2 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 Analog Scale (VAS) after consenting to 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]. Participants rated five statements (*I feel calm, I am tense, I feel upset, I am relaxed, I am worried*) on a 1–4 scale (*Not at all, Somewhat, Moderately, Very Much)*. The anchors were 0 and 20 indicating lowest to highest anxiety states. During the procedure, the same 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 and post procedure anxiety was reassessed with the STAI.

Our primary outcome measure was recall of maximum procedure pain 3–5 min post-procedure; the delay in recording maximum pain was planned to take advantage of the amnestic properties of N_2O/O_2. Pain was also measured at second coil insertion. Prior to discharge from the clinic, participants rated their pain level 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