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CLINICAL ARTICLE

A randomized controlled trial of nitrous oxide for intrauterine device insertion in nulliparous women☆

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ABSTRACT

Objective: To evaluate the effectiveness of inhaled nitrous oxide for pain management among nulliparous women undergoing intrauterine device (IUD) insertion. *Methods:* A double-blind, randomized controlled trial was conducted among nulliparous women aged 13–45 years who underwent IUD insertion at a US center between October 1, 2013, and August 31, 2014. Using a computer-generated randomization sequence, participants were randomly assigned to inhale either oxygen (O_2) or a mixture of 50% nitrous oxide and 50% oxygen (N_2O/O_2) through a nasal mask for 2 minutes before insertion. Only the person administering the inhalation agent was aware of group assignment. The primary outcome was maximum pain assessed 2 minutes after insertion via a 100-mm visual analog scale. Analyses were by intention to treat. *Results:* Forty women were assigned to each group. Mean maximum pain score at the time of insertion was 54.3 ± 24.8 mm for the N_2O/O_2 group and 55.3 ± 20.9 mm for the O_2 group ($P=0.86$). Adverse effects were reported for 6 (15%) women in the N_2O/O_2 group and 7 (18%) in the O_2 group ($P=0.32$). *Conclusion:* N_2O/O_2 did not reduce the pain of IUD insertion among nulliparous women.

ClinicalTrials.gov: NCT02391714

1. Introduction

Intrauterine devices (IUDs) provide safe, highly effective, and convenient reversible long-term contraception. Despite these advantages, IUDs were used by less than 3.6% of women aged 15–19 years in 2006–2008 in the USA [1]. Fear of pain during IUD insertion is a barrier for adolescents and nulliparous women [2]. Additionally, clinicians could be reluctant to offer IUDs to nulliparous women, whom they believe experience more pain with IUD insertion [3,4]. Because cervical cytology for cancer screening is now deferred until the age of 21 years in the USA [5], and urine testing is often used for sexually transmitted infection screening [6], few young nulliparous women have undergone a pelvic examination. Fear of discomfort associated with such an examination could compound the fear of pain from IUD insertion.

Nulliparous women experience moderate pain with IUD insertion [7–9]. Misoprostol, non-steroidal anti-inflammatory drugs, and local anesthesia have been studied, but not shown to reduce IUD insertion pain among nulliparous women [10–12]. Identification of effective interventions to reduce the pain of IUD insertion for nulliparous women could promote acceptability and utilization.

Nitrous oxide titrated with oxygen (N_2O/O_2) is an inhalation agent that affords safe, effective, non-invasive analgesic and anxiolytic with rapid onset and clearance [13]. It has a favorable adverse effects profile, and has been used for many years with excellent outcomes for procedural analgesia and anesthesia in outpatient clinics, including dentistry and emergency department settings [14–16]. N_2O/O_2 is attractive in the clinic because delivery systems are fairly inexpensive, training is not burdensome, and administration of the gas is noninvasive. To our knowledge, no studies have evaluated the use of N_2O/O_2 for IUD insertion among nulliparous women.

The primary objective of the present study was therefore to determine whether N_2O/O_2 at a 50%/50% concentration decreases pain as compared with oxygen alone (O_2) during IUD insertion among nulliparous women who choose a 52-mg levonorgestrel or copper T380A IUD.

2. Materials and methods

A randomized, double blinded, placebo-controlled trial of N_2O/O_2 versus O_2 for IUD insertion was conducted among nulliparous women attending the Center for Reproductive Health clinic at the University of New Mexico, Albuquerque, NM, USA, between October 1, 2013,

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and August 31, 2014. English-speaking nulliparous women aged 13–45 years who chose the 52-mg levonorgestrel or copper T380A for contraception were recruited. Women were included if they had never been pregnant or had not carried a pregnancy beyond 19 weeks and 6 days, were at least 4 weeks from the end of a pregnancy, and had a negative urine pregnancy test. Women younger than 18 years were eligible if accompanied by a parent or legal guardian who signed the informed consent. Participants were excluded if they were actively using prescribed opioids, benzodiazepines or illicit drugs, or had contraindications to IUD insertion or N_2O/O_2 administration, including respiratory infection, chronic obstructive pulmonary disease, intoxication, or inability to breathe through the nose. The University of New Mexico Health Science Center Human Research Review Committee approved the study (ref. no. 13-289) and all participants provided written informed consent before study participation.

Study team members recruited participants on the day of the IUD insertion procedure. Participants received routine clinical and preprocedural care and counseling. After providing informed consent, participants were randomly assigned to one of two groups via a randomization scheme in blocks of four, computer-generated by a statistician not involved in study recruitment. Randomization allocation was concealed in sequentially numbered opaque envelopes. Each envelope was opened by the person administering the inhalation agent immediately before the procedure, and the contents were not seen by other clinicians. A disposable scented nasal mask was fitted for all patients to ensure they were not aware of group assignment. The biostatistician was not masked to group assignment during data analysis.

A dedicated physician or nurse administered N_2O/O_2 or O_2 for 2 minutes, as per the randomization assignment, before the IUD insertion procedure. The N_2O/O_2 delivery system was concealed behind a screen to maintain masking of both the patient and the clinician performing the IUD insertion. N_2O/O_2 was titrated up to a fixed dose ratio of 50%/50% N_2O/O_2 before the IUD procedure; 100% O_2 was used in the control group. The control group did not receive any other medication. Participants were monitored for level of consciousness, ventilation status, and oxygenation during administration of the inhaled gas.

The IUD insertion procedure was similar for all participants. A bimanual examination was performed before speculum insertion. The cervix was cleansed with an antiseptic solution. A single-tooth tenaculum was placed on the cervix and a uterine sound was used to measure cavity length. The IUD was inserted via a standard insertion technique as described in the package leaflet. The bimanual examination denoted the beginning of the procedure and removal of the speculum marked the end.

The participants assessed their baseline pain, expected pain, IUD insertion pain, and pain at the time of discharge from the clinic via a 100-mm visual analog scale (VAS; 0 mm indicated no pain, 100 mm pain as bad as it can be). The primary pain outcome was maximum pain with IUD insertion assessed 2 minutes after completion of the procedure, which is the timepoint at which N_2O/O_2 is expected to be systemically cleared. Satisfaction with pain management during IUD insertion was assessed with a five-point Likert scale (very satisfied, satisfied, neutral, dissatisfied, and very dissatisfied) and 100-mm VAS (0 mm indicated very dissatisfied, 100 mm very satisfied). Women who reported being dissatisfied were able to describe in free text the reason why they were dissatisfied with their pain management. The physician who inserted the IUD recorded the procedure details and assessed the difficulty of IUD insertion on a 100-mm VAS (0 mm, very easy; 100 mm, most difficult). Physicians were also asked to guess whether the patient had received N_2O/O_2 or 100% O_2. Participants completed a demographic and medical history questionnaire before the procedure. Before discharge from the clinic, women also completed a questionnaire regarding their IUD insertion experience, which included a question asking them to guess whether they had received N_2O/O_2 or 100% O_2. All participants received a US$10 gift card for a local retail shop to compensate for the inconvenience of the study procedures.

Sample size was based on the assumption that a 15-mm difference on a 100-mm VAS is the minimal clinically important difference in pain [17]. In previous studies, mean pain scores (measured on a 100-mm VAS) for IUD insertion among nulliparous Hispanic and non-Hispanic white women were 61.9 ± 25 mm [8] and 55 ± 21 mm [7], respectively. Because the New Mexico population consists of primarily non-Hispanic white and Hispanic women, a pooled standard deviation (SD) of 23 was assumed. To detect a 15-mm difference in pain scores between the N_2O/O_2 and O_2 groups with an SD of 23, a sample size of 38 women per treatment group was necessary with a β value of 0.80 and an α value of 0.05. With an anticipated 5% drop out rate after randomization, the recruitment goal was established at 40 women per group.

Study data were collected and managed using Research Electronic Data Capture (REDCap) [18]. Different research coordinators entered the study data into the Double Data entry feature in REDCap to compare data entry results via the data comparison tool. SAS version 9.3 (SAS Institute, Cary, NC, USA) was used for all data analyses.

Data were analyzed by intention to treat. Normally distributed continuous variables were compared by parametric tests (*t* test and analysis of variance), and continuous variables that were not normally distributed were compared by non-parametric Wilcoxon-rank sum tests. Categorical variables were compared by Fisher exact test. $P<0.05$ was considered to be statistically significant.

3. Results

Among 161 women evaluated for enrollment, 93 (58%) were eligible (Figure 1). Of the 93 eligible women, 80 (86%) were enrolled; 40 were allocated to each group. The IUD insertion procedure was discontinued for one participant in the N_2O/O_2 group owing to the creation of a false tract, but she was included in the analysis (Figure 1).

The mean age of participants was 25.6 ± 5.8 years. Most women were single (52 [65%] participants), and were predominantly non-Hispanic white (43 [54%]) and Hispanic (29 [36%]). Most women had completed some college or were college graduates (73 [91%]), and most were employed either part- or full-time (63 [79%]). Most participants earned less than US$40 000 per year (51 [64%]). Characteristics of women in the N_2O/O_2 group were similar to those of the participants assigned to the O_2 group (Table 1).

Mean insertion pain scores at IUD insertion were similar among the N_2O/O_2 and O_2 groups ($P=0.86$) (Table 2). Baseline and expected pain, and pain at the time of discharge from the clinic were also similar between the two groups (Table 2). The 52-mg levonorgestrel IUD was selected by 67 (84%) participants. Mean insertion pain score was 57.5 ± 21.7 mm with the 52-mg levonorgestrel IUD and 43.4 ± 23.0 mm with the copper T380A IUD ($P=0.07$).

Use of adjunctive measures—e.g. the os-finder and dilators—was more common in the N_2O/O_2 group than in the O_2 group ($P=0.02$), whereas the procedure duration did not differ between the two groups ($P=0.14$) (Table 3). The obstetrics–gynecology faculty, family medicine faculty, and family planning fellows inserted all IUDs, with most inserted by the obstetrics–gynecology faculty (46 [58%]). Pain scores did not differ among the provider types (data not shown). One (3%) IUD insertion procedure was unsuccessful within the N_2O/O_2 group owing to the creation of a false tract.

Satisfaction with pain management was similar between the N_2O/O_2 and O_2 groups ($P=0.39$) (Table 2). Significantly more women in the N_2O/O_2 group than in the O_2 group were satisfied with their pain management on the Likert scale ($P=0.04$) (Table 2). Women reported their dissatisfaction with pain management as follows: “It hurt more than I expected;” “There needs to be better options for pain management;” and “I felt there was little to no pain control.”

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