Pain in diagnostic hysteroscopy: a multivariate analysis after a randomized, controlled trial

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Objective: To study which variables are able to influence women's experience of pain during diagnostic hysteroscopy.
Design: Multivariate analysis (phase II) after a randomized, controlled trial (phase I).
Setting: Endoscopic gynecologic center.
Patient(s): In phase I, 392 patients were analyzed. Group A: 197 women with carbon dioxide (CO_2); group B: 195 women with normal saline. In phase II, 392 patients were assigned to two different groups according to their pain experience as measured by a visual analogue scale (VAS): group VAS >3 (170 patients); group VAS ≤3 (222 patients).
Intervention(s): Free-anesthesia diagnostic hysteroscopy performed using CO_2 or normal saline as distension media.
Main Outcome Measure(s): Procedure time, VAS score, image quality, and side effects during and after diagnostic hysteroscopy.
Result(s): In phase I the median pain score in group A was 2, whereas in group B it was 3. In phase II the duration of the procedure, nulliparity, and the use of normal saline were significantly correlated with VAS >3. A higher presence of cervical synechiae was observed in the group VAS >3. The multivariate analysis revealed an inverse correlation between parity and a VAS >3, whereas the use of normal saline, the presence of synechiae in the cervical canal, and the duration of the hysteroscopy were all directly correlated to a VAS score >3.
Conclusion(s): Pain in hysteroscopy is significantly related to the presence of cervical synechiae, to the duration of the procedure, and to the use of normal saline; conversely, parity seems to have a protective role.
Clinical Trial Registration Number: NCT01873391. (Fertil Steril® 2014;102:1398–403. ©2014 by American Society for Reproductive Medicine.)
Key Words: Diagnostic hysteroscopy, pain, saline solution, carbon dioxide, distension media

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Diagnostic hysteroscopy is the gold standard in the study of uterine cavity morphology and in the diagnosis of endocavitary pathologies (1). Despite being considered an outpatient procedure (2) that is associated with a high success rate and a low complication rate (3), hysteroscopy is largely viewed as a painful procedure, poorly tolerated by patients (4) and often carried out under general or local anesthesia.

In an attempt to make the examination less painful, a new generation of hysteroscopes has been developed, characterized by being of smaller caliber and potentially less invasive (5–8). Other studies have resorted to pharmacologic approaches (9–11), which at times can be relatively invasive (10, 12), to find a solution for pain during hysteroscopy; but besides not reaching consensus on their actual effectiveness (13), those studies also altered the outpatient nature of the procedure (14).

Special attention has been paid to the role played by distension media during hysteroscopy (15), and despite the substantial literature available on the matter, results are often controversial (16–19) and even unreliable in some cases, owing to the limited number of enrolled patients (17, 20).

Ideally, an investigation should consider blinding on multiple levels (including the operator); nevertheless, because of the nature of these trials, the only ones who can be blinded are those who collect the data and the women who participate (21).

To investigate the relation between different variables and pain levels during diagnostic hysteroscopy, and considering that there are several variables with different natures among them, a multivariate approach is required: in this way, the distension medium, the pathologies, and the patients' characteristics can all be taken

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into consideration at the same time. To date, no report has been published with this methodology.

To include the distension media in our analysis, we first created a randomized, controlled trial using carbon dioxide (CO_2) or saline solution. At a later stage the same patients were analyzed according to the pain experience perceived during hysteroscopy, and a multivariate analysis was carried out. In this manner it was possible to include the distension media as an independent variable in the context of a multivariate logistic regression model.

MATERIALS AND METHODS

Phase I: Randomized, Controlled Trial

From June 2013 to January 2014 we conducted a prospective, randomized, controlled study of 603 patients who underwent diagnostic hysteroscopy at the "Arbor Vitae" Center for Endoscopic Gynecology (Clinica Nuova Villa Claudia, Rome, Italy). Institutional review board approval was obtained for data collection. The study protocol was registered in the ClinicalTrials.gov Protocol Registration System (ClinicalTrials.gov identifier: NCT01873391). Informed consent was obtained from all the patients.

All Italian-speaking patients were initially enrolled. Indications for a hysteroscopy were abnormal uterine bleeding, infertility, recurrent miscarriage, fibroids, polyps, uterine malformation, and endometrial thickening. Women with ongoing pregnancy, cervical carcinoma, pelvic inflammatory disease, or women who had previously undergone cervical surgery were not included.

To exclude factors that could influence the perception of pain, patients who had previously undergone diagnostic hysteroscopy were ruled out. In addition, exclusion criteria included the presence of excessive uterine bleeding and the execution of an endometrial biopsy during the procedure.

Patients allocated to the study were divided into two groups according to the distension media used for the procedure: carbone dioxide (CO_2) (group A) or normal saline (group B), in accordance with a previously generated randomized sequence. Randomization was performed by a statistical consultant (V.B.) using computer-generated numbers (StatsDirect version 2.7.2; StatsDirect Ltd.).

The distension medium was assigned before starting the diagnostic procedure by opening a sealed, opaque envelope containing the group allotment.

To avoid significant bias concerning hysteroscope diameter and shape, the hysteroscopy was performed using a rigid telescope with a diameter of 4 mm and a 30° fore-oblique covered with a single-flow examination sheath with a diameter of 5.1 mm (Hamou II; Karl Storz).

In group A an electronic hysteroflator (Hamou Hysteroflator; Karl Storz) was used at a flow rate of 30 mL/min and a maximum intrauterine pressure of 75 mm Hg. In group B normal saline was mechanically infused using a squeeze bag at a maximum pressure of 80 mm Hg. Patients were not allowed to follow the procedure on a monitor.

Two expert surgeons with the same abilities and educational background (M.G. and S.H.) indifferently performed all the procedures through vaginoscopy with both distension media according to the randomized allocation.

The cervical canal was explored using a 30° fore-oblique view, and the image was placed at a 6 o'clock position on the screen. The surgeons never resorted to the use of a tenaculum to grasp the cervix, nor did they resort to cervical dilatation or to the administration of prostaglandins.

Local or general anesthesia was not used, nor were analgesic or antispastic drugs administered before or after the procedure.

In women of fertile age, the procedure was carried out during the proliferative stage of the menstrual cycle. Medical history data were collected, such as age, pre- or postmenopausal state, parity, the number of previous cesarean sections, and the indication for the procedure. The duration of the examination was measured from the moment the hysteroscope was inserted into the external orifice of the uterus until its complete removal. In the case of unbearable pain or unsatisfactory vision quality of the uterine cavity, the procedure was stopped and the perceived level of pain was collected.

The main characteristics of the cervix were recorded, so as to describe its morphology (anteversion, retroversion, latero-deviation, normoversion, and mixed pattern) and the presence of synechiae, endocervical polyps, stenosis of the external orifice of the uterus, and isthmocele.

An individual's pain threshold is somewhat subjective: therefore, to better compare the groups and to obtain a reference point in the evaluation of pain, before starting the procedure patients were asked to quantify their menstrual discomfort on a visual analogue scale (VAS) from 0 to 10, where 0 corresponds to no pain and 10 to the worst pain imaginable. Using the same method, they were asked to express the pain they expected to perceive during the hysteroscopy (22).

To avoid shoulder tip pain, at the end of hysteroscopy we invited patients to remain in the supine position for a few minutes while taking deep breaths, to absorb the gas from the abdominal cavity.

Five minutes after the procedure, the patients were once again asked the same question, so as to quantify the pain actually experienced during the procedure, as well as the presence of symptoms like nausea, dizziness, or shoulder pain.

Phase II: Analysis According to the Pain Experience

The studied population was subsequently divided into two new groups according to the pain experienced during the procedure, regardless of the distension medium used. To investigate which variables were responsible for pain during the hysteroscopy, we defined a painful experience as all the procedures in which the patients reported a VAS score >3. We divided the patients into a first group with a VAS score >3 and a second group with a VAS score ≤ 3. These criteria were based on the widely approved standard in the literature, which assesses >3 as the perception of significant pain (22–24).

All the variables taken into consideration in phase I were analyzed through a bivariate analysis, to highlight the factors that could potentially and significantly influence the perception of pain in hysteroscopy. A multivariate analysis was