A randomized controlled study comparing carbon dioxide versus normal saline as distension media in diagnostic office hysterectomy: is the distension with carbon dioxide a problem?

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Objective: To compare two distension media, carbon dioxide (CO2) and saline, with regards to patient discomfort and the adequacy of the panoramic view in diagnostic hysteroscopy by the vaginoscopic approach.

Design: Randomized prospective study.

Setting: Tertiary referral centers for gynecologic care.

Patient(s): 264 patients randomly allocated to two groups: CO2 (132 women) and normal saline (132 women).

Intervention(s): Office hysteroscopy performed with a forward-oblique 30° telescope (total diameter 5.1 mm) and CO2 as the distension medium or with a forward-oblique 30° telescope (final diameter 5.1 mm) and saline solution as the distension medium.

Main Outcome Measure(s): Global operative time, pain experienced by patients using a visual analogue scale (VAS), severity of the pain (VAS), incidence of collateral effects (shoulder-tip pain, nausea, or dizziness), degree of difficulty, and view (VAS).

Result(s): Pelvic discomfort was comparable between groups, without statistically significant differences in intensity or degree of difficulty. However, the visual quality was statistically significantly higher when hysteroscopy was performed with CO2 as the distension medium.

Conclusion(s): No relevant difference in pain or technical difficulty was found between the two distension media, but CO2 was associated with better quality visualization. (Fertil Steril 2010;94:2319–22. ©2010 by American Society for Reproductive Medicine.)

Key Words: Carbon dioxide, CO2, normal saline, pain, office diagnostic hysteroscopy, view

Hysteroscopy represents the gold standard procedure for assessing the endometrial cavity and for the diagnosis of several endometrial conditions (1), a diagnostic role shared in the past with dilation and curettage, hysterosalpingography, and more recently two-dimensional and three-dimensional ultrasonography and sonohysterography (2-4). The technical limitations that hampered the diffusion of hysteroscopy, mainly related to the distension of the cervical canal and the uterine cavity (5), were resolved by the use of carbon dioxide (CO2) as a distending medium, on the basis of satisfactory canal and the uterine cavity (5), were resolved by the use of carbon dioxide as the distension medium.

The second technologic improvement occurred in 1996, when the Bettocchi Office Hysteroscope (Karl Storz, Tuttingen, Germany) incorporated a telescope of 2.9 mm diameter covered with a continuous-flow sheath and an operating sheath equipped with a channel for semirigid 5-Fr instruments (5.1 mm diameter) (8, 9). These technical features, together with the use of saline solution as the distension medium, simultaneously allowed diagnostic and therapeutic procedures (i.e., office hysteroscopic surgery) (10). The popularity of saline as the distension medium for hysteroscopy contributed to the discontinuation of CO2, as did the presumed greater pain during the examination, the vision compromised by the emergence of bubbles, the phrenic reflex, and the not-negligible need for a speculum (11).

Our prospective, randomized study compared the two distension media, CO2 and saline, with regards to patient discomfort and the adequacy of the panoramic view in diagnostic hysteroscopy by the vaginoscopic approach (12), without the use of a speculum or a single-tooth tenaculum forceps for grasping the cervix and without use of local or general anesthesia.

MATERIALS AND METHODS

Enrollment

Our study was conducted prospectively from February to May 2007, and a total of 290 consecutive women were found to be eligible for our study of
office diagnostic hysteroscopy. All patients (average age: 46.3 ± 10.4 years, mean ± standard deviation [SD], range: 22 to 74 years) who gave consent for diagnostic hysteroscopy underwent a physical examination after a detailed medical, obstetric, and gynecologic history was obtained (Table 1 shows the clinical and anthropometric details). The institutional ethics review committee approved the study, all women were fully informed of all aspects of the study, and informed consent was obtained before participation.

There was always an interval period ranging from 2 to 6 weeks between obtaining consent for women to enroll in the trial, randomization, and performing the hysteroscopy to give them sufficient time to consider their decision and opt out of the study. At the end of the selection, 16 women were lost at enrollment, and 10 patients had hysteroscopy in the meantime, so that 132 patients in each group: group A, CO2 as distension medium, and group B, saline solution as distension medium.

Inclusion and Exclusion Criteria
Inclusion criteria were the evaluation of abnormal uterine bleeding, suspected müllerian anomalies, the assessment of uncertain or abnormal findings on imaging studies, infertility, increased endometrial thickness, assessment of the endometrium in women taking tamoxifen, and cytologic endometrial hyperplasia. Exclusion criteria were patients with cervical carcinoma, menorrhagia or excessive bleeding at the time of hysteroscopy, pelvic inflammatory disease, and pregnancy. Surgeons involved in the study were skilled in both procedures, and the decision between the two approaches was made preoperatively according to the randomization. None of these patients were previously evaluated by sonohysterography.

Main Outcome Measures
Our study established whether compliance of patients differed based on distension media used in diagnostic hysteroscopy. To that end, after the hysteroscopic procedure was completed, we evaluated the patients’ pain by use of a visual analogue scale (VAS); the severity of the pain was expressed as a score ranging from 0 to 10 (13, 14). The patients also were asked to report their emotional status as “quiet” or “anxious” and record their answers. During each procedure, we recorded the global operative time, which included the time spent passing through the cervical canal.

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**Table 1**

<table>
<thead>
<tr>
<th>Clinical and anthropometric data related to the different distension medium used in the study: group A with CO2 and group B with normal saline.</th>
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<tbody>
<tr>
<td>Group</td>
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<tr>
<td>Mean ± SD age (in years)</td>
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<tr>
<td>Nulliparous (n, %)</td>
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<tr>
<td>Nulliparous with caesarean section (n, %)</td>
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<td>Multiparous with spontaneous delivery (n, %)</td>
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<td>Premenopausal (n)</td>
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<tr>
<td>Postmenopausal (n)</td>
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<tr>
<td>Retroverted uterus (n, %)</td>
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<tr>
<td>Orifice stenosis (n, %)</td>
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<td>Uterine malformations (n, %)</td>
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<td>Uterine synechiae</td>
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**Hysteroscopy Techniques**

We synchronized the examination with patient’s menstrual flow to perform the hysteroscopy on the 7th to 12th day of menstrual flow. All examinations were performed by the vaginoscopic approach (10, 12, 15) without the use of a speculum, single-tooth tenaculum forceps for grasping the cervix, or local or general anesthesia. In group A (CO2), we used a forward-oblique 30° telescope, 4 mm diameter, 24 cm length, covered with a single-flow examination sheath of 5.1 mm diameter (Hamou I; Karl Storz), and a hysteroflator for the CO2 (Hamou Hysteroflator; Karl Storz); the endouterine pressure did not exceed 100 mm Hg, and the flow was 80 ml/minute. In group B (normal saline solution), we used a forward-oblique 30° telescope, 2.9 mm diameter, 30 cm length (Karl Storz) with a 5.1 mm diameter continuous-flow sheath (Betocchi; Karl Storz); the manual pressure of infusion did not exceed 80 to 100 mm Hg.

In both cases, because the telescope has a forward-oblique vision of 30°, progression in the cervical canal was achieved by placing the cervical canal on the lower side of the monitor, entering the uterus. Endometrial biopsy samples were obtained with the use of a 5-Fr grasp (Karl Storz) when saline solution was the distension medium or Mazzon’s forceps (diameter 3 mm, length 30 cm, spread 1 cm; Karl Storz) with CO2, which was inserted in the single-flow sheath after the telescope removal. The telescope was then reinserted into the sheath to verify the appropriateness of the biopsy.

**Statistical Analysis**

In a recent large study involving 1144 patients undergoing outpatient hysteroscopy, the mean VAS pain score was 4.7 ± 2.5 (mean ± standard deviation [SD]) (16). On this basis, we assumed that the SD of the 10-cm VAS pain scores in each of our study groups would be close to 2.5 cm and that an underlying difference in mean pain score between the two distension media of 1.0 cm or greater would be of clinical significance. The sample-size calculation, computed by using a two-tailed test with an α level of 0.05 and 80% power, revealed that a sample size of 100 patients in each group would be needed to detect this difference and to detect a similar mean difference (1.0 cm) on the VAS for the confidence rate based on the operator for the hysteroscopic view, assuming a corresponding 2.5 cm (or less) SD for the VAS for confidence scores in each of the groups.

Data were analyzed with Prism software (GraphPad Software Inc., San Diego, CA) and were expressed as mean ± SD. The Kolmogorov-Smirnov test was used to evaluate whether values had a Gaussian distribution: the unpaired t-test was used to compute statistical significance, and chi-square and Fisher exact test to analyze differences between proportions. P<.05 was considered statistically significant.

**RESULTS**

After randomization, groups A and B were similar in age, parity, and body mass index as well as the prevalence of women who were nulliparous, nulliparous with previous caesarean section, multiparous with previous spontaneous delivery, and/or had a retroverted uterus (see Table 1). Moreover, the prevalence of cervical and/or endometrial diseases did not differ between groups (see Table 1).
Hysteroscopic evaluation was performed in all patients. Phrenic reflex occurred only in one patient in group A. The total procedure time required was comparable between the two groups (group A, 112 ± 14 seconds; group B, 109 ± 12 seconds; P > .05, data not shown), as was pelvic discomfort (VAS of experienced pain: group A, 4.1 ± 2.27; group B, 4.1 ± 2.20; P = .95) (see Table 1). When we evaluated differences in prevalence for the women who found hysteroscopy a very painful experience, the data were found to be superimposable between groups: group A, 7 out of 132 (5.3%), and group B, 8 out of 132 (6.1%) (P = .98). We also retrospectively evaluated the differences in the intensity of pain and the presence of cervical and/or endocavitary diseases: pain intensity did not differ between groups for patients with orifice stenosis, uterine malformations (intrauterine septum ≤ 0.5 cm in both groups, suspected after ultrasonography), and/or synechiae (VAS of pain in uterine disease; Table 2); however, pain intensity was statistically significantly higher (group A, 8.4 ± 1.27; and group B, 8.5 ± 1.13; P < .0001 for both) in the patients with these conditions than in patients without them (group A, 3.9 ± 2.1; group B, 3.8 ± 1.9).

When we evaluated for any correlation between the patient’s emotional state (i.e., quiet or anxious) before the hysteroscopy and the pain experienced during evaluation of the endometrial cavity, we found no correlation. Hormone status (i.e., menopausal vs. premenopausal status) also did not correlate with pain (P > .05, data not shown); however, nulliparous patients experienced more intense pelvic discomfort (group A, 6.4 ± 2.7; group B, 6.0 ± 2.2), as did women who had delivered by caesarean section (group A: 5.2 ± 1.6; group B: 5.3 ± 1.8) when compared with multiparous women who had had spontaneous deliveries (group A: 3.9 ± 1.9; group B: 3.8 ± 1.4) (P < .01 for both).

The degree of difficulty did not differ with the distension medium used, but the visual quality was statistically significantly higher (P < .001) when CO2 was used as the distension medium (VAS for visual quality: group A, 8.9 ± 1.85; group B, 7.0 ± 0.7; data not shown).

**DISCUSSION**

The uterine cavity is a potential space, so it must be distended to be inspected properly. Therefore, a distension medium (either fluids or CO2 gas) is introduced into this space throughout the hysteroscopy examination to expand and expose the intrauterine cavity. The choice of the type of the distension medium depends on the type of procedure: fluids can be used for both diagnostic and operative procedures, but CO2 distension is only for diagnostic procedures. When comparing CO2 with saline solution as the distension medium, many investigators have reported that CO2 is more often associated with pain, more side effects (mainly the stimulation of the phrenic reflex [11, 12, 15]), or gas bubbles that interfere with clear visualization of the uterine cavity (12, 16–23).

Our use of CO2 was not associated with any statistically significant increase in pain or side effects (i.e., phrenic reflex) because we allowed patients to remain lying for a few minutes while deep breathing, which cleared the gas from the abdominal cavity.

Typically, saline solution has been recommended for diagnostic hysteroscopy because it offers clearer vision of the uterine cavity and less pain while inserting instruments through the uterine cervix (8, 18, 21, 22). However, performing a hysteroscopic examination correctly will minimize pain symptoms, regardless of distension medium: the telescope is 30° forward-oblique, so progression through the cervical canal must be achieved by placing the cervical canal on the lower side of the monitor entering the uterus. If the cervical lumen appears in the middle of the monitor, the telescope is not well positioned—if the sharp point, characteristic of forward-oblique scopes, is directed against the posterior wall of the uterine channel, pain and bleeding result. Accordingly, we have found that proper technique in passing through the cervical canal is the most important factor in pain experienced by patients, independent of the differences in telescope diameters. We also found that pain perception was higher in patients who had orifice stenosis, uterine malformations, and/or synechiae when compared with those who did not have these problems, independent of the type of distension medium used.

In visualizing the uterine cavity, we found that visual quality was better when hysteroscopy was performed with CO2 distension, confirming the findings of previous studies (8, 18, 21, 22). The hysteroscope that we used with normal saline medium had a diameter of 2.9 mm; the 30° forward-oblique telescope was inserted into a system of Bettocchi sheaths (5.1 mm diameter), with continuous-flow and channel for semirigid 5-Fr instruments. In contrast, the telescope that we used with CO2 had a diameter of 4 mm; its size reasonably allowed a better panoramic vision, with optimum diffusion of light, and clearer and more defined views than could be obtained with a telescope of smaller diameter (i.e., 2.9 mm). The problem of “bubbles,” which has been described as the inevitable accompaniment of CO2, only occurs when the gas mixes with liquid; thus, bubbles can be minimized by keeping the sheaths and optics always dry.

Other reasons for better visualization with CO2 are the better index of refraction and the absence of an “algae effect” (fluctuations of the endometrial lining caused by saline solution). As a result, hysteroscopic visualization of endouterine structures or pathologies is finer with CO2 as distension medium than can be obtained with saline solution, and endometrial components such as vascular distribution, glandular outlets, surfaces, thickness, and color are better evaluated. Also, CO2 appears to be associated with a lower risk of germs, mucus, and cells spreading upward (23).

Our study demonstrates that the technical problems encountered during the performance of hysteroscopy have little to do with the distension medium used; rather, improper selection of patients and difficulty in navigating the cervical canal play greater roles. Indeed, with office hysteroscopy the selection of patients is paramount for success. Identifying patients who have anatomic cervical defects or are especially susceptible to pain (who may require anesthesia or analgesia rather than be subjected to a trial of pain tolerance) will increase successful outcomes.

| Table 2: Visual analogue scale (VAS) of pain intensity for distension medium: group A with CO2 and group B with normal saline. |
|-----------------|-----------------|-----------------|
| **Group A (n = 132)** | **Group B (n = 132)** | **P value** |
| Very painful (n, %) | 7 (5.3) | 8 (6.3) | .98 |
| VAS of experienced pain | 4.1 ± 2.27 | 4.1 ± 2.20 | .95 |
| VAS of pain in uterine diseases | 8.4 ± 1.27 | 8.5 ± 1.13 | .83 |

REFERENCES


