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Carbon dioxide in office diagnostic hysteroscopy: An open question. A multicenter randomized trial on 1982 procedures

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ABSTRACT

Objective: to compare carbon dioxide and saline solution distension in diagnostic hysteroscopies with regards to patient discomfort and procedural time and in accordance with the instrument diameter (5 mm vs 3.5 mm). The secondary outcome was to evaluate the role of the patient age and the obstetrical history on perception of pain and procedural time.

Study design: This is a prospective multicenter randomized study including 1982 patients that underwent office diagnostic hysteroscopy in: Policlinico Abano Terme, Università Cattolica del Sacro Cuore in Rome and Ente Ecclesiastico Ospedale Generale Regionale "F. Miulli" in Acquaviva delle Fonti. They were firstly randomized according to distension medium and secondly according to instrument diameter. Pain perception after the procedure was assessed by VAS (Visual Analogue Scale) score and procedural time was registered. Mann-Whitney U test was used to compare data.

Results: Lower pain score and procedural time were recorded with the employment of Carbon Dioxide ($p < 001$). Patient discomfort and procedural time were significantly influenced by the instrument diameter independent of the distension medium used, though in the subgroup where gas was employed VAS score after 1 min (VAS1) resulted lower compared to saline solution in both the traditional and mini-hysteroscopy procedures ($p < 001$).

Conclusion: Carbon dioxide and saline solution are both suitable distension media for outpatient diagnostic hysteroscopy; nonetheless, carbon dioxide confers advantages in terms of pain perception and procedural time.

Introduction

Diagnostic hysteroscopy could be considered the result of two hundred years of history characterized by technologic improvements that have contributed to the widespread employment of this procedure for assessing the endometrial cavity and for the diagnosis of several endometrial conditions [1]. Because of the feasibility of the technique and the reduced discomfort for patients, obtained through the introduction of small-diameter hysteroscopes (<3.5 mm) and the vaginoscopic "no touch" approach, diagnostic hysteroscopy has become a routinely outpatient procedure [2,3].

Notwithstanding, there are still several problems to face that are mainly related to pelvic pain, endometrial bleeding that may influence the image quality, side effects and patient satisfaction that can be associated with the distension medium used during the procedure [4].

In this field, for many years, carbon dioxide (CO2) was the only distension medium employed [5]; the popularity of saline solution (NaCl) as distension medium contributed to the discontinuation of CO2, thanks to its easy availability, safety and low cost [6]. In addition, in the era of "see and treat", the NaCl is the only distension medium that can be employed for operative procedures.

Based on these data, we conducted a randomized, multicenter study to compare the two different distension media CO2 and NaCl in women undergoing diagnostic hysteroscopy. The primary

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objective of the study was the assessment of patient discomfort and the procedural time with both distension media and in accordance with the instrument diameter (5 mm vs 3.5 mm). The secondary objective was to evaluate the possible role of the patient age and the obstetrical history on the perception of pain and procedural time.

Materials and methods

Our randomized study was conducted from November 2016 to April 2017 in three Italian centres:

- Department of Obstetrics and Gynaecology, Policlinico Abano Terme (Centre A).
- Department of Obstetrics and Gynaecology, Università Cattolica del Sacro Cuore in Rome (Centre B).
- Department of Obstetrics and Gynaecology, Ente Ecclesiastico Ospedale Generale Regionale "F. Miulli" in Acquaviva delle Fonti (BA) (Centre C).

All patients who gave written consent for diagnostic hysteroscopy underwent the procedure after an accurate medical, obstetric and gynecological history. The study was approved by the Institutional Review Board and all patients were informed of the study before the enrollment. It was a single-blinded (participant) study. The indications for performing diagnostic hysteroscopy were the following: suspected intrauterine lesions, abnormal uterine bleeding and/or infertility. Viable pregnancy, severe cardiovascular and/or respiratory diseases, acute infections and severe active bleeding were considered as exclusion criteria.

The procedures were carried out by the same four experienced gynecologists (RR, MG,LP) in the corresponding three centers. For patients in fertile age, the procedure was performed between the sixth and the twelfth day of the menstrual cycle. Randomization was reached using opaque sealed envelopes, containing computer-generated block randomization numbers, opened the day of the procedure. Two groups were obtained after the randomization on the basis of the distension medium employed: group A (vaginoscopic hysteroscopy with CO2) and group B (vaginoscopic hysteroscopy with NaCl). Carbon dioxide was delivered by an electronic HAMOU-hystero-insufflator (Storz, Tutlingen-Germany) adjusted to a flow rate of up to 60 ml/minute at a maximum pressure of 100 mmHg. The saline solution was instilled from a flexible 1000 ml bag wrapped in a pressure cuff connected to a manometer and pumped up to 100 mmHg. Illumination was provided by a 250-W Xenon light source with a fiber-optic cable. The images were viewed on a high-resolution color screen connected to the hysteroscope by a video-camera. Hysteroscopy was performed following the standardized vaginoscopic approach, without the use of a speculum or a single-tooth tenaculum forceps for clamping the cervix, as previously described [1,7]. No local anesthesia or systemic drugs were given to any patient.

In order to evaluate the role of the hysteroscopic diameter on the pain perception, group A and group B were further randomized, with the same method of randomization, to two other groups (Fig. 1). In particular, 485 patients in the CO2 group and 455 patients in NaCl group underwent the procedure with the conventional hysteroscopy set composed of a rigid optic (rod lens, 4.0 mm; 30-degree oblique vision) and 5 mm single-flow sheath (Karl Storz, Tuttlingen, Germany); 510 patients in the CO2 group and 532 patients in the NaCl group underwent the procedure with the mini-hysteroscopy set including a rigid optic (rod lens, 2.9 mm; 30 ° for oblique vision) and a 3.5 mm single-flow sheath (Karl Storz, Tuttlingen, Germany). To exclude the possible influence of other factors on the results obtained with the two different distension media, we performed two other subgroup analysis on the basis of the patient age (4 different groups: 20-39 years, 40-49 years, 50-60 years, over 60 years) and the obstetric history (nulliparous or parous women).

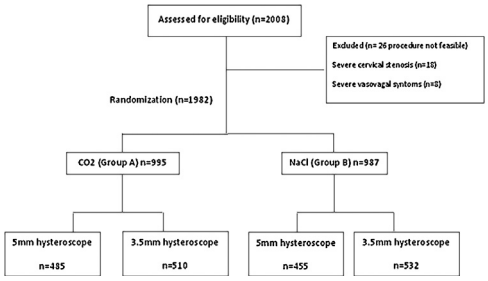

Fig. 1. Flow diagram of randomization of patients eligible for the study.

Outcome measures

The primary outcome measure was patient discomfort that was assessed through a visual analog scale (VAS 0= no pain; VAS 10= worst pain). These data were collected through a questionnaire that was administered by the nurse. Patients were asked to rate pain 1 min (VAS1) and 5 min (VAS5) after the end of the procedure and to point out any other symptoms like shoulder-tip pain. The procedural time was measured from the insertion of the hysteroscope into the vagina until its removal.

Statistical analysis

Results are presented as mean and standard deviation. Statistical analysis was performed by GraphPad Prism7 software. The distribution of data was tested by the Kolmorov-Smirnov test in order to verify whether the samples follow a specified distribution. We found that all variables were not normally distributed. The data from the study groups were compared by using Mann-Whitney U test. A p value of <0.05 was considered statistically significant. Based on the primary endpoint (the VAS score after the procedure and the procedural time) with the sample size employed our trial showed a statistical power of 100%.

Results

2008 women, enrolled for outpatient diagnostic hysteroscopy from November 2016 to April 2017 in three centers, aged between 18 and 65 years, were eligible for the study; in 26 of these women the procedure was not feasible (18 cases of severe cervical stenosis, 8 cases of severe vasovagal symptoms). Subsequently, in 1982 cases the diagnostic hysteroscopy was completed.

CO2 and NaCl were used for uterine distension in 995 patients (group A) and in 987 patients (group B) respectively. The first analysis showed that VAS score after 1 min (VAS1) and the procedural time were significantly lower in group A compared to group B (VAS1: 1.37 ± 0.05 vs 2.7 ± 0.06, respectively; $p < 0.01$; procedural time: 58.31 ± 0.8 s vs 76.62 ± 0.8 s, respectively; $p < 0.01$) (Fig. 2). After the second randomization on the basis of instrument diameter, the "mini-hysteroscopy group" ($n = 1042$) compared with the "standard hysteroscopy group" ($n = 940$) reported with less pain according to VAS1 and less procedural time, irrespective of the uterine distension medium used (VAS1: 1.25 ± 0.05 vs 1.82 ± 0.08, respectively; $p < 0.05$; procedural time 56.98 ± 0.98 vs 71.36 ± 1.32 s respectively; $p < 0.05$) (Fig. 3).

An additional analysis showed that in the group of patients who underwent mini-hysteroscopy, the VAS1 score was lower (1.21 ± 0.05 vs 1.97 ± 0.05, respectively; $p < 0.01$) and the procedural time was shorter when CO2 was employed rather than NaCl

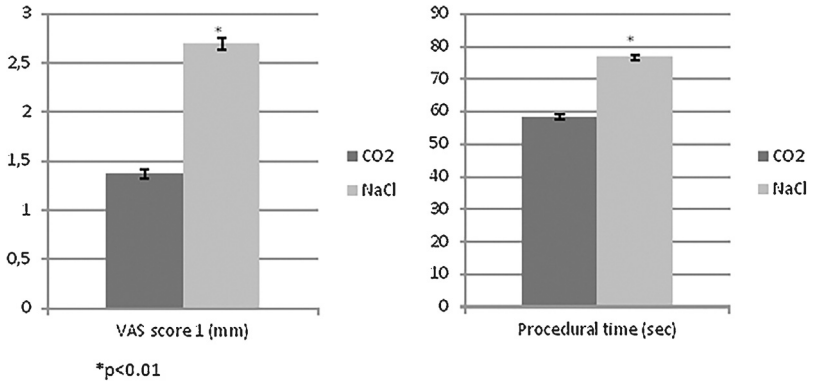

Fig. 2. VAS score 1 and procedural time in group A (N = 995) and group B (N = 987).

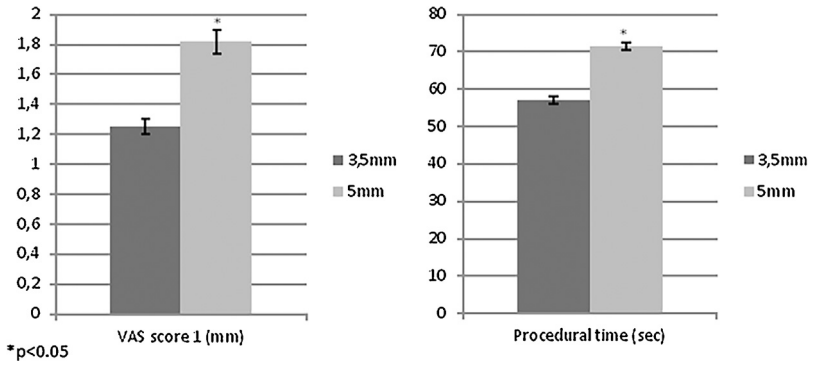

Fig. 3. VAS score 1 and procedural time according to the hysteroscope-diameter.

(54.6 ± 0.7 vs 58.8 ± 0.5 s). The same results were obtained in the group of women who underwent the standard hysteroscopy: pain scores (VAS1: 1.61 ± 0.08 vs 2.46 ± 0.08, respectively; $p < 0.01$) and time of hysteroscopy (64.4 ± 0.9 vs 75.8 ± 1.1 s) resulted significantly lower in the CO2 group compared to NaCl group (data not shown).

A further group sub-analysis was performed in order to evaluate the possible role of obstetrical history and patient age in influencing the perception of pain and the procedural time. We observed that pelvic discomfort, according to VAS1, was worse in nulliparous women (1.66 ± 0.05) than in parous (≥1 vaginal delivery) women (137 ± 0.07) ($p < 0.05$), independent of the distension medium used. In accordance with this result, also the procedural time resulted higher in the nulliparous patients, although these data did not reach the statistical significance. However, when taking into consideration the variable of the distension medium, the pain score was higher with the employment of saline solution in respect to carbon dioxide both in the nulliparous women (2.4 ± 0.08 vs 1.5 ± 0.07, respectively; $p < 0.01$) and in the parous women (2,5 ± 0.06 vs 1.27 ± 0.06, respectively; $p < 0.01$) (Fig. 4).

The final analysis was conducted after the allocation of the patients in four groups based on age (first group: 20–40 years; second group: 40–50 years; third group: 50–60 years; fourth

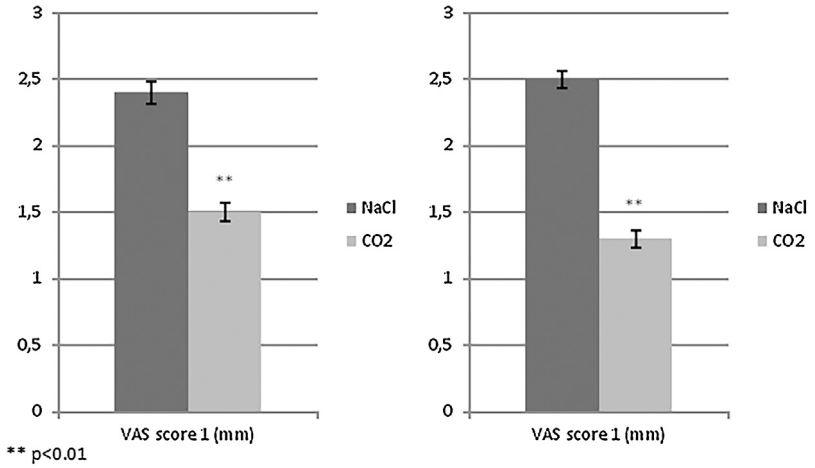

Fig. 4. VAS score 1 in nulliparous and parous women according to the distension medium employed.

group: over 60 years). VAS score increased with patients age although this trend did not reach the statistical significance (data not shown). As recorded in the other subgroup analysis, by correlating age and distension medium, pain scores were seen to be worse with the employment of NaCl compared to the CO2 in all four groups (Table 1).

We reported only 6 cases of shoulder tip pain in the group A. No other side effects and/or complications were noticed among all procedures.

Comments

Several randomized studies reported significantly lower patient discomfort and shorter procedural time, maintaining a good image quality of the uterine cavity, with the employment of saline solution [8–10] compared to gas. The systematic review and meta-analysis of ten randomized controlled trials published by Craciunas and collaborators in 2013 concluded that saline solution is superior to CO2 in terms of intensity of pain, incidence of shoulder-tip pain and rate of side effects, increasing women's satisfaction with the procedure [11]. Based on these data, NaCl may be considered more suitable for the clinical use. However, the validity of the showed results could be questioned by the undeniable bias that this review of literature included. The small sample size of several randomized trials, the heterogeneity of statistical methods, inclusion and exclusion criteria and the definition of side effects and measurements for pain, satisfaction or quality of view, make not possible to draw conclusions.

In light of this foreword, in the current randomized multicenter study, we aimed to assess the roles of uterine distension medium and instrument diameter in a large series of diagnostic procedures performed by three experienced hysteroscopists, in order to evaluate the influence of these two variables on the perception of pain and procedural time.

Unexpectedly, when we randomized patients on the basis of the distension medium used, patients belonging to the group A (C02) experienced a significant lower pain after diagnostic hysteroscopy and the procedural time resulted significantly shorter in this group compared to the group B (saline solution). These results appear to be independent of the instrument diameter, obstetrical history and/or age. This improvement in patient tolerability in the group A compared to the group B, registered immediately after the hysteroscopy, may be attributed to several factors: first of all, it could be explained by the significant shorter time of procedure registered with carbon dioxide that can be linked to its properties of excellent endoscopic medium concerning the visualization of the uterine cavity. It is well known that carbon dioxide has the same refractive index as air, providing clear images of endometrial cavity [12]. In addition, we hypothesized that the lower VAS score observed after 1 min in the CO2 group could be associated with the minimal pressure that was employed during the procedure with gas compared with fluid (60 mmHg vs 80–100 mmHg); indeed, as is common knowledge, the patient discomfort during hysteroscopy, as for any hollow viscus, is mainly influenced by the distension of the uterine cavity. Finally, the reasons of these findings may be associated with the stepwise distension of both the cervix and the uterine cavity that can be obtained by the employment of gas compared to a fluid medium.

Table 1
VAS score in the subgroups divided on the basis of patient age according to the distension medium employed.

	VAS score with NaCl (Group A:995 patients)	VAS score with CO2 (Group B: 987 patients)
20–39 years	1.92 ± 0.07*	1.29 ± 0.08
40–49 years	2.05 ± 0.06*	1.38 ± 0.08
50–60 years	2.10 ± 0.09*	1.39 ± 0.01
Over 60 years	2.57 ± 0.12*	1.53 ± 0.12

In a further analysis, we decided to appraise critically the role of the instrument size, the obstetrical history and the patient age on the perception of pain during the procedure.

As expected, after the second randomization we found that the instrument size (5 mm vs 3.5 mm) played a crucial role in the pelvic discomfort complained by patients; this result is in line with previous studies reporting that the employment of smaller instruments is closely related to the reduction of pain during hysteroscopy [13,14].

Nonetheless, the analysis obtained from the second randomization further confirmed the results obtained in the whole group of patients. Both in the subgroup of women that underwent a mini-hysteroscopy (hysteroscope size: 3.5 mm) and in the subgroup of women that underwent conventional hysteroscopy (hysteroscope size: 5 mm), the uterine cavity distension by carbon dioxide induced less pain as VAS1 and resulted associated with shorter procedural time and these findings may be explained by the hypotheses proposed for the whole group of patients.

Analyzing the obstetrical history and the different categories of patient age, we found that the nulliparous status was associated with more intensive pelvic discomfort and longer procedural time. These data are in agreement with a large analysis performed by Litta and coll.; in this study, indeed, irrespective of the distension medium used, the pelvic pain was significantly worse in nulliparous women than in parous women. However, when taking into consideration all patients and both distension media, pelvic discomfort resulted higher with saline solution compared to CO2 both in the nulliparous and parous women and this result is in accordance with the study previously cited [8].

By correlating patient age and distension medium, procedural time was seen to be higher in elderly patients while the VAS 1 score was not statistically associated with increasing age.

Finally, the present study revealed that the employment of carbon dioxide as distension medium and the smaller diameter of the instrument represent the major determinants for a well-tolerated procedure. These two features appeared to be more essential than age or obstetrical history in the perception of pain soon after the procedure (VAS1) and in the quantification of the procedural time. The level of expertise of the surgeons was not considered as a variable in our analysis because all the procedures were performed by the same three experienced operators. However, in accordance with the large study performed by Di Spezio Sardo and collaborators in 2008 [15] the high level of expertise should not influence the success rate of outpatient hysteroscopy.

It could be argued that the advantages showed by CO2 in terms of procedural time and pain perception may be not clinically relevant given the trend towards "see and treat" and the inability to employ gas for operative procedures. However, this trial would stress the concept that the carbon dioxide is a distension medium that for pure diagnostic procedures should be employed because of the comparable effectiveness in respect to saline solution and possible less discomfort for the patients.

In conclusion, the randomized design may lead to a valid conclusion: this study suggests that, only for pure diagnostic procedures, the carbon dioxide should not be abandoned. Actually, in experienced hands, it should be employed as an appropriate distension medium for office-based hysteroscopy because associated with less pain and slightly shorter procedural time compared to saline solution.

Conflicts of interest

All authors have no conflicts of interest to declare.

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None.

Author contribution

V.Tagliaferri: Manuscript writing/editing.
L.Ricciardi: Data collection.
R.Ricciardi: Data management.
L.R.Pinto: Data management.
A.Lanzone: Protocol/project development.
G.Scambia: Protocol/project development.
M.Guido: Protocol/project development, manuscript editing.

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