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Comparison of Efficacy between Nitrous Oxide Analgesia and Pericervical Analgesia in Office Operative Hysteroscopy with 16 Fr Mini-Resectoscope: A Randomized Clinical Pilot Study

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Office hysteroscopy; Pain control; Miniresectoscope; Nitrous oxide; Pericervical analgesia

1. Abstract

Pain is the primary cause of failure in hysteroscopy. It can be attributed to multiple causes, such as manipulation of the cervical canal, uterine distension due to the liquid distension media used during the procedure, operative procedures on the endometrium, up to the release of prostaglandins following manipulation of the cervix and uterine distension. After the advent of the Bettocchi hysteroscope, the real revolution in office hysteroscopic surgery occurred in the early 2000s with the development of the Bipolar Mini-resectoscope : it is especially due to this new instrument that the modern hysteroscopy has been reached, allowing the simultaneous diagnosis and treatment of intrauterine pathology without significant risks or complications for the patient, thus enabling the operating room and hospitalization only for extremely selected cases. To fully utilize the high performance of the Mini-resectoscope, and thus, to minimize access to the operating room, it is necessary to ensure adequate pain control for the patient undergoing office hysteroscopic surgery. For this reasons, this study aims to evaluate and compare the effectiveness of two methods (nitrous oxide – INO- analgesia and pericervical analgesia) in controlling pain during office operative hysteroscopy using Miniresectoscope (GUBBINI system; Tontarra Medizintechnik®, Tuttlingen, Germany).

2. Introduction

Pain is the primary cause of failure in hysteroscopy. It can be attributed to multiple causes, such as manipulation of the cervical canal [1], uterine distension due to the liquid distension media used during the procedure2, operative procedures on the endometrium (a possible cause of uterine contraction 3), and even the release of prostaglandins following manipulation of the cervix and uterine distension [2,3]. A first major revolution in the hystory of hysteroscopy occurred with the advent of the Bettocchi hysteroscope, a miniaturized 5 mm instrument that allowed, for the first time in the history of hysteroscopy, the execution of the so-called "see and treat" approach, combining diagnostic and operative performance ("Office Continuous Flow Operative Hysteroscope") [4]. Nevertheless, the real revolution in office hysteroscopic surgery occurred in the early 2000s with the development of the Bipolar Miniresectoscope [5]. This instrument, approximately 15-16 Fr in size, is equipped with a 0° optics of about 3 mm, a continuous flow system, and an operative channel for the insertion of electro-surgical loops: effective in the treatment of intrauterine pathologies,

it bridges the benefits in terms of patient comfort, invasiveness, and costs of office hysteroscopy with the operative possibilities of resectoscopy [5]. Indeed, the bipolar miniresectoscope allows for the avoidance of cervical dilation and enables an increasingly minimally invasive surgical approach with local anesthesia even for large intrauterine pathologies, substantially limiting access to the operating room and hospitalization, with undeniable economic advantages as well. It is due to all these discoveries and innovations that modern hysteroscopy has been reached, allowing the simultaneous diagnosis and treatment of intrauterine pathology without significant risks or complications for the patient, thus enabling the operating room and hospitalization only for extremely selected cases. Few studies in the literature compared the various methods of pain control during hysteroscopic examination. Among these, Ahmad et al. [6], for instance, compared the use of paracervical block and inhalational anesthesia during hysteroscopy: although both were found effective in pain control, the paracervical block was associated with a higher number of complications [1]. More recently, Solano et al.6 defined the administration of nitrous oxide as equally effective (but with many more advantages) compared to paracervical block with 1% lidocaine in pain control during hysteroscopy performed using the Bettocchi hysteroscope. Regarding the measurement of pain during hysteroscopy, most studies in the literature have used the Visual Analogue Scale (VAS): among the most recent studies, Del Valle Rubido et al. [7], in 2015 reported a mean VAS score of 3 (on a VAS scale from 0 to 10) for nitrous oxide and 5 for paracervical analgesia; Solano et al. [6], in 2021, using a VAS scale from 0 to 100, instead reported a mean VAS score of 34.7 ± 25.8 mm for nitrous oxide and 36.1 ± 22.9 mm for paracervical analgesia.

However, for the purposes of this study, it is important to consider two aspects: all the studies in the literature that compared various methods of pain control during hysteroscopy were conducted using the Bettocchi Hysteroscope and not the Mini-resectoscope; and more specifically, there are no studies comparing the use of nitrous oxide and pericervical analgesia during office operative hysteroscopy with a Mini-resectoscope. This study aims to evaluate and compare the effectiveness of two methods (inhaled nitrous oxide – INO- analgesia and pericervical analgesia, excluding the use of paracervical block due to the increased risk of complications reported in the literature [7,1,8] in controlling pain during office operative hysteroscopy with Mini-resectoscope.

3. Matherial and Methods

This study is a single-blind randomized clinical pilot study with third-party masked evaluation. Patients have been assigned to the two groups (intervention group: pericervical analgesia / control group: nitrous oxide) using the sealed envelope method. The pilot study took place at the Hysteroscopy Service of the "Degli Infermi "Hospital in Ponderano (Biella, Italy); it has been validated by the Interhospital Ethics Committee of Novara (CE 130/2023) and registered on ClinicalTrials.gov (ID NCT06092541). The study enrolled patients referred to the Hysteroscopy Service for various types of intrauterine pathologies (polyps, fibroids, endometrial anomalies, adhesions, uterine septa, among others).

3.1. The Inclusion Criteria Were:

• Nulliparous or primiparous women (those with a history of either Spontaneous Vaginal Delivery - SVD - or Cesarean Section - CS - with the latter comparable to nulliparous women as there was no previous cervical dilation)

• Age between 25 and 50 years

Exclusion criteria were:

- Age < 25 or > 50 years
- Multiparity
- Positive history of previous interventions involving the cervical canal (e.g., conization)

Patients assigned to the Intervention group received pericervical anesthesia before undergoing hysteroscopy.

Specifically, for the administration of pericervical analgesia, Mepivacaine 1.5% 10/15 ml (max dose 7 mg/kg) was used, and pericervical infiltration at a depth of 0.5 cm at 3 o'clock and 9 o'clock was performed. Upon the patient's acceptance at the Hysteroscopy Service, a verbal discussion were conducted with the Gynecologist regarding the office operative hysteroscopy procedure (Time 1), including:

- Explanation of the timelines of office operative hysteroscopy;
- Objectives of the office operative hysteroscopy;
- Type of obstetric/medical care and monitoring;
- Brief explanation of the study and request for participation.
- Types of analgesia provided by the study;
- Information related to discharge instructions.

Time 1 ended with the signing of the consent to participate in the study.

Time 2: Subsequently, pericervical analgesia was performed as described earlier, followed by office operative hysteroscopy using Miniresectoscope (GUBBINI system; Tontarra Medizintechnik®, Tuttlingen, Germany).

Time 3: After the procedure, patients were subjected to an assessment of the pain experienced using the Visual Analog Scale (VAS 0-10 cm - 0 no pain, 10 unbearable pain). The patients of the control group followed the same timelines, except for the type of analgesia, which in this case involved the administration of INO via bucconasal mask. The environment of the hysteroscopy service has been arranged with soft lighting and relaxing background music to allow patients to relax even before the procedure. Fifty patients were enrolled in six months (identified sample size as-

suming a pooled standard deviation of 2.5 units on a VAS scale from 0 to 10, to detect a difference of two points on the VAS scale between the two groups, with 80% power and a significance level of 5% 9), with 25 in the intervention group and 25 in the control group. Among these 50 patients, data of interest, in addition to inclusion criteria, were collected through the anamnestic interview before the procedure. Specifically, the following informations were collected: last menstrual period, prior uterine surgeries, any comorbidities, allergies, medications, and indication for hysteroscopic examination. For the purposes of the study, at the end of the procedure, enrolled subjects completed the Visual Analog Scale (VAS 0-10 cm) for pain assessment, to determine which of the two methods is more effective in pain control during office operative hysteroscopy using the Miniresectoscope. Regarding the blinding of the study, the allocation and participants were blinded, care providers were not blinded, and the outcome assessors and data analysts were blinded thanks to the insertion of data entered as group A and B and not as control and intervention. As for as the statistical analysis, possible confounding variables were collected through the aforementioned questionnaire, and in the case of statistically significant differences between the experimental and control groups, adjustment were made through stratification or logistic regression [10]. The outcome of this study were the difference in mean VAS scores between the two groups and the corresponding standard deviation were estimated in order to obtain an evidence-based measure based on the weighted mean difference (WMD) between means adjusted for sample size with respective 95% confidence intervals.

4. Results

In the present study, 50 women were recruited, 25 in the group A (pericervical analgesia) and 25 in the group B (INO), and no participants left or withdrawed before the termination of the study. There was a significant difference in the mean of the VAS scores between the 2 groups (p=0.002). Table 1 actually indicates means and standard deviation (SD) of VAS scores of the 2 groups; as shown in Table 1, the mean of VAS values of Group A was 3.12, with SD of 2.3; the mean of VAS values of Group B was 5.32, with SD of 2.58 : from these results derives a WMD of -2.12 (IC95%= -3.46 ; -0.78 , p<0.005), with a statistically significant difference in VAS values of group A compared to group B.

No adverse effect was reported in either group.

Table 1: Means and standard deviations of VAS scores of the 2 groups.

Group	Mean	SD	Frequency	*P-value*
A	3.16	2.2300972	25	
B	5.12	2.5871477	25	
Total	4.14	2.5873318	50	0.002

Abbreviation: SD, standard deviation.

5. Discussion

It is now well known that pain is the primary cause of hysteroscopy failure. For this reason, all efforts in the field of hysteroscopy in recent years have been focused on reducing discomfort during the procedure and consequently improving patient compliance. Among the main innovations that have contributed to the emergence of modern outpatient hysteroscopic surgery -a rapid method well tolerated by patients, with a significantly lower rate of postoperative risks and complications- we recall the use of saline solution as a means of uterine cavity distension, the transition from a monopolar to a bipolar circuit, the use of miniaturized instruments with operative performances, and the development of the "no-touch technique" vaginoscopic approach by Stefano Bettocchi.11

In this regard, numerous studies have highlighted the advantages of the vaginoscopic approach over the traditional one12: the atraumatic vaginoscopic technique has been shown to be faster, better tolerated by patients, and associated with fewer risks. In fact, the reduction of pain is primarily linked to the technique changes introduced in the initial phase of the procedure: while the insertion of the speculum and tenaculum forceps used to cause significant pain to patients before the advent of the vaginoscopic approach, the atraumatic entry into the vagina and the distension with liquid medium in vaginoscopy has made hysteroscopy increasingly painless and well tolerated by patients. The sensory innervation of the uterine fundus comes from the sympathetic pathway (T10-L1), while the sensory innervation of the cervix derives from the parasympathetic pathway (S2-S4) (Fig. 1-2): considering the innervation of the uterus and cervix, over the years, many studies have investigated the best strategies for pain control in hysteroscopy. Given these premises, since the early 2000s, many authors have studied the role of local anesthesia in hysteroscopy, focusing mainly on paracervical block and pericervical analgesia.

Regarding topical anesthesia, it is now established that the routine instillation of a local anesthetic directly into the uterine cavity should be avoided as it is not associated with a reduction in pain associated with office hysteroscopy8. The two techniques of local anesthesia that have proven effective in controlling pain during office operative hysteroscopy are paracervical block and pericervical instillation of local anesthetic.

Indeed, the initial data in the literature on the use of paracervical anesthesia already demonstrated a significant reduction in pain with the use of paracervical block compared to placebo or no treatment [13-17].

Two more recent systematic reviews18,19 identified six randomized controlled trials comparing paracervical injection of local anesthetics before hysteroscopic examination with controls (placebo or nothing). The results demonstrated a significant reduction in pain despite the heterogeneity of the studies [15]. Unlike the paracervical block, which is a peripheral nerve block, the pericervical

block acts as an infiltrative anesthetic by distending the tissues, causing a mechanical disruption of neural impulses: theoretically, this requires a less precise injection than the paracervical block and it appears to be easier and more reproducible among operators [20]. Furthermore, in the literature, the paracervical block has been found to be associated with a greater number of complications [1].

If the use of paracervical block appears to be associated with a significant reduction in pain compared to placebo or no treatment, when compared to another extensively studied method of pain control (the use of inhalation analgesia with nitrous oxide) , the latter seems to be more effective and with a lower rate of side effects.1 In fact, as reported by the most recent literature data6, paracervical block appears to be associated with a higher rate of side effects - abdominal pain, bleeding and pain at the injection site of the anesthetic, dizziness, nausea, and overall vasovagal adverse reactions - compared to inhalation analgesia with nitrous oxide. Nitrous oxide is a colorless, odorless, and non-explosive gas. At room temperature, it remains below its critical temperature, which is why it is stored in liquid form. When released at atmospheric pressure, it transforms into an inert gas and is therefore eliminated unchanged through the respiratory tract during breathing. It takes about 20 seconds to pass from pulmonary circulation to the central nervous system and 3-5 minutes to reach its peak [21]. It does not have serious gastrointestinal side effects and does not alter coagulation parameters [7]. Recently, there have been increasingly favorable literature data towards nitrous oxide; in fact, the equimolar mixture of 50% nitrous oxide and oxygen gas (inhaled nitrous oxide; INO) has been shown to be effective and safe for pain control due to its analgesic, anxiolytic, and amnesic properties. This mixture indeed produces a short-duration analgesic effect and is safe as it does not depress the cough reflex and respiration [7]. The first study evaluating the efficacy of INO compared to other options (including paracervical block) for pain control in hysteroscopic polypectomy was published by Del Valle Rubido et al. and showed promising results [7]. More recently, Solano Calvo et al, [6], demonstrated that, regardless of office hysteroscopic procedures, INO was as effective as 1% lidocaine paracervical block for pain control. Both interventions were more effective than the option without analgesics [22,6]. The results also suggest a better safety profile for nitrous oxide compared to other groups. In particular, vasovagal events were reported more in the paracervical block and no analgesics arms compared to the arm that used the nitrous oxide mixture [6]. From the literature currently available, it emerges that inhaled nitrous oxide has shown analgesic efficacy equivalent to that shown by paracervical and pericervical block with lidocaine, for outpatient hysteroscopic procedures using Bettocchi hysteroscope. However, nitrous oxide is much easier to administer and has therefore demonstrated a better safety profile and overall has been associated with greater patient satisfaction.

Considering these premises, our study is important as there are currently no studies comparing inhaled analgesia with nitrous oxide and pericervical anesthesia in outpatient hysteroscopic surgery with Miniresectoscope: on one hand the results of this study confirm how pericervical analgesia and nitrous oxide are both effective methods in controlling pain in office hysteroscopic surgery with a Mini-Resectoscope and, on the other, demonstrates the superiority of pericervical analgesia.

From the results of this study it is actually clear how pericervical analgesia allows the execution of increasingly complex procedures that may also require cervical canal dilation without causing discomfort to the patient, thus limiting the use of the 26 Fr Resectoscope, a surgical instrument significantly larger in caliber, to the operating room.

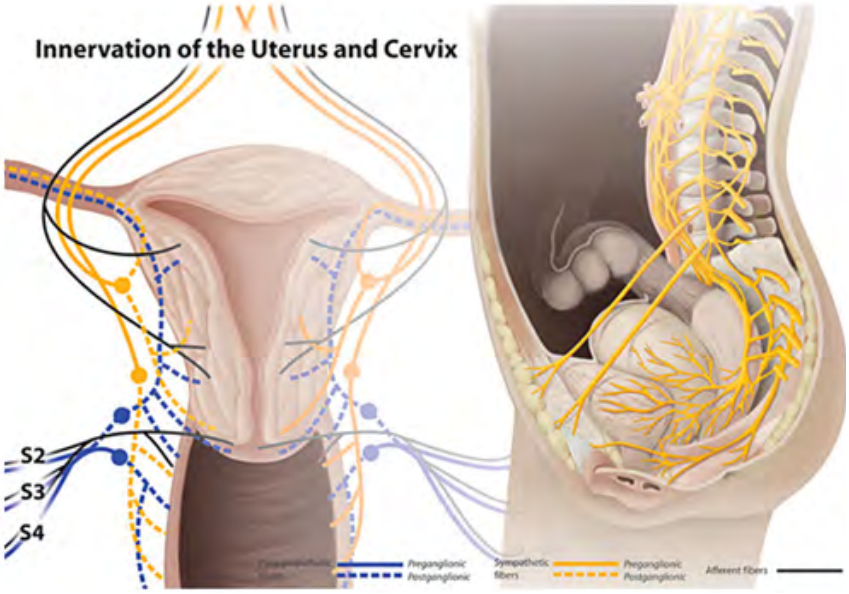

Figure 1: Innervation of the Uterus and Cervix.

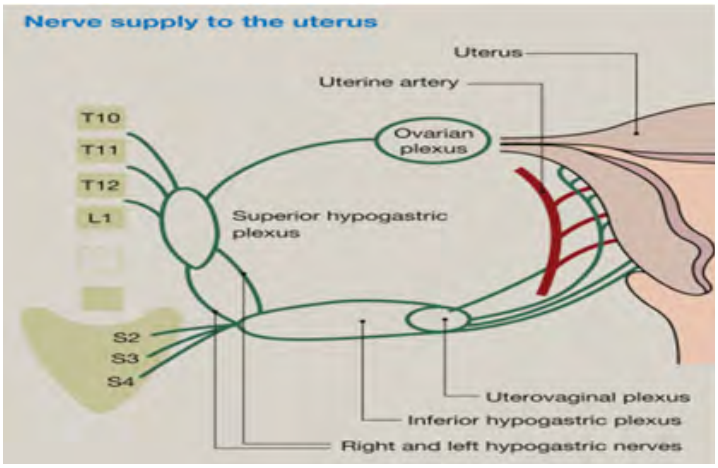

Figure 2: Nerve supply to the uterus.

6. Conclusion

From the results of this study, it is evident that good pain control significantly increases patient compliance with the hysteroscopic procedure, enabling the performance of increasingly complex interventions in an outpatient setting with rapid discharge, further reducing operating room admissions and thus healthcare costs, and, more broadly, increasing patient satisfaction and adherence to the procedure. Our study demonstrates how pericervical analgesia is a safe and effective method of pain control, allowing the execution of even complex surgical procedures in an office setting, fully exploiting the high performance of the Bipolar Mini-resectoscope, even in nulliparous or primiparous patients. This approach achieves high patient compliance and further limits access to the operating room. Nevertheless, further studies are needed before implementing this approach into daily clinical practice.

7. Funding

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