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Original Article

Analgesic Efficacy of Intrauterine Lidocaine Flushing in Hysterosalpingo-foam Sonography: A Double-blind Randomized Controlled Trial

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ABSTRACT **Study Objective:** To evaluate the efficacy of flushing the uterine cavity with lidocaine before hysterosalpingo-foam sonography (HyFoSy) to reduce procedure-related pain.

Design: A double-blind randomized controlled trial was conducted at the Department of Obstetrics and Gynecology, Shamir Medical Center, Israel between June 2020 and September 2020 involving 80 women undergoing a HyFoSy procedure.

Setting: University-affiliated medical center.

Patients: A total of 40 women were assigned randomly to the lidocaine group and 40 to the saline (placebo) group using a predetermined randomization code. Intrauterine instillation before the procedure consisting of either lidocaine 2% or normal saline alone was conducted, respectively.

Interventions: The primary outcome measure was the visual analog scale (VAS) pain score during the phase of intrauterine foam instillation reported by the women after the procedure. The VAS consisted of a 10-cm line ranging from 0 to 10 (anchored by 0 = no pain and 10 = very severe pain). On the basis of the VAS scores, the pain level ratings were classified as mild (rated 1−3), moderate (4−6), or severe (7−10).

Measurements and Main Results: The patient characteristics and obstetric data were found to be similar in both groups. Comparison of the VAS pain scores experienced during the procedure showed that women in the lidocaine flushing group rated the procedure less painful than the women in the saline group (3.0 ± 1.3 vs 6.3 ± 1.5, respectively; p = .001). The incidence of severe pain was significantly lower in the lidocaine group than the saline group (2.5% and 45.0%, respectively, p = .001).

Conclusion: Lidocaine flushing of the uterine cavity before HyFoSy significantly decreased the pain known to be caused by this procedure and had the advantage of no side effects. It is easily applied, relatively inexpensive, and may affect compliance with this procedure. Journal of Minimally Invasive Gynecology (2021) 28, 1484−1489. © 2020 AAGL. All rights reserved.

Keywords: HyFoSy; Infertility; Lidocaine; Pain; VAS

Tubal patency evaluation is an important step in the assessment of female infertility [1], and hysterosalpingography (HSG) is currently still used for this purpose. Its associated pain and discomfort, however, make this procedure unpleasant for patients [2,3]. Modern ultrasound-based procedures assessing uterine cavity and tubal patency using contrast are increasingly popular in infertility investigations [4] such that the HSG test, which was the most common source of information on the uterus, has declined [3].

Today, saline infusion sonography is part of the standard evaluation workup when evaluation of the uterine cavity is deemed necessary to test for infertility [5−7]. Saline,

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Data repository: https://figshare.com/s/94f1b76f9faf224752f3.
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however, is not a good contrast for assessing tubal patency because a more echogenic substance is needed to show flow within the tube [8]. In 2012, hysterosalpingo-foam sonography (HyFoSy) was introduced as a new technique for assessing fallopian tube patency. During the examination, the passage of a hyperechogenic foam composed of a mixture of gel and purified water can be visualized as it progresses from the uterine cavity through the fallopian tubes into the peritoneal cavity [9]. Mirroring the shortcomings of saline, hyperechogenic contrasts are not appropriate for evaluating the uterine cavity because they impede the identification of hyperechoic intracavitary lesions. The solution has been to use 2 different contrasts for ultrasound evaluation in infertility: first, the uterine cavity is evaluated with an anechoic contrast (saline), and then the patency of the uterine tubes is evaluated with a hyperechogenic contrast (HyFoSy).

As an office procedure, HyFoSy gives comparable results to HSG [10] but has the advantages of being an office procedure with no exposure to radiation and with lesser patient discomfort. The patient data collected include anatomy of the uterus and the ovaries, any pathologies such as endometriosis and adenomyosis, and tubal patency. The office setting may be more patient- friendly than the radiology department where HSG is performed on a hard flat X-ray table [10−12]. HyFoSy is well tolerated by most patients and has few adverse effects [10]. Although it has been reported to be less painful to women than HSG [11], approximately 50% stated that the HyFoSy examination was unpleasant [12], thus pointing to the need for effective pain relief.

Typically, HyFoSy is done in the physician's office or as a hospital outpatient. This precludes the use of a centrally acting analgesic, but parenterally administered oral analgesics with peripheral action may not relieve the pain quickly enough. Several studies have shown that the intrauterine application [13] of a topical anesthetic (lidocaine) is easy and safe [14] and can provide adequate analgesia during minor intrauterine gynecologic procedures including endometrial biopsy [15,16], curettage [15], sonohysterography [17], and office hysteroscopy [13,15,18]. This suggests that lidocaine administration could provide pain relief during HyFoSy.

The present study's aims were to compare the efficacy of flushing the uterine cavity with lidocaine before HyFoSy to reduce the level of pain experienced by women during this procedure.

Materials and Methods

This randomized, double-blind, placebo-controlled trial was conducted at the Department of Obstetrics and Gynecology, Shamir Medical Center, Israel between June 2020 and September 2020. The study was approved by the institutional ethics committee (# 0189-19) and registered as a clinical trial (trial registration number [ClinicalTrials.gov ID]: NCT 04433611). Written informed consent was obtained from all participants. Women who were referred for an assessment of tubal patency as part of their fertility workup were recruited. Women were excluded from the sample if they were allergic to lidocaine, had engaged in unprotected intercourse, had chronic pelvic pain, experienced profuse vaginal bleeding, or reported inflammation or infections of the genital tract (e.g., pelvic inflammatory disease or suspected sexually transmitted diseases [purulent vaginal discharge on speculum insertion], salpingitis, or tubo-ovarian abscess). Similarly, women with psychologic or neurologic lesions affecting sensation, a history of cervical surgery, or cervical stenosis were excluded.

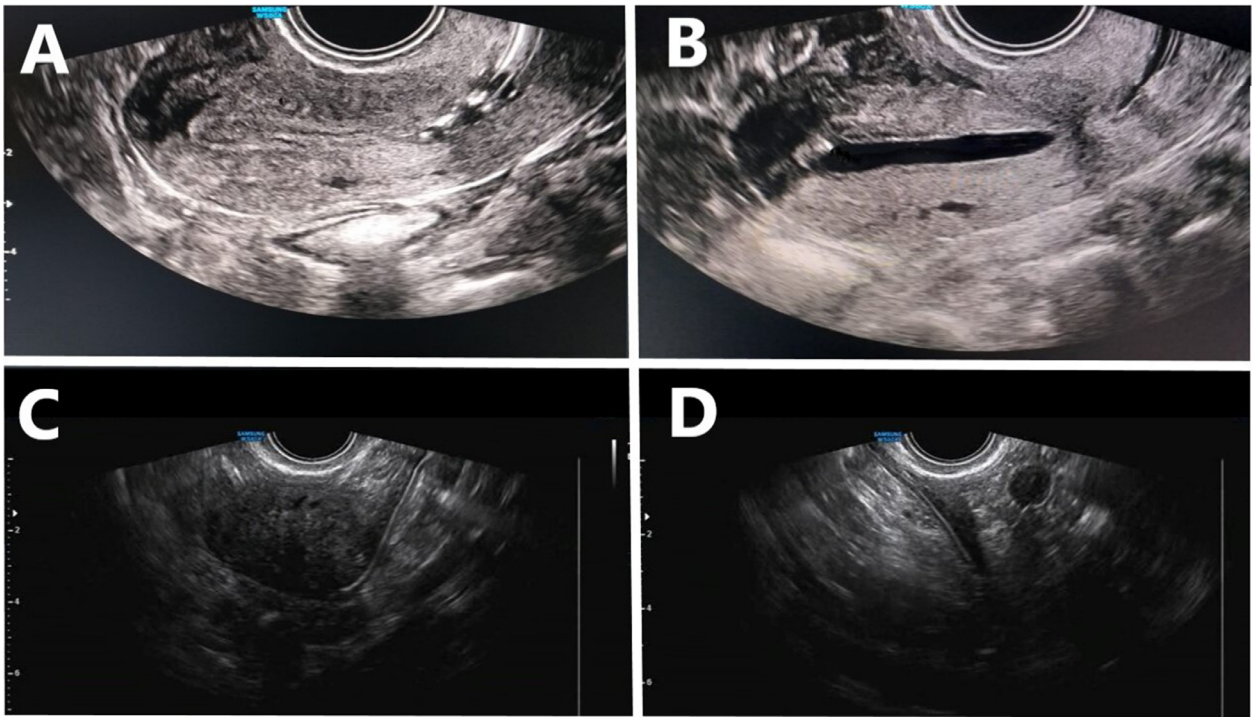
The women were assigned randomly to the treatment/placebo groups on the day the procedure took place by the research nurse on the basis of a randomization code. Half of the sample received the placebo, and the other half received the treatment. The treatment group received an intrauterine infusion of 10 mL 2% lidocaine (Rafa Laboratories, Jerusalem, Israel), whereas the placebo group received an intrauterine infusion of 10 mL 0.9 % normal saline immediately before the HyFoSy procedure. The syringes and their contents appeared identical: both syringes were the same size (10 mL) and disposable, and both solutions were colorless. Therefore, the women undergoing the procedure and also the sonographer were blind to group assignment.

Before the HyFoSy procedure, no premedication was administered. All women were scheduled before the 14th day of their ovulatory cycle and after the cessation of menstrual bleeding from their previous period. A baseline transvaginal scan to detect pelvic pathologies was performed after placing the woman in the supine position by 1 of 2 experienced clinicians. A vaginal speculum was introduced to visualize the cervix. After the cervix and the vagina were flushed with iodine solution, a balloon-less GIS catheter (GynaecologIQ, Delft, the Netherlands) [19] with a soft tapered tip was inserted into the endocervical canal for both the treatment and the placebo HyFoSy procedures (Fig. 1A). None of the women were subjected to a tenaculum or a cervical dilatator. Then, the ultrasound transducer was introduced vaginally after carefully removing the speculum to avoid moving the catheter. The administration of either the 2% lidocaine solution or the normal saline was introduced slowly into the uterine cavity through the catheter until achieving satisfactory distension and visualization of the uterine cavity (Fig. 1B). Foam was produced according to the manufacturer's instructions for the ExEm Foam kit (NOVUS Pharma Solutions, Sofia, Bulgaria) [9]. On the basis of direct ultrasound guidance, the foam was injected slowly through the GIS catheter to assess its passage (Fig. 1C and D) or blockage through the fallopian tubes. All examinations were conducted on a Samsung WS80A (Samsung, Seoul, South Korea) ultrasound system fitted with a V5−9 MHz endovaginal probe.

To obtain a baseline value for pain, all women were assessed before the procedure on a visual analog scale (VAS) as described in Katz and Melzack [20], which

Fig. 1

(A) Transvaginal midsagittal section of the uterus showing a catheter with a soft tapered tip inserted into the endocervical canal. (B) Transvaginal midsagittal section of the uterus showing uterine cavity distension during administration of the normal saline through the catheter. (C) Patent left tube (the right tube is not demonstrated in this plane). (D) Patent right tube (the left tube is not demonstrated in this plane).



consists of a 10-cm line marked at 1 end by 0 (no pain) and at the other end by 10 (severe pain). For purposes of reassessment after the HyFoSy examination, all patients indicated their perceived level of pain during the phase of intrauterine foam instillation on the VAS scale while seated in the waiting area [20]. The VAS scores were then categorized as mild (rated 1−3), moderate (4−6), or severe (7−10).

Statistical analyses implemented SPSS software (SPSS Inc., v.25 Chicago, IL). The descriptive variables are presented as the mean ± standard deviation. Frequencies are presented as percentages. Two-tailed *t* test, Fisher exact test, and Pearson chi-square test were employed as appropriate. A p-value of less than .05 was considered statistically significant. For purposes of statistical analysis, the sample size was recruited to be sufficient to detect 1-unit difference in pain scores ± 1 standard deviation between groups. This yielded an estimated sample of 27 women in each group to reject the null hypothesis of 0.05 at a power of 0.9. To compensate for missing data, 39 women were included in each group.

Results

A consecutive 85 women who referred for an assessment of tubal patency as part of their fertility workup were approached (Fig. 2). Of these 85 women, 5 (5.9%) were excluded because they were engaged in unprotected intercourse (n = 4) or had a tubo-ovarian abscess suspected during baseline transvaginal ultrasound examination before the HyFoSy procedure (n = 1).

The final sample was composed of 80 women: 40 were randomly assigned to the lidocaine flushing arm and 40 to the saline flushing arm. The patient characteristics and pain scores are presented in Table 1. Both groups emerged as similar in age, body mass index, duration of infertility, and primary infertility rate. No significant differences between groups were found for the risk factors for tubal occlusion (included history of tubal occlusion, previous ectopic pregnancy, previous pelvic infection, and endometriosis). Obstetric history was also similar in both groups as was the patency of both tubes on HyFoSy examination. All women who were recruited indicated no pain (baseline VAS score 0) before the procedure. However, ratings on the VAS during the procedure indicated that lidocaine flushing was associated with significantly less pain than ratings in the saline group; namely, 3.0 ± 1.3 vs 6.3 ± 1.5, respectively (p = .001). The incidence of severe pain was significantly lower in the lidocaine group than the saline group (2.5% and 45.0%, respectively, p = .001). HyFoSy revealed 2 cases of proximal tubal occlusion in each group (5.0%).

Finally, VAS score was analyzed according to parity. In the nulliparous lidocaine group of patients, significant pain

Fig. 2

Flow chart of study participants.

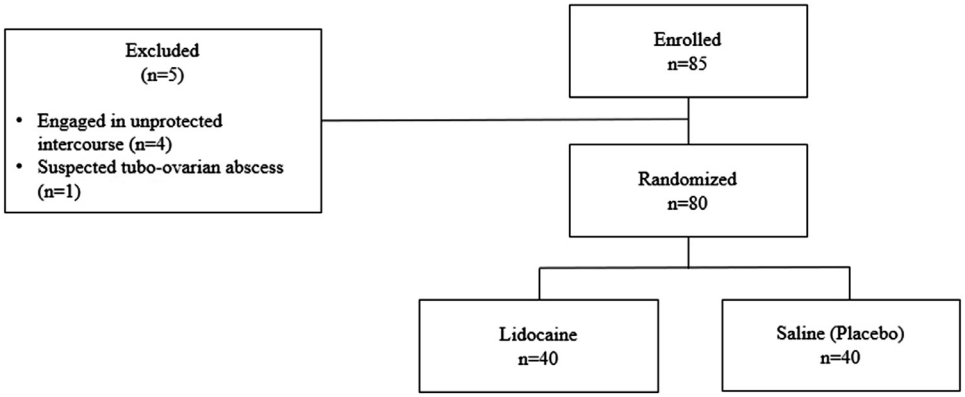


Table 1

Patient characteristics and pain scores

Parameter	Lidocaine n = 40	Saline n = 40	p-value
Age, yrs	32.7 ± 3.9	32.7 ± 2.6	.973*
BMI, kg/m^2	24.8 ± 4.6	22.1 ± 1.9	.081*
Duration of infertility, yrs	1.2 ± 0.5	1.4 ± 0.9	.327*
Primary infertility	13 (32.5)	19 (47.5)	.254*
Risk factors for tubal occlusion†	9 (22.5)	8 (20.0)	1.0‡
Bilateral tubal patency	37 (92.5)	36 (90.0)	1.0‡
Obstetric history			
Gravidity	1.1 ± 1.1	1.2 ± 1.6	.748*
Parity	0.6 ± 0.9	0.8 ± 1.3	.363*
Nulliparity	26 (65.0)	22 (55.5)	.494‡
Previous abortion	7 (17.5)	6 (15.0)	1.0‡
Previous dilation and evacuation	6 (15.0)	2 (5.0)	.263‡
Previous vaginal delivery	10 (25)	12 (30)	.803‡
Previous cesarean delivery	5 (12.5)	10 (25)	.251‡
VAS			
Score before the procedure§	0	0	
Score during the procedure§	3.0 ± 1.3	6.3 ± 1.5	.001*
Intensity during the procedure‖			
Mild	28 (70)	1 (2.5)	.001¶
Moderate	11 (27.5)	21 (52.5)	
Severe	1 (2.5)	18 (45.0)	
Tubal status			
Unilateral proximal occlusion	2 (5.0)	2 (5.0)	

BMI = body mass index; VAS = visual analog scale.
Data are presented as the number (%) or as the mean ± standard deviation.
* Two-tailed *t* test.
† Risk factors for tubal occlusion include history of tubal occlusion, previous ectopic pregnancy, previous pelvic infection, and endometriosis.
‡ Fisher exact test.
§ The VAS consisted of a 10-cm score line anchored by 0 and 10 (0 = no pain and 10 = very severe pain).
‖ The pain intensity was classified as mild (1−3), moderate (4−6), and severe (7−10) according to the VAS score.
¶ Pearson chi-square test.

relief was obtained by the use of lidocaine as compared with the saline group (3.0 ± 1.4 vs 6.3 ± 1.5, respectively, p = .001). Ratings on the VAS in patients who were multiparous indicated that lidocaine flushing was also associated with significantly less pain during the phase of intrauterine foam instillation than ratings in the saline group; namely, 3.0 ± 1.3 vs 6.2 ± 1.4, respectively (p = .001).

Discussion

Several studies have investigated the role of intrauterine application of lidocaine for pain reduction during minor intrauterine gynecologic procedures [13,15−18]. Guney et al [17] reported a statistically significant difference in pain reduction with the use of intrauterine lidocaine during, immediately after, and 20 minutes after sonohysterography only in the patients who were multiparous but not patients who were nulliparous. The explanation for this difference is not clear. Tenaculum use, which was more common in the nulliparous group, may have contributed to the greater pain experienced in this subgroup of patients [17].

This is the first trial to evaluate the efficacy of flushing the uterine cavity with lidocaine before HyFoSy to reduce the pain experienced by women during the phase of intrauterine foam instillation. The findings indicated that the women in the lidocaine treatment group reported significantly lower VAS pain scores than the placebo saline group. Furthermore, the incidence of severe pain levels was significantly lower in lidocaine group. Further subgroup ratings on the VAS score indicated that lidocaine flushing was associated with significantly less pain both in patients who were multiparous and patients who were nulliparous. None of the women were subjected to tenaculum use. In this study, a 2% lidocaine administration was selected as an intrauterine analgesic because it acts rapidly with a shorter duration

than mepivacaine, as is often used in studies in the literature studies. Reports have indicated that 2% lidocaine may be more effective than 1% [13,15,21].

Pain is the most crucial factor when performing ultrasound evaluations of the uterine cavity for tubal patency. Studies have shown that fear of pain can generate a withdrawal reflex to avoid potential harm and is part of the body's arsenal of defense mechanisms to ward off physical injury [3]. Any gynecologic procedure can be experienced as embarrassing, uncomfortable, and stressful, which may be amplified by the fear of pain. It is important in these cases to reduce these emotions by explaining the procedure before starting the examination, to insert the speculum gently, and most importantly, to inject the medium very slowly to avoid high intrauterine pressure. Szymoniak et al [22] asked 100 women to complete a survey on their attitudes and reactions to gynecologic examinations. Nearly 70% of the sample stated that they felt embarrassed and found the examination to be stress provoking. Almost half (47%) noted that they were the most highly embarrassed when getting into the stirrups position; roughly one-third found the examination embarrassing (30%), but sone-quarter of the women (21%) noted that the least embarrassing moment was the gynecologic examination itself.

The sources of pain experienced during HyFoSy may be caused by a levator ani muscle spasm as a result of vaginal and/or cervical manipulation [18] and the mechanical distension of the uterine walls during intrauterine instillation of contrast media that can lead to uterine cramps [10]. It is likely that the administration of lidocaine in the current study affected nerve endings within the endometrial mucosa [13,21]. Frankenhäuer's plexus, parasympathetic S2 to S4, controls the sensory innervation of the cervix and the lower uterine segment [23]. Nevertheless, the fundal region may be innervated from the ovarian nerve plexus [24].

Furthermore, although beyond the scope of the present study, lidocaine may also play a role in anti-infection prophylaxis beyond its analgesic effects [25]. The combination of the analgesic and antibacterial activity of lidocaine for women undergoing uterine and tubal assessments using a contrast medium should be further evaluated because of its broad potential benefits.

The current study had some limitations that need to be addressed: pain is a subjective feeling comprising both emotional and cognitive components, which makes its evaluation complex. Tolerance and response to pain differ across individuals. Thus, the VAS score may reflect the local population's perception of the severity of pain and discomfort, which may vary with respect to other populations. Furthermore, the current study was not designed to discriminate pain experienced during different phases of the procedure. Finally, the power analysis was set at a lower threshold to detect a 1-unit difference in pain scale, which may not be clinically relevant. Nevertheless, these findings are important because they clearly show a difference in pain perception between saline and lidocaine flushing. The strengths of this study lie in its prospective double-blinded assessment and the sufficient number of participants in each arm, and the results should encourage others to consider lidocaine as a pain attenuator.

To conclude, overall lidocaine flushing of the uterine cavity before HyFoSy was shown to significantly reduce the pain known to be caused by this procedure and had the advantage of no side effects. It is easily applied and may affect compliance with this procedure.

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