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Original Article

Efficacy of Oral Nifedipine, Naproxen, or Placebo for Pain Relief During Diagnostic Hysteroscopy in an Office Setting: A Randomized Pilot Study

Steffi van Wessel, MD, Julie Rombaut, MD, Astrid Vanhulle, MD, Mark Hans Emanuel, MD, PhD, Tjalina Hamerlynck, MD, PhD, and Steven Weyers, MD, PhD

From the Women's Clinic, Ghent University Hospital (Drs. Wessel, Rombaut, Vanhulle, Hamerklynck, Weyers), Ghent, Belgium, Women's Care, Bergman Clinics (Dr. Emanuel), Hilversum, Netherlands, and Department of Reproductive Medicine and Gynecology, University Medical Center (Dr. Emanuel), Utrecht, The Netherlands

ABSTRACT **Study Objective:** To compare nifedipine, naproxen, or placebo for pain relief during diagnostic hysteroscopy.
Design: Double-blind, randomized controlled pilot study.
Setting: University hospital.
Patients: Women scheduled for office diagnostic hysteroscopy (n = 60).
Interventions: Women received nifedipine (2 tablets of 10 mg), naproxen (2 tablets of 250 mg), or placebo (2 tablets of 500 mg lactose) 30 to 60 minutes prior to hysteroscopy.
Measurements and Main Results: Sixty patients were enrolled in the study (21 in the nifedipine group, 19 in the naproxen group, and 20 in the placebo group). The median pain scores during hysteroscope insertion, measured on a Visual Analog Scale (VAS), were 1 (interquartile range (IQR) 0−0), 2 (0−4) and 1 (0−1) in the nifedipine, naproxen and placebo group, respectively (P,14). The median VAS scores during hysteroscopy were 5 (IQR 2−7), 5 (4−8) and 5 (3−7) in the nifedipine, naproxen and placebo group, respectively (P,73). The median VAS scores immediately after hysteroscopy were 2 (IQR 0−4), 3 (0−6) and 3 (1−5) in the nifedipine, naproxen and placebo group, respectively (P,40). The median VAS scores 30 minutes after hysteroscopy were 1 (IQR 0−2), 1 (0−1) and 1 (0−2) in the nifedipine, naproxen and placebo group, respectively (P,63). Hysteroscope insertion failed in 1 case (naproxen group) because of cervica'l stenosis (P,32). Flushes, fatigue and vertigo, 30 minutes after the procedure, were significantly more prevalent in the nifedipine group compared to the naproxen ($p < .001$, p,03, p,03, respectively) and the placebo group ($p < .001$, p,01, p,01, respectively). Palpitations occurred only in the nifedipine group ($p < .001$). The day after the procedure, the headache was most prevalent in the nifedipine group compared to the naproxen group (p,001) and the placebo group (p,001).
Conclusion: In our pilot study, pain relief and success rates for office diagnostic hysteroscopy were not significantly different between nifedipine, naproxen, and placebo. Nifedipine was associated with more, albeit tolerable, side-effects. Journal of Minimally Invasive Gynecology (2023) 00, 1−7. © 2023 AAGL. All rights reserved.

Keywords: Diagnostic hysteroscopy; Efficacy; Naproxen; Nifedipine; Office hysteroscopy; Pain relief

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The authors declare that they have no conflict of interest.

Dutch Clinical Trial Registry (NL7750): currently available on https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-001020-19/BE).

No significant differences in pain relief during, or success of office diagnostic hysteroscopy were found comparing oral nifedipine, naproxen, or placebo, albeit with more side effects associated with nifedipine.

Corresponding author: Steffi van Wessel, MD, Women's Clinic, Ghent University Hospital, Corneel Heymanslaan 10, Ghent 9000, Belgium.
E-mail: steffi.vanwessel@uzgent.be

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Hysteroscopy is the gold standard for diagnosis and treatment of intrauterine pathology. Miniaturization and enhancements of hysteroscopes and hysteroscopic instruments have enabled procedures to be safely and effectively performed in office [1−3]. Moreover, compared to the ambulatory setting, office hysteroscopic procedures are equally acceptable to patients, and recovery is quicker [4].

Strategies to maximize patient's comfort include the use of saline, the vaginoscopic approach, and cervical ripening with misoprostol in selected patients [5−9].

A consensus on optimal method of pain relief for office hysteroscopy, however is lacking, and various methods have been described: oral analgesics (nonsteroid anti-inflammatory drugs (NSAIDs), opioids), and local anesthetics (intracervical, paracervical, intrauterine instillation, ectocervical application). For diagnostic hysteroscopy, there is no consistent, good-quality evidence of a clinically meaningful difference in safety or effectiveness of pain relief methods [10]. However, local anesthetics may be considered when performing a diagnostic or an operative hysteroscopy in postmenopausal women to reduce the failure rate related to pain [11].

Calcium channel blockers relax vascular smooth muscle cells by preventing calcium from entering the cells [12]. Dihydropyridines (nifedipine) cause vasodilation and are used in cardiovascular treatment. The pharmacologic characteristics imply it may also have a relaxing effect on the uterine smooth muscle cells and, therefore may decrease myometrial contraction-related pain [13,14]. It is used off-label for the treatment of preterm labor [15,16]. Nifedipine as pain relief during hysteroscopy has not yet been studied and has several advantages: oral administration, few contra-indications, and low cost.

The aim of this pilot randomized controlled trial (RCT) is to compare nifedipine with NSAIDs or placebo for pain relief during office diagnostic hysteroscopy.

Material and Methods

This double-blinded pilot RCT was performed at the Ghent University Hospital (Belgium) from May 2019 to June 2022. The study was approved by the Ethical Committee and registered at the Dutch Clinical Trial Registry (NTR NL 7750), amendments to speed up inclusions made during the trial can be found at EudraCT (https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-001020-19/BE) (preprocedural blood pressure ≥ 100 mm Hg systolic instead of 120 mm Hg and body mass index < 35 kg/m^2 instead of 30 kg/m^2). All women gave written informed consent.

Women aged 18 to 50 years, scheduled for diagnostic hysteroscopy in an office setting, with a body mass index < 35 kg/m^2 and preprocedural blood pressure ≥ 100 mm Hg systolic and ≥ 60 mm Hg diastolic, were eligible for inclusion. Exclusion criteria were menopause, cardiovascular diseases, hypotension (systolic pressure <100 and/or diastolic pressure <60 mm Hg), use of cardiovascular medication, pregnancy, breastfeeding, liver diseases, daily use of pain medication, gastric ulcers related to NSAIDs, use of CYP3A4-inhibitors, rifampicin or magnesium sulfate.

The intervention is nifedipine (2 tablets of 10 mg), a dihydropyridine which inhibits calcium influx and relaxes smooth muscle cells. It is short-acting (T_{Max} (time to maximum serum concentration) 0.5 to 2 hours, $T_{1/2}$(time to halve the serum concentration) 2−4 hours), it works in 20 minutes, and it is metabolized by CYP3A4. Common side effects (<10%) are malaise, (peripheral) edema, vasodilation, obstipation, and headache.

The control is naproxen (2 tablets of 250 mg) or placebo (2 tablets of 500 mg lactose). Naproxen, a propionic acid derivative, inhibits prostaglandin synthesis and is an analgesic, antipyretic, and anti-inflammatory drug. It is long-working (T_{max} 2-4 hours, $T_{1/2}$10−17 hours, T_{Max} 2−4 hours), and it works in 1 hour. Common side effects (1% −10%) are reflux, nausea, stomachache, abdominal pain, obstipation, headache, fatigue, dizziness, tinnitus, allergic skin reaction, ecchymosis, decreased thrombocyte aggregation, prolonged bleeding, peripheral edema, and dyspnea.

Patients were randomly assigned with a 1:1:1 allocation ratio to nifedipine (group A), naproxen (group B), or placebo (group C). Randomization was done by a computer-generated random allocation sequence (random.org). The treatment allocation was concealed by sequentially numbered, opaque, sealed envelopes kept by an independent person. Both the patient, the gynecologist, and the nurse assisting the procedure were blinded for the treatment allocation. Within a time frame of 30 to 60 minutes before the diagnostic hysteroscopy, the blood pressure was measured. Immediately thereafter, the randomization was done by the study nurse, and the patient received the treatment allocation blindfolded.

The diagnostic hysteroscopy was performed by staff members with similar experience. The 4.3mm Bettocchi hysteroscope (Karl Storz, Tuttlingen, Germany) was used. Saline was used as a distension medium and delivered by a pressure bag. A vaginoscopic approach was used without cervical ripening. After the procedure, the women were observed for 30 minutes to monitor the blood pressure and possible side effects. A telephone visit was scheduled the following day to monitor side effects.

The primary outcome was maximum pain intensity measured on a Visual Analog Scale (VAS) during hysteroscope insertion (from the vaginoscopy to the insertion of the hysteroscope into the cervix just beyond the external ostium), during the procedure (from beyond the external ostium until the moment just before the hysteroscope was removed from the uterine cavity), at the end of the procedure (just after complete removal of the hysteroscope from the uterus), and 30 minutes after hysteroscopy.

The secondary outcomes were success rate, duration of the hysteroscopy, hysteroscopy-related complication rate, medication-related side effects 30 minutes and the day after

the hysteroscopy, additional pain relief taken until the day after the procedure, patient's willingness to take the same medication again (registered the day after the procedure).

Since this was a pilot study, without existing literature on which to base accurate power calculations, no power calculation was performed. The sample size for this pilot study was therefore determined at 60 women. This study was performed to provide guidance for a future RCT.

Data were collected and managed using Research Electronic Data Capture tools hosted at Ghent University Hospital [17,18]. Research Electronic Data Capture is a secure, web-based software platform designed to support data capture for research studies, providing an intuitive interface for validated data capture, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages, and procedures for data integration and interoperability with external sources. Data were analyzed using the statistical program SPSS (version 28, IBM Corp., Armonk, NY). Continuous variables were summarized with descriptive statistics mean and standard deviation for data normally distributed and median and interquartile range (IQR) otherwise. Categorical data were presented as frequency and percentage. Continuous data were analyzed using the one-way analysis of variance test if the data were normally distributed or using the Kruskal Wallis test otherwise. Categorical data were analyzed using the chi-square test or Fisher exact test when numbers were small. The residuals from the linear regression model of the primary outcome (VAS score) were not normally distributed, therefore a Kruskal Wallis test was performed. Level of significance was set at $p < .05$.

A per protocol analysis was performed to assess the robustness of our findings, excluding any women that received their medication outside the defined time frame. A safety analysis was also performed.

Results

Sixty women were enrolled in the study (Fig. 1). Patient characteristics are shown in table 1. Women with complaints (fatigue, abdominal cramps, headache, and procedure-related stress) at the moment of the administration of the allocated treatment were not significantly different between the 3 groups (P .35).

Data regarding the diagnostic hysteroscopy is shown in table 2. The introduction failed in 1 case of the naproxen group because of cervical stenosis. The VAS scores at the start (P .14), during (P .73), at the end (P .40), and 30 minutes after the diagnostic hysteroscopy (P .63) were not significantly different between nifedipine, naproxen, and placebo. The proportion of women with a VAS score higher than 4 (57%, 61%, and 60%) was also not significantly different between the 3 groups (P 1.0). Overall, the reported

Fig. 1

Consort flow chart

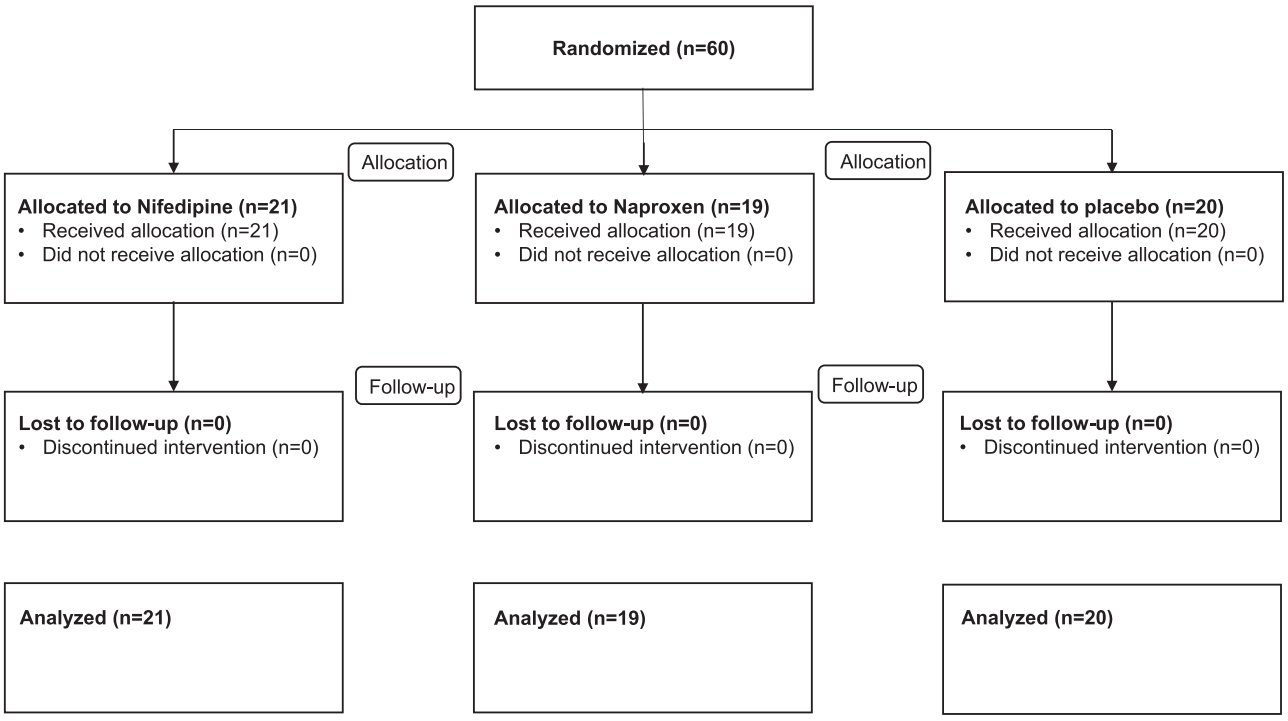

Table 1

Patient characteristics

Characteristic		Nifedipine (n = 21)	Naproxen (n = 19)	Placebo (n = 20)	P value
Age		34 ± 6	35 ± 7	33 ± 6	.74
BMI		25 ± 3	23 ± 4	24 ± 3	.26
Smoker		2 (10)	1 (5)	2 (10)	1.0*
ASA	0	18 (86)	18 (95)	18 (90)	.86*
	1	3 (14)	1 (5)	2 (10)	
Preprocedural systolic blood pressure (mm Hg)		125 ± 10	126 ± 10	125 ± 10	.90
Preprocedural diastolic blood pressure mm Hg)		78 ± 7	80 ± 5	81 ± 10	.40
Nulliparous		7 (33)	4 (21)	7 (35)	.60*
Cesarean section		3 (14)	2 (11)	4 (20)	.75*
Dysmenorrhea		15 (71)	12 (63)	13 (65)	.74†
Myomas		4 (19)	5 (26)	3 (16)	.85*
Adenomyosis		2 (10)	0 (0)	0 (0)	.23*
Endometriosis		0 (0)	2 (11)	3 (15)	.22*

ASA = American Society of Anesthesiologists; BMI = body mass index.
Data are mean ± SD or n (%).
p value from one-way analysis of variance unless otherwise specified.
* p value Fisher exact test.
† p value chi-square test.

VAS scores were the highest during the diagnostic hysteroscopy. The VAS scores at the other time points were low. In 6 cases, additional procedures (endometrial biopsy [pipelle] [n = 4], placement of an intrauterine device [n = 1], a vaginal examination [n = 1]) were performed subsequent to the diagnostic hysteroscopy. The median time between administration of the allocated treatment and the hysteroscopy was 77 minutes, 69 minutes, and 70 minutes in the nifedipine, naproxen, and placebo groups, respectively. The diagnostic hysteroscopy was performed outside the defined time frame in 3, 6, and 4 women of the nifedipine (range 64−77 minutes), naproxen (range 64−79 minutes, with one procedure being performed after 25 minutes), and placebo group, respectively, because of practical matters (P .42).

The postprocedural data is shown in table 3. The median systolic blood pressure 30 minutes after the diagnostic hysteroscopy was 115 mm Hg (IQR 109−123), 122 mm Hg (113−132) and 119 (113−124) in the nifedipine, naproxen and placebo group, respectively (P.19). The median diastolic blood pressure 30 minutes after the diagnostic hysteroscopy was 71 mm Hg (IQR 65−77), 77 mm Hg (69−81) and 76 mm Hg (71−84), respectively (P .04). Subgroup analysis showed a significant difference between nifedipine and placebo (P .02). Flushes, fatigue and vertigo, 30 minutes after the procedure, were significantly more prevalent in the nifedipine group compared to the naproxen (p <.001, p = .03, p = .03, respectively) and the placebo group (p <.001, p = .01, p = .01, respectively). Palpitations occurred only in the nifedipine group (p <.001). The day after the procedure, headache was most prevalent in the nifedipine group compared to the naproxen group (p = .001) and the placebo group (p = .001). Eleven women in the nifedipine group required additional medication for pain in the postprocedure period (paracetamol, ibuprofen, excedrin or diclofenac) compared to 2 women in the naproxen group (paracetamol or ibuprofen) (p = .004) and 5 women in the placebo group (paracetamol 500 mg, paracetamol) (P .03).

The per-protocol analysis led to similar conclusions.

Discussion

In our sample, we could not observe a statistically nor clinically significant difference between the randomization groups with respect to the mean ranking on the VAS scale and the probability of a VAS score higher than 4. Furthermore, the success ratio was high in all groups and not significantly different. However, the use of nifedipine was associated with significantly more side effects and the need for additional pain relief after the hysteroscopy. Nevertheless, the side effects would not refrain more patients from taking nifedipine again compared to naproxen or a placebo.

To our knowledge, this is the first report on the use of nifedipine as an analgesic method for office hysteroscopy. Calcium channel blockers prevent the passage of calcium into the muscle cells and prevent them from contracting. Therefore, it has analgesic potential.

We report on a well-designed RCT, blinding the outcome assessor and the participant and using an active reference treatment as well as a placebo. An objective parameter, the VAS score, was used to measure women's pain experience. Moreover, the VAS score was recorded at different time points up to 30 minutes after the hysteroscopic procedure. Furthermore, a safety analysis was

Table 2

Diagnostic hysteroscopy

Characteristic		Nifedipine (n = 21)	Naproxen (n = 19)	Placebo (n = 20)	p
Indication	AUB	8 (38)	4 (21)	2 (10)	.10
	Infertility	9 (43)	7 (37)	11 (55)	.50*
	Pain	1 (5)	1 (5)	0 (0)	.76
	Other	7 (33)	9 (47)	8 (40)	.68
Vaginoscopy		21 (100)	19 (100)	20 (100)	
Uterus	Anteversion	20 (95)	19 (100)	14 (70)	.01
	Retroversion	1 (5)	0 (0)	6 (30)	
Success		21 (100)	18 (95)	20 (100)	.32
Intrauterine pathology		10 (48)	8 (44)‡	7 (35)	.76*
Polyp		0 (0)	2 (11)	1 (5)	
Myoma		5 (24)	3 (16)	2 (10)	
Adhesions		1 (5)	0 (0)	1 (5)	
Placental remnants		1 (5)	1 (5)	1 (5)	
Niche		2 (10)	0 (0)	1 (5)	
Septum		1 (5)	1 (5)	1 (5)	
Adenomyosis		0	1 (5)	0 (0)	
Complications		0 (0)	0 (0)	0 (0)	
Additional procedure		4 (19)	0 (0)	2 (10)	.17†
Hysteroscopy duration (minutes)		2.2 (1.4−2.6)	2.3 (2.00−3.10)	2.0 (1.4−2.9)	.40†
VAS	Start of the procedure	1 (0−0)	2 (0−4)	1 (0−1)	.14†
	During the procedure	5 (2−7)	5 (4−8)‡	5 (3−7)	.73†
	After the procedure	2 (0−4)	3 (0−6)‡	3 (1−5)	.40†
	30 minutes after the procedure	1 (0−2)§	1 (0−1)‖	1 (0−2)§	.63†

AUB = abnormal uterine bleeding; VAS = Visual Analog Scale.
Data are median (Q25−Q75) or n (%).
p value from Fisher exact test unless otherwise specified.
* p valua chi-square test.
† p value Kruskal-Wallis test.
‡ 1 missing.
§ 2 missings.
‖ 5 missings.

performed, taking medication-related side-effects until the day after the procedure into account.

We do acknowledge that our study has some limitations. An important shortcoming is the small sample size and the lack of a sample size calculation. Since nifedipine was never used before for the indication of pain relief for hysteroscopy, our intention was to conduct a pilot study to determine whether a larger multicenter RCT is worth the effort. The lack of a statistically significant difference could be due to a lack of power. However, the estimated differences for the probability of a VAS score higher than 4 (57% in the nifedipine group, 61% in the naproxen group, and 60% in the placebo group) also do not seem to be clinically relevant. Another shortcoming is the fact that in 6 cases, additional procedures were performed. This could have influenced the VAS scores 30 minutes after the procedure. However, these VAS scores were low and not significantly different. The diagnostic hysteroscopy was performed outside the defined time frame in some cases, which is associated with day-to-day practice. Therefore, we could have underestimated the analgesic potential of nifedipine and naproxen. Still, pain relief was not different in the per-protocol analysis. Uterine retroversion was significantly more prevalent in the placebo group compared to the naproxen group (P .02). The retroverted position is a known risk factor for pain during outpatient hysteroscopy [19]. However, the VAS scores were not significantly different. Some VAS scores at 30 minutes were missing because they forgot to ask the patient. Lastly, the cervix itself is formed mainly by connective tissue [20]. Therefore, cervical pain (from distension and manipulation) might be unresponsive to nifedipine.

The literature regarding pain relief in-office diagnostic and operative hysteroscopy has expanded since the start of our study. The evidence for conscious sedation, local anesthesia, and analgesia, compared to no treatment, placebo, the same, another, or a different dose/scheme analgesic or anesthetic, has been examined by De Silva et al [21−23]. Conscious sedation and local anesthesia via any route of the genital tract are not recommended routinely. Regarding analgesia, NSAIDs reduce pain during and after the hysteroscopic procedures without an increase in side effects. The authors conclude that women without contraindications should be advised to take oral NSAIDs before the

Table 3

Postprocedural data

Characteristic		Nifedipine (n = 21)	Naproxen (n = 19)	Placebo (n = 20)	p
Side effects 30 minutes after the diagnostic hysteroscopy	Headache	2 (10)	1 (5)	1 (5)	1.0
	Fluid retention	2 (10)	0 (0)	0 (0)	.32
	Flushes	13 (62)	0 (0)	1 (5)	< .001
	Feeling unwell	5 (24)	5 (26)	2 (10)	.44
	Fatigue	9 (43)	2 (11)	1 (5)	.007
	Palpitations	7 (33)	0 (0)	0 (0)	< .001
	Vertigo	13 (62)	5 (26)	4 (20)	< .001
	Syncope	1 (5)	0 (0)	0 (0)	1.0
Side effects the day after the diagnostic hysteroscopy	Headache	17 (81)	3 (16)	4 (20)	< .001
	Fluid retention	2 (10)	0 (0)	0 (0)	.32
	Flushes	2 (10)	0 (0)	1 (5)	.77
	Feeling unwell	4 (19)	2 (11)	0 (0)	.13
	Fatigue	10 (48)	5 (26)	4 (20)	.15
	Palpitations	2 (10)	0 (0)	0 (0)	.32
	Vertigo	1 (5)	2 (11)	1 (5)	.68
	Syncope	0 (0)	0 (0)	0 (0)	
	Other	4 (19)	4 (21)	0 (0)	.10
Would the patient take the same medication?		11 (52)	10 (53)	11 (55)	1.0*
Did the patient take painkillers after the diagnostic hysteroscopy		13 (62)	3 (16)	5 (25)	.006

Data are n (%).
p value Fisher exact test unless otherwise specified.
* p value chi-square test.

hysteroscopic procedure, although the optimal route, dose, and timing of administration have yet to be determined. Transcutaneous Electrical Nerve Stimulation (TENS) is suggested as a suitable alternative for analgesia in case of contraindications for NSAIDs. The technique of TENS is based on the stimulation of specific dermatomes, which establishes a blockade at the dorsal horn, preventing pain from being transmitted to the upper nervous system. The 2 studies included in the meta-analysis of Da Silva and colleagues are heterogeneous in terms of TENS application (device, electrode placement, and settings) [23−25]. Therefore, we could not report on TENS as a standardized technique. Moreover, it entails logistical challenges (the necessity of a specific device and application before the procedure) when performed for office hysteroscopy.

A major limitation of the meta-analysis on analgesia of De Silva et al [23] is the methodologic, and clinical heterogeneity of the studies included. Hence, we believe more good-quality data are needed before one can recommend NSAIDs routinely.

Recently, a Cochrane review has been published on the use of nifedipine for pain relief in primary dysmenorrhea, which is the only gynecologic indication so far [26]. No new studies have been published since the start of our trial. Compared to placebo, nifedipine was effective for pain relief (odds ratio 9.04; 95% confidence interval [2.61 −31.31]), but the evidence was of low-quality and based on only 2 studies. The adverse event rate did not significantly differ from placebo (odds ratio 0.94; 95% confidence interval (0.07−4.20), and the most prevalent symptoms were headache and facial flushes.

The side effects of nifedipine were expected, but the prevalence is higher than those reported in the literature. An observational study of 40 women using nifedipine for severe, primary dysmenorrhea reported headache (38%), palpitations (13%), vertigo (8%), nausea (5%), and diarrhea (3%) [13]. Another observational study of 10 women using nifedipine for severe, primary dysmenorrhea reported an increased heart rate (100%), a decrease in diastolic pressure, and transient flushing [14]. Unfortunately, the reason for additional pain relief was not registered.

In our opinion future well-designed studies should focus more in detail on the efficacy of different types of NSAIDs for pain relief during diagnostic and operative hysteroscopy in an office setting. If the evidence for pain relief increases, the optimal route, dose, and timing of NSAIDs should be determined. Subsequently, a well-designed large-scale non-inferiority study should be performed to study alternative analgesia, such as nifedipine, which could offer an alternative to patients who cannot take NSAIDs. Meanwhile, office diagnostic hysteroscopy without analgesia, taking other pain-reducing strategies into account, is acceptable for most women.

Conclusion

In our pilot study, pain relief and success rates for office diagnostic hysteroscopy were not significantly different

between nifedipine, naproxen, and placebo. Nifedipine was associated with more, albeit tolerable, side effects.

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