A randomized double-blinded clinical trial to explore the clinical outcome of self-administered vaginal isonicotinic acid hydrazide (INH) administration 12 hours before hysterosalpingography in primarily infertile patients

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Abstract

Objective: The purpose of this study was to assess the clinical outcomes of using a combination of oral Ketoprofen and vaginal isonicotinic acid hydrazide (INH) for pain management during hysterosalpingography (HSG) vs using solely oral Ketoprofen.

Methods: The randomized controlled study was conducted between August 2020 and September 2021. Infertile women scheduled for HSG were randomized (1:1) to Ketoprofen with or without INH. All women received oral 150 mg Ketoprofen plus 900 mg vaginal INH or placebo tablets 12 hours before the procedure. The primary outcome was the participant's self-rated pain perception utilizing a 10-cm Visual Analogue Scale (VAS). During speculum insertion, cervical tenaculum application, dye injection, and 5 and 30 minutes following the procedure, the participants' self-rated pain was assessed using a 10-cm VAS.

Results: A total of 200 women participated (100 in each group). Oral Ketoprofen combined with vaginal INH substantially lowers the major VAS pain ratings during dye injection (4.23 ± 0.89 vs. 6.18 ± 0.90), 5-minute post-procedure (3.05 ± 0.95 vs. 5.81 ± 0.91), and 30-minute post-procedure (2.14 ± 0.74 vs. 4.69 ± 0.80), with p 0.01 at all phases. After using a speculum or tenaculum, there were no significant differences in VAS values. In terms of side effects, there was no significant difference between the study groups.

Conclusion: Adjuvant vaginal INH to oral Ketoprofen 12 hours before HSG may be considerably more effective than Ketoprofen alone in reducing the caused pain score during and 30 minutes after the HSG procedure.

Key words: Hysterosalpingography; INH, NSAIDs; infertile; pain.

Introduction

Infertility is described as a couple's failure to conceive after 12 months of unprotected sexual intercourse (1). Tubal abnormalities are estimated to be the cause of infertility in 30–40% of infertile people, hence tubal patency testing is crucial in their identification (2).

A radiographic evaluation of a women's genital tract is called hysterosalpingography (HSG). Examinable areas include the cervical canal, endometrial cavity, tubal lumen, and peri adnexal region. The National Institute for Health and Care Excellence suggests using HSG to check for tubal occlusion as part of a baseline infertility workup (3).

During cervical instrumentation, dye injection into the uterus, which produces distension, or peritoneal irritation owing to tubal leak, women may experience substantial pain (5).

Women's pain during HSG is essential since it may affect their compliance, decreasing the procedure's value. The greatest effective technique for pain mitigation during HSG is debatable in the literature. (6)

Nulliparity, a history of dysmenorrhea, anxiety, and a high degree of predicted pain are all risk factors that may enhance the amount of pain experienced (4, 5). Nonsteroidal anti-inflammatory medicines, topical anesthetic gel or spray, paracervical block, nitrous gas, misoprostol, and conscious sedation have all been used to alleviate pain during HSG, with mixed success. (7).

There are multiple randomized comparison trials for pain reduction utilizing HSG, according to a recent Cochrane systematic review. Despite the fact that the results of this systematic review reveal that only topical anesthetics provide significant pain relief, the authors recommend that large randomized controlled trials be conducted to investigate the effect of combining multiple analgesic classes on HSG-related pain (8).

Because the synthesis of prostaglandins from cervical manipulation and uterine distension can cause pain during HSG, a prostaglandin-synthetase inhibitor looks to be a promising pain-relieving method. NSAID given one hour before hysteroscopy will have the most analgesic impact throughout the procedure. After one 50 mg Diclofenac pill, mean peak plasma concentrations took 20–60 minutes to reach (9).

Oral non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to be ineffective in reducing pain during HSG or within 30 minutes in a variety of trials, with variable results. (10,11).

Cervical ripening can be caused by the nitric oxide donors isosorbide mononitrate and glyceryl trinitrate. Nitric oxide donors may be a better choice than prostaglandins for cervical ripening. (12)

Isonicotinic acid hydrazide (INH) is an anti-tuberculosis medication that helps the cervical ripening process. In term pregnancies, it was proven to be just as effective as misoprostol (13). According to some studies, the effect of INH on cervical ripening may be due in part to nitric oxide (NO) production in the cervix. INH injection has previously been shown to cause a significant increase in NO levels in rat red blood cells (RBCs), and it has been suggested that NO plays a critical role in the pathophysiology of INH-induced oxidative stress in RBCs (14).

The purpose of this study was to assess the clinical outcomes of using a combination of oral Ketoprofen and vaginal isonicotinic acid hydrazide (INH) for pain management during HSG vs using solely oral Ketoprofen.

Materials and Methods

A randomized, double-blind controlled study (ClinicalTrials.gov identifier NCT04500470; registered on August 3, 2020) was conducted at a tertiary university hospital between August 1, 2020, and September 30, 2021.

The hospital's Institutional Research Ethics Committee accepted the study's protocol (Aswu/352/3/19). Patients were counseled and signed a written informed consent form before enrolling in the study.

Eligible Participants

Women who visited our infertility department and underwent HSG for a primary infertility workup were asked to participate in the study. We included infertile women, aged 19–42 years old, who did not receive any analgesics in the 48 h before HSG.

The study excluded women having a history of cervical surgery, acute pelvic inflammatory illness, secondary infertility, NSAID contraindications, unexplained irregular uterine bleeding, or acute cervicitis. The study excluded women with persistent pelvic pain, irregular uterine bleeding, or a history of cervical surgery. Women who had an allergy to INH or had a medical condition that made it impossible for them to use it were also excluded, as did those who refused to take part in the trial.

Participants who qualified were divided into one of two groups. Group I women received 3 tablets (900 mg) of vaginal INH 12 hours before the procedure. Group II women received 1 placebo tablet to INH. All patients received 150 mg of Ketoprofen 1 hour before the procedure.

Randomization

Participants were randomly assigned to receive INH or a placebo vaginal tablet in a 1:1 ratio. A statistician who was not engaged in the study in any way created a computer-generated randomization table and placed the allocation data in serially numbered sealed envelopes. Each envelope contained a card indicating the sort of intervention. Only a study researcher opened the envelopes in the order of women's attendance. Allocation could not be modified once it had been completed.

All women were randomly allocated to one of two groups: (INH, group) received three 300 mg INH tablets virginally 12 hours before HSG, or (Placebo group) got three placebo tablets of the same size, color, and shape as INH tablets. The Faculty of Pharmacy's Pharmaceuticals department pharmacist made the placebo pills. The same pharmacist placed all the study drugs into unlabeled sterile boxes, so neither the physicians nor the ladies knew what they were getting (double-blind study).

Intervention

One of the study researchers approached all included women and collected their demographic characteristics: age, parity, residence, educational level, duration of infertility, history of dysmenorrhea or chronic pelvic pain, and history of previous HSG. He next gave the subjects an explanation of the common 10-cm visual analog scale (VAS) for pain assessment. (15). A VAS scale was used to measure the intensity of the pain (0 being no pain and 10 being the worst agony possible). Finally, he instructed the women to take the Ketoprofen oral tablet one hour before HSG and insert place the INH or placebo tablets as high as feasible in the vaginal canal 12 hours before their HSG appointment.

All of the female patients had HSG as an outpatient procedure while in the follicular phase of their menstrual cycle. A single experienced radiologist performed the HSG. On a fluoroscopic table, women were positioned in the dorsal lithotomy position. The radiologist inserted a sterile speculum into the vagina and used povidone-iodine to clean the cervix. A Rubin's cannula was then introduced into the cervical canal after the anterior lip of the cervix was gripped with a tenaculum. A 15 ml water-soluble contrast dye (Sodium amidotrizoate and meglumine at 76% Urografin® Bayer Hispania SL; Barcelona; Spain) was injected over 20

seconds into the uterine cavity.

Radiographic images were taken in the anteroposterior view when the uterine cavity was filled with the dye. All equipment was then taken away, and the women were given a 30-minute observation period within the clinic. The woman was asked to assess the level of discomfort during the operation using the same 10-point VAS on multiple sheets of paper by the research assistant who was standing next to her. Six different times during the procedure—baseline (expected pain), after speculum installation, after tenaculum implantation, after dye injection, and 5 and 30 minutes later—participants were asked to assess their level of discomfort.30 minutes after the surgery, all women were questioned about whether they needed any extra analgesics.

Ibuprofen 400 mg was made accessible to women as extra analgesia if necessary because it was widely available in our clinic. All women were asked to report any side effects occurring during the procedure and 30 min after HSG, such as syncope, dizziness, nausea, or vomiting.

Study Outcome

The main endpoint was the variation in mean pain score throughout the procedure. The number of women who required extra analgesics, the difference in the mean pain scores at 5 and 30 minutes after HSG, and the adverse effects of the study drugs were the secondary endpoints.

Sample size

Sample size calculation was based on the VAS score during the most painful step of the HSG procedure as reported by a randomized clinical trial (16). The most painful mean VAS score was 4.9 with a standard deviation (SD = 2.7) in the placebo group. We considered a 25% reduction to an overall VAS score of 3.7 (SD = 2) in the active treatment group would be significant. Considering an alpha error of 0.05, a statistical power of 85%, and a 10% rate of loss to follow-up. A sample size of at least 100 women in each group would be required.

Statistical Analysis

SPSS software, version 21, from Chicago, Illinois, USA, was used to analyze all data. When necessary, Fisher's exact test and the Chi-square test were utilized to compare groups. Quantitative data were described as means (SD) or medians, after testing for normality by the Kolmogorov-Smirnov test. In normally distributed variables, independent samples t-test was used for comparison between groups. P ≤0.05" was statistically significant.

Results

A total of 220 women were approached to take part in the study. Four women experienced irregular uterine bleeding, and eight women had already had intravenous analgesics prior to HSG, thus they were disqualified. In addition, eight women rejected to take part in the research. The remaining 200 women were divided into two groups at random (Fig. 1, the study flowchart).

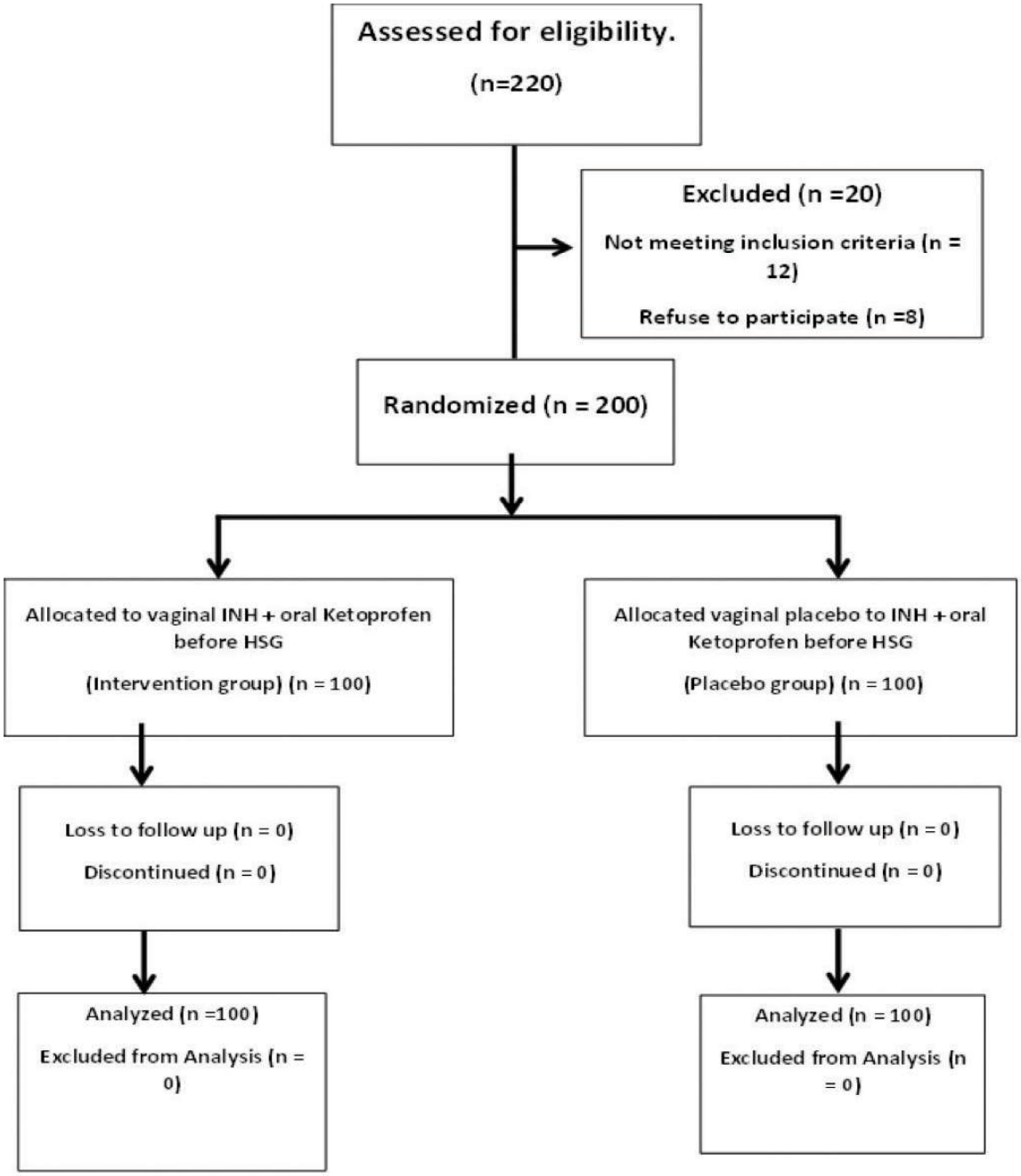
There was no significant difference between the two groups' baseline characteristics, such as age, BMI, length of infertility, place of residence, and educational level. (Table 1).

The pain score for each group was determined using a visual analog scale (VAS). There was no significant difference in pain score between the two groups during speculum and tenaculum application (p=0.7, p=0.7). However, in comparison to the placebo group, there was a substantial reduction in pain score during dye injection, 5- and 30-minutes following injection in the INH group, (P<0.001). In addition, women in the INH Group were more satisfied than those in the placebo group(P<0.001).

In comparison to the INH group, the addition of extra analgesic resulted in a substantial rise in the placebo group. P=0.013; however, there was no significant difference in the mean procedure duration between the two groups, p=0.719 (Table 2).

In terms of HSG result diagnosis, there were no significant differences between the two groups, (P = 0.9). (Table-3)

There was no significant difference between the research groups in terms of adverse effects. (Table-4)



Discussion

This is the first randomized, double-blind, placebo-controlled study in women with primary infertility to test the effectiveness of vaginal INH with oral Ketoprofen against oral Ketoprofen alone in lowering pain during and after HSG.

Adjuvant 900 mg vaginal INH utility 12 hours before HSG to 150 mg oral Ketoprofen one hour before HSG considerably reduced the caused pain scores during and 30 minutes after the HSG treatment as compared with Ketoprofen alone.

HSG is a valuable diagnostic method in the study of infertility. One of the most serious concerns with this therapy is difficulty reaching the interior cervical os. When there is significant cervical stenosis, an immature cervix, or severe anteflexion or retroflexion, cervical trauma or uterine perforation are more likely (17). Traditional cervical dilatation with Hegar's dilators may not be feasible in certain patients with very tight cervices or cervical abnormalities, regardless of parity (18). Furthermore, uterine sounding might be a challenge or a failure in particular disciplines. As a result, cervical softening is critical to the success of the procedure.

INH is a cervical ripening therapy that is still relatively new. According to the findings of a study conducted by Highlight et al. (19), vaginal INH is an effective medication for cervical ripening prior to labor induction in term pregnancies. When it comes to cervical dilatation, INH acts similarly to NO donors. According to the findings of several studies (20), INH impacts cervical dilatation via NO production.

The minimal clinically significant difference (MCSD) in VAS pain score was defined by Todd et al. (21) as the quantitative change in VAS pain score that is connected to the patient's subjective judgment of a little less or a little more discomfort. MCSD in acute pain ranged from 13 to 20 mm (22), (23), and changes in VAS pain score of less than 13 mm may be of low clinical relevance (24).

In our study, the difference in ease of insertion scores between the INH and placebo groups was more than 1.6, which was clinically significant.

In a study by Moore (25), pain sources during HSG were described as cervical instrumentation, pain secondary to uterine distention with contrast medium, and pain due to peritoneal irritation because of contrast leakage into the peritoneal cavity.

We hypothesized that cervical priming using INH as adjunctive to ketoprofen may decrease the filling pressure of the uterus with contrast media and decrease pain; our results indicated that INH reduces the VAS outcomes compared to those of the group that does not use INH.

The pain score in the area of dye injection was higher than 30 minutes following the procedure in both groups, according to the findings of this study. According to other research, the most painful element of the HSG process was injecting the dye into the uterine cavity (2, 18,).

Women who underwent vaginal INH were more satisfied than women in the placebo group when questioned about their satisfaction with the HSG procedure. There were no significant differences in side effects or procedure-related complications between the two groups. Many studies use our dose for cervical ripening, and they did not encounter any adverse drug reactions in either group specialty headache (19,26)

One study indicates that the mechanism(s) of action of INH may be similar to nitric oxide (NO) donors but without their frequent adverse effects, such as headache or hypotension.

The subjective assessment of pain in our study was limited by the fact that it might be influenced by patient characteristics or anxiety levels. Randomization and adequate

research design, however, were able to overcome this issue.

The randomized, double-blind, placebo-controlled design of our study is one of its strongest features. The ladies and the HSG radiologist were blinded, and sufficient sample size was acquired. In addition, we employed validated pain measures and evaluated women's satisfaction, which was not done in many previous studies. Finally, the trial was carried out at the same hospital with a single radiologist to exclude any inter-assessor variability in pain VAS assessment.

Conclusion

Adjuvant vaginal INH to oral Ketoprofen 12 hours before HSG may be considerably more effective than Ketoprofen alone in reducing the caused pain score during and 30 minutes after the HSG procedure.

Ethics declarations

Ethics approval and consent to part manuscript preparation icipate

Approval of the western Municipality and Faculty of Medicine was obtained. The ethical review board approved the study by a grant number of (Aswu/209/7/20) from Aswan university Review Board and Ethics Committee. ClinicalTrials.gov identifier NCT04500470; registered on August 3, 2020.

Every patient enrolled in the study counselled about the intervention and written informed consent was taken from each woman before performing any intervention.

Consent for publication

Not applicable

Availability of data and material

The data was obtained from case records of outpatient clinic in our department.

Competing interests

The authors declare that they have no competing interests.

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There was no funding received from the institution.

Authors' contributions

All authors agree to be accountable for all aspects of the work. NS: design, literature review, manuscript preparation. HS: conception and design, literature review, manuscript preparation: HM manuscript preparation, AT: manuscript preparation. HM: manuscript preparation, design preparation

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Figure legends

Figure 1: Consort flowchart showing enrollment of participants.

Table (1): Base line Characteristics in the study groups: -

Parameters	INH Group (n = 100)	Placebo Group (n = 100)	Test of significance
Age (year)	29.4±3.3	29.1 ±2.7	T=0.9, p=0.4
BMI	27 ±2.2	27.3 ± 2	T= 1.2, p= 0.2
Anticipated pain score	5.5 ± 1	5.5 ± 1.1	T=0.3 p=0.8
Duration of infertility (year)	4 ±1.3	4.04 ±1.3	T=0.3 p= 0.8
Residence (%): Urban Rural	 31 (31) 69 (69)	 37 (41) 63 (63)	Chi-squared test=0.8 P=0.4
Education level (%) Primary Secondary high	 35 (35) 42 (42) 23 (23)	 31 (31) 44 (44) 25 (25)	Chi-squared test=0.4 P=0.8
Position of uterus (%): AVF RVF Mid position	 70 (70) 22 (22) 8 (8)	 72 (72) 21 (21) 7 (7)	Chi-squared test=0.1 P=0.9

BMI (body mass index),

Variables are presented as mean and standard deviation, and number (percentage).

Table (2): The study outcomes in the study groups: -

Parameters	INH Group (n = 100)	Placebo Group (n = 100)	Test of significance
Duration of the procedure	12.9±1.3	12.8±1.7	T=0.3, p=0.7
VAS at speculum placement	3.01 ± 0.8	3 ± 0.9	T=0.3, p=0.7
VAS at tenaculum placement	4.02 ± 0.8	4.01 ± 0.9	T=0.1, p=0.9
VAS during dye injection	4.04 ± 0.8	6 ± 1.04	T=14.7, p < 0.001*
VAS 5 minutes post injection	3 ± 0.8	5 ± 0.9	T=17.4, p < 0.001*
VAS 30 minutes post injection	1.9 ± 0.7	4.1 ± 0.8	T= 19.6, p < 0.001*
Women satisfaction score	6.6 ± 1.1	4.4 ± 1.2	T= 13.5, p < 0.001*
Need for additional analgesia (%)	12 (12)	28 (28)	Chi-squared test=8 p= 0.005*

VAS (visual analogue scale). *Statistically Significant Difference

Variables are presented as mean and standard deviation, and number (percentage).

Table (3): Diagnosis of HSG (hysterosalpingogram) in the study groups: -

parameters	INH Group (n = 100)	Placebo Group (n = 100)	Test of significance
Diagnosis of HSG (%)			
Normal	53 (53)	50 (50)	Monte Carlo test
Uterine adhesion	1 (1)	2 (2)	
Uterine anomalies	6 (6)	7 (7)	P = 0.9
Unilateral tubal block	13 (13)	14 (14)	
Bilateral tubal block	9 (9)	8 (8)	
Peri tubal adhesion	18 (18)	19 (19)	

Variables are presented as number (percentage).

Table (4): Side effects in the study groups: -

parameters	INH Group (n = 100)	Placebo Group (n = 100)	Significance
Tenaculum site bleeding (%)	8 (8)	9 (9)	Chi-squared test=0.1, p= 0.8
Headache (%)	17 (17)	14 (14)	Chi-squared test=0.3, p= 0.6
Fever (%)	0	1 (1)	----
Chills (%)	0	0	----
Nausea (%)	3 (3)	5 (5)	Fisher s exact test, p= 0.7
Vomiting (%)	0	0	----
Diarrhea (%)	0	0	----