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Original Research Article

A randomized double blinded clinical trial to explore the clinical outcomes of vaginal isonicotinic acid hydrazide (INH) administration six hours prior to T380A intrauterine device insertion in persons delivered only by cesarean delivery☆,a

Nahla W. Shady[a,*], Hassan A. Farouk[b], Hany F. Sallam[a]

[a] Obstetrics and Gynecology Department, Aswan Faculty of Medicine, Aswan University, Aswan Governorate, Egypt
[b] Mansoura Insurance Hospital, Mansoura, Egypt

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ABSTRACT

Objective: To compare insertion pain and ease of insertion in participants with a prior caesarean delivery having copper intrauterine device (IUD) after pretreatment with isonicotinic acid hydrazide (INH) 900 mg vaginally or placebo.

Study design: From September 2020 to September 2021, we conducted a randomized, double-blind, placebo-controlled experiment at Aswan University Hospital in Egypt with participants who were delivered solely by caesarean delivery and desired copper T380A IUD insertion. The participants were randomly assigned to either vaginal INH or placebo six hours before IUD insertion in a 1:1 ratio. The primary objective of the research was the individuals' self-reported pain during cervical tenaculum placement, sound insertion, IUD insertion, and 5 minutes after the placement, as measured by a 10-cm visual analogue scale (VAS). Our secondary outcomes were ease of insertion, satisfaction, the need for analgesics, and adverse effects. IUD insertion ease was graded from 0 to 10 on a 10-cm VAS scale, with 0 suggesting very easy insertion and 10 denoting extremely difficult insertion.

Results: When compared to the placebo group, the INH group experienced considerably less pain during IUD insertion (2.9 ± 0.85*vs*.5.11 ± 0.82; $p < 0.01$), lower median ease of insertion score ($3(1-4)$*vs*.$5(3-6)$; $p < 0.01$), and better satisfaction (8.17 ± 0.69*vs*.5.57 ± 0.75). The two groups had comparable side effects.

Conclusions: Vaginal INH administered before IUD insertion reduce the amount of discomfort participants feel throughout the process in individuals who had previously only been delivered via CD. It also has the potential to make insertion easier.

Implications: In participants who were delivered solely by CD before, vaginal INH given prior to IUD placement reduces the amount of discomfort participants experience throughout the procedure. Furthermore, it could increase the ease of insertion.

1. Introduction

Long-acting reversible contraception (LARC) is a very successful method for reducing the number of unintended pregnancies across the world. The intrauterine device (IUD) is a procedure that provides many persons with long-term, dependable contraception [1].

IUDs are used by 15% of reproductive-aged people in developing regions, and 9% of reproductive-aged individuals in developed regions [2].

Various treatments to reduce pain perception during IUD placement have been reported [3].Oral ibuprofen, diclofenac, prostaglandins, local anesthetics such as lidocaine, lidocaine-prilocaine, and Nitric oxide donors have all been used [4,5].

Nulliparous people and individuals who have never given birth vaginally have more discomfort with IUD insertion [5,6].

Pain from IUD placement is low to moderate in most people [4]. Some individuals, however, are still concerned about the prospect

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* Corresponding author.
E-mail address: nahlagyn@yahoo.com (N.W. Shady).

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of pain or are more likely to be impacted by variables like nulliparity or a long interval after birth. Expected discomfort during insertion and provider worries about difficult insertion are two potential obstacles to IUD usage. Finding successful ways to make IUD insertion easier might lead to more interest in IUD uptake [7].

The nitric oxide donor's isosorbide mononitrate and glyceryl trinitrate, like the prostaglandin analog gemeprost, can cause cervical ripening. For cervical ripening before surgical procedures in the first trimester nitric oxide donors may be a better option than prostaglandins [8]. Isonicotinic acid hydrazide (INH) is an antituberculosis drug used sometimes to promote cervical ripening. It was shown to be just as effective as misoprostol in induction of labour in term pregnancies [9].

The impact of INH on cervical ripening may be attributable in part to nitric oxide generation in the cervix, according to some research. It has previously been demonstrated that INH injection induces a substantial rise in nitric oxide levels in rat red blood cells (RBCs), and it has been proposed that nitric oxide plays a key role in the pathophysiology of INH-induced oxidative stress in RBCs [10].

Unfortunately, there has been no research on the pharmacokinetics of IINH in the vaginal route; however, a study using INH 900 mg vaginally 6 to 8 hours for cervical ripening before office hysteroscopy found that INH 900 mg vaginally 6 to 8 hours before diagnostic hysteroscopy is effective for increasing ease of insertion and cervical softening change [11].We hypothesized that intravaginal INH could induce cervical ripening by increasing collagen solubility within 6 hours of administration

Because data on the efficacy of this agent on cervical ripening are still limited, we conducted this study to determine if INH 900 mg vaginally, given 6 hours before copper intrauterine device (IUD) insertion was more effective than placebo in reducing insertion discomfort in individuals who delivered only by CD and increasing ease of insertion.

2. Materials and methods

From September 1, 2020, to September 1, 2021, we conducted a double-blind, randomized, placebo-controlled research at the Gynecology Clinic of the Obstetrics and Gynecology department, Faculty of Medicine, Aswan University, Aswan, Egypt. We prospectively registered the study on clinicaltrials.gov, and the scientific departmental committee gave us ethical permission. After receiving a thorough description of the procedure, potential side effects, and problems, all those who agreed to participate signed a written informed consent form.

All of the trial's providers were gynecologists who had received advanced training in contraception.

We offered participation to all patients attending a family planning clinic and requesting copper T 380A IUD insertion if they were 18 years of age or older, did not take any analgesics within 48 hours before IUD insertion, had a negative pregnancy test, and had birth only by CD. We followed normal clinic practices for preprocedural counselling and evaluation; we obtained a thorough medical history and did abdominal and vaginal exams to rule out genital infections or tumors.

We excluded individuals who had a diagnosis of pelvic inflammatory illness, active vaginitis, or cervicitis within the past 3 months, were presently pregnant or were pregnant within six weeks of study admission or had a history of cervical surgery. Individuals with undiagnosed abnormal uterine bleeding, World Health Organization Medical Eligibility Criteria category 3 or 4 precautions to a copper IUD [12], fibroids or other uterine abnormalities distorting the uterine cavity, and a known allergy or contraindication to INH were also excluded.

On the day of study enrollment and IUD placement, participants filled out a demographics form, and the study nurse administered a urine pregnancy test to all of them.

We randomly assigned the participants in a 1:1 ratio into one of 2 groups: the INH group, who received INH 900 mg vaginally, and the placebo group, who received placebo tablets which were identical in shape, color, and consistency to the INH tablets. The placebo was designed by the department of pharmaceutical chemistry at Aswan University's Faculty of Pharmacy to be identical to INH pills in form, size, and color.

A statistician, not involved in the study, used computer randomizer software to generate random numbers table, and allocation was concealed in sequentially numbered sealed opaque envelopes. The statistician kept the key for the randomization scheme and allocation until study completion.

Tablets of INH and placebo were placed in opaque, sealed envelopes with consecutive serial numbers. They were utilized in the sequence in which the women were present. The allocation was kept a secret from the participants, provider, and suppliers.

Six hours before copper IUD insertion, the research nurse digitally placed INH or placebo pills into the posterior vaginal fornix of women without using a speculum. Participants had the option of sitting in the waiting area and watching TV or reading magazines or going home and returning 6 hours later for IUD placement.

After placing a speculum, cleaning the cervix with antiseptic, applying a single-toothed tenaculum, and sounding the uterus to measure its length, the inserting physicians inserted the IUD without using ultrasound guidance. We tested whether Hegar dilators with a diameter of four millimeters could pass through the internal cervical os without resistance prior to copper IUD placement to assess the degree of cervical dilation.

IUD insertions took place on the third to fifth day of the menstrual cycle. The IUD utilized was Copper T380A (ParagardT380A; Teva Pharmaceuticals USA, Inc. North Wales), and all of the providers employed the manufacturer's recommended procedure for IUD insertion [13].

The primary outcome was the mean difference in pain scores during IUD insertion between INH and placebo groups. On a 10 cm horizontal straight line, the VAS scale is rated from 0 to 10, with 0 indicating no pain and 10 indicating the greatest conceivable agony.

A research assistant stood behind the study participant and asked her to assess the severity of pain at four distinct points: during tenaculum placement, sound insertion, IUD insertion, and 5 minutes after the end of the procedure, using the same 10-point VAS with a different sheet of paper at each stage. Participants rated their pain at every time point, not from memory, by marking it on a different VAS at every time point

The secondary outcome measure was the difference in IUD insertion ease scores between study groups (as reported by physicians responsible for IUD insertion). This score is scaled from 0 to 10 on a 10-cm VAS scale, with 0 denoting very easy insertion and 10 denoting extremely difficult insertion.

Cervical dilation of less than 4 mm and the severity of patient-perceived pain at the time of tenaculum placement, during uterine sounding, and 5 minutes following the procedure, as measured by a visual analogue scale, were secondary outcomes.

The providers asked all participants about the need for any analgesics at 15 minutes after completing the procedure.

The providers reported ease of insertion using the ease of insertion score (ES) at the conclusion of the procedure. Twenty minutes post placement, women's satisfaction level with the IUD insertion were recorded on a VAS-like scale from 0 to 10 (with 0 = no satisfaction and 10 = maximum satisfaction).

We requested all patients to return to the clinic in 2 weeks for a string check and to complete a final questionnaire on patient sat-

Table 1
Baseline characteristics of 220 Egyptian women randomized to use vaginal INH or placebo 6 hours prior to IUD insertion.

Parameters	Placebo group (n = 110)	INH group (n = 110)	*p* value
Age (year)	28.9 ± 2.6	28.9 ± 2.9	0.961
BMI	25.3 ± 2.2	25.4 ± 2.3	0.57
parity	2.0 (1-4)	2.0 (1-5)	0.88
Hx of IUD insertion (%)	56 (50.9)	57 (51.8)	0.68
Residence (%):			
Urban	42 (38.2)	46 (41.8)	
Rural	68 (61.8)	64 (58.2)	0.58
Education (%):			
High	45 (40.9)	50 (45.5)	
Primary	65 (59.1)	60 (54.5)	0.49
Position of uterus (%):			
AVF	88 (80)	85 (77.3)	
RVF	12 (10.9)	14 (12.7)	
Mid position	10 (9.1)	11 (10)	0.88

All data are presented as mean and standard deviation, median (minimum-maximum) and number (percentage).
AVF, anteverted flexed; BMI, body mass index; IUD, intra uterine devise; RCT, randomized controlled trial; RVF, retroverted flexed.

isfaction; during that time, we also did a pelvic examination and TVS to rule out pelvic infection and copper IUD expulsion.

We assessed for fever (oral temperature 38°C), which was measured immediately before the procedure, nausea, vomiting, shivering, diarrhea, and cramps, all of which were recorded shortly before IUD placement to ensure that they were caused by the medication and not the insertion technique. We also documented tenaculum site haemorrhage 5 minutes after the procedure, vasovagal response, uterine perforation, unsuccessful insertions, and insertion time from speculum into speculum out.

Based on prior research [14,15], we determined the minimal clinically significant difference (MCSD) in pain reduction to be a 1.5-mm mean difference in the 10-mm VAS, with a standard deviation of 3.2 as indicated in a previous study [16], 90% power, and a 0.05 error. We required a sample size of 200 patients based on that. We increased the sample size by 10% to account for attrition and missing data, resulting in a total of 220 cases (110 patients per group). The sample size was calculated using OpenEpi version 3, an open-source calculator.

Data were entered and statistically analyzed using the Statistical Package for Social Sciences (SPSS) version 20. Quantitative data were described as means (SD) or medians, after testing for normality by Kolmogorov-Smirnov test. In normally distributed variables, independent samples t-test was used for comparison between groups, while in the non-normally distributed variables, Mann-Whitney U test was used for comparison between groups. "*p* value ≤0.05" was statistically significant.

Clinical trial registration number: NCT 04499989.

3. Results

We offered study participation to 260 individuals who delivered only by CD and excluded 40 persons: 30 did not fulfil the inclusion criteria, and 10 declined to participate (Fig. 1)

Participant characteristics are presented in Table 1; we found no differences between the groups.

The INH group had lower pain scores at all time points (Table 2). Physician reported outcomes also favored INH (Table 2).

There were no significant differences in terms of tenaculum site hemorrhage [9] (8.2%) in INH group compared with 8 (7.3%) participants in placebo group), abdominal cramps [14] (12.7%) in INH group) compared with 17 (15.5%) participants in placebo group), fever (one in INH group compared with no participant in placebo group), or nausea [4] (3.6%) in INH group compared with 2 (1.8%) participants in placebo group) after IUD insertion. *p* = (0.80,0.56,1.0, and 0.68). Chills, vomiting, diarrhea, failure of IUD insertion, and 2-week follow-up complication such as perforation, displacement, or expulsion were not recorded in either group.

4. Discussion

In this double-blinded randomized trial, we observed that copper IUD insertion was easier, with less resistance at the level of the internal cervical os and less insertion discomfort, when we compared INH 900 mg vaginally, given 6 hours before copper intrauterine device (IUD) insertion to placebo.

INH is a recently introduced medication for cervical ripening. Vaginal INH is an effective drug for cervical ripening prior to labor induction, according to the findings of a research done by Highlight et al [8]. INH works in a similar way as nitric oxide donors when it comes to cervical dilation.

Several randomized trials with nitric oxide donors have found that the force necessary to widen the cervix prior to a first-trimester abortion is reduced, even when the cervical diameter is less than 6 mm [17–19].Haghighi et al [11]. observed that administering vaginal INH before hysteroscopy reduced the amount of pressure required for cervical dilatation and made it easier to pass the hydroscope into the cervical canal.

Todd et al [20]. established the minimal clinically significant difference (MCSD) in VAS pain score as the quantitative change in VAS pain score that is linked with the subjective evaluation of a little less or a little more pain by the patient. Changes in VAS pain score of less than 13 mm may be of minimal clinical significance, while MCSD in acute pain varied from 13 to 20 mm [21].

The primary pain score difference between the INH and placebo groups in our research was more than 1.3, which was clinically significant.

The impact of nitric oxide donors on the ease of insertion of IUCD and the requirement for supplementary insertion procedures was studied in two studies [22,23].Both studies found no significant differences in provider ratings of the need for cervical dilatation or pain scores among all women randomized. The both studies lacked sufficient power to identify differences in pain perception and ease of insertion with just 24 women. Participants were given analgesia prior to IUCD insertion, which might have affected the pain score reported during IUCD insertion.

There were no significant differences in pain scores between the nitroprusside gel and the control groups in the first trial

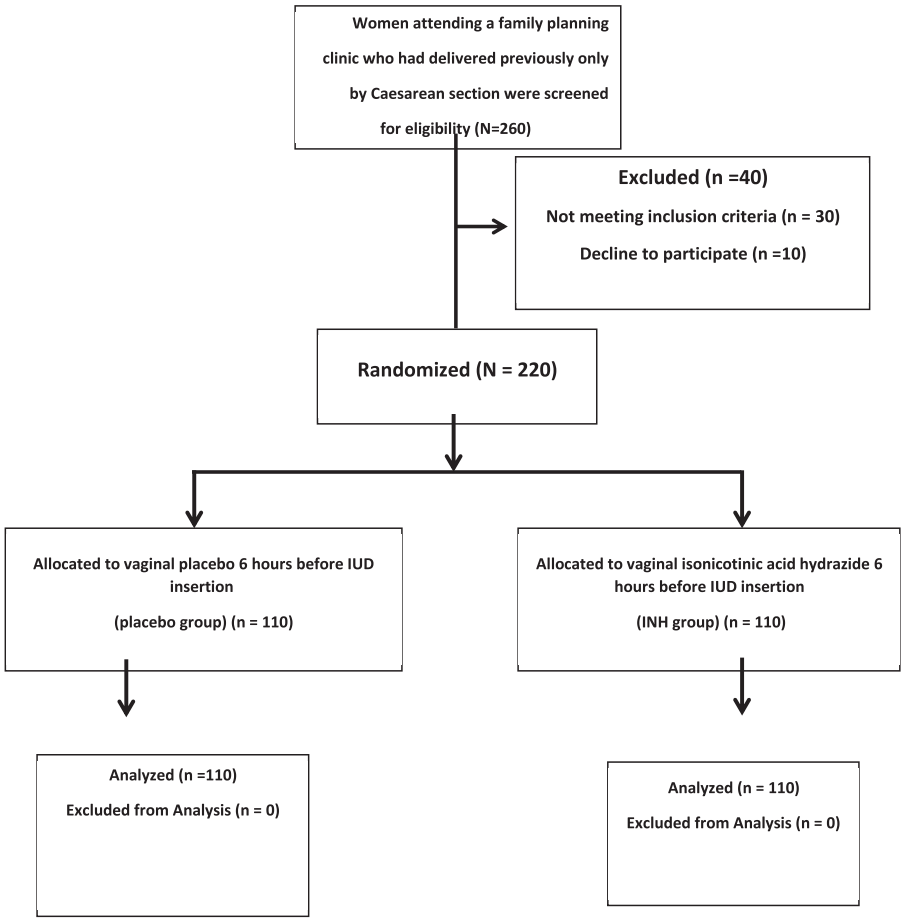

Fig. 1. Consort flowchart showing enrollment of participants in vaginal INH, and placebo groups given six hours before copper IUD insertion.

Table 2
Outcomes in a clinical trial of vaginal INH versus placebo used six hours prior to IUD insertion among Egyptian women with previous cesarean delivery

Parameters	placebo group (n = 110)	INH group (n = 110)	*p* value
Pain reported using VAS			
VAS tenaculum placement	4.0 (3-5)	2.0 (1-3)	<0.01
VAS sound insertion	4.1 ± 0.8	2.9 ± 0.8	<0.01
VAS IUD insertion	5.3 ± 0.79	3.9 ± 0.8	<0.01
VAS 5 minutes post insertion	3 (3-5)	2 (1-3)	<0.01
Request for additional analgesia (%)	27 (24.5)	5.0 (4.5)	<0.01
Participant satisfaction score[b]	5.5 ± 0.7	8.1 ± 0.6	<0.01
Duration of the procedure(minutes)	3.5±0.7	3.5±0.7	0.92
Ease of insertion score[a]	5 (3-6)	3 (1-4)	<0.01
Cervical dilatation			
>4 mm	47 (42%)	77 (72%)	<0.01

All data are presented as mean and standard deviation (t-test was used for comparison between groups), median (minimum-maximum) and number (percentage), and Mann-Whitney U test was used for comparison between groups).
VAS, visual analog scale RCT: randomized controlled trial.
[a] Ease of insertion score was rated on a scale from 0 to 10. (a lower score indicated easier).
[b] Female satisfaction score was rated on a scale from 0 to 10. (a higher score indicated greater satisfaction).

(mean = 32.4 vs 26.5, respectively) [23]. There may be a difference between this study and our experiment. It's conceivable that the period between nitroglycerin and IUD insertion was too short in their trials, or that our drug dose was high enough, to allow for cervical remodeling.

The study has certain limitations, such as the fact that it only looked at one kind of IUD since the levonorgestrel IUD is not frequently used in Egypt owing to its expensive cost, therefore the data is only applicable to copper IUDs.

Furthermore, the six-hour wait between the administration of the study drug and the IUCD insertion was particularly long. Participants may either wait in a comfortable waiting room with plenty of entertainment or go home and return 6 hours later for IUCD placement. However, many patients may find it difficult and inconvenient to wait 6 hours for a brief IUCD insertion in most clinics. This disadvantage can be solved in clinical practice by teaching the patient to self-administer the drug at home and return to the clinic 6 hours later for IUCD insertion.

Vaginal INH was associated with less IUD-insertion pain among women with a previous cesarean delivery. Gynecologists reported the insertions as easier.

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