
The impact of self-administered vaginal isonicotinic acid hydrazone (INH) administration 12 hours prior to levonorgestrel-releasing intrauterine system in women delivered only by elective cesarean section: A randomized double blinded clinical trial

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Abstract

Objective: To evaluate if self-administered 900 mg Isonicotinic Acid Hydrazone (INH) vaginally reduced pain during the insertion of the Levonorgestrel releasing intrauterine system (52 mg LNG-IUS) among women with elective caesarean section (CS).

Methods: This was a double-blinded, single-center, randomized controlled trial. 12 hours before 52 mg LNG-IUS insertion, 220 women were randomly allocated to receive INH 900mg vaginally or placebo. The mean pain score during 52 mg LNG-IUS insertion was our primary endpoint. Mean pain scores during tenaculum application, uterine sounding, and 10 minutes after insertion were our secondary outcomes, as were ease of insertion, satisfaction score, need for further analgesics, and side effects. On a 10-cm VAS scale, IUD insertion ease was assessed from 0 to 10, with 0 signifying very easy insertion and 10 denoting extremely difficult insertion. Fisher's exact test and Chi square test were used for comparison between groups, as appropriate. The student t test was used to compare quantitative data between the two groups.

Results: When compared to the placebo group, the INH group experienced significantly less pain during IUD insertion (4.13 ± 0.98 vs. 6.22 ± 0.895 ; $P < 0.001$) and 10 minutes after insertion (2.63 ± 0.82 vs. 4.52 ± 0.79), easier IUD insertion (2.67 ± 0.83 vs. 5.56 ± 0.87 ; $p < 0.01$), and higher satisfaction (7.25 ± 0.77 vs. 4.74 ± 0.87). When compared to the placebo group, the INH group required fewer extra analgesics ($P < 0.001$). The two groups had similar side effects.

Conclusions: In women who had solely delivered via elective CS, self-administered 900 mg INH vaginally before 52 mg LNG-IUS insertion reduces pain scores during LNG-IUS insertion, making insertion easier and increasing women's satisfaction, with tolerable side-effects.

Key words: Cesarean delivery; intrauterine device; Isonicotinic Acid Hydrazone; pain

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key message

- **What is already known on this topic:** Seeking for alternatives to improve the patients' experience at intrauterine device insertion is an important topic, since the fear of pain during intrauterine device insertion can discourage some potential users.
- **What this study adds:** In women who delivered only by elective cesarean section, vaginal INH self-administered 12 hours prior to 52 mg LNG-IUS placement has the ability to reduce the amount of pain women experience throughout the procedure. Furthermore, it may increase the ease of insertion.
- **How this study might affect research, practice or policy:** INH can simply be utilised to aid in the insertion of 52 mg LNG-IUS. One disadvantage of an intervention that must be provided 12 hours before to 52 mg LNG-IUS placement is that it is ineffective for same-day IUD insertion. However, INH was not used on the same day of the 52 mg LNG-IUS placement in our trial, needs to be addressed in future research.

Introduction

Levonorgestrel releasing intrauterine system (52 mg LNG-IUS) has shown to be a highly effective method of decreasing unplanned births across the world. 52 mg LNG-IUS is a procedure that provides long-term, reliable contraception to many women (1).

The use of LNG-IUS varies by country, although it is used by anywhere from 2% to 75% of contraceptive users worldwide. (2). The insertion procedure, however, is associated with a great deal of pain, which may discourage some women from using it (3).

When compared to placebo, oral and local analgesics, as well as cervical priming, can reduce 52 mg LNG-IUS placement-related discomfort, although their routine usage is still debatable. Predictive indicators may aid healthcare providers in identifying women who are at risk of discomfort(4).

Women who have never given birth vaginally are considered to have more discomfort following 52 mg LNG-IUS insertion (5). Two possible barriers to IUD use include expected pain during insertion and provider concerns about problematic insertion. Finding effective techniques to make IUD insertion less difficult might result in more 52 mg LNG-IUS insertions.(6)

Isonicotinic acid hydrazide (INH) is an anti-tuberculosis medication that helps the cervical ripening process. In term pregnancies, it may be just as effective as misoprostol (7) . Although misoprostol is effective for cervical ripening, it does not reduce pain related to IUD insertion (8). According to some study, the effect of INH on cervical ripening may be due in part to nitric oxide (NO) production in the cervix (9,10).

We conducted this study to evaluate if 900 mg of vaginal INH given 12 hours before insertion of a 52 mg LNG-IUS was more effective than placebo for decrease pain scores and increase the ease of insertion among women with elective caesarean section (CS).

Materials and methods

Study design

From August 2021 to December 2022, we conducted a randomized, double-blinded, placebo-controlled trial in a family planning clinic of a tertiary referral hospital in Aswan, Egypt. After receiving protocol approval from the institutional ethical review board (ASWU/202/7/20), we prospectively registered the study in the clinicaltrials.gov registry (number NCT04500028). Every

participant signed a written informed consent form.

study population

We clinically assessed all women who requested 52 mg LNG-IUS insertion at the Family Planning Clinic throughout the research period and offered them to participate if they did not have any contraindications for insertion based on WHO eligibility criteria and were solely delivered by elective CS.

All the women in the study were non-pregnant, between the ages of 18 and 45, and had not taken any analgesics in the 48 hours before to the 52 mg LNG-IUS insertion.

The study excluded women with uterine anomalies such as congenital deformities, endometrial lesions, adenomyosis, fibroids, or intrauterine adhesions. The study excluded women who had Chronic pelvic pain including dysmenorrhea, irregular uterine bleeding, or a history of cervical surgery, and active vaginitis, cervicitis, or pelvic inflammatory disease within the past 3 months. Women who had an allergy to INH, had a medical condition that prevented them from using it, or women with known psychiatric disorders and chronic use of antidepressants or anticonvulsants were also ruled out, as were those who refused to take part in the study.

Recruitment

Following an explanation of the conventional 10-cm visual analogue scale, one investigator from our research team recorded the participants' baseline characteristics. To establish eligibility and rule out any contraindications, we performed a history taking, abdominal and pelvic examinations, and transvaginal ultrasonography (TVS) using the Sonoace R5 apparatus (Samsung Medison). To rule out pregnancy, the clinic nurse administered a urine pregnancy test to all participants.

LNG-IUS insertion procedure

For insertion, each woman was given LNG-

IUS (Mirena®, Bayer HealthCare, Berlin, Germany). The IUD was inserted during menstruation, on days ranging from the third to the fifth of the menstrual cycle.

Before starting the procedure, we reported all drug-related side symptoms such as nausea, vomiting, stomach cramps, diarrhea, fever (oral temperature 38 °C), and shivering

LNG-IUS insertion was performed by two of the research investigators who was familiar with IUD insertion using the manufacturer's recommended procedure of 52 mg LNG-IUS (Mirena®, Bayer HealthCare, Berlin, Germany).

The providers inserted a speculum into the vagina and used povidone-iodine to clean the cervix. Then, using a single toothed tenaculum, they grabbed the anterior lip of the cervix for fixation of the uterus and inserted uterine sound for uterine length measurement, followed by 52 mg LNG-IUS placement.

Randomization and interventions

The participants were randomly assigned to one of two groups: the INH group, which received 900-mg INH tablets vaginally, or the placebo group, which received placebo tablets that were identical in form, color, and consistency to the INH tablets. A statistician who was not involved in the study generated a random numbers table using computer randomizer software (<http://www.graphpad.com/quickcalcs/index.cfm>), and the allocation was hidden in sequentially numbered sealed opaque envelopes. Until the trial was over, the statistician maintained the key to the randomization method and allocation.

According to the randomization procedure, a single pharmacist made the placebo tablets and packed both INH and placebo tablets into boxes that were then placed in sequentially numbered opaque sealed envelopes. The only person who knew what was in the envelopes was the pharmacist, and neither

the clinicians nor the women knew what kind of medication was inside. The clinic nurse opened the envelopes in the order in which the women arrived at the clinic and dispensed the pills in the sealed boxes. The clinic nurse taught how to store the research medications properly and made sure that all patients had refrigerators.

All patients were given a second appointment for IUD placement and directed to insert the study medicines vaginally 12 hours before to the planned appointment, according to the clinic nurse. One day before IUD installation, an investigator called all participants to remind them to take their medication.

Patients in Group I received a placebo to INH (placebo group) 12 hours prior to the insertion of the 52 mg LNG-IUS, whereas those in Group II received 900 mg vaginal INH (INH group).

All women reported their perceived level of pain at different time points: during tenaculum placement, during sounding of the uterus, during IUD insertion, and 10 minutes after the procedure with the use of the 10-cm VAS (in which 0 corresponds to no pain and 10 to the worst possible pain imaginable).

The duration of IUD insertion as well as immediate problems such as uterine perforation, failure of insertion, and vasovagal response were documented. The providers reported the ease of IUD placement using the ease of insertion score after the procedure was completed (ES). The ES was determined using a graded VAS-like scale ranging from zero to ten, with ten indicating extremely difficult insertion and zero indicating very simple insertion.

All women rated their pain severity on a 10-cm VAS scale after 10 minutes of the procedure and expressed their satisfaction with IUD placement on a 10-cm VAS scale (with 0 = no satisfaction and 10 = maximum satisfaction). We also inquired about post-operative bleeding or spotting, as well as the need for further analgesics. Ibuprofen

400 mg orally was given if needed, as it is a safe and effective medication that is readily available in our clinic.

The participants also mentioned the medication's side effects. Headache, nausea/vomiting, stomach cramps, chills, fever, and diarrhea.

We requested all participants to return to the clinic in one month for a string check and to complete a final questionnaire about patient satisfaction; during that time, we also did a pelvic examination and TVS to rule out pelvic infection and 52 mg LNG-IUS expulsion. We reminded them by phone prior to the appointment, and we scheduled home visits for those who were unable or unwilling to return for follow-up.

Study outcomes

The difference in pain VAS ratings during IUD insertion was the main result. The VAS scale is graded from 0 to 10 on a 10 cm horizontal straight line, with 0 representing no pain and 10 indicating the worst imaginable pain. On a VAS sheet, the participant was asked to select the point that corresponded to the level of pain she had experienced.

The difference in IUD insertion ease ratings across study groups was the secondary end measure (as reported by physicians responsible for IUD insertion). On a 10-cm VAS scale, this score ranges from 0 to 10, with 0 indicating very simple insertion and 10 indicating exceedingly difficult insertion.

The difference in pain VAS scores during tenaculum application, at the placement of uterine sound, 10 minutes after IUD placement, the women's level of satisfaction at the end of insertion, the number of women who require additional analgesics after insertion, and the medication's side effects were among the secondary outcomes.

Sample size

The sample size was calculated using the Open Epi software program, version 2.3.1(11). Based on earlier research (12, 13),

we assumed a minimum clinically important difference (MCID) in VAS pain score to be 1.5 cm and based on Samy et al. (14) trial which reported the mean VAS with LNG-IUS insertion in placebo group (6.4cm); we needed a sample size of 100 women in each group with 90% power and an α error of 0.05 to detect this MCID with INH use. To account for attrition and missing data, we raised the sample size by 10%, resulting in a total of 220 cases (110 patients per group).

Statistical Analysis

Data were entered and statistically analyzed using the Statistical Package for Social Sciences ((SPSS Inc., Chicago, IL.) version 23. Qualitative data were described as numbers and percentages. Fisher's exact test and Chi square test were used for comparison between groups, as appropriate. 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. Because this study used a within-subjects design, linear mixed model (LMM) was used. Odds ratios and their 95% confidence interval were calculated. "p value ≤ 0.05 " was considered to be statistically significant.

Patient and public involvement

There was no direct patient and public involvement in the design of the study.

Results

We screened 250 individuals requesting 52 mg LNG-IUS placement for study eligibility; 30 patients were excluded, 25 patients did not fulfil the inclusion criteria, and 5 patients refused to participate. As a result, the remaining 220 patients were divided into two groups, each with 110 patients. Patients in Group I received a placebo to INH (placebo

group), whereas those in Group II received vaginal INH prior to the insertion of the 52 mg LNG-IUS (INH group). (See Figure 1).

Table 1 shows that the baseline characteristics of the study participants were similar in both groups. The two groups revealed no significant differences in terms of age, weight, height, body mass index (BMI), gravidity, location, education, previous IUD insertion history, time since last birth, and uterine position. The uterine position was anteverted in most cases in both groups

Table 2 shows in addition, there was no statistically significant difference in the mean duration of IUD placement between the two groups ($p=0.934$).

women in the INH group had significantly lower pain scores during the LNG-IUD insertion process than the placebo group, as determined by the visual analogue scale (VAS) during tenaculum placement, sound insertion, IUD insertion, and 10 minutes after the procedure. women in the INH group had significantly higher satisfaction scores compared with those in the placebo group.

Providers reported significantly more ease of insertion in the INH group compared with the placebo group.

In addition, as compared to placebo group, the requirement for additional analgesic was significantly reduced in INH group. ($p<0.001$). (Table 2)

Table 3 shows there were no significant differences related to the complication of the insertion procedure as tenaculum site bleeding, abdominal cramps, fever, headache, headache, vomiting, and failure of insertion. No reported cases of diarrhea or chills. (Table 3).

Discussion

Self-administering INH vaginally 12 hours before LNG-IUS insertion reduces pain at all stages of 52 mg LNG-IUS insertion, with no significant difference in procedure time and

greater women's satisfaction, according to the current study. It also makes IUD placement easier for women who have previously just had a CS.

This is the first randomized, double-blind, placebo-controlled study to assess the efficacy of vaginal INH 900 mg against placebo in decreasing insertion pain and enhancing 52 mg LNG-IUS insertion ease in women who only had a CS.

Because the CS rate has been steadily increasing in our country in recent years, and the IUD is the most popular contraceptive method among Egyptian women, it was necessary to investigate ways to reduce pain and make IUD insertion easier for those who only delivered by elective CS to avoid unintended pregnancies (15, 16). Due to the existence of a scar at the internal os impairing softening of the cervix, previous CD resulted in higher pain levels after IUD insertion and more insertion failures (13).

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

Even when the cervical width is less than 4 mm, the force required to expand the cervix prior to a first trimester abortion is decreased in several randomized studies using NO donors (17-20).

Two investigations looked at the effect of nitric oxide donors on the ease of insertion and the need for further insertion procedures. (21,22) and both show that, there were no significant differences in pain scores between the nitroprusside gel and the control groups. There may be a difference between these studies 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. Furthermore, the authors of these studies indicate that a bigger sample size may have shown significantly different results as the number of participants

only 12 in each group.

The ease of insertion score in the INH group was lower than in the placebo group, indicating that insertion was easier for providers in the INH group

Initial cervical dilatation and dilatation length were longer with vaginal misoprostol than with Foley catheter with vaginal isosorbide mononitrate, according to El-Khayat et al. (23), but there was no significant difference in the procedure duration or difficulty in dilation between the two groups. It's conceivable that their lack of statistical significance is attributable to different sample sizes or methods than those used in the current study.

Women who underwent INH insertion were more satisfied than women in the placebo group when questioned about their satisfaction with 52 mg LNG-IUS insertion. There were no significant differences in side effects or procedure-related problems between the two groups. In our trial, there were four unsuccessful insertions (three in the placebo group and one in the INH group), all of which were caused by a very tight cervical os. After the operation, women in the placebo group needed more analgesics than women in the INH group, and this proves the clinical value and implications of INH administration.

The requirement for cervical dilatation was reduced in the INH group than in the placebo group, implying that insertion was easier for doctors in the INH group.

In a recent study (24), 315 doctors who had inserted the LNG-IUS in nulligravida's reported a relative risk of 2.0 (95 percent confidence range, 1.2–3.2) for a problematic insertion when compared to parous women. The degree of difficulty, on the other hand, was inversely linked to the number of insertions conducted by each professional, with doctors who had performed less than 10 insertions having a higher risk of difficulty (relative risk, 2.2; 95 percent confidence range, 1.6–3.1).

Strengths and limitations

This research provides several advantages. This is the first experiment to explicitly examine the effect of INH on pain at the time of 52 mg LNG-IUS implantation in women delivered only by cesarean section, as previously mentioned. We were able to reduce possible biases that an unblinded or observational study would have introduced by using a prospective, double-blinded, randomized control trial to compare the two treatment arms. We were also able to examine the effect of INH on pain at the time of 52 mg LNG-IUS insertion since we excluded women who had taken other pain medicines on the day of insertion. Finally, an adequate sample size with sufficient power to detect any significant differences between groups using CONSORT guidelines for clinical trials.

The study's main limitation was the requirement for two visits for IUD placement. In addition, the need to be administered 12 hours prior 52 mg LNG-IUS placement is that it not useful for same-day 52 mg LNG-IUS. Patients need two visits: one to pick the medication and another to insert the IUD. This is, however, typical procedure for our family planning clinic, and it allows us to provide better counselling and patient decision-making on the 52 mg LNG-IUD contraception. However, INH was not used on the same day of the 52 mg LNG-IUS placement in our trial, which is one of the study flaws that needs to be addressed in future research.

The subjective evaluation of pain in our study was restricted 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.

Women in the vaginal INH group were more likely to report clinically significant lower pain scores during vulsellum application which

may not explained. The variations in pain perception between the two groups during tenaculum application may be attributed to the effect of INH on cervical ripening and the effect of No on cervical tissue perception of pain. Another drawback was that we did not measure discomfort at different time periods following the operation. Some baseline factors, such as provider experience and time since the previous birth, may have influenced pain and ease of insertion results. However, due to the strong resemblance of these features in the two groups, this hypothesis was ruled out.

INH can simply be used to facilitate IUCD implantation. However, the basic mechanism of cervical ripening is unknown. More study is needed to identify the mechanisms of action and clinical effectiveness of INH in comparison to alternative therapies for cervix softening prior to IUCD implantation, as well as the optimal dosage and timing of INH for cervix softening before to IUCD implantation.

Research implications

To corroborate our findings, more well-designed RCTs on this topic are needed. Future RCTs should compare INH to other drugs for pain alleviation during LNG-IUS insertion, with women who have other risk factors for greater pain scores during LNG-IUS insertion, such as nulliparity, included. However, in the future, more investigation into the efficacy of INH given on the same day as the 52 mg LNG-IUS insertion is needed.

Conclusions

In women who had solely delivered via elective CS, self-administered 900 mg INH vaginally before LNG-IUS insertion reduces pain scores during 52 mg LNG-IUS insertion, making insertion easier and increasing women's satisfaction, with tolerable side-effects.

Compliance with ethical standards**Conflict of interest**

The authors declare that they have no conflict of interest.

Ethical approval

The study protocol was approved by the Ethics Committee of Aswan University Faculty of Medicine (Aswu/202/7/20). ClinicalTrials.gov identifier: NCT04500028

The study was in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

Authors contribution:

NS: design, literature review, manuscript preparation. HS: conception and design, literature review, manuscript preparation. AT: literature review, manuscript preparation.

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Figure legends

Figure 1: Consort flowchart showing enrollment of participants