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Original Article

Effect of topical glyceryl trinitrate cream on pain perception during intrauterine device insertion in multiparous women: A randomized double-blinded placebo-controlled study

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ABSTRACT

Objective: Intrauterine contraceptive device (IUD) insertion-related pain presents a push beyond the decline of women to use IUD for family planning. We aimed to investigate the analgesic effect of glyceryl trinitrate cream (GTN) in reducing pain during IUD insertion.
Materials and methods: We conducted a randomized double-blinded placebo-controlled study (NCT02708251, clinicaltrials.gov) in a tertiary University hospital. Reproductive-aged women requesting Copper IUD for contraception were considered. Eligible women for IUD insertion were randomized (1:1) to glyceryl trinitrate cream (GTN arm) or Placebo. Three minutes before IUD insertion, 1 ml of GTN cream or placebo was applied to the cervical lip at the planned tenaculum site, followed by 1 ml placed in the cervical canal up to the level of the internal os using a Q-tip applicator. Our outcomes were the participant's self-rated pain perception utilizing a 10-cm Visual Analogue Scale (VAS) during cervical tenaculum placement, uterine sound and IUD insertion, then 15 min post-procedure.
Results: 100 women were enrolled and randomized to GTN arm (n = 50) or placebo (n = 50). Women in the GTN arm reported lower VAS scores during tenaculum placement, sound and IUD insertion (median: 2 vs. 4, $p < 0.0001$; 2.5 vs. 4.5, $p < 0.001$;3 vs. 5.5, $p < 0.0001$, respectively). Higher ease of insertion score was also determined among GTN arm (mean ± SD: 6.9 ± 1.15 vs. 4.7 ± 1.38, $p < 0.0001$). Additionally, women in the GTN arm were more satisfied by the end of the insertion (92% vs. 74%, $p = 0.003$).
Conclusion: Application of cervical GTN cream before IUD insertion seems to reduce the induced pain with subsequent easy insertion.

Introduction

Intrauterine contraception (IUC) provides long-term, reversible contraception equal in efficacy to tubal sterilization [1]. Depending on the country, the use of intrauterine devices (IUDs) ranges from 2% to 75%. On average, 15% of reproductive-aged women in developing countries and 9% in developed countries use IUDs [2].

Pain can be perceived during all steps of IUD insertion including the application of the tenaculum to the cervical lip, sounding the uterus, and advancing the IUD introducer through the cervical canal inside the uterine cavity [3,4]. The levels of pain that women experienced during IUD insertion vary in published reports. Most women experience mild to moderate discomfort during IUD insertion. Rarely, the pain is severe and associated with vasovagal episode. Predictors of pain during IUD insertion include nulliparity, age greater than 30 years, longer inter-pregnancy interval, history of dysmenorrhea, and not currently breastfeeding [5].

Nitric oxide (NO) donors have reported effects on the animal and human cervix [6]. In randomized trials, both nitroglycerin (glyceryl trinitrate) and isosorbide mononitrate tablets have been shown to induce cervical ripening with minimal side effects compared to placebo when administered vaginally for the management of first-trimester abortion [7].

One study demonstrated that nitroglycerin 0.5 mg applied vaginally was associated with a decrease in the force needed to

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dilate the cervix to 8 mm compared to placebo [6]. Since NO donors are smooth muscle relaxants, they are expected to induce cervical softening without causing uterine cramping, which is the most recognized side effect of misoprostol [8].

Therefore, the objective of this study was to evaluate the analgesic effect of topical application of glyceryl trinitrate (GTN) cream during IUD insertion.

Materials and methods

This study was a randomized, double-blinded placebo-controlled trial (ClinicalTrials.gov ID: NCT02708251). The ethical review board of the Faculty of Medicine of Assiut University approved the study. The study was conducted between October 2016 and March 2017. The participants were identified and recruited from the family planning clinic at Woman's Health Hospital, Assiut University, Egypt.

Inclusion and exclusion criteria

We included multiparous women aged (18–50 years) who have not taken any analgesia or anxiolytics in the 24 h before IUD insertion and who have not received misoprostol before insertion. We excluded women with category 3 or 4 conditions for IUD insertion according to the WHO Medical Eligibility Criteria for contraceptive use. Also; we excluded women with known hypersensitivity to GTN and those with a history of migraine or chronic headache.

Informed consent was sought for participation after discussing the nature of the study. After that, the participants entered the screening phase of the study. This phase included history taking and clinical examination by two investigators (SSA, ER).

Randomization

Randomization was performed by a computer-generated random table. Eligible women were randomized to either group I: GTN group or group II: placebo group. Allocation concealment was carried out using serially numbered closed, opaque envelopes. Each envelope was labeled with a serial number and had a card noting the intervention type. The allocation was never changed after opening the closed envelopes.

Intervention

The participants who were allocated to group I (GTN group) received 1 mL of glyceryl trinitrate cream which was applied to the anterior cervical lip and another 1 mL which was inserted into the cervix up to the level of the internal cervical os using Q-tip applicator. Whereas the participants who were allocated to group II (placebo group) received the same amount of an inert cream of similar appearance, color, and consistency. The placebo cream was manufactured in the Department of Pharmaceuticals, Faculty of Pharmacy, Assiut University. After a three minute waiting period, the IUD was inserted in the standard fashion.

Study outcomes

The primary outcome was the difference in pain visual analog scale (VAS) scores during the IUD insertion. The secondary outcomes included the difference in pain scores during each other step of IUD insertion, the difference in ease of insertion score, the difference in women's satisfaction score, and the side effects of the used medication.

Follow-up schedule

We gave participants a 10-point VAS and asked them to indicate their perceived pain score with insertion (This validated pain scale uses a 10 cm line to represent the continuum of 'no pain at 0′ to 'worst imaginable pain at 10′ [9].

Technique of IUD insertion

With the patient in the lithotomy position, one of the study investigators (AMA) performed a bimanual examination, placed the speculum, and cleansed the upper vagina and the ectocervix with povidone-iodine then the IUD was inserted utilizing the standard producer approved technique for each IUD type, including placement of a tenaculum and uterine sounding. No cervical dilation was used for any IUD insertion in this study.

Participants were asked to mark pre-insertion pain expectations initially, and then to mark their pain score according to the VAS in each step of IUD insertion including placement of the tenaculum for cervical traction, uterine sounding, the passage of the applicator tube and insertion of the device. Pain score for the IUD insertion was immediately obtained. A "global pain score" reflecting the patient's overall assessment of the pain for the overall procedure was obtained at 15 min post-procedure. Any complications related to the insertion (i.e., perforation, expulsion) were recorded. Perforation is diagnosed during insertion if the sound or IUD inserter passes for a long distance inside the uterus or sudden pain and bleeding occurs during insertion. Additionally, all cases confirmed to have IUD in place immediately after insertion using pelvic ultrasound examination.

Sample size

Preliminary data from for women undergoing IUD insertion found a mean pain score of 4 (SD = 2.5) on a 10-point scale for the placebo group. We considered a 2-cm difference in the mean score as a clinically important difference. Forty-three women per arm were required to reach 90% power with an alpha (type I) error of 0.05. Anticipating the possibility of 15% loss in study participants, fifty cases were included in each arm of the study.

Statistical analysis

The data were collected and entered into a Microsoft Access database and were analyzed using the Statistical Package for Social Science (SPSS Inc., Chicago, version 21). The demographic characteristics and baseline data were compared between the groups. The outcome variables were presented as medians and compared using the Mann-Whitney test. For dichotomous variables, chi-square was used to estimate the significance value. For analysis, $p < 0.05$ was considered to be significant.

Results

One hundred and eight women were identified. However, eight women were excluded from the study (three had contraindications to IUD insertion, two with a history of migraine, and three with a history of chronic headache). One hundred women consented to participate and were randomized to both groups (Fig. 1).

Table 1 shows that both groups were homogenous in baseline socio-demographic data without statistically significant differences. Table 2 shows that there was a statistically significant difference between both groups at all steps of IUD insertion. Women in GTN group reported lower pain score at tenaculum application ($p < .0001$), at uterine sounding ($p < 0.001$), at IUD insertion ($p < 0.0001$) and 15 min post procedure ($p = 0.009$).

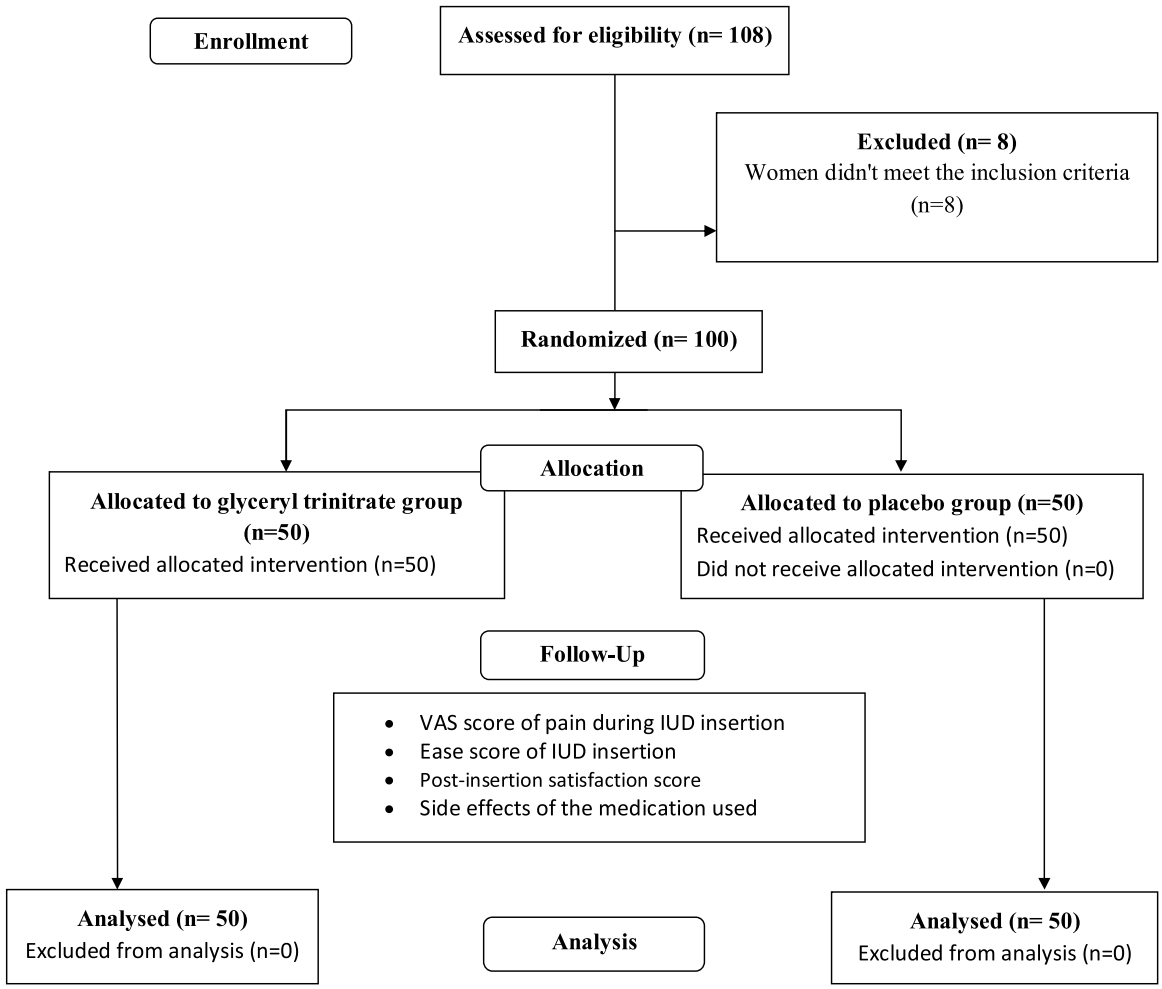

Fig. 1. The study flowchart.

Higher ease of insertion score was also determined among GTN arm (mean ± SD: 6.94 ± 1.15 vs. 4.74 ± 1.38, p < 0.0001). Additionally, women in the GTN arm were more satisfied by the end of the insertion (92% vs. 74%, p = 0.003). No difference between both groups regarding the duration of IUD insertion (p = 0.125). Furthermore, no cases of perforation or failed insertion were observed in the study.

Table 1
The baseline characteristics of the study participants.

Characteristics	GTN group	Placebo group	P-value
Age	29.58 ± 6.44	30.04 ± 7.76	0.747
Parity	2.90 ± 1.39	2.56 ± 1.30	0.371
Residency			0.316
Urban	22 (44%)	29 (58%)	
Rural	28 (56%)	21 (42%)	
Previous cesarean section	19 (58%)	25 (50%)	0.705
Previous miscarriage	15 (30%)	12 (24%)	0.423
Educational level			0.535
Primary	41 (82%)	37 (74%)	
High	9 (18%)	13 (26%)	
Previous IUD insertion	25 (50%)	29 (58%)	0.567
lactating	36 (72%)	37 (74%)	0.797
Not lactating	14 (28%)	13 (26%)	

GTN; glyceryl trinitrate, IUD; intrauterine device.

Discussion

To the best of our knowledge, this is the first trial to study the effect of cervical glyceryl trinitrate on the pain associated with copper IUD insertion. Our results have shown that GTN significantly reduced the pain perceived during tenaculum placement, sound insertion, IUD insertion, 15 min post-insertion and increases the ease of insertion score, compared with placebo.

Steps of the IUD insertion procedure that may cause pain include the application of the tenaculum to the cervix to stabilize

Table 2
The study outcomes according to the medication used prior to the procedure.

Study Outcomes	GTN group	Placebo group	P-value
VAS tenaculum placement*	2	4	< 0.0001
VAS sound insertion*	2.5	4.5	< 0.001
VAS IUD insertion*	3	5.5	< 0.0001
VAS 15 minutes post-insertion*	2	3.5	0.009
Ease of insertion score	6.94 ± 1.15	4.74 ± 1.38	< 0.0001
Duration of insertion (min)	6.82 ± 0.92	6.82.± 1.55	0.125
Failure of insertion	0	0	————
Perforation	0	0	————
Satisfaction	46 (92%)	37 (74%)	0.003

GTN; glyceryl trinitrate, VAS; visual analog scale, IUD; intrauterine device.
* Data are presented as medians.

the uterus and provide traction for straightening the cervical canal, sounding the uterus, advancing the introducer tube through the cervix, and irritation of the endometrial cavity when the device is deployed [10].

Nitric oxide (NO) donors, including nitroglycerin, nitroprusside, isosorbide mononitrate and isosorbide dinitrate, have effects on the animal and human cervix [6]. Two pilot studies examined NO donors versus placebo for pain relief during IUD insertion. The experimental interventions were nitroprusside 10 mg as 1% aqueous gel administered immediately before IUD insertion in Bednarek et al. study and 1 mL of 0.5 mg nitroglycerin ointment at 30–45 minutes before the procedure in Micks et al. study [10,11]. Meta-analysis of these two small trials showed no effect of the intervention on pain during IUD insertion [12]. Previous study compared GTN with lidocaine ointment in pain relief of anal fissure and proved its efficacy [13].

Our results showed that women in the GTN group had significantly lower pain scores compared to those in the placebo group during all steps of IUD insertion. In contrast to Bednarek et al. who showed no significant difference between the groups in pain scores at tenaculum placement (51.6 mm in the placebo group versus 55.5 mm in the lignocaine group; $p = 0.33$). The study arms did not differ significantly in pain scores during IUD insertion ($p = 0.28$) [10]. The same was observed in Micks et al. study, vaginal application of 0.5 mg nitroglycerin ointment before IUD insertion did not decrease pain with IUD insertion among nulliparous women ($p = 0.56$) [11]. Both studies found no significant difference between nitroglycerin ointment group and placebo group regarding IUD insertion pain. These findings may be attributed to the small number of participants (12 women in each group) and to a long time between the application of ointment on the cervix and the insertion (30–45 min before IUD insertion) in Micks et al. study [12].

The strengths of our study include that it was a double-blinded randomized controlled trial in which with neither the participants nor the clinicians were aware of the group allocation. Also, we included women from different educational levels, as this may be a contributing factor for their perception of pain. Therefore, our results could be generalized to the female population in our community. Finally, we were able to recruit our calculated sample size to achieve sufficient power to detect a statistically significant difference in our primary outcome.

However, our study is not without limitations. Firstly, we did not study the effect of cervical GTN cream on pain perception during insertion of levonorgestrel intrauterine system (LNG-IUS), as the LNG-IUS is not widely available in our community due its high cost. Secondly, the subjectivity in reporting pain score through the VAS. And lastly, we only included multiparous women in our study as the acceptability of IUD among nulliparous women in our community is low.

Conclusion

Our study concluded that the use of local glyceryl trinitrate cream before copper IUD insertion in multiparous women reduces pain and increases the satisfaction rate for this effective contraceptive method.

Conflict of interest

No conflict of interest to be declared.

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