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Original Article

Effect of oral diclofenac potassium plus cervical lidocaine cream on pain perception during hysterosalpingography: A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Objective: The current study aims to investigate the analgesic effect of combining oral diclofenac potassium and cervical lidocaine cream for alleviating pain during HSG.
Study design: A randomized double-blind controlled trial.
Setting: Assiut University Hospital, Assiut, Egypt.
Materials and methods: Reproductive-aged infertile women scheduled for HSG were recruited and randomized (1:1) to diclofenac plus lidocaine or Placebo group. All women received oral 50 mg diclofenac potassium or placebo tablets one hour before HSG, then 3 ml of lidocaine 5% cream or placebo was applied to the anterior cervical lip, followed by 3 ml placed in the cervical canal using a sterile needless syringe. The study outcomes was the participant's self-rated pain perception utilizing a 10-cm Visual Analogue Scale (VAS) during speculum placement, cervical tenaculum placement, injection of the dye, 5 min and 30 min post-procedure.
Results: One hundred forty women were enrolled (n = 70 in each group). Oral diclofenac plus lidocaine cream significantly reduce the median VAS pain scores during injection of the dye (4 vs. 7), 5 min post-procedure (2 vs. 4) and 30 min post-procedure (1 vs. 2.5) with p = 0.0001 at all steps. No significant differences in VAS score after speculum or tenaculum placement.
Conclusions: Utility of oral diclofenac potassium one hour before HSG combined with cervical lidocaine 5% cream significantly alleviate the induced pain during and 30 min after the HSG procedure.

1. Introduction

Infertility is the failure of a couple to conceive after ≥12 months of regular unprotected sexual intercourse [1]. In 30–40% of cases, Tubal abnormalities may stand behind the cause of infertility and evaluation of tubal patency is so crucial in their diagnostic workup [2]. Hysterosalpingography (HSG) is a reliable, simple and cost effective method for evaluation of tubal patency. Besides that, it can be used for evaluation of an intrauterine pathology and mullerian anomalies [3]. Although it is a minor gynecological procedure, considerable pain can be experienced by women during cervical instrumentation, injection of the dye in the uterus causing its distension, or from peritoneal irritation secondary to tubal spill [4].

Pain is transmitted from the uterus through two different pathways; Parasympathetic one (S2-S4) provides sensory innervation to lower part of the uterus with the cervix and sympathetic (T10-L1) provides sensory innervation to the uterine fundus [5]. The pain felt by women during HSG is relevant as it might affect their cooperation during the procedure, thereby limiting the value of HSG. In the literature, there is a divergence regarding the best method that can be used for pain relief during HSG.

A recent Cochrane systematic review (2015) shows a number of randomized comparative studies for pain relief with HSG [6]. Although the result of this metaanalysis shows that only topical anesthetics verified effective pain relief, they expressed the need of large randomized controlled trials for investigating the effect of combining different analgesia classes on HSG-related pain [6].

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Local anesthetics have been extensively studied for a variety of different indications involving the genital mucosa, including lidocaine gel, Lidocaine-prilocaine cream, benzocaine 20% gel and mepivacaine gel [7]. Lidocaine is one of the most commonly used local anesthetics [8]. Studies evaluating topical lidocaine formulations for pain relief during HSG provide low evidence of reduction of pain only during the procedure but not within 30 min after it [9–11].

Several studies reported that oral non-steroidal anti-inflammatory drugs (NSAIDs) are not effective in reducing pain neither during HSG nor within 30 min [12–14]. However, a recent study demonstrated significant pain reduction during HSG with oral diclofenac potassium [15].

The aim of the current study is to investigate the effect of combining oral diclofenac potassium and cervical lidocaine cream for pain relief during HSG.

2. Materials and methods

Our hypothesis that lidocaine cream can block the pain arising from the cervix due to tenaculum application and cannula insertion through the cervical canal. Additionally, diclofenac potassium can block the pain arising from the uterus due to injection of the dye and peritoneal irritation secondary to its spill.

The current study was a prospective, randomized, double-blind, placebo-controlled trial, conducted in Assiut University Hospital, Egypt between the 1st of March and the 30th of September 2016. The Institutional Research Ethical Review Board approved the study. This trial was registered at Clinical Trials.Gov (NCT02709590).

All women attended our Infertility Clinic and scheduled for HSG were invited to participate. All eligible participants included in the study signed a written informed consent before participation after explaining the nature of the study. We included infertile women, aged 19–42 years old, and did not receive any analgesics or misoprostol in the 24 h prior to HSG. We excluded women with hypersensitivity to NSAIDs or local anesthetics. Additionally, women with undiagnosed irregular uterine bleeding, acute cervicitis and suspected pregnancy were excluded.

Participants were randomized in a 1:1 ratio to receive active or placebo treatment. A statistician, not otherwise involved in the study, prepared a computer generated randomization tables and placed the allocation data in a serially numbered sealed envelopes. Each envelope had a card noting the intervention type inside. The envelopes opened only by a study researcher according to the order of attendance of women. Once allocation had been done, it could not be changed.

We randomly assigned all participants into one of two groups: **(Study group):** women received 50 mg diclofenac potassium tablet (Cataflam®; Novartis, Stein, Switzerland) plus topical lidocaine anesthetic cream (Lignocaine 5%®; The Nile Co., Egypt) placed into the cervix prior to HSG, and **(Placebo group):** women received a placebo tablet of the same size, color and shape of diclofenac plus an inert placebo cream created to be identical in consistency, odor and color to the lidocaine cream. A single pharmacist was responsible for the manufacturing of the placebo tablets and cream then packaging of preparations into unlabeled sterile boxes, so neither the clinicians nor the women knew the type of the preparation (double-blind study).

One of the study researchers approached all included women and collected their demographic characteristics: age, parity, residence, educational level, previous miscarriages, vaginal or cesarean delivery, type and duration of infertility, history of dysmenorrhea or chronic pelvic pain, and history of previous HSG. Then, he explained the standard 10-cm visual analog scale (VAS) to the participants for pain scoring [16]. The severity of pain was assessed with VAS (with 0 = no pain and 10 = worst imaginable pain). Finally, he instructed the women to take the tablet one hour before HSG.

All women were in the follicular phase of their menstrual cycle and underwent HSG as an outpatient procedure. A single experienced radiologist performed the HSG. Women were placed in the dorsal lithotomy position on a fluoroscopic table. The radiologist placed a sterile speculum into the vagina and cleansed the cervix with povidone-iodine. Three minutes prior to HSG, 3 ml of the study cream was placed on the anterior lip of the cervix by a Q-tip applicator, followed by 3 ml injected by a sterile needless 5 ml syringe into the cervical canal. Then, the anterior lip of the cervix was grasped with a tenaculum and a sterile Rubin's cannula was inserted into the cervical canal. A 15 ml water-soluble contrast dye (Sodium amidotrizoate and meglumine at 76% Urografin® Bayer Hispania SL; Barcelona; Spain) was injected over 20 secondsinto the uterine cavity. Radiographic images were taken in the anteroposterior view when the uterine cavity was fully filled with the dye. Finally, all instruments were removed, and women were observed in the clinic for 30 min.

A research assistant standing beside the woman asked her to rate the intensity of pain experienced during the procedure using the same 10-point VAS with a different sheet of paper at every point. Participants were asked to rate the intensity of pain six time points; at baseline (anticipated pain), after speculum placement, after tenaculum placement, after injection of the dye, 5 and 30 min following the end of the procedure. All women were asked about the need for any additional analgesics at 30 min post-procedure. Women were offered ibuprofen 400 mg as an additional analgesic if needed as it was readily available in our clinic. All women were asked to report any side effects occurring during the procedure and 30 min after HSG, such assyncope, dizziness, nausea or vomiting. The duration and the results of HSG were also included in the final analysis.

The primary outcome was the difference in mean pain score during the procedure. The secondary outcomes included the difference in mean pain scores at 5 and 30 min after HSG, the number of women who need additional analgesics, and the side effects of the study medications

Sample size calculation was based on the VAS score during the most painful step of the HSG procedure as reported by Liberty et al. in a randomized clinical trial [17]. The most painful mean VAS score was 4.9 with 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 will be significant. Considering an alpha error of 0.05, a statistical power of 80% and a 10% rate of loss to follow-up. A sample size of at least 68 women in each group would be required.

All data were analyzed using SPSS software Chicago, IL, USA, version 21. Comparison between categorical variables in both groups was done by Fisher's exact test and continuous variables were compared using. For statistical analysis, we tested the different pain scores for normality by Shapiro-Wilkes test and they were not normally distributed, so they are presented as median scores and compared using the Mann-Whitney test. We considered P value < 0.05 as a significant value.

3. Results

One-hundred fifty-two women were approached to participate in the study. Twelve women have been excluded: three women had irregular uterine bleeding and four women had already

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