Original Article

Effect of Vaginal Dinoprostone Plus Oral Diclofenac Potassium on Pain Perception During Hysterosalpingography in Infertile Patients

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ABSTRACT

Objective: To compare the clinical results of utilizing a combination of oral diclofenac potassium and vaginal dinoprostone for pain management during hysterosalpingography (HSG) versus using only oral diclofenac potassium.

Material and Methods: From September 2020 to September 2021, researchers at Aswan University Hospital conducted a randomized controlled trial. Reproductive-aged infertile women who were scheduled for HSG were administered diclofenac plus vaginal dinoprostone or diclofenac plus placebo to vaginal dinoprostone. All women were given vaginal dinoprostone or placebo six hours before the surgery, which was applied to the upper vagina by the patient, followed by oral 50 mg diclofenac potassium tablets one hour before HSG. The participants' self-rated pain experience was measured using a 10-cm Visual Analogue Scale (VAS) during speculum installation, cervical tenaculum implantation, dye injection, and 5 and 30 minutes after the operation.

Results: Two hundred women were enrolled (n = 100 in each group). Oral diclofenac plus vaginal dinoprostone significantly reduces the main VAS pain scores during injection of the dye (4.18 ± 0.90 vs. 6.23 ± 0.89), 5 min post-procedure (3.81 ± 0.91 vs. 5.05 ± 0.95) and 30 min post-procedure (2.69 ± 0.80 vs. 4.14 ± 0.74) with $p < 0.01$ at all steps. There were no significant variations in VAS scores after using a speculum or tenaculum.

Conclusion: Utility of adjuvant vaginal dinoprostone six hours before HSG to oral diclofenac potassium one hour before HSG significantly more effective than diclofenac potassium for alleviate the induced pain during and 30 min after the HSG procedure.

Key Words: Dinoprostone, hysterosalpingography, infertile, NSAIDs, pain.

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INTRDUCTION

After 12 months of unprotected sexual intercourse, infertility is defined as a couple's inability to conceive[1]. Tubal abnormalities are thought to be the cause of infertility in 30–40% of individuals, making tubal patency testing critical in their diagnosis process[2].

Hysterosalpingography (HSG) is a critical step in the assessment of tubal patency and the uterus in the absence of comorbidities, and the National Institute for Health and Care Excellence recommends utilizing HSG to screen for tubal occlusion[3].

Hysterosalpingography (HSG) is a simple, safe, and economical method of determining tubal patency. It can also be used to look for Mullerian anomalies and intrauterine diseases[4].

Women may suffer significant discomfort during cervical instrumentation, dye injection into the uterus, which causes distension, or peritoneal irritation due to tubal leak[5].

The discomfort experienced by women during HSG is important since it may impair their compliance, lowering the procedure's value. In the literature, the best effective strategy for pain reduction during HSG is controversial[6]

Nulliparity, a history of dysmenorrhea, anxiety, and high expected pain levels are all risk factors that might increase the amount of pain experienced[4,5]. Nonsteroidal anti-inflammatory drugs, topical anesthetic gel or spray, paracervical block, nitrous gas, misoprostol, and conscious sedation have all been investigated to reduce discomfort during HSG; nevertheless, the results have been confusing and conflicting[7].

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According to a recent Cochrane systematic review, there are several randomized comparative studies for pain reduction using HSG[8]. (2015). Despite the fact that the results of this meta-analysis show that only topical anesthetics give considerable pain relief, they advocate for large randomized controlled trials to look into the effect of mixing different analgesic classes on HSG-related pain[8].

Because the production of prostaglandins from cervical manipulation and uterine distension may induce discomfort during HSG, utilizing a prostaglandin-synthetase inhibitor during the procedure appears to be a viable pain-relieving strategy. An NSAID administered one hour before to hysteroscopy will achieve its maximum analgesic effect during the operation. Mean peak plasma concentrations took 20–60 minutes to attain after one 50 mg Diclofenac tablet[9].

Oral non-steroidal anti-inflammatory medicines (NSAIDs) have been unproven in various studies to reduce pain during HSG or within 30 minutes, with mixed outcomes[10,11].

Dinoprostone also known as natural prostaglandin E2, increases cervical dilatation, effacement, and softening, which mimics the normal process of pregnancy, potentially through enhanced collagenase release[12]. The activity of a vaginal dinoprostone suppository begins within 10 minutes and lasts for up to 2–3 hours[13].

Indeed, vaginal dinoprostone was found to be more effective than misoprostol for cervical softening, with fewer side effects and procedure-related problems before outpatient hysteroscopy[14].

The purpose of this study is to investigate how effectively oral diclofenac potassium and vaginal dinoprostone work together to alleviate HSG pain.

MATERIALS AND METHODS

Between 1st of September 2020 and 30th of September 2021, a randomized, double-blind controlled experiment (ClinicalTrials.gov identifier NCT04500509; registered on August 5, 2020) was undertaken at a tertiary university hospital. The study's protocol was approved by the hospital's Institutional Research Ethics Committee. Before being included in the trial, the patients underwent counselling and signed a written informed consent form.

Eligible Participants

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

The following were the criteria for exclusion: a) dinoprostone contraindications (cardiovascular disease, hypertension, severe asthma, glaucoma, renal failure, or allergy to prostaglandins); b) NSAIDs contraindications (previously reported adverse reaction; c) history of cervical surgery, presence of acute pelvic inflammatory disease; d) secondary infertility women; and e) women with unexplained irregular uterine bleeding, acute cervicitis, or probable pregnancy.

Eligible participants were allocated to 1 of 2 groups. Group I women received 1 tablet (3 mg) of vaginal dinoprostone (prostin E2; Pharmacia & Upjohn, Puurs, Belgium) 6 hours before the procedure. Group II women received 1 placebo tablet to dinoprostone. All patients received 50 mg diclofenac potassium tablet (Cataflam®; Novartis, Stein, Switzerland) 1 hours before the procedure.

Randomization

Patients were assigned to one of two study groups in a 1:1 ratio using a two-block randomization list designated I or II. A statistician who was not otherwise involved in the study created the randomization list using a computer-generated random table.

The assigned groups were concealed within serially numbered sealed opaque envelopes that were only unlocked following enrolment. Each envelope contained a card indicating the sort of intervention. The envelopes belonged to one of the study's scientists, who was not involved in the patients' treatment. HSG was planned at a later visit after the women were accepted into the research, and the sealed envelopes were opened by the study investigator in the order in which the women arrived.

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. Then, he explained the standard 10-cm visual analog scale (VAS) to the participants for pain scoring[15]. 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 diclofenac potassium oral tablet one hour before HSG and insert place the dinoprostone or placebo tablet as high as feasible in the vaginal canal 6 hours before their HSG appointment.

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. 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 seconds into 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 as syncope, dizziness, nausea or vomiting. The duration and the results of HSG were also included in the final analysis.

Study Outcome

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

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 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 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

All data were analyzed using SPSS software Chicago, IL, USA, version 21. -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. Odds ratios and their 95% confidence interval were calculated value ≤0.05" was statistically significant.

RESULTS

Two hundred twenty patients complaining of infertility and will subjected to HSG were asked to participate in our study ,20 patients were excluded as 15 patients not meeting inclusion criteria and 5 patients refuse to participate (Figure 1).

The remaining 200 patients were randomized to 2 groups each group comprised of 100 patients.

There was no significant difference between the base line characteristics for the two groups such as their age, body mass index (BMI), and duration of infertility, residence, and education level. (Table-1).

Table 1: Base line Characteristics in the study groups

Parameters	Group I (n = 100)	Group II (n = 100)	*P value*
Age (year)	30.44±3.24	30.07 ±2.71	0.382
BMI	26.05 ±2.08	26.21 ± 2.11	0.590
Anticipated pain score	6.6 ± 17.0	6.4 ± 16.2	0.463
Duration of infertility (year)	3.99 ±1.31	4.06 ±1.27	0.705
Residence (%):			
Urban	39 (39)	41 (41)	
Rural	61 (61)	59 (59)	0.773
Education level (%):			
Primary	46 (46)	44 (44)	
Secondary	36 (36)	36 (36)	0.928
high	18 (18)	20 (20)	
Position of uterus (%):			
AVF	78 (78)	75 (75)	
RVF	12 (12)	14 (14)	0.881
Mid position	10 (10)	11 (11)	

BMI (body mass index), CS (caesarian section),

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

Pain scoring for each group was assessed by visual analogue scale (VAS), there was no significant difference between the two groups with respect to pain score during speculum and tenaculum placement. P= (0.707, 0.432), However there was a significant reduction in pain score during dye injection, 5 and 30 minutes after injection in group II compared to group I, p= (0. 0001,0.0001,0.0001, and 0.0001). Also, the satisfaction level among women was higher in group II compared to group I. p= (0.0001), The additional of extra analgesic was significant increase in group I compared to group II. P= (0.023), however no significant difference in the mean duration of the procedure between the two groups, p= (0.619) (Table 2).

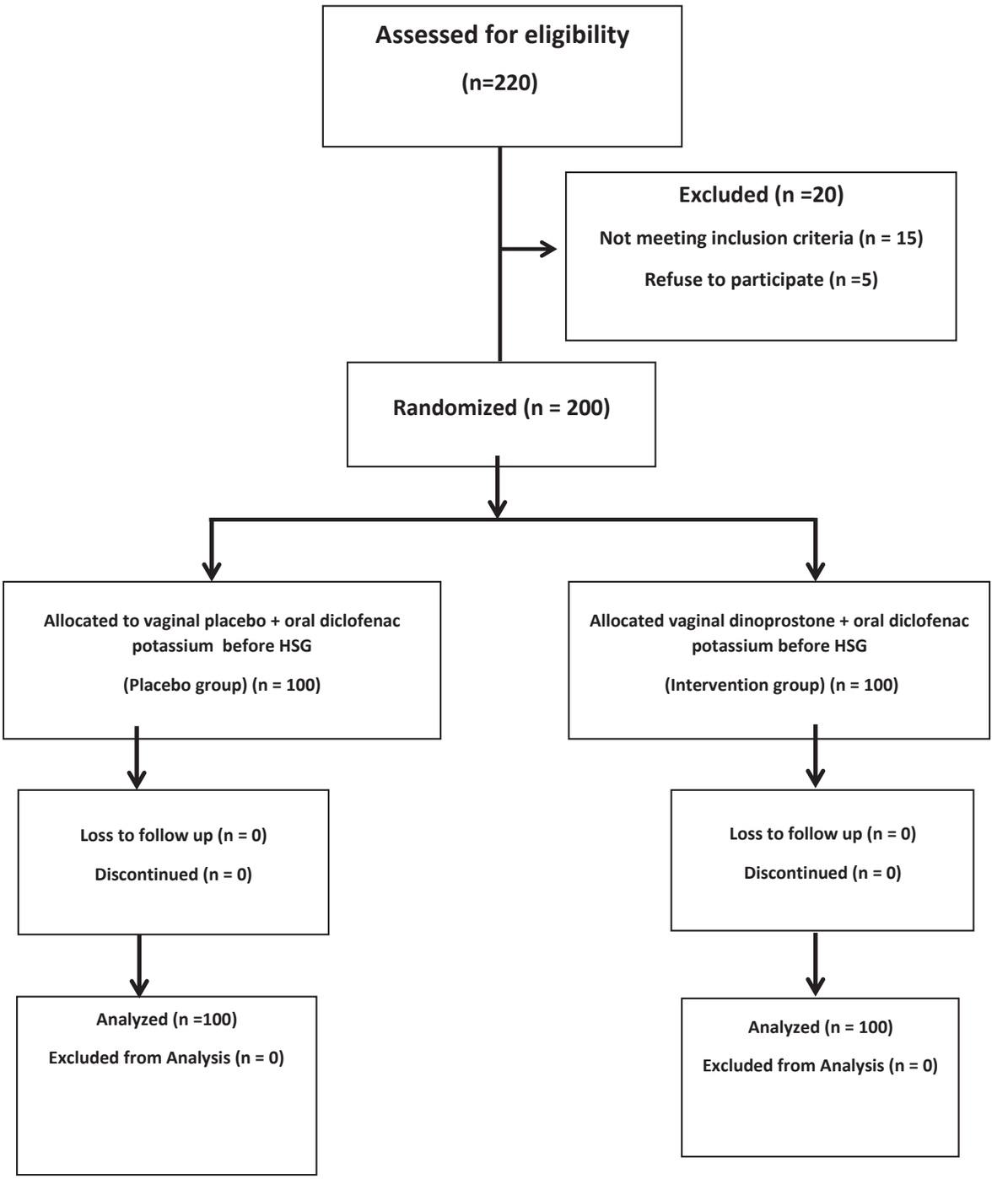

Fig. 1: Consort flowchart showing enrollment of participants

Table 2: The study outcomes in the study groups

Parameters	Group I (n = 100)	Group II (n = 100)	*P value*
Duration of the procedure	11.93±1.17	11.85±1.10	0.619
VAS at speculum placement	2.97 ± 0.78	3.01 ± 0.72	0.707
VAS at tenaculum placement	5.16 ± 0.87	4.25 ± 1.29	0.432
VAS during dye injection	6.23 ± 0.89	4.18 ± 0.90	0.0001*
VAS 5 minutes post injection	5.05 ± 0.95	3.81 ± 0.91	0.0001*
VAS 30 minutes post injection	4.14 ± 0.74	2.69 ± 0.80	0.0001*
Women satisfaction score	4.76 ± 0.87	6.97 ± 1.15	0.0001*
Need for additional analgesia (%)	27 (27)	14 (14)	0.023*

VAS (visual analogue scale). *Statistically Significant Difference
Variables are presented as mean and standard deviation, and number (percentage)

There were no significant differences between the two groups in the diagnosis of HSG result. P = (0.990) (Table 3). There was no significant difference between the research groups in terms of adverse effects. (Table 4).

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

Parameters	Group I (n = 100)	Group II (n = 100)	*P value*
Diagnosis of HSG (%)			
Normal	59 (59)	58 (58)	
Uterine adhesion	4 (4)	5 (5)	
Uterine anomalies	5 (5)	7 (7)	0.990
Unilateral tubal block	11 (11)	11 (11)	
Bilateral tubal block	9 (9)	8 (8)	
Peri tubal adhesion	12 (12)	11 (11)	

Variables are presented as number (percentage)

Table 4: Side effects in the study groups

Parameters	Group I (n = 100)	Group II (n = 100)	*P value*
Tenaculum site bleeding (%)	8 (8)	9 (9)	0.801
Abdominal cramp (%)	17 (17)	14 (14)	0.561
Fever (%)	0	1 (1)	1.000
Chills (%)	0	0	----
Nausea (%)	2 (2)	4 (4)	0.683
Vomiting (%)	0	0	----
Diarrhea (%)	0	0	----

DISCUSSION

This is the first randomized, double-blind, placebo-controlled trial in women with primary infertility to compare the efficacy of vaginal dinoprostone plus oral diclofenac potassium in reducing discomfort during and after HSG against oral diclofenac potassium alone.

Adjuvant vaginal dinoprostone utility six hours before HSG to oral diclofenac potassium one hour before HSG considerably reduced the caused discomfort during and 30 minutes after the HSG treatment as compared with diclofenac potassium alone.

In the research of infertility, HSG is a useful diagnostic technique. However, difficulties penetrating the internal cervical os is one of the most significant issues with this treatment. Cervical trauma or uterine perforation are more likely when there is substantial cervical stenosis, an immature cervix, or extensive anteflexion or retroflexion[17]. Traditional cervical dilation with Hegar's dilators may not be possible in some patients, regardless of parity, who have very tight cervices or cervical anomalies[18]. Furthermore, for some subjects, sounds may be a difficulty or a failure. As a result, cervical softening is essential for the procedure's success.

Dinoprostone is widely used for cervical ripening before gynecologic transcervical procedures. Dinoprostone is primarily used in transcervical procedures to increase the baseline cervical diameter and reduce pain during instrumentation. Although Dinoprostone is widely used in patients who undergo office hysteroscopy, studies report conflicting results as to whether routine administration of Dinoprostone has beneficial effects[19].

In a study by Moore[20], pain sources during HSG were described as cervical instrumentation, pain secondary to uterine distention with contrast medium, and pain due to peritoneal irritation as a result of contrast spilling into the peritoneal cavity.

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

The pain score at the area of dye injection was higher than 30 minutes following the surgery 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[2,18,19].

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.

CONCLUSION

When compared to diclofenac potassium alone, the use of adjuvant vaginal dinoprostone six hours before HSG to oral diclofenac potassium one hour before HSG considerably reduced the caused pain during and 30 minutes after the HSG procedure.

ETHICS DECLARATIONS

Ethics approval and consent to participate

Approval of the western Municipality and Faculty of Medicine was obtained. The ethical review board approved the study by a grant number of (Aswu/203/8/20) from Aswan university Review Board and Ethics Committee. ClinicalTrials.gov identifier NCT04500509; registered on August 5, 2020.

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

AVAILABILITY OF DATA AND MATERIAL

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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.

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CONFLICT OF INTERESTS

There are no conflicts of interest.

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