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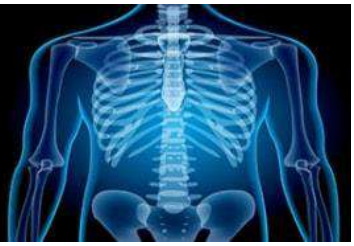

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**Kiridi EK**
[a] Department of Radiology, Niger Delta University Teaching Hospital, Okolobiri, Bayelsa State, Nigeria
[b] Silhouette Radiodiagnostic Consultants, Yenagoa, Bayelsa State, Nigeria

**Oriji PC**
Department of Obstetrics and Gynaecology, Federal Medical Centre, Yenagoa, Bayelsa State, Nigeria

**Ugwoegbu JU**
Department of Radiology, Federal Medical Centre, Owerri, Imo State, Nigeria

**Ubom AE**
Department of Obstetrics, Gynaecology and Perinatology, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Osun State, Nigeria

**Abasi IJ**
Department of Obstetrics and Gynaecology, Niger Delta University Teaching Hospital, Okolobiri, Bayelsa State, Nigeria

**Corresponding Author:**
**Oriji PC**
Department of Obstetrics and Gynaecology, Federal Medical Centre, Yenagoa, Bayelsa State, Nigeria

# Effect of diclofenac as a prophylactic analgesic during hysterosalpingography in Bayelsa State, South-South Nigeria: A randomized controlled trial

**Kiridi EK, Oriji PC, Ugwoegbu JU, Ubom AE and Abasi IJ**

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**Abstract**
**Background:** Pain is the most frequent side effect of hysterosalpingography, with up to 72% – 80% of women reporting varying degrees of pain during and after the procedure.
**Objective:** To evaluate the efficacy of diclofenac for pain relief in infertile women undergoing hysterosalpingography.
**Materials and Methods:** This randomised controlled trial was conducted at the Radiology Departments and Infertility Clinics of the Federal Medical Centre, Yenagoa, and Niger Delta University Teaching Hospital, Okolobiri, both in Bayelsa State, Nigeria, from July 2021 – March, 2022. Three hundred and eighty infertile women undergoing hysterosalpingography were randomised into two groups. Women in Group I were administered diclofenac, while the women in Group II received placebo, prior to the procedure. Pain scores at different steps of the procedure were recorded using the Visual Analog and Numerical Rating Scales. Data were analysed using the Statistical Product and Service Solutions for Windows®, version 25. Student's t-test was used to compare sample means, while the chi-square test was used to compare the proportion of women in the two study groups, who expressed pain at the different steps of the procedure.
**Results:** Insertion of speculum was the step associated with the least pain during the procedure, the mean pain score at this step being 1.14 ± 1.25. Instillation of contrast media had the highest mean pain score of 4.72 ± 2.13. The pain scores at all steps of the procedure, 30 minutes and 24 hours after the procedure, were significantly lower in the diclofenac group compared to the placebo group (p=0.001).
**Conclusion:** Diclofenac is superior to placebo for the control of hysterosalpingography-associated pain.

**Keywords:** Hysterosalpingography, infertility, pain, diclofenac, placebo, Bayelsa

## Introduction
Hysterosalpingography, first described by Carey in 1914, is the non-invasive fluoroscopic evaluation of the female genital tract following injection of a radio-opaque medium through the cervical canal [1, 2]. The National Institute for Health and Care Excellence recommends hysterosalpingography as the investigation of choice for assessing tubal patency in infertile women without comorbidities such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis [3].
Pain is the most frequent side effect of hysterosalpingography, with up to 72% – 80% of women reporting varying degrees of pain during and after the procedure [1]. The pain severity peaks at the time of instillation of the contrast medium until 5 minutes after the procedure, begins to rapidly wane between 5-10 minutes after the procedure, becoming mild 30 minutes following the procedure [4]. Causes of pain during hysterosalpingography include cervical instrumentation, uterine distension by the contrast medium, and peritoneal irritation from tubal spillage of contrast into the peritoneal cavity [4, 5]. Grasping and applying traction on the cervix with a tenaculum, as well as distension of the uterus with contrast medium, locally release prostaglandins that mediate the uterine cramps associated with hysterosalpingography [4, 5].
The pain experienced by women during and after hysterosalpingography can prevent them from fully cooperating with the procedure, thereby limiting its usefulness, and these women may refuse to undertake other similar diagnostic investigations for fear of pain [6, 7].

Pain relief is therefore an important consideration in women undergoing hysterosalpingography. Various analgesic agents have been proposed for pain relief during hysterosalpingography, including systemic drugs such paracetamol, non-steroidal anti-inflammatory drugs (NSAIDS), and opioids, application of topical analgesics to the cervix, intrauterine analgesic instillation, and paracervical block [2, 6-8]. There is however, no consensus on the ideal analgesic or the optimal timing of analgesic administration during hysterosalpingography [8, 9].

A Cochrane Review by Hindocha *et al*. while concluding that only topical anaesthetics and intravenous opioids were beneficial for pain relief during hysterosalpingography, found insufficient evidence to draw conclusions on the efficacy of other analgesic agents [5]. Hassa *et al*. found that oral diclofenac, an NSAID, administered before the procedure, was more effective for pain relief during hysterosalpingography compared with vaginal misoprostol or no analgesic [6]. Also, Gupta *et al*. reported that women who received oral naproxen, another NSAID, prior to hysterosalpingography, recorded lower pain scores both immediately and 30 minutes after the procedure compared to women who received intrauterine instillation of lignocaine, though the differences were not statistically significant [8]. On the other hand, a systematic review and meta-analysis by Ahmad *et al*. demonstrated no significant evidence of benefit for pain relief during and within 30 minutes after hysterosalpingography, with the use of both oral NSAIDs and local anesthetics. They recommended more randomized controlled trials (RCTs) to provide evidence on the optimal route of administration and dose of local anaesthetics, and the efficacy of oral analgesics [9]. The objective of this RCT was to evaluate the efficacy of diclofenac for pain relief in infertile women undergoing HSG in Bayelsa State, South-South Nigeria.

## Materials and Methods

**Study setting:** This randomised controlled trial was conducted at the Radiology Departments and Infertility Clinics of the Federal Medical Centre, Yenagoa and Niger Delta University Teaching Hospital, Okolobiri, both in Bayelsa State, Nigeria. It was conducted between July, 2021-March, 2022. These two study centers are tertiary health institutions that provide specialized gynecological services to women in Bayelsa State, and serve as referral centers for other hospitals in Bayelsa State, and surrounding Rivers and Delta States, both in South-south Nigeria.

**Sample size:** The sample size for this study was calculated using the formula:

$n = (Z\alpha + Z\beta)^2 \times 2 \times p\,(1 - p) / d^2$ [10]

Where n = minimum sample size

$Z\alpha$ = 95% confidence level = 1.96

$Z\beta$ = 20% $\beta$ error (at 80% power) = 0.84

p = prevalence of infertility which was 12.1% (0.121) from a previous study [11].

d = expected margin of error = 10% = 0.1

Substituting into the formula,

$n = (1.96 + 0.84)^2 \times 2 \times 0.121(1 - 0.121) / (0.1)^2$

$n = 7.84 \times 0.242 \times 0.879 / 0.01$

$n = 1.667 / 0.01$

n = 166.7 (minimum sample size per group)

Allowing an attrition rate of 10% (16.7), n = 183.4, rounded off to 190.

The sample size was therefore calculated to be 190 per group, giving a total of 380 study participants.

**Study randomization:** Three hundred and eighty eligible infertile women undergoing hysterosalpingography were enrolled in the study. Following adequate counselling, explaining the aim and possible benefits of the study, as well as the procedure, and written informed consent was obtained from all the study participants. Their baseline sociodemographic, gynecologic and infertility characteristics were obtained and recorded in the study proforma. The women were equally randomized (1:1 ratio) into two groups –I and – II by means of a computer-generated list of random numbers (generated from www.randomization.com). The allocating team and the team performing the hysterosalpingography were different, to prevent selection bias. Women in Group I were administered intramuscular diclofenac (Voltaren®, manufactured by GSK) 75 mg stat, while the women in Group II received a placebo of 3 ml of water for injection manufactured by Medlab Pharmaceuticals, India.

**Inclusion and exclusion criteria:** All infertile women undergoing hysterosalpingography, who consented to participate in the study, and completely filled the consent/questionnaire form, were included in the study. Exclusion criteria included abnormal uterine/vaginal bleeding, on-going menstruation, cervicovaginal discharge, cervical stenosis/cervical pathology, evidence of pelvic inflammatory disease, previous history of contrast hypersensitivity, history of allergy to diclofenac, and all patients that declined consent or incompletely filled the consent form and questionnaire.

**Procedure**: Hysterosalpingography for the women was performed during the proliferative phase of the menstrual cycle (7th – 10th day). Prior to the procedure, intramuscular diclofenac 75 mg stat was given to the women in Group I, while placebo (3 ml of water for injection, manufactured by Medlab Pharmaceuticals, India) was given to the women in Group II. The procedure started after five minutes of administration of intramuscular diclofenac/placebo. Protective lead apron and eye shield were put on by the radiologists performing the hysterosalpingography. After passing urine to empty her urinary bladder, the woman was initially placed in the supine position on the x-ray table. A scout radiograph of the antero-posterior view of the pelvis was taken. She was then placed in the lithotomy position, and draped to ensure privacy. The Visual Analogue Scale (VAS) [12] was used to document the level of pain expressed by the patients at different stages of the procedure, by an assistant who was blinded to the randomization (Figure 1).


**Fig 1:** Visual Analogue Scale [12]

After hand-washing and putting on sterile gloves, under a good light source, a sterile Cusco's speculum was inserted into the vagina to expose the cervix. The ecto-cervix was cleaned with savlon solution, and the anterior lip of the cervix was then grasped with a tenaculum. A self-retaining hysterosalpingography cannula was inserted into the cervix, and the speculum was removed for the patient's comfort. Urographin, a water-soluble, high osmolar contrast medium (10 – 20 ml) was warmed to body temperature, and injected slowly into the endometrial cavity. Three radiographs to outline the endometrial cavity, fallopian tubes and intraperitoneal spillage were obtained respectively. At completion of the procedure, the cannula was removed, the woman's vulva cleaned, and she was asked to dress up.

The hysterosalpingography films were reported by the Consultant Radiologist. The outcome of the procedure was discussed with the women. Thirty minutes after the procedure, the level of pain that the women felt were recorded with the use of the Numerical Rating Scale (Figure 2) [13]. This is the commonest scale used in the grading of pain. The patient rates the level of pain on a scale of 0 – 10. A score of 0 indicates no pain, 1 – 3 suggests mild pain, 4 – 6 suggests moderate pain, and 7 – 10 suggests severe pain [13].

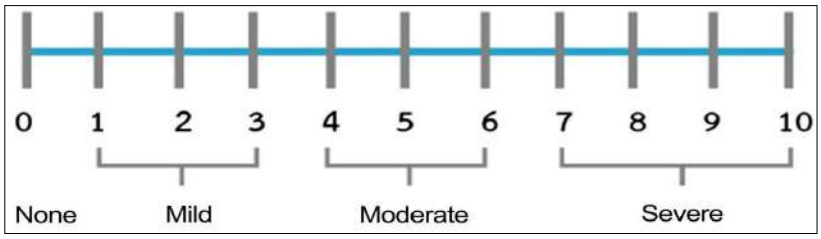


**Fig 2:** Numerical Rating Scale (NRS) [13].

**Outcome measures:** The primary outcome measures were pain scores at the different steps of the procedure, and 30 minutes and 24 hours after the procedure. The secondary outcomes included differences in pain scores, and presence of any adverse effect in the women in any of the groups.

**Data analysis:** Data obtained were entered into a pre-designed proforma, and were analysed using Statistical Product and Service Solutions for Windows® version 25 (SPSS Inc.; Chicago, USA). The results were presented in frequencies and percentages for categorical variables, and mean and standard deviation for continuous variables. Student's t-test was used to compare sample means, while the chi-square test was used to compare the proportion of women who expressed pain at the different steps of the procedure, including 30 minutes and 24 hours after the procedure, between the two groups. P-value < 0.05 was considered statistically significant.

**Ethics:** Ethical approval for this study was obtained from the Hospitals' Research and Ethics Committees, and the study was registered with the Pan African Clinical Trial Registry (PACTR202203544008183).

## Results

### Sociodemographic characteristics

There were 190 women recruited and randomised into each of the study groups, making a total of 380 women. The mean age of women in the study was 33.8±4.1 years with a standard deviation of 4.1. Women in the diclofenac group had a mean age of 33.8 ± 4.3 years while those in the placebo group had a mean age of 33.7 ± 3.8 years, with no significant difference (t = 0.15; p=0.880) in the mean ages of the women in the two groups (Table 1). In both groups, majority (148, 38.9%) of the women were aged between 36-40 years, and there was also no significant difference in the age distributions of the study groups ($\chi^2 = 0.71$; p=0.702).

Majority (175, 46.1%) of the women had tertiary level of education. Sixty-eight (17.9%) women were professionals, 73 (19.2%) were civil servants, 75 (19.7%) were unemployed, while traders and artisans were 77, 20.3%, and 87, 22.9%, respectively (Table 1). The occupational distribution of the women was also not significantly different ($\chi^2 = 3.99$; p=0.406). None of the women was underweight, about a quarter (90, 23.7%) had normal weight, while 234, 61.6%, and 56, 14.7%, and were overweight, and obese, respectively (Table 1).

### Gynecologic and infertility characteristics

The parity distribution in the diclofenac and placebo groups was similar ($\chi^2 = 0.92$; p=0.632) (Table 2). One hundred and twenty-one (63.7%) women in the diclofenac group and 115 (60.5%) women in the placebo group were nulliparous. About 3 in 5 (235, 61.8%) women attained menarche between 11 and 14 years (121 (63.7%) and 114 (60.0%) in the diclofenac and placebo group, respectively), showing no statistical difference ($\chi^2 = 0.55$; p=0.460) between the two groups (Table 2). Duration of marriage ($\chi^2 = 0.71$; p=0.557),

number of children ($\chi^2 = 0.11$; p=0.740), type ($\chi^2 = 0.10$; p=0.750) and duration of infertility ($\chi^2 = 0.66$; p=0.720) were also not statistically different between the two study groups (Table 2).

**Table 1:** Sociodemographic characteristics of women undergoing hysterosalpingography

| Characteristics | Total n = 380 (%) | Study Groups | | Test of significance | p-value |
|---|---|---|---|---|---|
| | | Diclofenac n = 190 (%) | Placebo n = 190 (%) | | |
| **Age group (years)** | | | | | |
| 26 – 30 | 114 (30.0) | 55 (28.9) | 59 (31.1) | 0.71 | 0.702 |
| 31 – 35 | 118 (31.1) | 57 (30.0) | 61 (32.1) | | |
| 36 – 40 | 148 (38.9) | 78 (41.1) | 70 (36.8) | | |
| **Mean age ± SD in years** | 33.8 ± 4.1 | 33.8 ± 4.3 | 33.7 ± 3.8 | 0.15 | 0.880 |
| **Level of education** | | | | | |
| Primary | 55 (14.5) | 30 (15.8) | 25 (13.2) | 0.53 | 0.766 |
| Secondary | 150 (39.5) | 74 (38.9) | 76 (40.0) | | |
| Tertiary | 175 (46.1) | 86 (45.3) | 89 (46.8) | | |
| **Occupation** | | | | | |
| Unemployed | 75 (19.7) | 40 (21.1) | 35 (18.4) | 3.99 | 0.406 |
| Civil servant | 73 (19.2) | 38 (20.0) | 35 (18.4) | | |
| Trader | 77 (20.3) | 38 (20.0) | 39 (20.5) | | |
| Professional | 68 (17.9) | 38 (20.0) | 30 (15.8) | | |
| Artisan | 87 (22.9) | 36 (18.9) | 51 (26.8) | | |
| **Body mass index (kg/m$^2$)** | | | | | |
| Normal weight | 90 (23.7) | 42 (22.1) | 48 (25.3) | 3.13 | 0.210 |
| Overweight | 234 (61.6) | 114 (60.0) | 120 (63.2) | | |
| Obesity | 56 (14.7) | 34 (17.9) | 22 (11.5) | | |
| Mean weight (kg) | 75.9 ± 9.9 | 78.6 ± 8.6 | 80.3 ± 9.3 | 1.85 | 0.065 |
| Mean height (m) | 1.64 ± 0.05 | 1.61 ± 0.06 | 1.62 ± 0.05 | 1.76 | 0.078 |
| Mean body mass index (kg/m$^2$) | 28.4 ± 3.9 | 28.6 ± 3.7 | 29.3 ± 4.0 | 1.78 | 0.077 |

**Table 2:** Gynecologic and infertility characteristics of women undergoing hysterosalpingography

| Characteristics | Total n = 380 (%) | Study Groups | | Test of significance | p-value |
|---|---|---|---|---|---|
| | | Diclofenac n = 190 (%) | Placebo n = 190 (%) | | |
| **Parity** | | | | | |
| Nulliparity | 236 (62.1) | 121 (63.7) | 115 (60.5) | 0.92 | 0.632 |
| Primiparity | 79 (20.8) | 40 (21.1) | 39 (20.5) | | |
| Multiparity | 65 (17.1) | 29 (15.3) | 36 (18.9) | | |
| **Median parity (range)** | 0 (0 – 5) | 0 (0 – 5) | 0 (0 – 1) | 4.79 | 0.001 |
| **Age at menarche (years)** | | | | | |
| 11 – 14 | 235 (61.8) | 121 (63.7) | 114 (60.0) | 0.55 | 0.460 |
| 15 – 19 | 145 (38.2) | 69 (36.3) | 76 (40.0) | | |
| **Mean age at menarche ± SD in years** | 13.8 ± 1.6 | 13.7 ± 1.6 | 14.1 ± 1.5 | 2.87 | 0.004 |
| **Duration of marriage (years)** | | | | | |
| 1 – 5 | 217 (57.1) | 104 (54.7) | 113 (59.5) | 1.71 | 0.557 |
| 6 – 10 | 137 (36.1) | 71 (37.4) | 66 (34.7) | | |
| > 10 | 26 (6.8) | 15 (7.9) | 11 (5.8) | | |
| **Mean duration of marriage ± SD in years** | 5.1 ± 3.1 | 4.9 ± 2.8 | 5.2 ± 1.2 | 0.36 | 0.175 |
| **Number of children** | | | | | |
| None | 261 (68.7) | 132 (69.5) | 129 (67.9) | 0.11 | 0.740 |
| 1 – 2 | 119 (31.3) | 58 (30.5) | 61 (32.1) | | |
| **Median number of children (range)** | 0 (0 – 2) | 0 (0 – 2) | 0 (0 – 1) | 0.86 | 0.388 |
| **Type of infertility** | | | | | |
| Primary | 141 (37.1) | 72 (37.9) | 69 (36.3) | 0.10 | 0.750 |
| Secondary | 239 (62.9) | 118 (62.1) | 121 (63.7) | | |
| **Duration of infertility (years)** | | | | | |
| ≤ 2 | 132 (34.7) | 64 (33.7) | 68 (35.8) | 0.66 | 0.720 |
| 3 – 5 | 178 (46.8) | 88 (46.3) | 90 47.4) | | |
| >5 | 70 (18.5) | 38 (20.0) | 32 (16.8) | | |
| **Mean duration of infertility ± SD in years** | 3.6 ± 2.0 | 3.5 ± 1.4 | 3.8 ± 2.4 | 1.48 | 0.138 |

**Duration of procedure and pain scores at different steps of hysterosalpingography**

The mean duration of the hysterosalpingography procedure was 4.3±0.9 minutes. The mean procedure duration was similar (t = 1.14; p=0.253) in the two groups (4.4 ± 0.9 minutes in the diclofenac group, and 4.3 ± 0.8 minutes in the placebo group).

The insertion of speculum was the step associated with the least pain perception during the procedure, with the mean pain score at this step being 1.14 ± 1.25. Instillation of

contrast media was associated with the highest level of pain perception in this study. The overall mean pain score during contrast instillation was 4.72 ± 2.13. The mean pain score at this step was 3.38 ± 1.46, and 5.56 ± 2.35, in the diclofenac and placebo groups, respectively (Table 3, Figure 3). Pain perception was significantly lower (p=< 0.05) at all steps of the procedure in the diclofenac group than in the placebo group (Table 3). Mean pain score at grasping of the cervix was 1.54 ± 0.79 in the diclofenac group, but was as high as 3.60 ± 0.49 in the placebo group, showing significant statistical difference (t = 30.57; p=0.001). The pain perception at 30 minutes post-procedure revealed a mean score of 197 ± 1.10 in the diclofenac group, with the mean pain score as high as 4.58 ± 1.31 in the placebo group (Table 3, Figure 3).

The severity of pain perception in the women at the different steps of the procedure are presented in Table 4, with 116 women (61.1%) and 40 (21.1%) expressing no pain at insertion of the speculum in the diclofenac and placebo groups, respectively; 18, 9.5% women expressed moderate pain in the placebo group, while only one woman in the diclofenac group expressed moderate pain. This observed difference was statistically significant ($\chi^2 = 69.22$; p=0.001). Twenty-four hours after the procedure no woman in the diclofenac group reported moderate and severe pain (Table 4). Though no woman reported severe pain in the placebo group 24 hours after the procedure, as high as 114 women (60.0%) reported moderate pain (Table 4). Pain perception was significantly different (p= < 0.05) at all steps of the procedure between the two study groups (Table 4).

**Table 3:** Duration of procedure and pain scores at different steps of hysterosalpingography

| Characteristics | Total n = 380 (%) | Study Groups | | Chi-square (p-value) |
|---|---|---|---|---|
| | | Diclofenac n = 190 (%) | Placebo n = 190 (%) | |
| **Mean duration of procedure (mins)** | 4.3 ± 0.9 | 4.4 ± 0.9 | 4.3 ± 0.8 | 1.14 (0.253) |
| **Mean pain scores ± SD at different steps of the procedure** | | | | |
| Insertion of speculum | 1.14 ± 1.25 | 0.42 ± 0.62 | 1.85 ± 1.31 | 13.63 (0.001) |
| Grasping of the cervix | 2.57 ± 2.57 | 1.54 ± 0.79 | 3.60 ± 0.49 | 30.57 (0.001) |
| Insertion of cannula | 3.81 ± 2.15 | 2.59 ± 1.46 | 5.02 ± 2.04 | 13.3 (0.001) |
| Instillation of contrast media | 4.72 ± 2.13 | 3.88 ± 1.46 | 5.56 ± 2.35 | 8.36 (0.001) |
| 30 minutes post-procedure | 3.28 ± 1.78 | 1.97 ± 1.10 | 4.58 ± 1.31 | 21.03 (0.001) |
| 24 hours post-procedure | 2.14 ± 2.08 | 0.37 ± 0.66 | 3.92 ± 1.37 | 32.09 (0.001) |

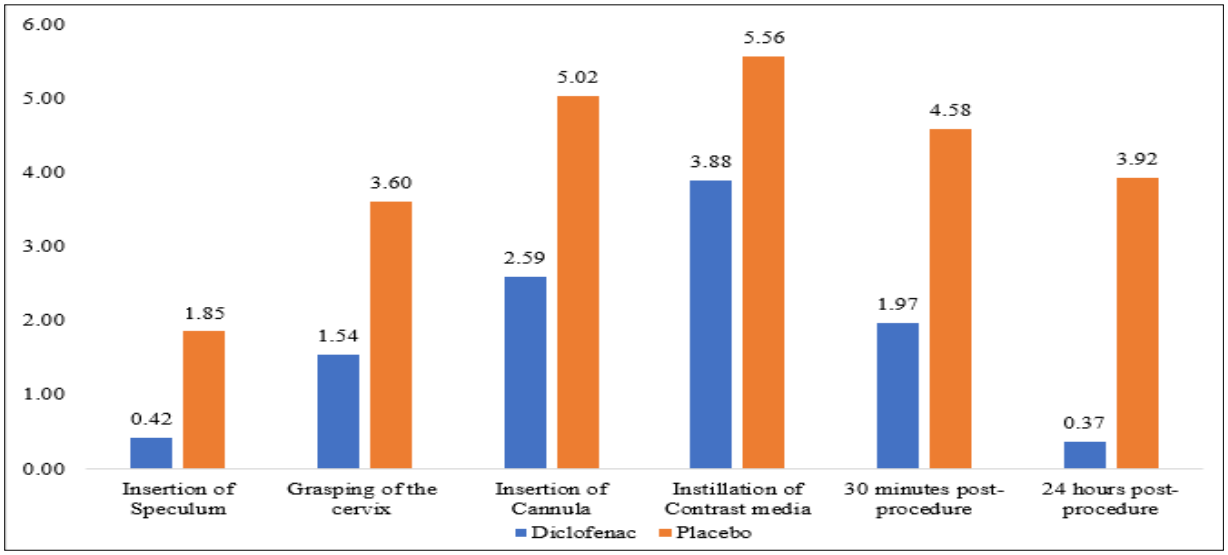


**Fig 3:** Mean pain scores at different steps of hysterosalpingography in both groups

**Table 4:** Severity of pain at different steps of hysterosalpingography

| Characteristics | Total n = 380 (%) | Study Groups | | Chi-square (p-value) |
|---|---|---|---|---|
| | | Diclofenac n = 190 (%) | Placebo n = 190 (%) | |
| **Severity of pain at insertion of speculum** | | | | |
| None | 156 (41.1) | 116 (61.1) | 40 (21.1) | 69.22 (0.001) |
| Mild | 205 (53.9) | 73 (38.4) | 132 (69.5) | |
| Moderate | 19 (5.0) | 1 (0.5) | 18 (9.5) | |
| **Severity of pain at grasping of the cervix** | | | | |
| Mild | 264 (69.5) | 188 (98.9) | 76 (40.0) | 155.24 (0.001) |
| Moderate | 116 (30.3) | 2 (1.1) | 114 (60.0) | |
| **Severity of pain at insertion of cannula** | | | | |
| Mild | 201 (52.9) | 163 (85.8) | 38 (20.0) | 168.15 (0.001) |
| Moderate | 140 (36.8) | 26 (13.7) | 114 (60.0) | |
| Severe | 39 (10.3) | 1 (0.5) | 38 (20.0) | |

| | | | | |
|---|---|---|---|---|
| **Severity of pain at instillation of contrast media** | | | | |
| Mild | 108 (28.4) | 72 (37.9) | 36 (19.0) | 39.21 (0.001) |
| Moderate | 200 (52.6) | 104 (54.7) | 96 (50.5) | |
| Severe pain | 72 (18.9) | 14 (7.4) | 58 (30.5) | |
| **Severity of pain 30 minutes post-procedure** | | | | |
| None | 11 (2.9) | 11 (5.8) | 0 (0.0) | 237.87 (0.001) |
| Mild | 216 (56.8) | 176 (92.6) | 40 (21.1) | |
| Moderate | 153 (39.7) | 3 (1.6) | 150 (78.9) | |
| **Severity of pain 24 hours post-procedure** | | | | |
| None | 137 (36.1) | 137 (72.1) | 0 (0.0) | 255.10 (0.001) |
| Mild | 129 (33.9) | 53 (27.9) | 76 (40.0) | |
| Moderate | 114 (30.0) | 0 (0.0) | 114 (60.0) | |

## Discussion

Hysterosalpingography is the major investigative modality used in the evaluation of women with infertility. One of the main side effects of hysterosalpingography is procedure-associated pain. The thought of this side effect leads to significant anxiety and stress prior to the procedure [1, 14]. Pain can make a patient decline hysterosalpingography or even reduce her cooperation during the procedure. The sources of pain during hysterosalpingography are insertion of vaginal speculum, grasping of the cervix, insertion of cannula, uterine distension by contrast media and peritoneal irritation from spillage of contrast media into the peritoneal cavity [15]. Pain is subjective in nature, and hence, difficult to record its perception reproducibly and reliably. Therefore, we used the Visual Analogue Scale and the Numerical Rating Scale to assess pain in this randomised controlled trial.

Our study revealed that the mean and modal age-group of the women were 33.8 ± 4.1 years, and 36 – 40 years, respectively. Similar mean age and/or modal age range have been reported by other studies within and outside Nigeria [16–24]. Majority of these women had tertiary level of education. Many women now delay childbearing for a number of reasons, which include career. Fecundity declines as a woman ages [25]. Therefore, with the delay of childbearing globally, more women may present for infertility evaluation within the modal age-group observed in this study. Another plausible reason for the age distribution in this study may be due to the fact that many women in our environment have preference for alternative/non-medical care, which includes visit to traditional birth attendants, prayer houses, maternity homes, and other non-orthodox places, before presenting to a specialist for expert care.

Our study revealed that majority of the women were overweight and obese. There are elevated levels of androgens in circulation in obese women, which contribute to anovulation and menstrual irregularities. This in turn reduces fecundity and response to infertility treatment. An association between obesity and infertility has been reported by various studies, as the prevalence of obesity in the population of infertile women remains high [26]. In this study, the most common cause of infertility was secondary, and this observation is in tandem with the reports of many authors [18, 23, 24, 27, 28]. A plausible explanation for this may be due to post-abortion sepsis and pelvic inflammatory diseases, that may have complicated previous induced abortions. Sexually transmitted infections, post-operative/ procedure infections, and puerperal sepsis from previous deliveries supervised by unskilled/traditional birth attendants, which is very common in our environment, may be other plausible reasons for the high proportion of women with secondary infertility in our study.

Our study revealed that diclofenac was superior to placebo for the control of hysterosalpingography-associated pain. This observation is in agreement with the findings of other authors, who reported that non-steroidal anti-inflammatory drugs (including diclofenac) were better than placebo for the relief of hysterosalpingography-associated pain [6, 8, 29], and recommended non-steroidal anti-inflammatory drugs as the drug of choice for pain relief during hysterosalpingography [8,30]. Diclofenac is a non-steroidal anti-inflammatory drug. It has an analgesic and an anti-inflammatory effect, and its duration of action can be up to eight hours. It acts by inhibiting prostaglandin synthesis by inhibiting cyclooxygenase-1 and cyclooxygenase-2 enzymes [31].

In this study, the pain scores were significantly lower at all the steps, as well as 30 minutes and 24 hours post-hysterosalpingography in the diclofenac group than in the placebo group. In the study by Hassa *et al*.,[6] pain perception during the procedure was lower in women who received diclofenac compared to those who had misoprostol or no medication, but there was no difference in pain scores between the three groups 30 minutes after the procedure. In our study, pain perception was highest in both groups of women during instillation of contrast media. This is in consonance with the reports of various authors who noted that pain perception was higher during instillation of contrast media [2, 32–36]. However, Liberty *et al*., reported that it was during the insertion of cervical instruments that their patients expressed the most pain [37].

The role of pre-procedure counselling in pain relief cannot be downplayed, as anxiety and stress have been known to enhance the procedure-associated pain of hysterosalpingography [38]. The women that participated in this randomised controlled trial were counselled on the procedure, its benefits and the possible complications, prior to the procedure.

The strength of this randomised controlled trial lies in the fact that it is a two-centre, prospective study, where both the clinicians and the patients were blinded to the interventions used for each group of women. The allocating team and the team performing the hysterosalpingography were different. This eliminated the risk of selection bias. All the hysterosalpingography procedures were performed by only two Consultant Radiologists, which reduced performance bias, and improved the reproducibility and validity of our study findings. The limitation of this randomised controlled trial lies in the fact that it is hospital-based. A more robust population-based randomised controlled trial with a larger sample size is recommended.

## Conclusion

Our study revealed that diclofenac is superior to placebo for pain relief at all steps of hysterosalpingography, and up to 24 hours after the procedure. We recommend diclofenac as an

effective prophylactic analgesia during hysterosalpingography.

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**Conflict of interest**
The authors declare that there are no conflicts of interest.

**Authors' contributions**
EKK wrote the research protocol, carried out hysterosalpingography and collected data. PCO conceptualized the research topic, collated data, wrote the methodology, results, discussion and the first draft of the manuscript. JUU reported hysterosalpingography films. AEU wrote the introduction. IJA managed literature searches. All the authors read and approved the final manuscript.

**Ethical approval**
This prospective, descriptive, cross-sectional study was examined and approved by the Research and Ethics Committees of the hospitals, and the study was registered with the Pan African Clinical Trial Registry (PACTR202203544008183).

**References**

1. Omidiji OA, Toyobo OO, Adegbola O, Fatade A, Olowoyeye OA. Hysterosalpingographic findings in infertility - what has changed over the years? Afr Health Sci. 2019;19(2):1866-74.
2. Unlu BS, Yilmazer M, Koken G, Arioz DT, Unlu E, Dogan Baki E. Comparison of four different pain relief methods during hysterosalpingography: a randomized controlled study. Pain Res Manag. 2015;20(2):107-11.
3. Overview. Fertility problems: assessment and treatment. Guidance. NICE [Internet]. [cited 2022 Mar 31]; Available from: https://www.nice.org.uk/guidance/cg156
4. Ahmad G, Duffy J, Watson AJS. Pain relief in hysterosalpingography. Cochrane Database Syst Rev. 2007;(2):CD006106.
5. Hindocha A, Beere L, O'Flynn H, Watson A, Ahmad G. Pain relief in hysterosalpingography. Cochrane Database Syst Rev [Internet] 2015 [cited 2022 Mar 31];(9). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006106.pub3/full?contentLanguage=en
6. Hassa H, Oge T, Aydin Y, Burkankulu D. Comparison of nonsteroidal anti-inflammatory drugs and misoprostol for pain relief during and after hysterosalpingography: prospective, randomized, controlled trial. J Minim Invasive Gynecol. 2014;21(5):762-6.
7. Duffy JMN, Ahmad G, Watson AJS. Pain relief during hysterosalpingography: a national survey. Hum Fertil Camb Engl. 2008;11(2):119-21.
8. Gupta N, Ghosh B, Mittal S. Comparison of oral naproxen and intrauterine lignocaine instillation for pain relief during hysterosalpingography. Int J Gynaecol Obstet. 2008;102(3):284-6.
9. Ahmad G, Attarbashi S, O'Flynn H, Watson AJS. Pain relief in office gynaecology: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2011;155(1):3-13.
10. Araoye MO. Subjects Selection. In: Research Methodology with statistics for Health and Social sciences. Ilorin. Nathadex publishers, 2003, 115-129.
11. Menuba IE, Ugwu EO, Obi SN, Lawani LO, Onwuka CI. Clinical management and therapeutic outcome of infertile couples in southeast Nigeria. Ther Clin Risk Manag. 2014;10:763-8.
12. Yeung AWK, Wong NSM. The Historical Roots of Visual Analog Scale in Psychology as Revealed by Reference Publication Year Spectroscopy. Front Hum Neurosci, 2019, 13.
13. Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. Ann Rheum Dis. 1978;37(4):378-81.
14. Kinci M, Yeşilçinar İ, Acavut G, Karasahin K. The opinions and thoughts of the women who had applied hysterosalpingography for the first time: Letter to editor. J Turk-Ger Gynecol Assoc, 2018, 19.
15. Oriji PC, Kiridi EK, Abasi IJ, Ubom AE, Ugwoegbu JU. Predictive factors for the severity of procedure-associated pain in infertile women undergoing hysterosalpingography in Bayelsa State, South-South Nigeria. Int J Trop Dis Health. 2022;43(5):43-54.
16. Aduayi OS, Akanbi GO, Akintayo AA, Aduayi VA. Hysterosalpingography findings among women presenting for gynecological imaging in Ado-Ekiti, South western Nigeria. Int J Reprod Contracept Obstet Gynecol. 2017;5(6):1906-11.
17. Okafor CO, Okafor CI, Okpala OC, Umeh E. The pattern of hysterosalpingographic findings in women being investigated for infertility in Nnewi, Nigeria. Niger J Clin Pract. 2010;13(3):264-7.
18. Olatunji AA, Jagun OE, Toyobo OO, Ashaolu OA, Adekoya OA. Hysterosalpingogram findings among women with infertility in Ogun State, Nigeria. Ann Health Res. 2017;3(2):75-81.
19. Danfulani M, Haruna Y, Mohammed M, Ahmed S. Hysterosalphingographic findings in women with infertility in Sokoto North Western Nigeria. Afr J Med Health Sci. 2014;13:19.
20. Igoh EO, Chom ND, Pam SD, Ekedigwe JE, Ani CC, Atsukwei D, *et al*. Risk factors for abnormal tubal hysterosalpingographic findings in women presenting with infertility in Jos. Jos J Med. 2015;9(1):47-52.
21. Imo AOC, Sunday-Adeoye I. Radiological Assessment Of The Uterus And Fallopian Tubes In Infertile Women At Abakaliki, Nigeria. Niger J Clin Pract. 2008;11(3):211-5.
22. Kiguli-Malwadde E, Byanyima RK. Structural findings at hysterosalpingography in patients with infertility at two private clinics in Kampala, Uganda. Afr Health Sci. 2004;4(3):178-81.
23. Kiridi EK, Oriji PC, Ugwoegbu JU, Abasi IJ. Hysterosalpingography Findings among Women Presenting for Infertility Evaluation in Bayelsa State, South-South Nigeria. J Adv Med Med Res. 2022;34(5):717.
24. Kiridi EK, Oriji PC, Abasi IJ, Ubom AE, Ugwoegbu JU. Predictors or abnormal findings in infertile women

undergoing hysterosalgography in Bayelsa State, South-South Nigeria. Int J Clin Obstet Gynaecol. 2022;6(2):22-30.
25. Maheshwari A, Hamilton M, Bhattacharya S. Effect of female age on the diagnostic categories of infertility. Hum Reprod Oxf Engl. 2008;23(3):538-42.
26. Zain MM, Norman RJ. Impact of obesity on female fertility and fertility treatment. Womens Health Lond Engl. 2008;4(2):183-94.
27. Makwe CC, Ugwu AO, Sunmonu OH, Yusuf-Awesu SA, Ani-Ugwu NK, Olumakinwa OE. Hysterosalpingography findings of female partners of infertile couple attending fertility clinic at Lagos University Teaching Hospital. Pan Afr Med J. 2021;40:223.
28. Udobi S, Aronu M. Hysterosalpingographic findings in women with infertility in Awka, Anambra State, South-East Nigeria. Niger J Surg Sci. 2017;27(2):47-47.
29. Peters AA, Witte EH, Damen AC, Holm JP, Drogendijk AC, vd Velde EA, *et al*. Pain relief during and following outpatient curettage and hysterosalpingography: a double blind study to compare the efficacy and safety of tramadol versus naproxen. Cobra Research Group. Eur J Obstet Gynecol Reprod Biol. 1996;66(1):51-6.
30. Anserini P, Delfino F, Ferraiolo A, Remorgida V, Menoni S, De Caro G. Strategies to minimize discomfort during diagnostic hysterosalpingography with disposable balloon catheters: a randomized placebo-controlled study with oral nonsteroidal premedication. Fertil Steril. 2008;90(3):844-8.
31. Diclofenac (Topical) Monograph for Professionals [Internet]. Drugs.com [cited 2022 Apr 1];Available from: https://www.drugs.com/monograph/diclofenac-topical.html
32. Jain S, Inamdar DB, Majumdar A, Jain DK. Effectiveness of paracervical block for pain relief in women undergoing hysterosalpingography. J Hum Reprod Sci. 2016;9(4):230-5.
33. Hacivelioglu S, Gencer M, Cakir Gungor A, Kosar S, Koc E, Cosar E. Can the addition of a paracervical block to systemic or local analgesics improve the pain perceived by the patient during hysterosalpingography? J Obstet Gynaecol. 2014;34(1):48-53.
34. Robinson RD, Casablanca Y, Pagano KE, Arthur NA, Bates GW, Propst AM. Intracervical block and pain perception during the performance of a hysterosalpingogram: a randomized controlled trial. Obstet Gynecol. 2007;109(1):89-93.
35. Szymusik I, Grzechocińska B, Marianowski P, Kaczyński B, Wielgoś M. Factors influencing the severity of pain during hysterosalpingography. Int J Gynaecol Obstet. 2015;129(2):118-22.
36. Abbas A, Abo-Elela N, Mosa E. Effect of oral hyoscine-N-butyl bromide on pain perception during hysterosalpingography: A randomized, double-blind, placebo controlled trial. Middle East Fertil Soc J. 2017;23(1):57-62.
37. Liberty G, Gal M, Halevy-Shalem T, Michaelson-Cohen R, Galoyan N, Hyman J, *et al*. Lidocaine-prilocaine (EMLA) cream as analgesia for hysterosalpingography: a prospective, randomized, controlled, double blinded study. Hum Reprod Oxf Engl. 2007;22(5):1335-9.
38. Kiridi EK, Oriji PC, Abasi IJ. Effect of pre-procedure anxiety levels on post-procedure pain scores in women undergoing hysterosalpingography in South-South Nigeria. Int J Trop Dis Health. 2022;43(2):33-43.