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Original Research Article

Comparison of paracetamol and diclofenac as prophylactic analgesics during hysterosalpingography in Bayelsa State, South-South Nigeria: a randomized controlled trial

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ABSTRACT

Background: Hysterosalpingography is the investigative modality of choice for the evaluation of the uterine cavity, fallopian tubes, and adjacent peritoneal cavity. Objective were to compare the effectiveness of paracetamol and diclofenac in pain relief during hysterosalpingography.
Methods: This 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 June 2021-March, 2022, and 380 infertile women undergoing hysterosalpingography were equally randomised into two groups. Group I received paracetamol, while group II received diclofenac prior to the procedure. Data were analysed using statistical product and service solutions for Windows® version 25. Student's t-test was used to compare sample means, and the Chi-square test was used to compare the proportions.
Results: The women experienced the least pain during insertion of speculum, with an overall mean pain score at this step of 0.8±0.9, while the most painful step was instillation of contrast, the overall mean pain score at this step being 4.3±1.9. While 38, 20.0%, women in the paracetamol group expressed severe pain during contrast instillation, only 14, 7.4%, women in the diclofenac group expressed severe pain at this step, and this was statistically significant (χ^2=22.05; p=0.001). The mean pain scores at all steps of the procedure were significantly higher in the paracetamol group than in the diclofenac group (p≤0.005).
Conclusions: Compared to paracetamol, diclofenac is a more effective analgesic for pain relief during hysterosalpingography.

Keywords: Hysterosalpingography, Pain, Paracetamol, Diclofenac, Bayelsa

INTRODUCTION

Infertility is the inability of a couple to achieve pregnancy despite 12 months of adequate and regular unprotected sexual intercourse. Tubal pathology is the major cause of secondary infertility, and is implicated in about 40% of all cases of infertility.[1] Despite the development of other diagnostic tools such as hysteroscopy, laparoscopy, and magnetic resonance imaging, hysterosalpingography remains the most commonly used diagnostic modality for evaluating tubal patency in infertile women.[2] Hysterosalpingography is the non-invasive fluoroscopic evaluation of the female genital tract following injection of a radio-opaque medium through the cervical canal.[3,4]

The major drawback of hysterosalpingography is pain,[5] which is expressed in up to 72-80% of women undergoing the procedure.[3] These women experience mild to severe pain during and after hysterosalpingography, and it is one of the reasons some women decline to undergo this investigative modality.[5] The causes of pain during hysterosalpingography are insertion of vaginal speculum, grasping of the cervix, insertion of intra-cervical cannula, uterine distension by the contrast media, and peritoneal irritation from tubal spillage of contrast media into the peritoneal cavity.[6,7] Grasping and applying traction on cervix with a tenaculum and distension of uterus with contrast medium, locally release prostaglandins that mediate uterine cramps associated with hysteron-salpingography.[6,7]

Various analgesic agents have been used for pain relief during hysterosalpingography, including systemic drugs such paracetamol, non-steroidal anti-inflammatory drugs, and opioids, application of topical analgesics to the cervix, intrauterine analgesic instillation, and paracervical block.[4,8-10] There is however, no consensus on the ideal analgesic or the optimal timing of analgesic administration during hysterosalpingography.[10,11]

Paracetamol is an analgesic and an antipyretic. Its action is similar to that of non-steroidal anti-inflammatory drugs, and it is frequently preferred due to its superior tolerance. Paracetamol inhibits cyclooxygenase (COX) enzymes -1 and -2.[12] This results in the inhibition of prostaglandin synthesis.[12] Diclofenac is a non-steroidal anti-inflammatory drug. It has an analgesic and an anti-inflammatory effect, with a duration of action of up to eight hours. Abdominal symptoms (nausea, vomiting, abdominal pain, peptic ulcer disease, gastrointestinal bleeding) constitute the major side effects of diclofenac. These side effects limit its tolerance, and precludes its use in women with peptic ulcer disease. Like paracetamol, it also inhibits prostaglandin synthesis by inhibiting COX-1 and 2 enzymes, but unlike paracetamol, it additionally as an anti-inflammatory effect.[13]

The objective of this randomised controlled trial is to compare the effectiveness of paracetamol and diclofenac for pain relief in infertile women undergoing hysterosalpingography in Bayelsa State, South-South Nigeria.

METHODS

Study design and setting

This randomized 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 over a nine-month period, from June 2021-March 2022. The two study centres, both tertiary health institutions, provide specialised gynaecological services to women in Bayelsa State, and serve as referral centres for other hospitals in Bayelsa State and surrounding Rivers and Delta States, in South-South Nigeria.

Sample size

The sample size for this study was calculated using the formula: [14]

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

Where, n=minimum sample size, Zα=95% confidence level=1.96, Zβ=20% β error (at 80% power)=0.84, p=prevalence of infertility which was 12.1% (0.121) from a previous study Southern Nigeria.[15] d=expected margin of error = 10% = 0.1, Substituting these values into the sample size formula,

$n=(1.96+0.84)^2\times2\times0.121(1-0.121)/(0.1)^2$

$n=7.84\times0.242\times0.879/0.01$

$n=1.667/0.01$

n=166.7 (minimum sample size per group)

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

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

Three hundred and eighty infertile women undergoing hysterosalpingography were enrolled in the study. They were assigned into two groups by computer-generated randomisation. Women in group I will receive intramuscular paracetamol 600 mg (4 ml), while the women in group II will receive intramuscular diclofenac 75 mg (3 ml). Following adequate counselling, written informed consent was obtained from all women. Allocating team and team performing hysterosalpingography different, to help prevent selection bias.

Inclusion and exclusion criteria

All infertile women undergoing hysterosalpingography, who consented to participate in the study by completely filling the study consent/ questionnaire form, were included in the study.

Women who were menstruating, those with abnormal uterine/vaginal bleeding, cervicovaginal discharge, cervical stenosis/cervical pathology, evidence of pelvic inflammatory disease, previous history of contrast hypersensitivity, history of allergy to paracetamol or/and diclofenac, and women that declined consent or incompletely filled the consent form and questionnaire, were excluded from the study.

Randomization

The study participants were recruited from the infertility clinics of the study centres. Eligible women who consented to participate in the study were equally randomized into two groups I and II. The aim of the study, the procedure and the likely benefits were explained to the women. Their baseline sociodemographic and gynaecological characteristics were obtained and recorded on a purpose-designed proforma. Afterwards, the women were referred to the radiology departments of the study centres for hysterosalpingography.

Procedure

Hysterosalpingography for the study participants was performed during the proliferative phase of the menstrual cycle (7^{th}-10^{th} day). Protective lead apron and eye shield were worn by the radiologists performing the procedure. Intramuscular paracetamol (Drugamol®, manufactured by Drugfield Pharmaceuticals, Nigeria) 600 mg stat was given to the women in group I, while intramuscular diclofenac (Voltaren®, manufactured by GSK) 75 mg stat was given to the women in group II. After five minutes of administering either of the medications, the procedure was started.

After passing urine to empty her urinary bladder, the patient 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)[16] was used to document the level of pain experienced by the women at different stages of the investigation, by an assistant who was blinded to the randomisation (Figure 1).

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 ectocervix was cleaned with Savlon® solution. 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 the end of the procedure, the cannula was removed, the vulva was cleaned, and she was asked to dress up.

The hysterosalpingography films were reported by the consultant radiologists. The outcome of the procedure was discussed with the women. Thirty minutes and 24 hours after the procedure, the level of pain that the women felt were recorded with the use of the numerical rating scale (Figure 2).[17] 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.[17]

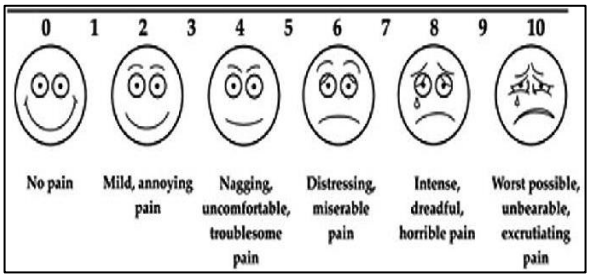

Figure 1: Visual analogue scale.

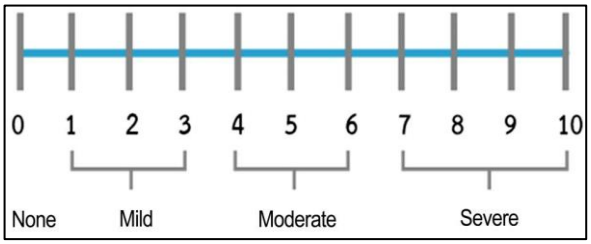

Figure 2: Numerical rating scale (NRS).[17]

Study outcome measures

The primary outcomes were pain scores during 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 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, and 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<0.05 was considered statistically significant.

Ethics

Ethical approval for this study was obtained from the hospitals' research and ethics committees. The study was registered with the Pan African Clinical Trial Registry (PACTR202204689887542).

RESULTS

Sociodemographic characteristics

Out of the 380 study participants, 33 (8.7%), 94 (24.7%), 122 (32.1%) and 135 (33.5%) were aged 18-25 years, 26-30 years, 31-35 years and 36-40 years, respectively (Table 1). The age distributions of study participants showed no significant difference (χ^2=3.86; p=0.277) between both groups of participants. The mean ages of women in the paracetamol and the diclofenac groups were 33.2±4.7 years, and 33.7±3.8 years, respectively (Table 1). There were 36 (18.9%) traders, 38 (20.0%) professionals and 60 (31.6%) civil servants in the paracetamol group. In the same vein, there were 35 (18.4%) traders, 39 (20.5%) professionals and 55 (28.9%) civil servants in the diclofenac group, showing no significant difference (χ^2=0.46; p=0.928) between the two groups, with respect to occupation (Table 1). Mean weight, height and body mass index were 79.8±14.1 kg, 1.66±0.16 m and 29.3±6.1 kg/m^2 in the paracetamol group, respectively, and in the diclofenac group, 77.7±8.5 kg, 1.64±0.15 m and 28.6±3.7 kg/m^2, respectively (Table 1). The anthropometric measurements were not significantly different (p≥0.05). The body mass index categories between the two groups were also not significantly different statistically (χ^2=2.19; p=0.334).

Table 1: Sociodemographic characteristics of women undergoing hysterosalpingography.

Characteristics	Total, n=380 (%)	Study groups, n=190 (%)		Test of significance	P value
		Paracetamol	Diclofenac		
Age group (years)					
18-25	33 (8.7)	18 (9.5)	15 (7.9)	3.86	0.277
26-30	94 (24.7)	40 (21.1)	54 (28.4)		
31-35	122 (32.1)	58 (30.5)	64 (33.7)		
36-40	135 (35.5)	74 (38.9)	61 32.1)		
Mean age ± SD in years	33.4±4.3	33.2±4.7	33.7±3.8	1.27	0.206
Level of education					
Primary	43 (11.3)	18 (9.5)	25 (13.2)	4.61	0.100
Secondary	154 (40.5)	78 (41.1)	114 (60.0)		
Tertiary	183 (48.2)	94 (49.5)	89 (46.8)		
Occupation					
Civil servant	115 (30.3)	60 (31.6)	55 (28.9)	0.46	0.928
Professional	77 (20.3)	38 (20.0)	39 (20.5)		
Trader	71 (18.7)	36 (18.9)	35 (18.4)		
Unemployed	117 (30.8)	56 (29.5)	61 (32.1)		
Body mass index categories (kg/m^2)					
Normal	154 (40.5)	76 (40.0)	78 (41.1)	2.19	0.334
Overweight	90 (23.7)	40 (21.1)	50 (26.3)		
Class I obesity	136 (35.8)	74 (38.9)	62 (32.6)		
Mean weight (kg)	78.7±12.3	79.8±14.1	77.6±8.5	1.84	0.066
Mean height (m)	1.65±0.15	1.66±0.16	1.64±0.15	1.22	0.219
Mean body mass index (kg/m^2)	28.8±5.9	29.3±6.1	28.6±3.7	1.35	0.178

Table 2: Gynaecologic and infertility characteristics of women undergoing hysterosalpingography.

Characteristics	Total, n=380 (%)	Study groups, n=190 (%)		Test of significance	P value
		Paracetamol	Diclofenac		
Parity					
Nulliparity	227 (59.7)	112 (58.9)	115 (60.5)	0.64	0.726
Primiparity	74 (19.5)	40 (21.1)	34 (17.9)		
Multiparity	79 (20.8)	38 (20.0)	41 (21.6)		
Median parity (range)	0 (0-5)	0 (0-1)	0 (0-5)	4.87	0.001
Age at menarche (years)					
11-14	218 (57.4)	104 (54.7)	114 (60.0)	1.07	0.300
15-19	162 (42.6)	86 (45.3)	76 (40.0)		

Continued.

Characteristics	Total, n=380 (%)	Study groups, n=190 (%)		Test of significance	P value
		Paracetamol	Diclofenac		
Mean age at menarche ± SD (years)	14.3±1.9	14.9±1.9	13.6±1.6	6.74	0.001
Duration of marriage (years)					
1-5	282 (74.2)	139 (73.2)	143 (75.3)	0.52	0.771
6-10	57 (15.0)	31 (16.3)	26 (13.7)		
11-15	41 (10.8)	20 (10.5)	21 (11.1)		
Mean duration of marriage ± SD (years)	4.8±3.8	5.6±4.5	4.1±2.8	0.86	0.388
Number of children					
None	155 (40.8)	126 (66.3)	129 (67.9)	0.11	0.744
1-2	125 (32.9)	64 (33.7)	61 (32.1)		
Median number of children	0 (0-2)	0 (0-1)	0 (0-2)	3.76	0.001
Type of infertility					
Primary	65 (17.1)	36 (18.9)	29 (15.3)	0.91	0.341
Secondary	315 (82.1)	154 (81.1)	161 (84.7)		
Duration of infertility (years)					
<5	159 (41.8)	71 (37.4)	88 (46.3)	5.46	0.065
6-10	186 (48.9)	96 (50.5)	90 (47.4)		
11-15	35 (9.2)	23 (12.1)	12 (6.3)		
Mean duration of infertility ± SD (years)	4.1±3.7	4.4±4.0	3.1±1.4	4.33	0.001

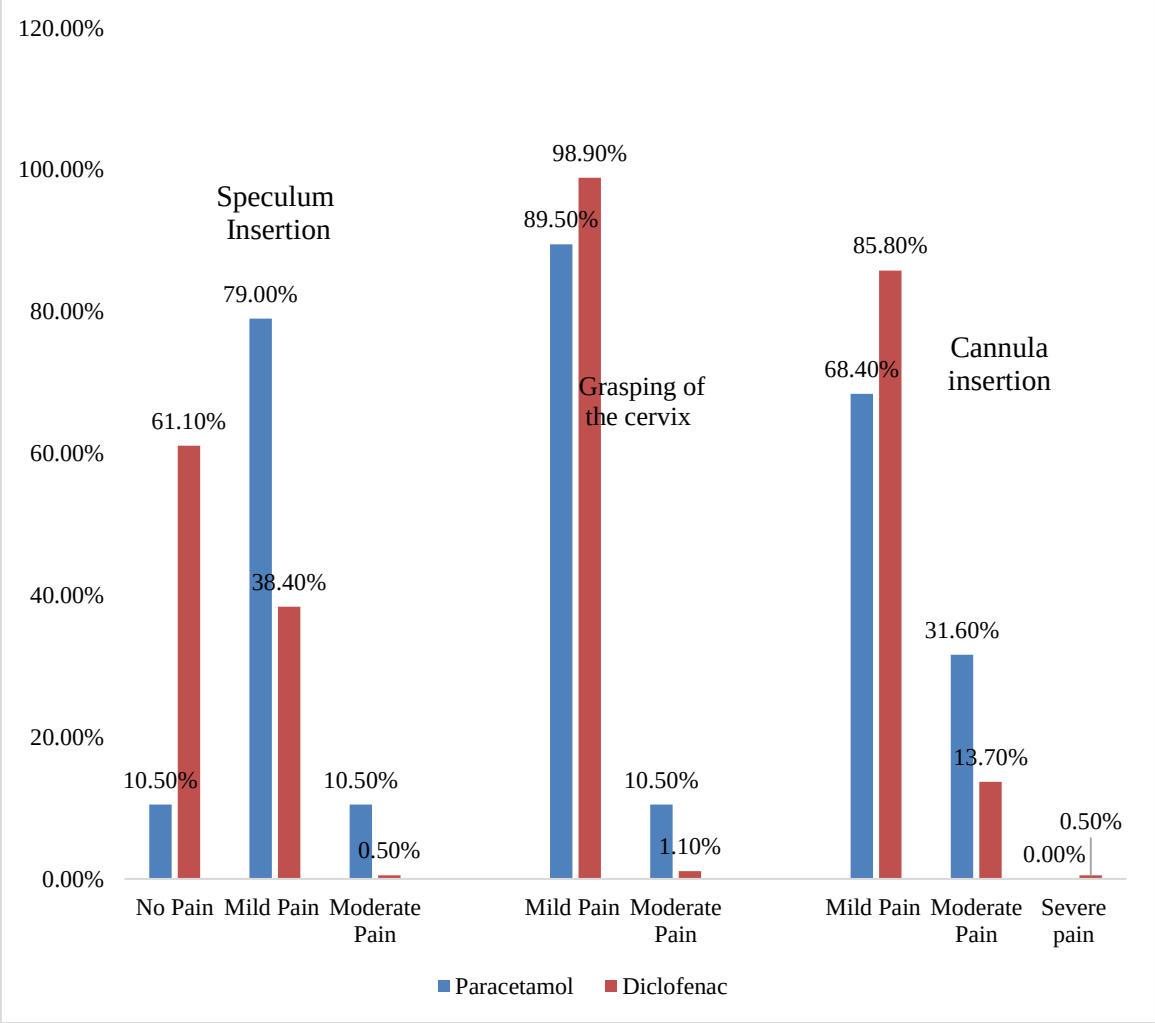

Figure 3: Severity of pain during insertion of speculum, grasping of the cervix and insertion of cannula.

Gynaecologic characteristics

About three in every five (57.4%) women attained menarche between the ages of 11 and 14 years, and 162 (42.6%) women, between the ages of 15 and 19 years (Table 2). In both study groups, women were evenly distributed in relation to age at menarche (χ^2=1.07; p=0.300). However, the median age of menarche showed a significant difference between the two groups (U test=6.74; p=0.001). Majority of the women (154, 81.1%) had secondary infertility in the paracetamol group, and 161, 84.7%, in the diclofenac group. This did not also show any statistical difference (χ^2=2.19; p=0.334). Twenty-three (12.1%) women in the paracetamol group had infertility for 11-15 years, while twelve (6.3%) women in the diclofenac group had infertility for the same length of time (Table 2). This observed difference in duration of infertility between the two groups was not significant statistically (χ^2=5.46; p=0.065).

Duration of procedure and pain scores at different steps of hysterosalpingography

The mean duration of hysterosalpingography in this study was 4.6±1.9 minutes. It was slightly higher (4.8±2.2 minutes) in the paracetamol group than the diclofenac group (4.6±0.9 minutes). Table 4 and Figure 3 shows that the difference in mean duration of procedure between the two study groups was not statistically significant (t test-1.15; p=0.247).

The mean pain scores at different points of the procedure were significantly higher in the paracetamol group than in the diclofenac group (p≤0.05) (Table 4). The mean pain score during insertion of speculum was 1.2±1.0 in the paracetamol group, and 0.4±0.6 in the diclofenac group, with a significant statistical difference (t test=9.21; p=0.001). Grasping of the cervix had a mean pain score of 2.4±1.1 in the paracetamol group, and 1.5±0.8 in the diclofenac group, with a significant difference (t test=8.68; p=0.001). Mean pain score was 3.1±1.2 and 4.8±2.2 at the instillation of contrast media and 30 minutes post-procedure, respectively, in the paracetamol group, and was significantly lower (p≤0.05) in the diclofenac group, for both instillation of contrast (3.9±1.5) and 30 minutes post-procedure (2.0±1.1).

During instillation of contrast media, while 38 (20.0%) women experienced mild pain in the paracetamol group, 72 (37.9%) women expressed mild pain in the diclofenac group, and while 38 (20.0%) women in the paracetamol group expressed severe pain at this step, only 14 (7.4%) women in the diclofenac group experienced severe pain. These differences were statistically significant (χ2=22.05; p=0.001). Table 4 and Figures 3 and 4 shows the level of pain perceived by the women in both study groups, during and after the procedure.

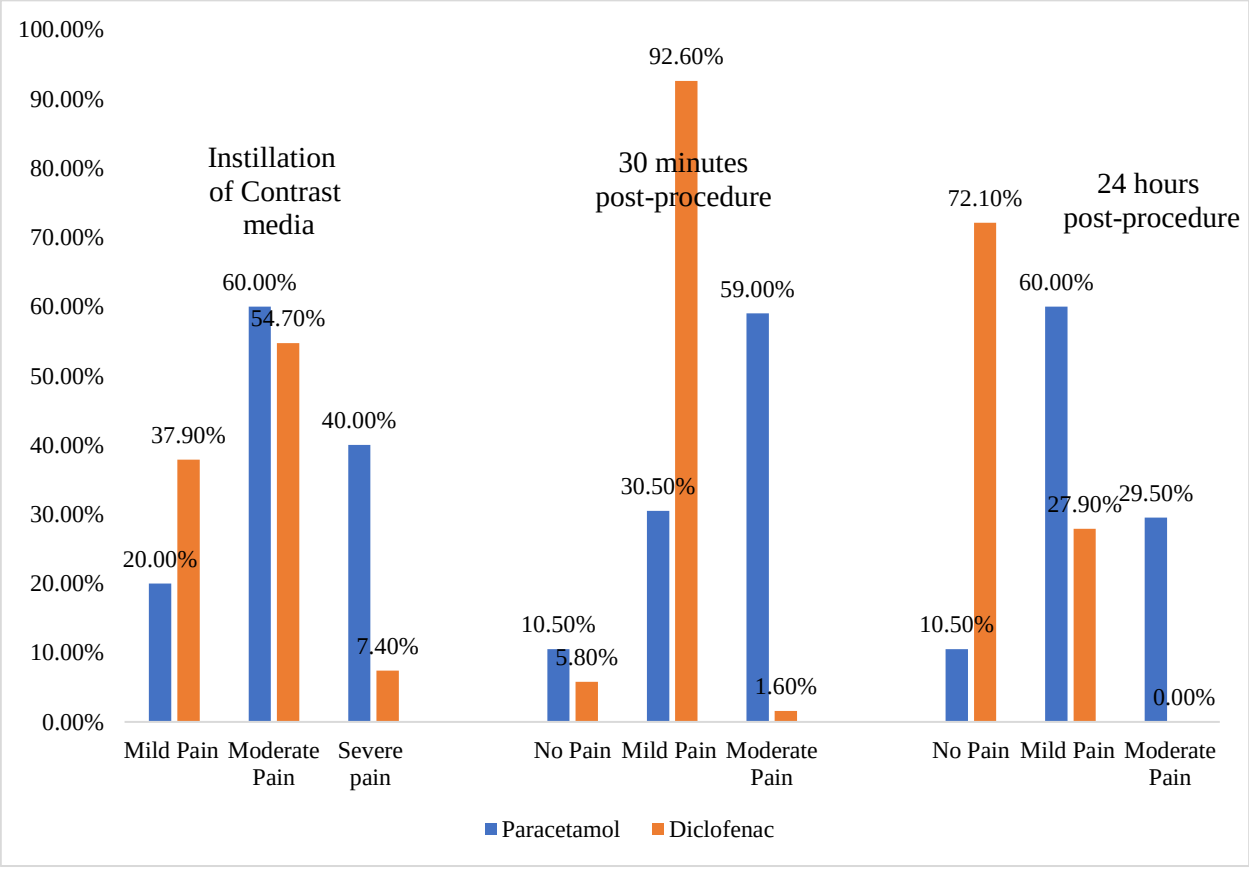

Figure 4: Severity of pain at instillation of contrast media, 30 min and 24 h post-procedure.

Table 3: Duration of procedure and pain scores at different stages of hysterosalpingography.

Characteristics	Total, n=380 (%)	Study groups, n=190 (%)		Students t test (p value)
		Paracetamol	Diclofenac	
Duration of procedure	4.6±1.9	4.8±2.2	4.6±0.9	1.15 (0.247)
Mean pain scores ±SD at the different steps of hysterosalpingography				
Insertion of speculum	0.8±0.9	1.2±1.0	0.4±0.6	9.21 (0.001)
Grasping of the cervix	2.0±1.1	2.4±1.1	1.5±0.8	8.68 (0.001)
Insertion of canula	2.8±1.3	3.1±1.2	2.6±1.5	4.05 (0.001)
Instillation of contrast media	4.3±1.9	4.8±2.2	3.9±1.5	4.76 (0.001)
30 minutes post-procedure	2.8±1.7	3.6±1.6	2.0±1.1	11.38 (0.001)
24 hours post-procedure	1.6±1.6	2.8±1.4	0.6±0.7	21.30 (0.001)

Table 4: Severity of pain at the different steps of hysterosalpingography.

Characteristics	Total, n=380 (%)	Study groups, n=190 (%)		Chi-square (p value)
		Paracetamol	Diclofenac	
Pain severity at insertion of speculum				
None	136 (35.8)	20 (10.5)	116 (61.1)	111.54 (0.001)
Mild	223 (58.7)	150 (79.0)	73 (38.4)	
Moderate	21 (5.5)	20 (10.5)	1 (0.5)	
Pain severity at grasping of the cervix				
Mild	358 (94.2)	170 (89.5)	188 (98.9)	15.59 (0.001)
Moderate	22 (5.8)	20 (10.5)	2 (1.1)	
Pain severity at insertion of cannula				
Mild	293 (77.1)	130 (68.4)	163 (85.8)	18.15 (0.001)
Moderate	86 (22.6)	60 (31.6)	26 (13.7)	
Severe	1 (0.3)	0 (0.0)	1 (0.5)	
Pain severity at instillation of contrast media				
Mild	110 (28.9)	38 (20.0)	72 (37.9)	22.05 (0.001)
Moderate	218 (57.4)	114 (60.0)	104 (54.7)	
Severe	52 (13.7)	38 (20.0)	14 (7.4)	
Pain severity 30 minutes post-procedure				
None	31 (8.2)	20 (10.5)	11 (5.8)	165.43 (0.001)
Mild	234 (61.6)	58 (30.5)	176 (92.6)	
Moderate	115 (30.2)	112 (59.0)	3 (1.6)	
Pain severity 24 hours post-procedure				
None	157 (41.3)	20 (10.5)	137 (72.1)	166.47 (0.001)
Mild	167 (43.9)	114 (60.0)	53 (27.9)	
Moderate	56 (14.7)	56 (29.5)	0 (0.0)	

DISCUSSION

Pain relief during hysterosalpingography is crucial, as procedure-associated pain is a major reason women decline to undergo this investigative modality and/or uncooperative during the procedure. In our study, the highest pain scores in both the paracetamol and diclofenac groups were recorded at instillation of contrast media, with more than a tenth of the women experiencing severe pain at this step. Similarly, other authors have reported instillation of contrast as the most painful step in hysterosalpingography.[4,18–21] Studies have shown that hysterosalpingography-associated pain peaks at the time of instillation of the contrast medium until 5-10 minutes after the procedure, when it begins to wane, and becomes mild 30 minutes following the procedure.[6,22] Uterine distension during contrast instillation locally release prostaglandins that mediate the uterine cramps at this step of the procedure.[6,7] Pain at this step can be significantly reduced by using a smaller amount of contrast, and slow injection of the contrast, which allows time for the contrast to spread through the uterine cavity without causing undue uterine distension.[23]

Similar to the findings of Unlu et al and Karaman et al the least painful hysterosalpingography step in our study was insertion of speculum.[4,24] Speculum insertion during routine pelvic examination and gynaecological procedures, including hysterosalpingography, can however, be associated with considerable discomfort/ pain. Fear of pain at speculum insertion may negatively affect women's uptake of these procedures. Having the

patient empty her bladder prior to positioning for the procedure, using an appropriate-sized speculum, plastic speculum and warming the speculum prior to insertion can reduce the pain experienced with speculum insertion during hysterosalpingography.[25]

In this study, women in the diclofenac group experienced significantly lesser pain at all steps of hysteron-salpingography, compared to those in the paracetamol group, with significantly less women in the diclofenac group reporting severe pain at contrast instillation, the most painful step of the procedure. At this step, compared with the paracetamol group, the diclofenac group experienced 18.75% less pain, which was clinically significant. According to Costello et al a 15% reduction in pain score during hysterosalpingography is considered clinically significant.[26]

Even though nonopioid analgesics, including paracetamol, are the most widely used systemic analgesics for pain prophylaxis during hysterosalpingography, paracetamol has not been demonstrated to be an effective analgesic for pain relief during hysterosalpingography.[7,9,27] This is explained by the fact that paracetamol has no anti-inflammatory action, and is therefore unlikely to have a significant effect on pain mediated by prostaglandin release from uterine distension or cervical instrumentation, two recognized causes of pain during hysterosalpingography.[7] Elson et al therefore recommended the use of a non-steroidal anti-inflammatory drug as prophylactic analgesic for hysterosalpingography.[27] Whereas Ahmad et al found no significant evidence of benefit of using non-steroidal anti-inflammatory drugs for pain relief during, within 30 minutes and more than 30 minutes after hysterosalpingography, and recommended more randomized controlled trials for further evidence, in our study, diclofenac provided effective analgesia up to 24 hours after the procedure.[11] Baseline demographic and gynaecologic characteristics, such as age, parity, type and duration of infertility influence pain perception during hysterosalpingography.[21] There were no statistically significant differences in these characteristics between our two study groups.

The strength of this randomised controlled trial is domiciled in the fact that it is a two-centre, prospective study, where both the clinicians and the patients were blinded to the intervention used for each group of women. The allocating team and the team performing the hysterosalpingography were different. This removed the risk of selection bias. Only two consultant radiologists performed all the hysterosalpingography procedures. This therefore, reduced performance bias, and improved the reproducibility and validity of our study findings. The limitation of this randomised controlled trial is that it is a hospital-based study. A more robust randomised controlled trial with a larger sample size is recommended.

CONCLUSSION

Diclofenac is more effective than paracetamol for pain relief at all steps of hysterosalpingography, providing effective analgesia up to 24 hours after the procedure. The authors recommend the use of diclofenac as prophylactic analgesia for hysterosalpingography.

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