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Original Research Article

Effect of paracetamol as a prophylactic analgesic in infertile women undergoing hysterosalpingography in Bayelsa State, South-South Nigeria: a randomised controlled trial

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ABSTRACT

Background: Hysterosalpingography is the primary 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 placebo in pain reduction during hysterosalpingography.
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 February, 2021-July, 2021. Three hundred and eighty infertile women were assigned into two groups. Women in group I received paracetamol, while the women in group II received placebo. 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 proportion of women who expressed pain at the different steps of the procedure.
Results: Pain ratings among women in the placebo group were higher than those of women in the paracetamol group at all the stages of the procedure. The highest pain scores were recorded during the instillation of contrast media in both study groups, but higher in patients in the placebo group.
Conclusions: Our study revealed that paracetamol was superior to placebo in the control of hysterosalpingography-associated pain. However, pain scores high in the 2 groups during instillation of contrast media into uterine cavity.

Keywords: Hysterosalpingography, Pain, Paracetamol, Placebo, Bayelsa

INTRODUCTION

Infertility is the most frequent reason for gynaecological consultations in Nigeria.[1] Female factors account for about 30% of cases of infertility, 30% are due to male factors, and 30%, due to a combination of male and female factors, while in 10% of cases, there is no identifiable cause.[2] The causes of female infertility vary

from one environment to the other, and may result from anovulation, tubal factors, uterine or cervical factors. Tubal factor is the most common cause of female infertility in our environment, owing to the high prevalence of sexually transmitted diseases, puerperal, post-abortion and post-operative sepsis.[3]

Hysterosalpingography is the investigative modality of choice for the evaluation of tubal patency in infertile women.[4] It is affordable, readily available, reliable, easy to perform, with minimal complications, and does not require anesthesia. This investigative modality has a sensitivity, specificity, positive predictive value, and negative predictive value of 88%, 87%, 71%, and 94%, respectively.[5] Despite these advantages, its major drawback is procedure-associated pain.[6] Many women experience mild to severe pain during and after hysterosalpingography, and this is one of the reasons some women decline undergoing the procedure.[6]

Various pharmacological and non-pharmacological modalities have been used for the control of the procedure-associated pain in hysterosalpingography, with varying results. These include paracetamol, non-steroidal anti-inflammatory drugs, opioids, paracervical block with lignocaine, intrauterine instillation of lignocaine, hyoscine-n-butyl bromide, balloon catheter as against the rigid catheter, and oil-based contrast media as against water-based media.

Paracetamol is an analgesic and antipyretic. Its action is similar to that of non-steroidal anti-inflammatory drugs (NSAIDs), and it is frequently preferred, due to its superior tolerance. Paracetamol inhibits cyclooxygenase (COX) 1 and 2 enzymes, resulting in the inhibition of prostaglandin synthesis.[7] There is paucity of published data on use of paracetamol as prophylaxis for control of pain during hysterosalpingography. Therefore, objective were randomised controlled trial to compare effectiveness of paracetamol in pain reduction during hysteron-salpingography in Bayelsa State, South-South Nigeria.

METHODS

Study design, period and location

This randomised controlled trial was conducted over a six-month period, from February 2021-July 2021, 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. These two tertiary health institutions provide specialized gynaecological services to women in Bayelsa State, and serve as referral centres for other hospitals in Bayelsa State, as well as the neighbouring Rivers and Delta States, in South-South Nigeria.

Sample size determination

The sample size for this study was calculated using the formula:[8]

$$N = \frac{(Z\alpha + Z\beta)^2 \times 2 \times P(1-P)}{d^2}$$

Where, N=minimum sample size per study group, 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.[9] d=expected margin of error=10%=0.1

The calculation was done as

$$N = \frac{(1.96 + 0.84)^2 \times 2 \times 0.121(1-0.121)}{(0.1)^2} = \frac{1.667}{0.01}$$

N=166.7.

Putting into consideration an attrition rate of 10% (16.7), N=183.4, adjusted to 190.

With a calculated sample size of 190 per study group, this gives a total of 380 study participants.

Inclusion and exclusion criteria

Infertile women referred for hysterosalpingography, who gave consent and completely filled consent/ questionnaire form, were included in study. Exclusion criteria included abnormal uterine/ vaginal bleeding before the procedure, on-going menstruation, pregnancy, cervicovaginal discharge, cervical stenosis/ cervical pathology, evidence of pelvic inflammatory disease, previous history of contrast hypersensitivity, history of allergy to paracetamol, and all patients that declined consent or incompletely filled the consent form and questionnaire.

Study participants recruitment and randomization

Three hundred and eighty eligible infertile women undergoing hysterosalpingography were enrolled in the study, from the gynaecological clinics of the study centres, after adequate counselling and obtaining written informed consents from them, for participation in the study. The aim of the study, the procedure and the likely benefits to the patients were explained to them, prior to recruiting them for the study. Their age, level of education, occupation, parity, body mass index and other relevant patients' information were obtained and documented. Afterwards, they were referred to the radiology departments for hysterosalpingography.

Eligible women who consented to participate in the study were equally randomized into two groups (1:1 ratio) by means of a computer-generated list of random numbers (generated from www.randomization.com). Women in group I were administered 600 mg (4 ml) of intramuscular paracetamol (Drugamol®), manufactured by Drugfield Pharmaceuticals, Nigeria, while the women in group II received a placebo of 4 ml of water for injection, manufactured by Medlab pharmaceuticals, India. The allocating team and the team performing the hysterosalpingography were different, to prevent selection bias.

Procedure

Hysterosalpingography for the women was performed during the proliferative phase of the menstrual cycle (7th - 10th day). Protective lead apron and eye shield were worn by the radiologists performing the procedure. 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.

Intramuscular paracetamol 600 mg (4 ml) was given to the women in group I, while placebo (4 ml of water for injection) was given to the women in Group II. After five minutes of administering intramuscular paracetamol or water for injection, following hand-washing and wearing of 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, and the anterior lip of the cervix was grasped with a tenaculum. A self-retaining hysterosalpingography cannula was inserted into the cervix, following which the Cusco's 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, through the cannula. Three radiographs to outline the endometrial cavity, fallopian tubes and intraperitoneal spillage of contrast, respectively, were obtained. A 0-10 cm visual analogue scale (VAS, 0=no pain, 10=worst possible pain) was used to document the level of pain experienced by the patients at different steps of the procedure, by an assistant, who was blinded to the randomisation (Figure 1).[10]

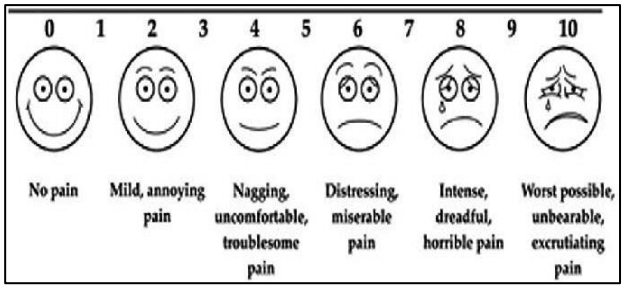

Figure 1: Visual analogue scale.[10]

At the end of the procedure, the cannula was removed, the vulva was cleaned, and the patient was asked to dress up. The hysterosalpingography films were reported by consultant radiologists in the study centres. 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).[11] This is the commonest scale used in the grading of pain. The patients rated the level of pain on a scale of 0-10. A score of 0 indicated no pain, 1-3 suggested mild pain, 4-6, moderate pain, and 7-10 suggested severe pain.[11]

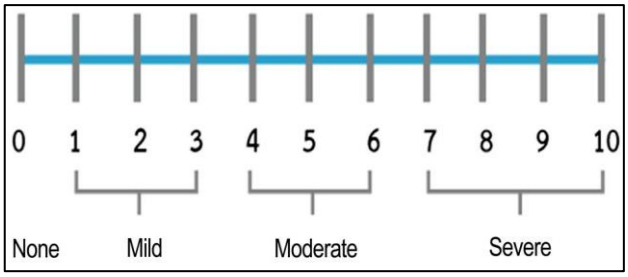

Figure 2: Numerical rating scale (NRS).[11]

Study outcome measures

The primary outcomes included pain scores during of the different steps of the procedure and immediately 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.

RESULTS

Socio-demographic characteristics

Three hundred and eighty women participated in the study, and they were equally randomized into the two study groups (190 women per study group). The mean age of the total study population was 33.5±4.5 years. The mean age of women in the paracetamol group was 33.2±4.6 years, while in the placebo group, it was 33.8±4.3 years. The modal age-group of the total study population was 36-40 years (126, 33.2%) (Table 1). There was no significant difference in age between the two study groups (t test=1.34; p=0.182).

In the paracetamol group, 18 (9.5%), 38 (20.0%) and 134 (70.5%) women, respectively, while in the placebo 20 (10.5%), 34 (17.9%) and 136 (71.6%) women, respectively, had primary, secondary and tertiary level of education, with no statistical difference ($\chi 2=0.34$; p=0.182) between the two groups. Table 1 further shows

that participants in the two study groups were not significantly different with respect to their occupation (χ^2=3.41; p=0.332) and body mass index categories (χ^2=1.06; p=0.787). All participants in the study were married.

Gynaecological and infertility characteristics

Table 2 shows that about 8 in 10 (294, 77.4%) women who participated in the study were nulliparous, married for between 1-10 years (303, 79.7%), with secondary infertility (304, 80.0%). The distribution of women in the two study groups in relation to parity (χ^2=0.61; p=0.737), duration of marriage (χ^2=3.69; p=0.297), number of children (χ^2=0.46; p=0.497), type of infertility (χ^2=0.26; p=0.608) and duration of infertility (χ^2=2.05; p=0.359) were not significantly different.

Presenting gynaecological symptoms and history

As shown in Table 3, the most common gynaecological history was a history of induced abortion (238, 62.6%). Other gynaecological presenting symptoms and history were chronic pelvic pain (188, 49.5%), dysmenorrhoea (182, 47.9%) and spontaneous abortion (114, 30.0%). Furthermore, the occurrence of induced abortion (64.2% vs 61.1%), chronic pelvic pain (51.6% vs 47.4%) and dysmenorrhoea (50.5% vs 45.3%) were higher in the placebo group than in paracetamol group. However, these differences were not statistically significant (p≥0.05).

Pain perception and scores in the paracetamol and placebo groups

Table 4 shows the perception of pain among the women while undergoing hysterosalpingography. The mean pain scores of the women in the placebo group were significantly higher than the pain scores of women in the paracetamol group at all the steps of the procedure (Table 4 and Figure 3). The highest pain scores were recorded during the instillation of contrast medium, with an overall mean pain score of 5.32±2.09 at this step (Table 4). Table 4 shows that at this step, the mean pain score was significantly higher (t test=5.01) in the placebo group (5.84±1.81) than in the paracetamol group (4.80±2.23). The least pain in both groups was experienced during insertion of speculum, the overall mean pain score at this step being 1.53±1.21.

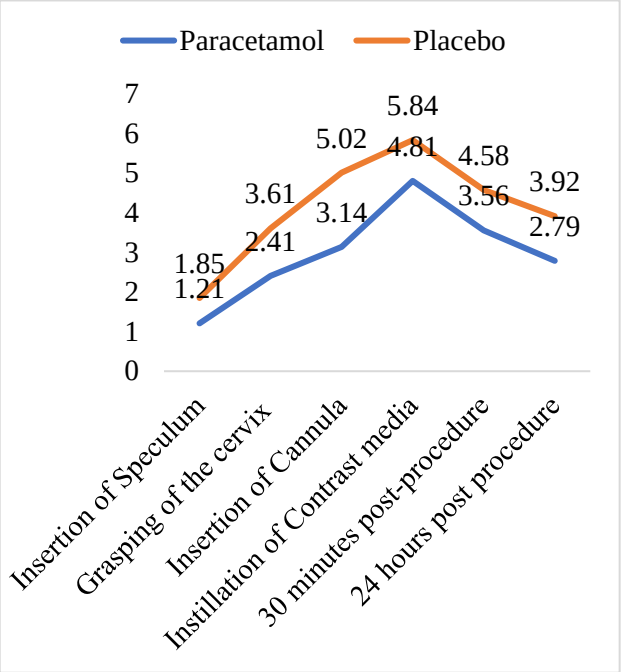

Figure 3: Mean pain scores at different stages of hysterosalpingography.

The severity of pain perceived at the point of instillation of contrast media was compared between the two groups. While 38 (20.0%) women in the paracetamol group had severe pain, 58 (30.6%) women experienced severe pain in placebo group at this step of procedure. In the paracetamol group, 38 (20.0%) and 114 (60.0%) expressed mild and moderate pain, respectively, while in the placebo group, 28 (14.7%) and 104 (54.7%) women experienced mild and moderate pain, respectively, during the instillation of contrast medium (Table 4). This observed difference in the perception of pain between the two study groups was statistically significant (χ2=6.14; p=0.046).

Table 1: Socio-demographic characteristics of women undergoing hysterosalpingography.

Characteristics	Total, n=380 (%)	Study groups		Test of significance	P value
		Paracetamol, n=190 (%)	Placebo, n=190 (%)		
Age group (years)					
18-25	34 (8.9)	18 (9.5)	16 (8.4)	0.39[a]	0.941
26-30	105 (27.6)	50 (26.3)	55 (28.9)		
31-35	115 (30.3)	58 (30.5)	57 (30.0)		
36-40	126 (33.2)	64 (33.7)	62 (32.6)		
Mean age±SD in years	33.5±4.5	33.2±4.6	33.8±4.3	1.34[b]	0.182
Level of education					
Primary	38 (10.0)	18 (9.5)	20 (10.5)	0.34[a]	0.843
Secondary	72 (18.9)	38 (20.0)	34 (17.9)		
Tertiary	270 (71.1)	134 (70.5)	136 (71.6)		

Continued.

Characteristics	Total, n=380 (%)	Study groups		Test of significance	P value
		Paracetamol, n=190 (%)	Placebo, n=190 (%)		
Occupation					
Civil servant	153 (40.3)	80 (42.1)	73 (38.4)	3.41[a]	0.332
Professional	23 (6.1)	15 (7.9)	8 (4.2)		
Trader	135 (35.5)	63 (33.2)	72 (37.9)		
Unemployed	69 (18.2)	32 (16.8)	37 (19.5)		
Body mass index					
Normal weight	154 (40.5)	76 (40.0)	78 (41.1)	1.06[a]	0.787
Overweight	86 (22.6)	40 (21.1)	46 (24.2)		
Class I obesity	104 (27.4)	56 (29.5)	48 (25.3)		
Class II obesity	36 (9.5)	18 (9.5)	18 (9.5)		
Mean weight (kg)	80.1±11.9	79.8±14.0	80.3±9.3	0.37[b]	0.711
Mean height (m)	1.66±0.07	1.65±0.09	1.66±0.03	0.29[b]	0.768
Mean body mass index (kg/m^2)	29.2±0.07	29.3±6.1	29.2±4.0	0.15[b]	0.882

[a]Chi-square test; [b]Students' t test.

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

Characteristics	Total, n=380 (%)	Study groups		Chi-square	P value
		Paracetamol, n=190 (%)	Placebo, n=190 (%)		
Parity					
Nulliparity	294 (77.4)	144 (75.8)	150 (78.9)	0.61	0.737
Primiparity	40 (10.5)	22 (11.6)	18 (9.5)		
Multiparity	46 (12.1)	24 (12.6)	22 (11.6)		
Duration of marriage (years)					
1-5	184 (48.4)	90 (47.4)	94 (49.5)	3.69	0.297
6-10	119 (31.3)	58 (30.5)	61 (32.0)		
11-15	47 (12.4)	22 (11.6)	25 (13.2)		
>16	30 (7.9)	20 (10.5)	10 (5.3)		
Number of children					
None	270 (71.1)	138 (72.6)	132 (69.5)	0.46	0.497
1-2	110 (28.9)	52 (27.4)	58 (30.5)		
Type of infertility					
Primary	76 (20.0)	36 (18.9)	40 (21.1)	0.26	0.608
Secondary	304 (80.0)	154 (81.1)	150 78.9)		
Duration of infertility (years)					
<5	236 (62.1)	122 (64.2)	114 (60.0)	2.05	0.359
6-10	108 (28.4)	48 (25.3)	60 (31.6)		
11-15	36 (9.5)	20 (10.5)	16 (8.4)		

Table 3: Presenting gynaecological symptoms and history of women undergoing hysterosalpingography.

Characteristics	Total, n=380 (%)	Study groups		Chi-square	P value
		Paracetamol, n=190 (%)	Placebo, n=190 (%)		
Dysmenorrhea					
Yes	182 (47.9)	86 (45.3)	96 (50.5)	1.05	0.305
No	198 (52.1)	104 (54.7)	94 (49.5)		
Chronic pelvis pain					
Yes	188 (49.5)	90 (47.4)	98 (51.6)	0.67	0.412
No	192 (50.5)	100 (52.6)	92 (48.4)		
Pelvic inflammatory diseases					
Yes	66 (17.4)	36 (18.9)	30 (15.8)	0.65	0.417
No	314 (82.6)	154 (81.1)	160 (84.2)		

Continued.

Characteristics	Total, n=380 (%)	Study groups		Chi-square	P value
		Paracetamol, n=190 (%)	Placebo, n=190 (%)		
Spontaneous abortion					
Yes	114 (30.0)	60 (31.6)	54 (28.4)	0.45	0.502
No	266 (70.0)	130 (68.4)	136 (71.6)		
Induced abortion					
Yes	238 (62.6)	116 (61.1)	122 (64.2)	0.40	0.525
No	142 (37.4)	74 (38.9)	68 (35.8)		

Table 4: Pain perception in the paracetamol and placebo groups at different steps of hysterosalpingography.

Characteristics	Total, n=380 (%)	Study groups		Chi-square (p value)
		Paracetamol, n=190 (%)	Placebo, n=190 (%)	
Severity of pain during instillation of contrast medium				
Mild	66 (17.4)	38 (20.0)	28 (14.7)	6.14 (0.046*)
Moderate	218 (57.4)	114 (60.0)	104 (54.7)	
Severe	96 (25.2)	38 (20.0)	58 (30.6)	
Mean pain scores ±SD at different steps of the procedure				
Insertion of speculum	1.53±1.21	1.21±1.01	1.85±1.31	5.35 (0.001*)
Grasping of the cervix	3.01±1.06	2.41±1.13	3.60±0.49	13.29 (0.001*)
Insertion of cannula	4.08±1.90	3.14±1.51	5.02±2.04	11.10 (0.001*)
Instillation of contrast media	5.32±2.09	4.80±2.23	5.84±1.81	5.01 (0.001*)
Thirty minutes post-procedure	4.07±1.53	3.56±1.57	4.58±1.31	6.88 (0.001*)
Twenty-four hours post-procedure	3.35±1.50	2.79±1.42	3.92±1.37	7.87 (0.001*)

Note: *Statistically significant.

DISCUSSION

The most frequent side effect of hysterosalpingography is the pain associated with the procedure. Up to 80% of women believe hysterosalpingography is painful, and as a result, they express significant anxiety prior to the procedure.[12,13] The pain and anxiety (from fear of pain) can prevent women from fully cooperating with the hysterosalpingography procedure or even make them decline undergoing the procedure.[14] Sources of pain during hysterosalpingography include insertion of speculum, grasping of the cervix, insertion of cervical speculum, uterine distension by contrast media and peritoneal irritation from spillage of contrast into the peritoneal cavity.[15]

Pharmacologically, nonopioid analgesics, including paracetamol, are the most widely used systemic analgesics for pain prophylaxis during hysterosalpingography.[14] Specifically, paracetamol has been recommended as an alternative analgesic for hysterosalpingography.[16] Evidence for the efficacy of paracetamol in relieving pain during and after hysterosalpingography is however conflicting, hence the need for more randomized controlled trials like ours.[16-18] In as much as our study observed that paracetamol was more effective than placebo for the overall reduction of hysterosalpingography-associated pain, there was significant pain at the point of instillation of contrast media. This finding is in tandem with the findings of several authors, who reported that pain is expressed most by patients at the point of instillation of contrast media into the uterine cavity.[15,19-22] Any pain relief method that will effectively control the pain at this step of hysterosalpingography would have significantly solved the issue of hysterosalpingography-associated pain. The role of counselling prior to hysterosalpingography cannot be over emphasised, as stress and anxiety can increase hysterosalpingography-associated pain.[6]

The mean and modal age group of our study participants were respectively, 33.5±4.5 years, and 36-40 years, with majority of the women possessing tertiary level education. Other studies within and outside Nigeria have reported similar mean age and/or modal age range.[23–31] Globally, many women are now delaying childbearing for various reasons, including career. As a women ages, the ability to conceive declines.[32] The age distribution of our study participants may also be explained by the fact that especially in our environment, infertile women often do not seek specialist care first. They would usually first wait passively, consult general practitioners, or patronize alternative/unorthodox care givers, before presenting to a specialist.

Majority of the patients in our study were overweight and obese. In obese women, there is increased levels of androgens in circulation, which contributes to anovulation and menstrual irregularities. This in turn leads to reduced ability to conceive and response to fertility treatment. The prevalence of obesity in the

population of infertile women is high, and many studies have reported an association between obesity and infertility.[33] Secondary infertility was the most common cause of infertility in this study. This is in agreement with the findings from many studies.[25,30,31,34,35] An explanation for this may be due to post-abortion sepsis and pelvic inflammatory diseases, that may have complicated previous induced abortions. Over 60% of the women in our study had had at least one previous induced termination of pregnancy. Other reasons for the high proportion of women with secondary infertility in our study may be due to 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.

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 intervention 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 therefore, 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 randomised controlled trial with a larger sample size is recommended.

CONCLUSSION

Paracetamol has been recommended as an alternative analgesic for hysterosalpingography. Our study confirmed that it is significantly more effective than placebo as an analgesic during hysterosalpingography, providing effective analgesia at all steps of the hysterosalpingography procedure, and up to 24 hours following the procedure. The authors therefore recommend that paracetamol should be considered as an effective alternative analgesic to NSAIDs, opioids, topical and local anaesthetics, during hysterosalpingography.

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