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Efficacy and safety of diclofenac suppository for postoperative pain relief after diagnostic hystero-laparoscopy and dye test: A double-blind, placebo-controlled, randomized trial

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ABSTRACT

Objective: To determine the efficacy and safety of rectal diclofenac for relieving postoperative pain following diagnostic hystero-laparoscopy and dye test (dHLD).

Methods: A prospective, double-blind, placebo-controlled, randomized trial was conducted among women who underwent dHLD to evaluate fertility. The women received either rectal diclofenac with intramuscular pentazocine or intramuscular pentazocine with rectal placebo for postoperative analgesia. The median pain scores at different time points were assessed as the primary outcome measures using the Numerical Rating Scale for pain. The secondary outcome measures were analgesic consumption, time at which first analgesic was requested, satisfaction with pain relief and any adverse events.

Results: In total, 108 participants were analysed (54 in each group, 1:1 ratio). The median score for postoperative pain was lower for the diclofenac group compared with the placebo group at 4 h (52.53 vs 56.47; $p = 0.507$), 6 h (50.48 vs 58.52; $p = 0.174$), 8 h (51.42 vs 57.65; $p = 0.296$), 10 h (51.35 vs 57.65; $p = 0.285$) and 12 h (52.45 vs 56.55; $p = 0.485$) post surgery, although the difference was not significant ($p > 0.05$). Seventeen participants required rescue analgesia with 30 mg of pentazocine: 11 at 4 h post surgery [5 (62.5 %) vs 6 (66.7 %)], three at 6 h post surgery [2 (25.0 %) vs 1 (11.1 %)], two at 8 h post surgery [1 (12.5 %) vs 1 (11.1 %)], and one at 12 h post surgery [0 vs 1 (11.1 %)] for the diclofenac and placebo groups respectively ($p = 0.713$). There were no significant differences in postoperative adverse effect profiles, overall patient satisfaction, and need for rescue analgesia between the two groups ($p > 0.05$).

Conclusions: Postoperative use of rectal diclofenac and pentazocine is safe, but did not significantly improve pain scores, patient satisfaction and need for rescue analgesia following dHLD, compared with patients who received pentazocine and placebo. While a multi-modal approach to pain relief following dHLD does not appear to be significantly beneficial, a multi-centre study is needed to confirm or refute these findings.

1. Introduction

Diagnostic hystero-laparoscopy and dye test (dHLD) is an essential tool for the evaluation of female infertility [1–3], and is the gold standard investigation for tubal patency [1]. dHLD offers the opportunity for detailed, direct viewing and evaluation of the uterine cavity; endometrium; tubal morphology and patency; and uterine, ovarian and adnexal pathology [1–3]. These fine details are often missed in routine

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clinical examination and ultrasound scan, and awareness can lead to use of additional beneficial therapeutic interventions in some cases [1].

Infertility remains a challenge to couples and gynaecologists, and women who present for dHLD often wish to return home and resume work rapidly after the procedure, without experiencing any pain or absence from work. Thus, any form of intervention that can alleviate pain will have a positive impact on patient quality of life [4]. Timely and effective relief of postoperative pain therefore forms an essential aspect of hystero-laparoscopic procedures, as it will have a significant effect on patient comfort and satisfaction in the immediate postoperative period. Diagnostic hysteroscopy entails evaluating the uterine cavity using a small-diameter hysteroscope [5,6]. Laparoscopy, on the other hand, provides direct visual access to the pelvis and peritoneal cavity using a minimal access technique to evaluate the anatomy of the uterus, and study the ovaries and fallopian tubes in detail so that detected abnormalities can be treated [6,7].

Although dHLD is performed under general anaesthesia, the postoperative pain can be enormous [8]. Several factors contribute to the pain experienced at hysteroscopy, including manipulation/dilatation of the cervix, distension of the uterus, and irritation of the peritoneum by spilled distension medium [5]. The pelvic splanchnic nerves conduct pain stimuli from the cervix and vagina, while the hypogastric nerves conduct pain stimuli arising from structures within the peritoneal cavity, including the uterine body [5]. Additionally, manipulating the cervix and distension of the uterus will result in delayed pain caused by the release of prostaglandins [5,9,10]. Systematic reviews have reported various results for pain experienced based upon the distension media used, although fewer vasovagal episodes have been reported with the use of saline compared with carbon dioxide [9,10]. At laparoscopy, the incision made to the skin and subcutaneous tissues will result in tissue trauma/damage which, in turn, causes pain via stimulation of peripheral nociceptors [11]. Also, the inflammatory response to tissue damage may activate the nociceptors and produce a sensation of pain [11,12]. Inflammatory mediators may also be released due to rapid distension of the peritoneal cavity during insufflation, resulting in rupture of blood vessels and trauma to the nerve endings [13]. Shoulder tip and upper abdominal pain are common after laparoscopic procedures [14].

Various short- or medium-acting sedatives, narcotics, non-steroidal anti-inflammatory drugs (NSAIDs) and local anaesthetics have been used during endoscopic procedures as adjuncts to anaesthesia to relieve pain in the postoperative period [4]. The amount of pelvic pain after hysteroscopy may be related to the prostaglandin level; laparoscopic tubal manipulations and chromotubation lead to the release of prostaglandins, which may lead to frequent nociceptive stimuli and the sensation of pain [13]. Prostaglandin synthase inhibitors (NSAIDs) may therefore be effective in ameliorating this type of pain [13].

Conflicting outcomes have been reported from previous studies that evaluated the use of NSAIDs for relieving postoperative pain following endoscopic procedures. While some prospective, randomized controlled studies that compared NSAIDs and placebo found that NSAIDs had better outcomes than placebo in relieving postoperative pain or decreasing the need for top-up analgesia after laparoscopic procedures [15–18], other studies [19–22] revealed no significant beneficial effect of NSAIDs in comparison with placebo. These studies showed different outcomes due to variations in dose, route of administration, and particular NSAID used.

There appears to be a lack of consensus on the use of NSAIDs alone or as an adjunct to reduce pain in the postoperative period following endoscopic procedures. However, administering NSAIDs in the postoperative period resulted in a significant reduction in opioid consumption in the first 24 h after surgery, as well as opioid-induced nausea, vomiting and sedation [23,24]. While the use of diclofenac via oral and parenteral routes [17,18,20] and at varying doses (50, 75 and 100 mg) has been studied for postoperative pain relief following laparoscopic procedures, few studies are available on the rectal route [15] of administration. Use of the rectal route, in the form of suppositories, has the advantages of a reduced hepatic first-pass effect, absence of gastric mucosa irritation, and significant local and systemic levels for various drugs [25]. However, the insertion process may be discomforting for patients. The literature search did not identify any publications on the use of rectal diclofenac for relieving postoperative pain following dHLD in a Nigerian population. Therefore, this study aimed to determine if the use of rectal diclofenac is safe and effective for relieving postoperative pain after dHLD.

2. Materials and methods

This study was a two-centre, prospective, double-bind, placebo-controlled, randomized study on 108 women evaluated for infertility at Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Nigeria and Life Specialist Hospital Limited (LIFE), Nnewi, Nigeria between October 2020 and April 2021. NAUTH is a tertiary health institution, and LIFE is a private specialist hospital. Both hospitals have accreditation for postgraduate training of doctors in gynaecological endoscopy under the West African College of Surgeons in the Faculty of Obstetrics and Gynaecology, and offer varied services including laparoscopic surgery, and gynaecological and fertility clinic services.

All included women provided written informed consent for study participation. The study protocol was approved by the NAUTH Ethics Committee (Approval No. NAUTH/CS/66/VOL.13/VER111/52/2020/063) and LIFE. The trial was also prospectively registered with the Pan African Clinical Trial Registry: https://pactr.samrc.ac.za/ with registration number of **PACTR202102546768103**. Women booked for dHLD on account of infertility at the gynaecology clinic and outpatient department of NAUTH and LIFE, respectively, were recruited by the researcher or trained research assistants based on the inclusion criteria. All recruited subjects underwent the procedure.

Preoperatively, the researcher or trained research assistants educated recruited participants in the use of the Numerical Rating Scale (NRS) for pain, with scores ranging from 0 to 10 (score of 0 = no pain, score of 10 = unimaginable severe pain). The NRS for pain was used because it is authenticated, widely accepted as appropriate for the evaluation of pain [26], and the patient does not need to remain in hospital for the entire evaluation period. The participants were randomized using randomly permuted blocks (blocks of four, allocation ratio 1:1) with available online software (http://www.randomization.com) by an autonomous individual who was not part of the study. This process was carried out prior to commencement of the study to generate number codes for the participants. Sealed and serially coded envelopes were used for allocation concealment. The coded envelopes randomized the patients to either rectal diclofenac or rectal placebo. Allocated participants were matched with the corresponding envelopes.

2.1. Study procedure

Individual participants were serially administered the treatment indicated in their envelope. Diclofenac suppositories (Bliss GVS Pharma Ltd, Mumbai, India) were sourced from the Nigerian outlet, and a uniform brand of Lofnac (diclofenac sodium suppository 100 mg) was used for all cases. A rectal placebo containing ascorbic acid, produced by the Pharmacy School of Nnamdi Azikiwe University, Awka, Nigeria was used in this study. Both drugs were stored in a theatre refrigerator in coded envelopes under the care of an independent perioperative nurse. The independent staff anaesthesiologist (who was not part of the study) utilized the hospitals' usual intra- and postoperative pain medication (i.e. pentazocine 30 mg). As such, the same anaesthesia and intramuscular analgesia were given to all participants (both cases and controls) during and after dHLD. The first dose of intramuscular pentazocine for postoperative analgesia was given at the end of the procedure, as when an independent nurse (who did not participate in the study) administered the suppository matching the code allocated to the participant before the participant recovered from general anaesthesia. Therefore, both the

participants and the outcome assessors (researcher and/or trained research assistants) were unaware of the interventions given to individual participants at the time of assessment, as the independent nurse administered the suppository (diclofenac/placebo) at the time of perineal cleansing, usually at the end of the procedure. The codes were broken at the end of the study.

dHLD was performed in the study centres under ketamine-induced general anaesthesia and 100 % oxygen ventilation delivered via a face mask [4]. Hysteroscopy was performed first using a 30° 2.9-mm rigid hysteroscope and 3.8-mm diagnostic sheath (Karl Storz, Tuttlingen, Germany). The cervix was exposed using a Sim's speculum, the anterior cervical lip was grasped with a tenaculum, and the hysteroscope was introduced gently into the uterine cavity after visualizing the external os and cervical canal. Normal saline was used as the distension medium at room temperature, delivered through a hystero-pump at preset pressure of 100 mmHg. The uterine cavity, including the endometrium and tubal ostia, was evaluated. The hysteroscope was withdrawn thereafter, and a uterine cannula was fitted into the cervical canal at the end of diagnostic hysteroscopy.

Diagnostic laparoscopy and dye test followed, using a 10-mm laparoscope (Karl Storz). The closed-access technique was used for all patients as the primary entry approach. Pneumoperitoneum was achieved with CO_2 insufflation via a Veress needle, introduced through a standard superior umbilical crease approach or a Palmer's point entry approach (where there was a subumbilical midline scar). The initial 'stab' incision was extended to 10–12 mm before introducing the trochar/cannula. A laparoscope, connected to a camera for video monitoring/recording and light source, was introduced to view the abdominal and pelvic organs. Tubal patency was tested using methylene blue dye injected via the fitted uterine cannula. Pelvic anatomy was evaluated by visualizing the uterus, ovaries and fallopian tubes to identify possible abnormalities, adhesions and endometriosis.

Postoperatively, the NRS for pain scores of individual participants were evaluated in the recovery room using a continuous 0–10-point scale every 2 h from 4 h post surgery to 12 h post surgery. At a score > 3 or following the patient's request, 30 mg intramuscular pentazocine was administered. The participants were monitored by the outcome assessors for adverse effects. At the end of the study (i.e. 12 h post surgery), the patients were asked by the assessors to rank their satisfaction with pain relief subjectively as satisfactory, good, fair or poor. The participants were also counselled on the findings during dHLD, as well as further treatment options, and were discharged home. Participants that were stable and discharged prior to 12 h post surgery were followed up via telephone calls to obtain the relevant data.

2.2. Outcome measures

The primary outcome measures were the median pain scores at 4, 6, 8, 10 and 12 h post surgery using the NRS for pain. The secondary outcome measures were analgesic requirement, time point when first request for additional analgesia was made, proportion of women requiring additional analgesic agent, patient satisfaction, and any adverse events.

2.3. Sample size determination

The sample size was determined from the formula used in sample size calculation for two population mean continuous outcome after substituting pain scores at 6 h post surgery, in accordance with a previous study by Arab et al. [27]: $n = 2[(Z_\alpha + Z_\beta)\,\sigma/(\mu 1 - \mu 2)]^2$, where $n =$ minimum sample size; Z_α (Z at 95 % confidence interval) $= 1.96$; Z_β [value of Z at 90 % power (1-Beta] $= 1.282$; σ (standard deviation of difference) $= 1.71$; $(\mu 1 - \mu 2)$ = mean difference $= 7.0–5.82 = 1.18$ according to Arab et al. [27]; $N = 2[(1.96 + 1.282)\ 1.71/1.18]^2$; $N = 2\ (4.698)^2 = 44.14$. This was approximated to 45. Therefore, there were 45 participants in the intervention group and another 45 participants in the control group. Considering an attrition rate of 20 %, 54 participants were recruited in each arm of the study. The total sample size was 108 $(54 + 54 = 108)$.

3. Statistical analysis

The data were evaluated for completeness prior to analysis. Data analysis was performed using Statistical Package for Social Sciences Version 25 (IBM Corp, Armonk, NY, USA). Data were presented in tables and charts, while continuous data were presented as mean ± standard deviation. Categorical variables were analysed using Chi-squared test where appropriate (or Fisher's exact test for smaller groups with frequencies <5), while continuous data were analysed using *t*-test if parametric. The differences in median postoperative pain scores between the two groups were compared using Mann–Whitney *U*-test. $p \leq 0.05$ was considered to indicate significance.

4. Results

Of the 158 participants that were assessed for study eligibility, 12 declined to participate, 20 did not meet the inclusion criteria because they were undergoing either laparoscopy and dye test alone or hysteroscopy alone, and 18 were excluded for other reasons which included prior history of gastric or duodenal ulcer, known asthmatic or prior reaction to NSAIDs. Therefore, 108 participants who met the inclusion criteria were randomized into the diclofenac group ($n = 54$) and the placebo group ($n = 54$). Fig. 1 shows the study flowchart.

Table 1 summarizes the sociodemographic variables of both groups. There was no significant difference in baseline sociodemographic and clinical data between the two groups.

Table 2 compares the mean age and body mass index (BMI) of the two groups. While the mean age of participants in the diclofenac group was higher than that of the placebo group (36.37 ± 5.52 vs 34.51 ± 5.62 years, respectively), the weight, height and BMI were higher in the placebo group. None of the differences were significant ($p > 0.005$). The mean duration for dHLD was 20.63 ± 7.20 min. There was no significant difference in the procedure time between the two groups.

Table 3 compares postoperative pain scores at 4, 6, 8, 10 and 12 h post surgery between the two groups. Participants in the diclofenac group had lower pain scores compared with the placebo group throughout the study period, although the difference was not significant. Fig. 2 is a graphical representation of the comparison of pain scores between the two groups.

Tables 4 and 5 compare the occurrence of postoperative adverse effects and overall patient satisfaction, respectively. There was no significant difference in the occurrence of postoperative complications and overall patient satisfaction between the two groups ($p > 0.05$).

The requirement for rescue analgesia, timing, and dose of rescue analgesia given are shown in Table 6. All participants received a single dose of 30 mg intramuscular pentazocine at the end of the procedure. Seventeen (15.7 %) participants had additional need for rescue analgesia with 30 mg intramuscular pentazocine at various points: eight (47.1 %) were in the diclofenac group and nine (52.9 %) were in the placebo group. There was no significant difference in the requirement for rescue analgesia between the two groups ($p > 0.05$).

The occurrence of shoulder tip pain and duration of hospital stay are shown in Table 7. Twenty-two participants (20.4 %) experienced shoulder tip pain: 12 (22.2 %) were in the diclofenac group and 10 (18.5 %) were in the placebo group. This difference was not significant ($p > 0.05$). The mean duration of hospital stay for all the participants within the study period was 6.70 ± 1.2 h. More participants had early discharge from the hospital at 4 h and 6 h post surgery in the diclofenac group compared with the placebo group [29 (53.7 %) vs 21 (38.9 %)]; this difference was not significant ($p > 0.05$).

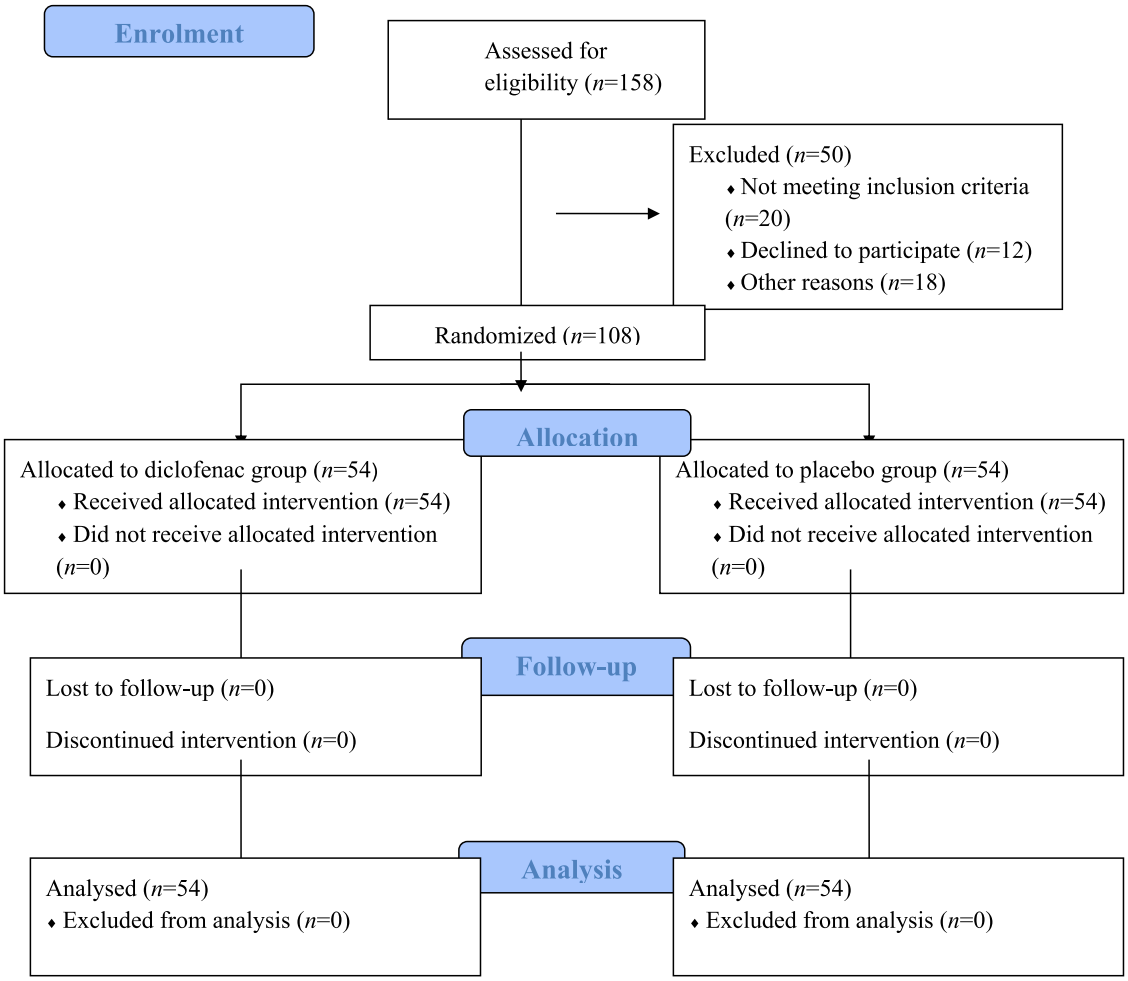

Fig. 1. Flowchart for the study.

5. Discussion

The motivation for this study was that conflicting outcomes have been reported from previous studies that evaluated the use of NSAIDs for relieving postoperative pain following endoscopic procedures. Additionally, literature searches have not identified any publications on the use of rectal diclofenac for relieving postoperative pain following diagnostic hystero-laparoscopy in a Nigerian population. It is therefore noteworthy that this study appears to be the first randomized controlled study in Nigeria involving the use of rectal diclofenac in the control of postoperative pain following dHLD without additional procedures.

This study showed that the use of rectal diclofenac did not reduce postoperative pain significantly following day-case dHLD. Compared with the placebo group, participants in the diclofenac group had lower pain scores, needed less rescue analgesia with pentazocine at first postoperative review, were discharged earlier from hospital, and had higher satisfaction with pain relief; however, these advantages did not reach significance.

This study did not find a significant reduction in the pain scores of participants in the diclofenac group compared with the placebo group throughout the study period. This finding was similar to the results of Crocker and Paech [19], Hovorka et al. [20], Shapiro and Duffy [21], and Windsor et al. [22], which documented a non-significant difference in pain scores between groups that received NSAIDs and placebo. However, the present finding differs from the studies by Gillberg et al. [15] and Van et al. [16], which reported that NSAIDs had better outcomes than placebo in relieving postoperative pain. In a prototype study in the Netherlands by Van et al. [16], rectal naproxen 500 mg was given as premedication to infertile patients undergoing combined outpatient hystero-laparoscopy under general anaesthesia. While Van et al. [16] observed a significant reduction in postoperative pain using rectal naproxen, rectal diclofenac did not reduce postoperative pain following dHLD significantly in comparison with placebo. Hassa et al. [28] were also unable to demonstrate a benefit in pain reduction with the use of 100 mg rectal diclofenac 60 min before outpatient hysteroscopy in a randomized controlled trial in nulliparous infertile women. Similarly, a Cochrane review meta-analysis did not demonstrate any significant reduction with NSAIDs or opioid analgesics during or after the procedure [29]. Nevertheless, the Royal College of Obstetricians and Gynaecologists Green-top Guideline Number 59 advises that women without contraindications should receive a standard dose of NSAIDs 1 h before hysteroscopy to reduce pain in the immediate postoperative period [30]. This may not be the case for patients undergoing dHLD under general anaesthesia, as a 4–6-h fast is usually required before the procedure. A plausible explanation for this peculiar finding could be that the intra-operative analgesics used by the anaesthetist and intramuscular pentazocine given at the end of the procedure may have masked the analgesic effect of rectal diclofenac. Diclofenac and pentazocine administered at the same time will both have a rapid onset of action, with plasma half-lives of approximately 1.2–2 h [31] and approximately 2 h [32], respectively. Whereas pain relief with pentazocine lasts for a maximum of 2–3 h [32], the duration of action of a single dose of diclofenac may be much longer (6–8 h) and may persist in synovial fluid for > 11 h [31,33]. Rectal diclofenac without pentazocine may unmask the analgesic benefits of diclofenac as a possible stand-alone analgesic agent for postoperative pain relief following dHLD.

Table 1
Sociodemographic variables in the diclofenac and placebo groups.

Sociodemographic variable	Total (%)	Group (%)		χ^2-value[a]	*p*-value
		Diclofenac ($n = 54$)	Placebo ($n = 54$)		
Age (years)					
23–28	15 (13.89)	6 (11.1)	9 (16.7)		
29–34	27 (25.00)	11 (20.4)	16 (29.6)		
35–40	49 (45.37)	28 (51.8)	21 (38.9)	3.526	0.474
41–46	16 (14.81)	8 (14.8)	8 (14.8)		
47–52	1 (0.93)	1 (1.8)	0 (0.0)		
BMI (kg/m^2)					
Normal	10 (9.26)	6 (11.1)	4 (7.4)		
Overweight	69 (63.89)	32 (59.3)	37 (68.5)	1.073	0.585
Class 1 obesity	29 (26.85)	16 (29.6)	13 (24.1)		
Parity					
0	69 (63.89)	31 (57.4)	38 (70.4)		
1	21 (19.44)	11 (20.4)	10 (18.5)		
2	12 (11.11)	9 (16.7)	3 (5.6)	3.757	0.440
3	4 (3.70)	2 (3.7)	2 (3.7)		
4	2 (1.85)	1 (1.8)	1 (1.8)		
HIV status					
Negative	104 (96.3)	51 (94.4)	53 (98.2)	1.038	0.308
Positive	4 (3.7)	3 (5.6)	1 (1.8)		
Marital status					
Divorced/separated	1 (0.93)	0	1 (1.8)		
Married	99 (91.67)	50 (92.6)	49 (90.7)	1.010	0.603
Single	8 (7.41)	4 (7.4)	4 (7.4)		
Educational status					
Primary	1 (1.0)	0	1 (1.8)		
Secondary	13 (12.0)	4 (7.4)	9 (16.7)	3.306	0.191
Tertiary	94 (87.0)	50 (92.6)	44 (81.5)		
Occupation					
Artisan	5 (4.63)	3 (5.6)	2 (3.7)		
Business	30 (27.78)	14 (25.9)	16 (29.6)		
Civil servant	38 (35.19)	19 (35.2)	19 (35.2)	1.753	0.781
Professional	22 (20.37)	13 (24.1)	9 (16.7)		
Unemployed	13 (12.04)	5 (9.3)	8 (14.8)		
Ethnicity					
Igbo	101 (93.52)	53 (88.9)	48 (93.5)	3.819	0.051
Non-Igbo	7 (6.48)	1 (11.1)	6 (6.5)		
Place of residence					
Rural	16 (14.81)	7 (13.0)	9 (16.7)	0.293	0.588
Urban	92 (85.19)	47 (87.0)	45 (83.3)		
Total	**108 (100.0)**	**54 (100.0)**	**54 (100.0)**		

BMI, body mass index; HIV, human immunodeficiency virus.
[a] Fisher's exact test was used for smaller groups with frequencies < 5.

This study also revealed that there was no significant difference ($p = 0.678$) in the side effect profile after administration of rectal diclofenac with intramuscular pentazocine following dHLD compared with the control group that received intramuscular pentazocine with rectal placebo. Previous randomized controlled studies comparing various doses and routes of diclofenac with placebo – carried out by Gilberg et al. [15] (50 mg diclofenac given rectally), Wilson et al. [18] (75 mg diclofenac given intramuscularly) and Edwards et al. [34] (75 mg diclofenac given intramuscularly) – found no significant difference in the occurrence of side effects between the two groups. The non-significant side effect profiles (nausea, vomiting and chest pain) seen in the diclofenac group in the present study corroborate with the above randomized studies as well as a non-randomized study by Naz et al. [35], suggesting that the use of rectal diclofenac is safe. Additionally, NSAIDs do not depress the respiratory centre or cause the psychological/physical dependency seen with opioids. Rectal diclofenac is user friendly and most appropriate in women with gastric upset, nausea and vomiting; and for drowsy patients in whom the oral route is prohibited [35], as seen in patients following diagnostic hystero-laparoscopy. This may further justify the use of rectal diclofenac.

In this study, no significant difference in overall patient satisfaction was found after administration of intramuscular pentazocine with rectal diclofenac following dHLD in comparison with the control group receiving intramuscular pentazocine with rectal placebo. Very few studies actually evaluated patient satisfaction with pain relief. As observed by Van et al. [16], participants in the diclofenac group ambulated earlier, had earlier discharge from hospital, and had higher satisfaction with pain relief, but these differences were not significant ($p > 0.05$).

Similar to other studies [15,18,20,34] that used diclofenac (oral, intramuscular and rectal), the present study did not find a significant difference in the need for rescue analgesia and duration of hospital stay between the diclofenac group and the placebo group. In a review article

Table 2
Mean age, weight, height, body mass index (BMI) and duration of procedure in the diclofenac and placebo groups.

Variable	Total mean	Group (mean ± SD)		*t*-value	*p*-value
		Diclofenac ($n = 54$)	Placebo ($n = 54$)		
Age (years)	35.44 ± 5.62	36.37 ± 5.52	34.51 ± 5.62	1.726	0.087
Weight (kg)	80.02 ± 13.99	79.50 ± 14.92	80.53 ± 13.12	-0.380	0.704
Height (m)	1.67 ± 0.08	1.67 ± 0.09	1.68 ± 0.08	-0.454	0.650
BMI (kg/m^2)	28.17 ± 2.55	28.08 ± 2.61	28.27 ± 2.52	-0.372	0.710
Duration of procedure (min)	20.63 ± 7.20	20.79 ± 6.64	20.48 ± 7.78	0.226	0.821

SD, standard deviation.

Table 3
Mann–Whitney *U*-test showing the differences in median postoperative pain scores assessed at different time points in the diclofenac and placebo groups.

Postoperative pain	Diclofenac ($n = 54$) (mean rank score)	Placebo ($n = 54$) (mean rank score)	Mann–Whitney *U*	z-value	*p*-value
4 h post surgery	52.53	56.47	1351.50	-0.664	0.507
6 h post surgery	50.48	58.52	1241.00	-1.360	0.174
8 h post surgery	51.42	57.58	1291.50	-1.045	0.296
10 h post surgery	51.35	57.65	1288.00	-1.070	0.285
12 h post surgery	52.45	56.55	1347.50	-0.699	0.485

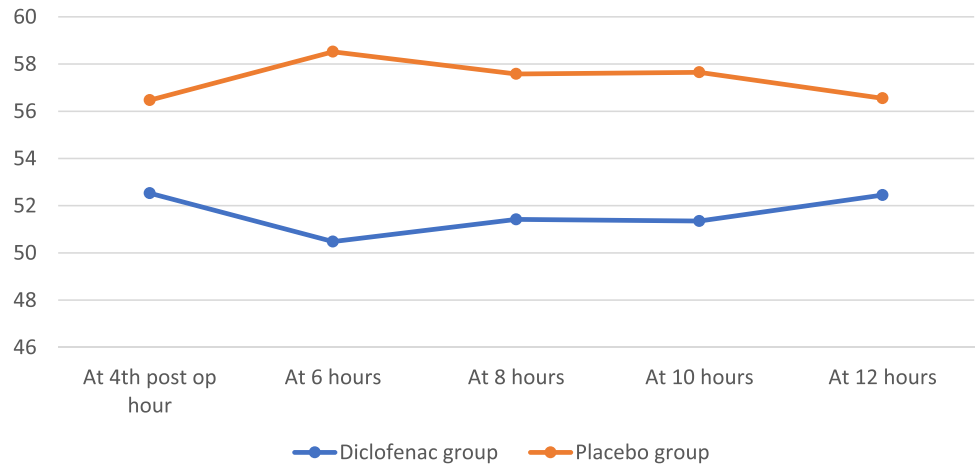

Fig. 2. Line graph comparing the median severity of postoperative pain assessed at 4, 6, 8, 10 and 12 h post surgery.

Table 4
Occurrence of postoperative adverse effects between the diclofenac and placebo groups.

Postoperative adverse effects	Total (%)	Group (%)		χ^2-value[a]	*p*-value
		Diclofenac ($n = 54$)	Placebo ($n = 54$)		
Nausea	16 (14.8)	7 (13)	9 (16.7)		
Chest pain	1 (0.9)	1 (1.8)	0 (0.0)		
Vomiting	16 (14.8)	8 (14.8)	8 (14.8)	3.143	0.678
Nausea, vomiting	1 (0.9)	1 (1.8)	0 (0.0)		
None	74 (68.5)	37 (68.5)	37 (68.5)		

[a] Fisher's exact test was used for smaller groups with frequencies < 5.

Table 5
Overall patient satisfaction between the two modalities in the diclofenac and placebo groups.

Variable	Total (%)	Group (%)		χ^2-value[a]	*p*-value
		Diclofenac ($n = 54$)	Placebo ($n = 54$)		
Satisfaction with pain relief					
Fair	21 (19.4)	10 (18.5)	11 (20.4)		
Good	38 (35.2)	17 (31.5)	21 (38.9)	0.978	0.613
Satisfactory	49 (45.4)	27 (50.0)	22 (40.7)		

[a] Fisher's exact test was used for smaller groups with frequencies < 5

of 20 prospective randomized controlled comparisons of NSAIDs with placebo by Alexander [13], 13 studies showed that NSAIDs were superior to placebo in reducing pain or reducing the requirement for additional analgesia after laparoscopy/laparoscopic procedure, whereas seven studies showed no significant benefit of NSAIDs compared with placebo. This review showed heterogeneity in various NSAIDs used (fenoprofen, indomethacin, ketorolac, naproxen, diclofenac and tenoxicam) and route of administration (oral, rectal, intramuscular and intravenous). Gilberg et al. [15] and Hovorka et al. [20] found that diclofenac was effective for postoperative pain relief for patients that underwent diagnostic laparoscopy, but was not sufficiently potent to reduce pain after laparoscopic tubal ligation. The addition of hysteroscopy may have diminished the expected analgesic effect of diclofenac in

Table 6
Rescue analgesia administered, time and dose administered in the diclofenac and placebo groups.

Variable	Total (%)	Group (%)		χ^2-value[a]	*p*-value
		Diclofenac ($n = 54$)	Placebo ($n = 54$)		
Rescue analgesia administered					
No	91 (84.3)	46 (85.2)	45 (83.3)	0.069	0.792
Yes	17 (15.7)	8 (14.8)	9 (16.7)		
Time ($n = 17$)					
4 h post surgery	11 (64.7)	5 (62.5)	6 (66.7)	1.370	0.713
6 h post surgery	3 (17.6)	2 (25.0)	1 (11.1)		
8 h post surgery	2 (11.7)	1 (12.5)	1 (11.1)		
12 h post surgery	1 (5.9)	0 (0.0)	1 (11.1)		
Dose					
30 mg pentazocine	17 (100.0)	8 (47.1)	9 (52.9)	-	-

[a] Fisher's exact test was used for smaller groups with frequencies < 5

Table 7
Shoulder tip pain and duration of hospital stay in the diclofenac and placebo groups.

Variable	Total (%)	Group (%)		χ^2-value[a]	*p*-value
		Diclofenac ($n = 54$)	Placebo ($n = 54$)		
Shoulder tip pain					
No	86 (79.6)	42 (77.8)	44 (81.5)	0.228	0.633
Yes	22 (20.4)	12 (22.2)	10 (18.5)		
Duration of hospital stay (h)					
4–6	50 (46.3)	29 (53.7)	21 (38.9)		
7–9	55 (50.9)	24 (44.4)	31 (57.4)	2.504	0.286
10–12	3 (2.8)	1 (1.8)	2 (3.7)		
Mean duration (± SD) (h)	6.70 ± 1.2				

SD, standard deviation.
[a] Fisher's exact test was used for smaller groups with frequencies < 5.

the present study, as experienced in the laparoscopic tubal ligation arm [15,20,34], and in patients who underwent outpatient hysteroscopy and endometrial biopsy [34].

Evidence that the use of NSAIDs increases recovery or hospital discharge is not consistent [13]. NSAIDs (diclofenac in this case) appear to be ineffective for shoulder tip pain, as seen in the present study. The occurrence of shoulder tip pain and duration of hospital stay did not differ significantly between the two groups ($p > 0.05$). A similar finding was observed by Crocker and Paech [19]; they reported that more participants had shoulder pain (as seen in the present study) and chest pain in the indomethacin group compared with the placebo group.

The clinical implication of the present study is that optimum postoperative pain relief following dHLD remains an issue of interest to every gynaecologist, with the aim of providing effective and safe analgesia at all times. Several factors definitely contribute to pain associated with dHLD. Despite recent pharmacological advances, effective relief of postoperative pain remains a challenge [36]. Given the complexity and multi-factorial aetiology of postoperative pain, a multi-modal approach in the use of analgesics is preferred, and entails using more than one drug, each with a different mechanism of action, in order to achieve a synergistic and additive effect, reducing the dose of each drug and minimizing associated side effects [3]. Nevertheless, the present study showed that the administration of intramuscular pentazocine alone at the end of dHLD may suffice for postoperative pain relief, and the addition of rectal diclofenac to the analgesic regimen did not show a significant or clinically important reduction in overall postoperative pain.

A strength of this study was its double-blind randomized design, which significantly reduced the detection bias introduced by the outcome assessors, and performance bias introduced by the participants, as seen in previous studies. In this study, rectal diclofenac or rectal placebo was administered in the operating theatre before the participant recovered from general anaesthesia. The study was a placebo-controlled study, so the risk of bias was greatly reduced. The main limitation of this study was the fact that participants did not have to remain in the hospital throughout the study period, as they were counselled and discharged as soon as they recovered fully from anaesthesia. This may have introduced some bias in the pain assessment. Nevertheless, participants were followed-up via telephone calls to obtain the relevant information. Single incision diagnostic laparoscopy was used in this study, whereas many gynaecologists use two or more ports. This would make it difficult to extrapolate the findings of this study to situations where more than one port was used for diagnostic laparoscopy. The use of opioids at the same time as diclofenac may have masked the expected analgesic effect of diclofenac. Several factors may have contributed to the negative findings regarding the efficacy of rectal diclofenac for postoperative pain relief in this study, including the route of administration, sample size, combination therapy with pentazocine, pain assessment tools, patient heterogeneity, and placebo responses. The methodology used for self-description and self-scoring of pain by patients is subject to large variability between individuals. Some patients may find it difficult to translate subjective sensations into numerical scores. The current sample size is small and prone to type II error. The non-significant trend observed may have been associated with an individually significant improvement in postoperative course for several of these individual patients. Further research with consideration of these factors may provide additional insights into the efficacy and safety of diclofenac for pain management in gynaecological endoscopy procedures.

In conclusion, postoperative use of combined rectal diclofenac and intramuscular pentazocine is safe but did not significantly improve pain scores, patient satisfaction, and need for rescue analgesia following dHLD compared with patients who received intramuscular pentazocine and rectal placebo. While a multi-modal approach to pain relief following dHLD does not appear to be significantly beneficial, a multicentre study with a large study population is needed to confirm or refute these findings, and possibly determine if the differences observed could reach significance.

CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare no conflict of interest.

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