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Rectal Indomethacin Versus Rectal Diclofenac Sodium for Reducing Pain Associated with Diagnostic Office Hysteroscopy

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Abstract

Background: Office hysteroscopy is a common surgical procedure but the optimal method of pain reduction is not known.
Objectives: The objective of our study was to study the effect of rectal diclofenac sodium and indomethacin during diagnostic office hysteroscopy.
Methods: This prospective study was conducted in Infertility and Reproductive Endocrinology Department of Istanbul University, Istanbul Faculty of Medicine, between December and March 2018. Indication of office hysteroscopy infertility or recurrent miscarriage which are included in the study. Patients received either 100 mg rectal indomethacin or diclofenac sodium one hour prior to office hysteroscopy. The patients who did not receive any medication formed the control group. End points included measures of pain among 30 patients in each group. Office hysteroscopy is performed. The perception of pain was evaluated for every subject during, immediately after, and 30 min after the office hysteroscopy with the use of the score on a visual analogue scale (VAS). One-way ANOVA test, Kruskal-Wallis test and χ^2 test was performed for statistical analysis P value was < 0.05, the result was considered as statistically significant.
Results: A total of Ninety patients were included in the study. The baseline characteristics of the three study groups were similar, except for mean gravidity. The gravidity was higher in the control group (P = 0.047) but the mean number of parity and number of normal vaginal births, which could affect the pain scores, were comparable between three groups. The duration of hysteroscopy was not statistically different in the study groups (P = 0.555). The study found no statistically significant difference in the pain scores among the groups during, immediately after, and 30 min after the procedure (P = 0.777, P = 0.774, P = 0.618, respectively).
Conclusions: There is no statistically significant beneficial effect of either medication compared with any medication with regard to mean pain scores during and after diagnostic office hysteroscopy.

Keywords: Office Hysteroscopy, Pain, Non-Steroidal Anti-Inflammatory Drugs, Diclofenac Sodium, Indomethacin

1. Background

Hysteroscopy is a common gynecologic procedure for diagnosing intrauterine pathology (1). It can be performed in an outpatient setting; which is called outpatient or office hysteroscopy (2). Office hysteroscopy is indicated for the evaluation of women with abnormal uterine bleeding, infertility, recurrent miscarriage, and removal of lost intrauterine devices. Although the procedure is well tolerated, most patients experience pain (3, 4).

The optimal method of pain reduction during outpatient hysteroscopy is not known. Several agents have been used to reduce pain including rectal, oral or intramuscular nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and local anesthesia. There are few studies in the management of the most effective pain relieve drug with the least possible adverse effects and the suitable method in reducing pain associated with office hysteroscopy (5).

Indomethacin and diclofenac sodium are both non-specific, non-steroidal antiinflammatory agents, which inhibit cyclooxygenase (COXOral NSAIDs cause gastric irritation, nausea, and vomiting. The intramuscular (IM) route can carry some complications such as pain at the injection site, abscess formation, and necrosis (6). In literature, diclofenac has also been associated with streptococcal myositis, necrotizing fasciitis, tissue necrosis and death (7-13). On the other hand, the rectal mucosa has a rich vascular and lymph supply. Drugs are quickly absorbed and the analgesic effect begins more quickly than the oral

route. Additionally, first pass metabolism is avoided in rectal administration (14-22).

Indomethacin and diclofenac sodium have been repeatedly studied for pain reduction during hysteroscopy; however, the rectal route has rarely been studied, even though rectal administration has many advantages. The aim of this study was to evaluate the effectiveness of 100 mg rectal indomethacin and 100 mg rectal diclofenac sodium in reducing pain associated with outpatient diagnostic office hysteroscopy. Secondary measures were adverse effects, complications, failure rate, and procedure time.

2. Methods

This was a prospective study that was conducted over a 4-month period after obtaining approval from the Research Ethics Committee (No: 2017.12.1.03.012.r1.019).

First, the study was explained to the patients and afterwords, they were invited to participate . Ethical approval was obtained, and all patients provided written informed consent. Inclusion criteria were being aged 18 - 45 years and having an indication for office hysteroscopy (infertility or recurrent miscarriage). The exclusion criteria were patients with known cardiac disease, gastritis or peptic ulcer, asthma, acute porphyria, hepatitis, renal failure, women undergoing menopause, and allergy to indomethacin or NSAIDs. Women with a possible pregnancy, lower genital tract infection, and lactating women were also excluded.

The eligible patients were divided into three groups according to the medication that was given. Patients who received 100 mg rectal indomethacin formed group 1, patients who received 100 mg rectal diclofenac sodium comprised group 2, and patients who received no medication constituted group 3. The latter one served as our control group. All patients in groups 1 and 2 received the medication one hour before the procedure. The study ended when 30 patients were included in each group.

2.1. Operation

The procedure was performed in the lithotomy position. The hysteroscope that we used was a 30-degree angle 2.9-mm rigid hysteroscope with 3.8-mm diagnostic sheath [Karl Storz, Germany]. The vaginoscopy approach was used in all cases (the use of speculum and tenaculum was needed in two patients who were excluded from the study). The vaginoscopy approach is defined as gently introducing hysteroscope into the uterine cavity after visualization of the cervix and identification of the external os. The distension medium that was used was saline at roon temperature and the pressure was set at 100 mm Hg. The uterine cavity and tubal ostia were systematically visualized. Patients were informed beforehand that if a uterine lesion was found during officehysteroscopy, treatment would be scheduled for another session.

The patients' perception of pain was assessed for each patient during, immediately after, and 30 min after the procedure with the use of the score on a visual analogue scale (VAS). A VAS score of 0 indicates that the patient has no pain and a score of 10 indicates that the patient experiences the worst possible experienced pain. To assess the pain during the procedure, the operator explained the VAS score to the patient before the operation, and asked the patients for a VAS score three times; the patients gave points that they thought corresponded to their pain. All patients stayed in the clinic for at least 30 min and until all pain disappeared; all patients were pain free before leaving the clinic. Adverse effects were also recorded.

2.2. Statistical Analysis

2.2.1. Sample Size Calculation

To our knowledge this is the first study to investigate the role of rectal indomethacin and rectal diclofenac sodium in reducing office hysteroscopy- associated pain. Therefore we did not have previous data to help calculate the required sample size. We included the first 90 patients because it was a single-center study.

2.2.2. Statistical Tests

Statistical analyses were performed using the IBM SPSS Statistics version 22.0 software. Normal distribution of continuous variables was evaluated using the Shapiro-Wilk test. The one-way ANOVA test was used for normally distributed variables, which are expressed as mean $\pm$ standard deviation. The Kruskal-Wallis test was used for non-normally distributed variables; these are expressed as median (minimum - maximum). The χ^2 test was used to compare categorical variables between the groups, and frequencies and percentiles are given. Statistically significance was defined as P value of < 0.05.

3. Results

Ninety patients were included in the study that were classified into three groups of 30 patients; diclofenac, indomethacin, and no medication (control). There was one patient in each group in whom there was difficulty in passing through the cervical canal. We could not enter the cavity due to cervical stenosis in these patients. One patient in the control group and one patient in the diclofenac group required cervical tenaculum use. These patients were excluded. A total of 85 patients were evaluable in the final analysis.

The baseline characteristics of the three study groups were comparable. There were no significant differences between the groups (except except for mean gravidity. The gravidity was higher in the control group (P = 0.047) but the mean number of parity and number of normal vaginal births, which could affect the pain scores, were comparable between the groups. The duration of hysteroscopy was not statistically different in the study groups (P = 0.555).

The VAS pain scores in the study groups are shown in Table 2. There was no significant difference in the pain scores among the groups during the procedure, immediately after, and 30 min after the procedure (P = 0.777, P = 0.774, P = 0.618, respectively; Table 3).

We experienced one adverse effect and one complication. One patient in the diclofenac group had flushing, itching, and dizziness. One patient in the indomethacin group had a vasovagal reaction; she developed bradycardia, hypotension, dizziness, faintness, and sweating.

4. Discussion

The objective of this prospective study was to determine pain during and after office hysteroscopy, according to the use of rectal indomethacin and rectal diclofenac sodium compared with controls. To the best of our knowledge, there are no previous reports in the literature prospectively comparing rectal indomethacin and rectal diclofenac sodium with a control group for pain management during office hysteroscopy. We found no statistically significant beneficial effect of either medication compared with no medication with regard to mean pain scores during the procedure, immediately after, and 30 min after the procedure. The groups were also comparable in terms of procedure time.

Several randomized controlled trials studied the use of several analgesics before hysteroscopy to reduce the pain associated with the procedure. To our knowledge, five trials studied the use of NSAIDs (14-18). Nagele et al. Tam and Yuen, and Issat et al. compared NSAIDs with placebo (15, 16, 18). Nagele et al. performed a double-blind, placebo-controlled trial with 95 patients and found that when 500 mg mefenamic acid was given one hour before hysteroscopy, it had no significant benefit in the discomfort experienced during the procedure but significantly reduced pain after hysteroscopy (15). The authors concluded that this finding was in agreement with the known post-operative analgesic benefits of prostaglandin synthesis inhibitors (16). Tam and Yuen published a randomized, double-blind, placebo-controlled trial about the efficacy and safety of oral diclofenac sodium in outpatient hysteroscopy and endometrial biopsy (17). They gave 50 mg diclofenac sodium tablets and found that pain scores did not differ significantly between the diclofenac sodium and placebo groups, neither were there any beneficial effects 30 minutes after the procedure. More recently, Issat et al. performed a placebo-controlled study to assess the efficacy of I.V. ketoprofen versus intravaginal misoprostol for pain relief during outpatient hysteroscopy (18). They found that 400 μg vaginal misoprostol 4 hour before the procedure was beneficial in reducing pain but their ketoprofen group's VAS score was comparable with that of the placebo group (18). Our data are consistent with all these data; we found no beneficial effects with either indomethacin and diclofenac sodium in reducing pain during office hysteroscopy.

Even though our study found no difference in pain scores between patients using NSAIDs and those with no medication, NSAIDs are a majorcomponent of simple 'low-technology' pharmacologic control of acute and chronic pain. They can be given by intravenous, intramuscular, rectal and oral routes for postoperative pain. Medications administered per rectum (PR) work for both local or systemic treatment, as the rectal mucosa has a blood and lymph supply that is capable of effective systemic absorption. On the other hand, the rectum is underused as a route for safe administration of drugs. The reason is probably the intimacy of the site compared with more frequently used routes, such as oral or intravenous/intramuscular injection. Rectal administration has several advantages, though. Drugs administered PR have a faster action than via the oral route and a higher bio-availability. Rectal administration also reduces adverse effects such as gastric irritation, nausea, and vomiting. There is no need for a I.V. catheterization, and the risks of IM injections are also excluded. For all these reasons, we investigated rectal NSAIDs in the management of pain caused by office hysteroscopy (19-23).

The strength of our study is its prospective nature and the existence of a control group. The limitations of our study include the fact that it was not a randomized, placebo-controlled study, and that all results were based on the subjective perception of pain. The low number of patients in the 3 groups can also be evaluated as a limitation of the current study. Additionally, we did not test different doses and times of administration; 100 mg rectal NSAIDs one hour before the operation may not be the optimal administration.

In conclusion, we were unable to demonstrate a benefit in pain reduction with use of rectal diclofenac sodium and indomethacin one hour before outpatient hysteroscopy. This finding is in accordance with previous studies; future research should study new drugs to decrease the pain perception during office hysteroscopy rather than studying different routes or doses of NSAIDs.

Table 1. Baseline Characteristics, Hysteroscopy Indications of the Groups[a]

	Groups			P Value
	Indomethacine (n = 29)	Diclofenac Sodium (n = 27)	No Medication (n = 27)	
Age (years)	29.43 ± 5.12	29.04 ± 5.92	32.14 ±5.14	0.073[b]
Body mass index (kg/m^2)	23.63 ± 3.24	24.89 ± 3.42	25.60 ± 3.41	0.139[b]
Gravida	1 (0 - 4)	0 (0 - 4)	2 (0 - 5)	0.047[c]
Parity	0 (0 - 3)	0 (0 - 2)	0 (0 - 3)	0.355[c]
Vaginal delivery	0 (0 - 3)	0 (0 - 1)	0 (0 - 2)	0.676[c]
Duration of the procedure (minutes)	1 (0.5 - 4)	1 (1 - 20)	1 (0.5 - 10)	0.555[c]
Indication				0.109[d]
Infertility	21 (75)	22 (81.5)	17 (65.4)	
Recurrent abortion	7 (25)	5 (18.5)	6 (23.1)	
Both	0	0	3 (11.5)	

[a] Age and body mass index are presented as mean ± SD. Gravida, parity, number of vaginal deliveries and duration of operation are presented as medians (minimum - maximum). Indications are presented as frequencies and percentages.
[b] One-way ANOVA.
[c] Kruskal-Wallis.
[d] χ^2 test.

Table 2. Pain Scores in the Indomethacin, Diclofenac Sodium and Control Groups[a]

	Groups		
	Indomethacine	Diclofenac Sodium	No Medication
Pain during the op.	5.33 ± 3.57	4.82 ± 2.99	4.91 ± 2.79
Pain within 30 min after the op.	1.83 ± 2.54	1.32 ± 1.90	1.61 ± 2.10
Pain 30 min after the op.	0.71 ± 1.50	0.29 ± 0.58	0.64 ± 1.45

Abbreviation: Op, operation.
[a] Data are presented as mean ± SD.

Table 3. Comparison Between Pain Scores in the Indomethacin, Diclofenac Sodium and Control Groups[a]

	Groups			P Value[b]
	Indomethacin	Diclofenac Sodium	No Medication	
Pain during the op.	5 (0 - 10)	4.5 (1 - 10)	5 (0 - 10)	0.777
Pain within 30 min after the op.	0 (0 - 8)	0 (0 - 5.5)	1 (0 - 7)	0.774
Pain 30 min after the op.	0 (0 - 6)	0 (0 - 2)	0 (0 - 7)	0.618

[a] Data are presented as medians (minimum - maximum).
[b] Kruskal Wallis

Footnote

Conflict of Interests: All authors declare no conflicts of interest.

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