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Research Article

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Preemptive Analgesia In Diagnostic Hysteroscopy

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Abstract

Objective: *To evaluate the preemptive analgesic effect of rofecoxib during the performance of a diagnostic hysteroscopy.*

Methods: *Randomized double-blind placebo-controlled trial. 55 patients were studied; 27 took rofecoxib and 28 took a placebo two hours before the beginning of the procedure.*
The instrument used to measure pain was a numeric scale from zero to ten, with zero representing "no pain" and ten representing "the worst possible pain." The patient selected a number to describe the intensity of the pain at five points: before the procedure, during the passing of the hysteroscope through the internal orifice of the cervix, at the distension of the uterine cavity, during the biopsy and at the moment of discharge. The ANOVA (F-test) and the Mann Whitney U-test were used. Statistical significance was set at 5% ($p < 0.05$).

Results: *The results demonstrated that there was no statistically significant difference between the groups at the five evaluated phases when analyzed as a set ($F = 1,477$; $p > 0,231$). During the passage of the instrument through the internal orifice of the cervix, the median score given by the patients was 3 in the rofecoxib group and 5 in the control group, with 50% of the ratings distributed among the lower and upper quartiles (3-5 in the rofecoxib group and 3.5-6.5 in the control group). However, there was a statistically significant difference among patients in the rofecoxib group at the moment of "passage of the instrument through the internal orifice of the cervix" ($p = 0.004$), as well as in pre-menopausal patients ($p = 0.002$) and those who had normal delivery ($p = 0.004$).*

Conclusions: *The use of 50 mg of rofecoxib was not superior to placebo in the alleviation of pain during diagnostic hysteroscopy. Nevertheless, rofecoxib was superior to placebo for pain reduction at the moment of passing the hysteroscope through the cervix for normal delivery and pre-menopausal patients.*

Keywords: Diagnostic Hysteroscopy, Pain Control, Rofecoxib.

1. Introduction

The use of analgesics before the beginning of nociceptive stimuli is a new clinical concept in the treatment of sharp pain, called preemptive analgesia. With the objective of preventing the central and peripheral sensitization which occurs in response to painful stimuli, avoiding chronic pain [1-3].

Diagnostic hysteroscopy is a valuable tool for the visual examination of the endocervical canal and the uterine cavity and is recommended for investigation of the principal causes of abnormal uterine bleeding, the diagnosis and follow-up of hyperplasias, the diagnosis and follow-up of trophoblastic disease, determining the need of and controlling uterine surgery, Müllerian alterations, amenorrhea, sterility and the location of foreign bodies [4-7]. The use of the hysteroscope in the clinic or doctor's office substitutes procedures of higher risk and cost, that is, it has an important role in avoiding hospital stays, "blind" uterine curetting in patients without alterations in the uterine cavity [8-11].

Yang e Vollenhoven relate that the principal complaint of patients submitted to outpatient diagnostic hysteroscopy is the pain and is also the most common reason in the failure to carry out this exam

[4,5,7,12].

Various methods of systemic analgesia and local anesthesia have been tested in an attempt to reduce the discomfort associated with outpatient diagnostic hysteroscopy, nevertheless, with controversial results. Downes and Al-Azzawi used a point system (1 to 10) to evaluate the acceptability of outpatient hysteroscopy [7,13]. In another study, lidocaine (1%) with adrenaline was injected into the cervix and did not prove to be superior to placebo. No technique of local anesthesia has been convincingly effective [5,14-17].

The analgesic rofecoxib was suspended from the market in September 2004 because of side effects when prescribed for chronic pain. It was a selective inhibitor of the enzyme cyclooxygenase-2 (COX-2), offering relief of acute pain, similar to other analgesics of the AINE group which do not inhibit the enzyme cyclooxygenase-1 (COX-1) which is responsible for physiological functions. Besides this, it did not compromise platelet aggregation, did not cause gastric toxicity, physical or psychological dependency, respiratory depression, and, consequentially, presented a low index of complications in the treatment of acute pain [18,19]. Its analgesic efficacy was observed in several clinical models of acute pain: after dental surgery, after orthopedic surgery and during primary dysmenorrhea [19,20]. Bracco et al. observed the beginning of analgesia within 31 minutes after dental surgery, with a single dose of 50mg of rofecoxib and Ehrich et al. in 45 minutes [21,22]. The recommended dose for the treatment of acute pain was 50mg by mouth with an analgesic effect of 24 h [20].

There exists no direct and objective way to evaluate with precision the intensity of pain. Nevertheless, in order to interpret the intensity of pain for each patient, there exist some instruments by which such a subjective thing can be tentatively measured. A numeric gradation is simple and the most widely used tool. On a scale of zero to ten, with zero representing “no pain” and ten corresponding to “the worst possible pain,” the patient selects a number to describe the intensity of her pain [23].

The objective of this study was to evaluate the efficacy of rofecoxib in the reduction of intensity of pain during diagnostic hysteroscopy or in its various phases and to evaluate the intensity of the pain.

2. Methods

Between January 30th, 2003 and January 29th, 2004, patients cared for in one of the clinics of diagnostic hysteroscopy at the Hospital de Base do Distrito Federal were evaluated by means of a questionnaire created for this study, which gathered the following information:

a) personal data (name. phone number, address, date of birth);

b) verification of eligibility, that is, screening for criteria of inclusion (abnormal uterine bleeding, foreign bodies, secondary amenorrhea, suspicions of sterility, altered ultrasound, asymptomatic illness and Müllerian alterations);

c) screening for criteria of exclusion (current pregnancy, pelvic infection, heavy uterine bleeding, uterine perforation, cervical cancer, advanced renal insufficiency, sensitivity to rofecoxib, current use of analgesics and unsatisfactory hysteroscopies); menstrual history; number of normal deliveries, surgical deliveries and miscarriages; current medications- hormonal and non-hormonal.

Sixty patients were randomly selected and allotted numbers. The numbers were set in a randomly ordered chart anonymity was guaranteed by means of sealed envelopes. Five hysteroscopies were unsatisfactory, so there remained 55 patients: 27 in the rofecoxib group and 28 in the control group. Seven other patients did not sign the terms of consent and, thus, did not participate in the study; nevertheless, they still received diagnostic hysteroscopy.

After explaining the use of the numeric scale, the patient was asked about the greatest pain felt in her life and which number she would assign to it (0-10), her expectations about the pain she would feel during the hysteroscopy procedure (0-10), and then that she would be assigning a number (0-10) to her pain during these steps of the procedure: the passing of the hysteroscope through the internal orifice of the cervix, the distension of the uterus with CO2, the biopsy (first fragment), and upon discharge (30 minutes after the procedure in the waiting room). Also registered were any complications, the findings of the hysteroscopic procedure, the lab report and the anatomopathological results.

With the patient in lithotomy position, a bimanual exam was carried out to evaluate the size and position of the uterus. The insertion of the speculum followed in order to expose the cervix for antiseptic treatment with povidone.

The procedure was initiated by inserting a rigid hysteroscope, 2.9 mm in diameter, with a hysteroscopic sheath of 3.7mm and STORZ (Tuttlingen, Germany) optics at a 30° angle into the external orifice of the cervix. The uterine cavity was distended with a CO2 infusion via a STORZ (Tuttlingen, Germany) hysteroflator with a flux of 50 ml/min and 75 mmHg pressure.

The exam was based on the panoramic vision of the uterine cavity, uterine horns, the orifices of the fallopian tubes, the point of view of the endometrial glands and the endocervical canal. The total time of the procedure was chronometrically measured from the introduction of the hysteroscope into the external orifice of the cervix until the removal of the apparatus. The final step consisted of carrying out a biopsy with 3.5 mm Citelli Rongeur forceps.

During the procedure, the patient was asked to rate the intensity of the pain in the five phases of the exam mentioned above. The frequency distribution of the diagnostic hysteroscopy indications showed that the most prominent was altered ultrasound, with abnormal uterine bleeding or not, in 81.4% of the patients in

the rofecoxib group and 89.2% in the control group. The most common hysteroscopic finding in the two groups was functional endometriosis, that is, that the uterine cavity had no organic alteration. After this, atrophic endometriosis, polyps, diffuse endometrial thickening and submucous myomas in the rofecoxib group. The second most common finding in the control group was endometrial polyps, followed by diffuse endometrial thickening and atrophic endometriosis.

The study was approved by the Research Ethics Commission of the Universidade de Brasília, according to Brazilian law. Informed consent forms were signed by all patients.

3. Statistical Analysis

The authors expected that pain would be reduced by 50%, and this was estimated by a total sample size of 60, with a power of 80% and type 1 error of 0.005.

Seeing that the numeric scale results did not follow the presuppositions of normality (Shapiro-Wilk test), the descriptive analysis was presented by means of Box plot –median, quartiles, maximum and minimum values and outliers.

In order to verify the perceptual difference of pain among the groups for each phase (expectation, internal orifice, distention, biopsy and discharge), the ANOVA test was used. The Greenhouse-Geisser Epsolon test was used to make adjustments to the degrees of freedom when the presuppositions of sphericity were not found.

Of specific interest, the internal orifice phase was investigated separately from the other phases by means of the Mann-Whitney U test.

In order to compare the differences of pain perception between the pre- and post-menopausal participants, as well as between those having had normal and non-normal deliveries, the Mann-Whitney U test was also used. Statistical significance was set at 5% ($p< 0.05$). To analyze the data, the Statistical Package for the Social Sciences (SPSS) version 11.5 for Windows was used.

4. Results

The mean age of the patients studied was 45.1 years for the rofecoxib group and 41.5 for the placebo group, 25.9% and 17.8%, respectively, were post-menopausal and 11.1% and 10.7%, respectively, were nulliparae.

As to type of delivery among the patients studied, 74.0% had given birth normally in the rofecoxib group, compared to 78.5% in the control group. There were no significant differences between the two groups regarding the duration of the diagnostic hysteroscopy (Table 1).

Caracteristics	*Rofecoxib n = 27*	*Control n = 28*
Age (years; extremes)	45.1 (32-60)	41.5 (24-65)
Hormonal state, n (%) Pre-menopause Post-menopause	 20 (74.0) 7 (25.9)	 23 (81.1) 5 (17.8)
Delivery method, n (%) Normal Non-normal	 20 (74.0) 7 (25.9)	 22 (78.5) 6 (21.4)
Duration of hysteroscopy (average)	2’39”	2’44”

Table 1. Caracteristics of patients and procedure in rofecoxib and control groups.

As far as the worst pain previously felt by the patients, 62.9% of the rofecoxib group reported labor pain, followed by biliary colic, at 7.4%. In the control group, 53.5% reported labor pains, with caesarian post-operative in second place, at 14.2% (Table 2).

Worst pain felt	*Rofecoxib*		*Controle*	
	n	*%*	*n*	*%*
Labor	17	62.9	15	53.5
Post-operative Cesarean	1	3.7	4	14.2
Renal colic	1	3.7	2	7.1
Biliary colic	2	7.4	1	3.5
Dysmenorrhea	2	7.4	1	3.5
Toothache	1	3.7	2	7.1
Head trauma	1	3.7	0	0

Puerperal infection	1	3.7	0	0
Hysterosonography	1	3.7	1	3.5
Earache	0	0	1	3.5
Miscarriage	0	0	1	3.5
Total	27	100	28	100

Table 2. The worst previous pain felt by the patient.

Study phases	Rofecoxib	Placebo
Patient expectations	5 (4-7)	5 (4.2-7.7)
Moment of internal orifice	3 (1.5-4.5)	5 (3.2-6.7)
Moment of distention of the uterine cavity	2 (1-4)	2,5 (1.2-4.7)
During the biopsy	5 (3-8)	6 (5-8)
Upon discharge	1 (1-2)	1 (1-2)

Table 3. Median and interquartile amplitude of the values of the numeric scale, in centimeters, of the groups treated with rofecoxib (n=27) and placebo (n=28), in the five phases of the study.

In table 3, it is of interest that, between the 25th and the 75th percentiles, the distribution of the ratings was similar in the following phases: expectations of pain, distention of the uterine cavity, performance of the biopsy and discharge. Of the numeric ratings given by the patients, the median was 5 for expectation of pain in both groups; in the distention phase it was 2 in the rofecoxib group and 2.5 in the control group; in the biopsy phase, it was 5 in the rofecoxib group and 6 in the control group, and in the discharge phase it was 1 for both groups.

Nevertheless, the same did not occur in the internal orifice of the cervix phase. The median was 3 in the rofecoxib group and 5 in the control group, with 50% of the patient ratings distributed among the inferior and superior quartiles; in the rofecoxib group they were between 3 and 5 and in the control group between 3.5 and 6.5.

Thus, the results obtained in the descriptive analysis of the values of the numeric scale (in centimeters) for the rofecoxib and control groups, in the five phases of the study, when analyzed as a set, showed that there was no statistically significant difference between the groups (sphericity test $p > 0.801$; $F = 1.477$; $p > 0.231$). Nevertheless, considering separately the internal orifice of the cervix phase , a statistically significant difference was encountered in favor of the rofecoxib group ($p = 0.004$) (Figure 1).

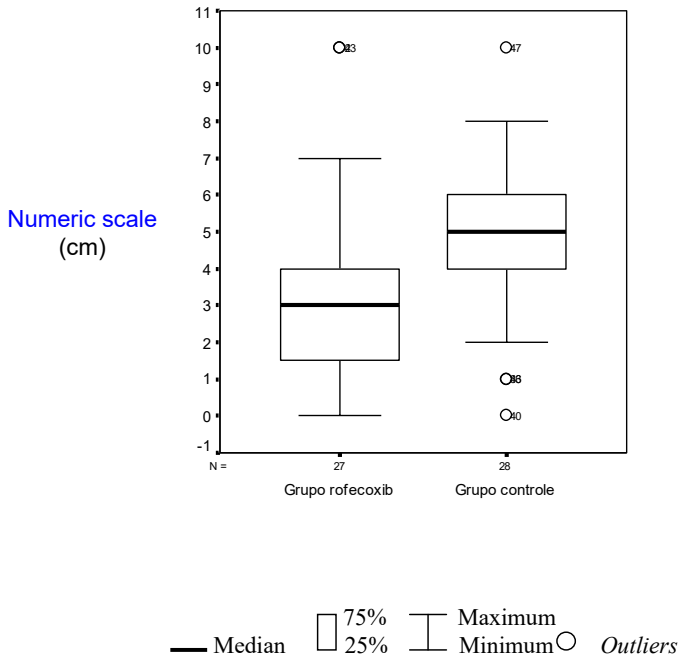

Figure 1. Descriptive analysis of the values of the numeric scale, in centimeters, of the participants of the rofecoxib and control groups in the *internal orifice* phase of the hysteroscopy.

In Figure 2, in the internal orifice phase, of the pre-menopausal participants, the median was 3 in the rofecoxib group and 5 in the control group. The ratings given by the patients, distributed among the inferior and superior quartiles were between 1 and 4 in the rofecoxib group and between 3.5 and 6 in the control group; in the descriptive analysis, as well, a statistically significant difference in favor of pre-menopausal patients in the rofecoxib group was found (p = 0.002).

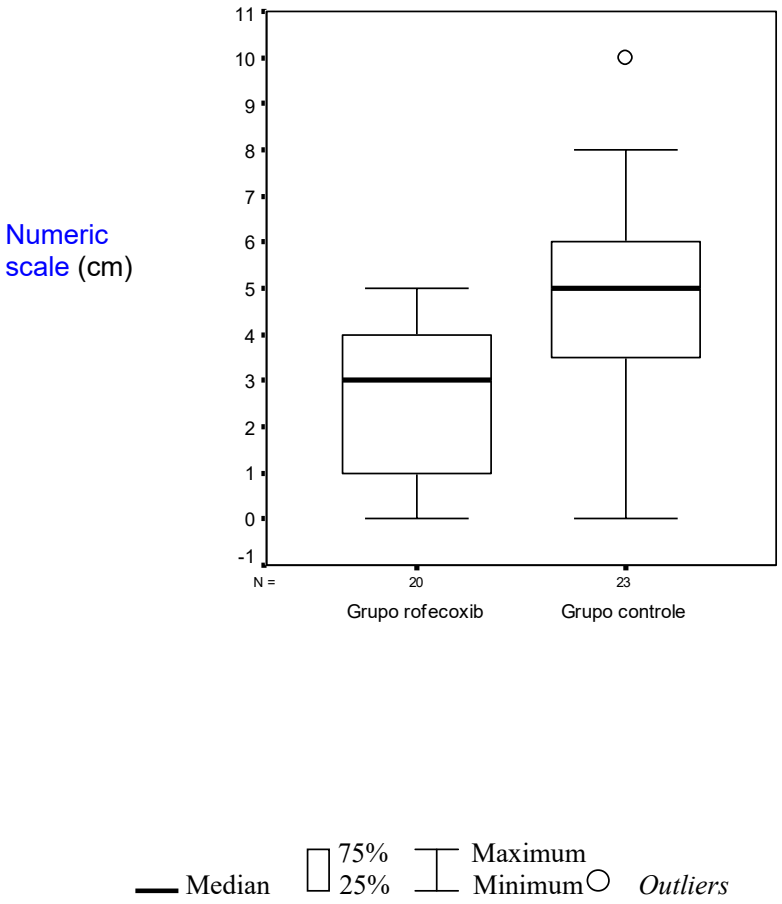

Figure 2. Descriptive analysis of the values of the numeric scale, in centimeters, of the premenopausal participants (rofecoxib versus control) in the *internal orifice* phase.

Nevertheless, there was no statistically significant difference between the participants in menopause compared to the other groups (rofecoxib e controle) (p = 0.561).

A statistically significant difference for the internal orifice phase was encountered in the descriptive analysis of the values of the numeric scale (in cm) in favor of the participants of the rofecoxib group who had had normal deliveries (p = 0.004), with 50% of the ratings between 4 and 6 with a median of 5. Consequently, no statistically significant difference was found among the two study groups for those who had not had normal deliveries (p = 0.628) (Figure 3).

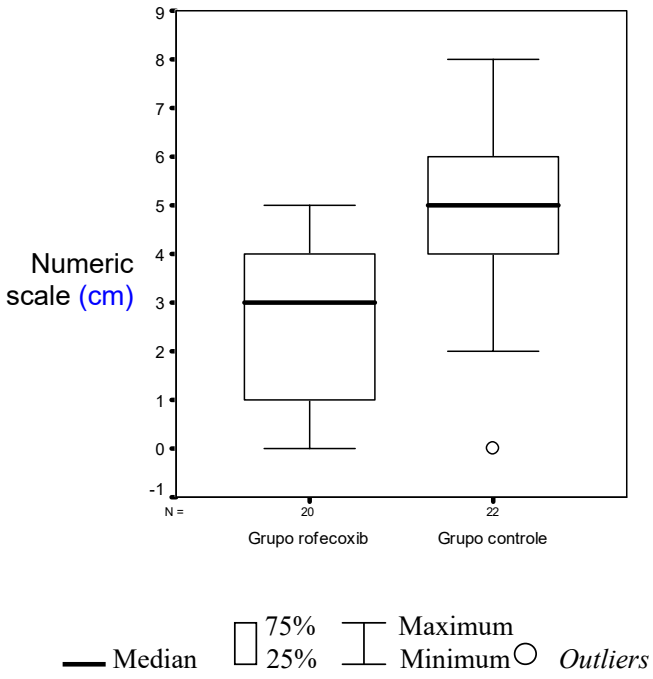

Figura 3. Box Plot of the values of the numeric scale, in centimeters, of normal delivery participants (rofecoxib versus controle),in the internal orifice phase.

5. Discussion

The purpose of this study was to evaluate the analgesic effect of rofecoxib during diagnostic hysteroscopy, with the intention of reducing pain caused by the exam. The consequences of untreated or inadequately treated pain manifest themselves psychosomatically throughout the principal systems of the organism. From an emotional point of view, pain provokes insomnia, anxiety, irritability, and the patient may become depressed. The release of catecholamines leads to tachycardia, as well as an increase in systolic volume, cardiac work, and consumption of oxygen. It can prolong patient stay in the hospital or delay the patient's return to normal activities, and, consequently, bring about negative economic repercussions [23].

The pain caused by similar injuries is experienced differently by each person. The plasticity related to pain represents persistent functional alteration or somatic memory produced in the organism by damage or other pathological events. The neuronal complexity and plasticity of pain involve physiological mediators, such as the cause and degree of the lesion, as well as psychosocial factors of a situational class (expectations, relevance and control of the situation), an emotional class (stress, coping style, fear and frustration), and a personal class (previous history of pain, cognitive and cultural level) [24].

The worst pain previously felt by the patients in the present investigation was labor pain in 62.9% of the rofecoxib group and 53.5% of the control group. All of the patients in the study had had significant pain-related experiences in the past. They were questioned about their previous pains in order to refresh their memories for a clearer comparison to the diagnostic hysteroscopy. Seeing that both groups had previous histories of intense pain in the same proportions, this factor did not influence the results of the study.

The use of analgesics before beginning nociceptive stimuli is a new clinical concept in the treatment of sharp pain, called preemptive analgesia. Its objective is to prevent central and peripheral sensitivity which occurs in response to painful stimuli, while leaving intact the physiological response to pain, avoiding chronic pain [25]. The selective inhibitors of COX-2 have shown efficacy and safety in the alleviation of post-operative pain (sharp) as preemptive analgesia [20].

The means of distention used in this study also did not influence the intensity of the pain experienced by the patients. Litta et al., in evaluating the discomfort causes in patients after diagnostic hysteroscopy with CO2 or with saline solution, using a visual analogical scale (0 = no pain; 100 = worst pain imaginable), recorded that of a total of 415 patients (CO2, n = 201; saline solution, n = 214), after hysteroscopy, pelvic discomfort was greater in nulliparae (pain index 39.0 ± 26.5) than in (especially premenopausal) multiparae (30.4 ± 25.9) [26].

For all patients, pelvic discomfort was generally minimal, nevertheless it was greater for those in whom saline been used, compared to CO2. In this study CO2 was used to distend the uterine cavity, however the means of distention did not contribute

to any abnormal pain increase in the patients.

The descriptive analysis of the values of the numeric scale (in cm) of rofecoxib and control groups, in the five phases of the study, demonstrated that there was no statistically significant difference between the two groups when analyzed as a set (sphericity test $p > 0.801$; $F = 1.477$; $p > 0.231$).

In a similar study of 92 patients using 50 mg of sodium diclophenate and a placebo, the index of pain intensity (for 89 of them) upon insertion of the hysteroscope was 4.3 ± 3.0 and 3.6 ± 2.7, during the exam 3.0 ± 2.5 and 3.0 ± 2.9, in the biopsy 4.3 ± 3.0 and 4.8 ± 3.2 upon discharge 1.1 ± 1.3 e 1.2 ± 1.7, in the diclophenate and control groups, respectively. In this study the biopsy was the most painful phase of the exam for both groups. Thus, these researchers did not encounter any beneficial effect of sodium diclophenate for pain relief in any phase of the hysteroscopy, including the biopsy [5].

Other researchers, analyzing 60 patients randomized in three groups, with the objective of investigating the analgesic effects of 50 mg of rofecoxib taken orally one hour before performing outpatient arthroscopy, compared them to patients who received 50 mg of rofecoxib orally after the procedure and to patients who received a placebo. The results demonstrated that the use of rofecoxib one hour before surgery resulted in lower indices of pain than in the other two groups [27].

Several studies using local intra-uterine transcervical anesthesia, paracervical blockage, lidocaine spray and lidocaine gel found that each of these was ineffective in pain reduction in the performance of endometrial biopsy- the part of the exam frequently considered to be the most painful [7,11,12,28].

De Iaco et al. demonstrated that 34.8% of patients submitted to diagnostic hysteroscopy experienced intense pain, even when performed with atraumatic techniques and by experienced surgeons [29]. The biopsy is considered the most painful part of the exam in the majority of studies, being compatible with the results of our investigation. Non-steroid anti-inflammatories are not effective in the treatment of intense pain, unless associated with an opiate [30].

The present study demonstrated that, at the moment of passing the hysteroscope through the internal orifice of the cervix, a statistically significant difference was found the descriptive analysis in favor of premenopausal patients in the rofecoxib group ($p = 0.002$), which is to say that hormonal state influences the intensity of pain. Postmenopausal patients, because of the hypoestrogen state, have genital atrophy, which could explain why among these participants in both groups no statistically significant difference was found ($p = 0.561$).

Upon comparing the patients who had undergone normal delivery with those who had not, the authors encountered a statistically significant difference in the internal orifice of the cervix. These patients experienced less pain than those in the control group who had the same characteristics.

During the biopsy phase, 66.6% of patients in the rofecoxib group and 89.2% of patients in the control group experienced moderate to intense pain, which is compatible with the majority of studies, where this was found to be the most painful phase.

The principal disadvantage of the numeric scale is the supposition that pain is a unidimensional experience. Though the intensity of pain is an important dimension, the word “pain” clearly refers to an interminable variety of attributes [24].

This study allows the conclusion that, in spite of being useful as a preemptive analgesic while passing the hysteroscope through the internal orifice of the cervix, no statistically significant difference was encountered between the two groups during the five phases of the exam when studied as a set.

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