RESEARCH ARTICLE

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The Efficacy of Oral Etoricoxib in Pain Control During Colposcopy-Directed Cervical Biopsy: A Randomized Control Trial

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Abstract

Objective: To investigate the effectiveness and safety of oral etoricoxib administration before colposcopic procedure for pain relief during and after colposcopy. **Methods:** A prospective double-blind, randomized controlled trial was conducted at the colposcopy unit of Thammasat University Hospital, Thailand from August 2022 to January 2023. The participants were women undergoing colposcopy. They were allocated into two groups: etoricoxib group and control group. Thirty minutes prior to colposcopy, the participants received etoricoxib or placebo tablet. A numerical rating scale was used to evaluate pain upon speculum insertion, 3% acetic acid application, directed cervical biopsy (CDB), endocervical curettage (ECC), and 10 minutes and 24 hours after colposcopy. **Result:** One hundred and ten women were recruited and were divided equally into study and control groups. The mean age of participants was 42.6 years old. One-fourth of cases (29/110) had cervical intraepithelial neoplasia grade 2 or more histology. Subjects in etoricoxib group had less median pain scores during CDB, ECC, and 10-minute and 24-hour post procedure than the control group with statistical significance. Both groups had comparable side effects. **Conclusion:** Administration of oral etoricoxib 30 minutes before colposcopy could reduce pain during and up to 24-hour post colposcopy with minimal side effects.

Keywords: Colposcopy- pain score- etoricoxib- side effect

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Introduction

Colposcopy is a standard procedure following abnormal cervical cancer screening. All steps of procedure especially colposcopic directed biopsy (CDB) and endocervical curettage (ECC) made pelvic discomfort, pelvic pain, and anxiety (Darweesh et al., 2020; Wittenborn et al., 2022).

The pain sensation of cervix is innervated by the superior hypogastric plexus. During colposcopy, CDB and ECC are performed for histopathological study. Pain from the procedure is usually classified as mild to moderate pain (Michail et al., 2021). Pain relief methods can be divided into two groups: non-pharmacological and pharmacological methods. The non-pharmacological methods include forced coughing, listening to music as well as video during colposcopy. However, inconclusive outcomes were reported (Karaman et al., 2019; Hecken et al., 2022). The pharmacological methods include administration of local anesthesia agents such as lidocaine spray (Wongluecha et al., 2017; Karaman et al., 2019), prilocaine intracervical injection (Kiviharju et al., 2017) and oral analgesic drugs ibuprofen (Church et al., 2001) and tramadol (Darweesh et al., 2020). The outcomes of pharmacological methods varied in effectiveness to reduce pain during and after colposcopy.

Systematic reviews reported that local cervical anesthesia administration has no statistically significant outcomes in pelvic pain reduction during colposcopy (Mattar et al., 2019). Whereas some oral analgesias were found to significantly decrease pain (Darweesh et al., 2020). So, low-potency oral analgesia should be offered for pain reduction, while high-potency analgesias such as meperidine or morphine may not be recommended. Oral nonsteroidal anti-inflammatory drug (NSAIDs) such as ibuprofen has been reported to provide no statistical significance in pain reduction from colposcopy when compared to a placebo (Church et al., 2001). Meanwhile, oral tramadol which is a low-potency synthetic opioid showed significant pain reduction from colposcopy. Nevertheless, side effects from tramadol including nausea,

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vomiting, and dizziness were reported (Darweesh et al., 2020).

Cyclooxygenase-2 (COX-2) is an enzyme induced by proinflammatory stimuli and has been mentioned to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. Selective COX-2 inhibitor works preferentially and has fewer gastrointestinal (GI) adverse effects compared to tramadol. Etoricoxib is an oral selective COX-2 inhibitor. The onset of action and duration were approximately 25 min and 20 hours, respectively (Moore RA et al., 2015). The advantages of etoricoxib include its oral route of administration, easy application, long duration, and reduction in upper GI tract risk of harm rate ratio by approximately 0.54-0.7 compared to non-selective COX inhibitor (Walker C, 2018).

The aim of this study was to investigate the effectiveness and safety of oral etoricoxib administration before colposcopic procedure for pain relief during and after colposcopy.

Materials and Methods

We conducted a prospective double-blind, randomized controlled trial at the colposcopy unit of Thammasat University Hospital, Thailand. This study was approved by the human research ethics committee of Thammasat University (MTU-EC-OB-1-342/64) and registered at the Thai Clinical Trials Registry (TCTR20220712004).

Recruited participants were patients who had estimated immediate or 5-year cumulative cervical intraepithelial neoplasia grade 3 or higher (CIN3+) risk of equal and more than 4 or 5 %, respectively according to 2019 ASCCP management guidelines (Perkins RB et al., 2020). Exclusion criteria were pregnancy or breastfeeding, previous pelvic radiation, history of painkiller usage within 24 hours, and contraindication to etoricoxib (severe hepatic and renal impairment, peptic ulcer, upper GI bleeding, colitis, heart failure, uncontrolled hypertension, cardiovascular disease, on anticoagulants and oral contraceptive pills). After written informed consent, all participants were divided into two groups. The study and control groups were administrated orally 90-mg etoricoxib or a placebo tablet 30 minutes prior to colposcopy, respectively. The random numbers were computerized and generated by a box of four patterns. Etoricoxib and a placebo of the same appearance were put into sealed, plastic with sequential serial numbers by a nursing officer. The participants were asked to blindly select either etoricoxib or placebo tablet. The colposcopic procedure was performed by two gynecologic oncology fellows under the supervision of certified colposcopy experts. The physicians, nursing officers, and researchers were also blinded to subject allocation.

Pain scores were evaluated at baseline (before etoricoxib or placebo administration), during the procedure (speculum insertion, 3% acetic acid application, CDB, and ECC), and post-procedure (after the procedure at 10 minutes and 24 hours). The severity of pain was recorded by a numerical rating scale (NRS) from zero (no pain) to ten (maximum pain). Patient characteristics were collected. Side effects of etoricoxib namely nausea, vomiting, dizziness, palpitation, hypertension, tachypnea, and rash were recorded. The primary outcome was a comparison of pain scores at each step of the procedure between etoricoxib and placebo. The secondary outcome was side effects related to etoricoxib administration.

The G-power program version 3.1.7 (UCLA, LA, USA) was used by Mann-Whitney U test for sample size calculation. The level of 0.85 was set for effect size. Type 1 error and power of 0.05 and 0.8, respectively were used for calculation. Sample size in the current study was 55 cases per arm. Data were analyzed by using commercial statistic software (SPSS version 23). Continuous data were represented by mean and standard deviations. Categorized data and side effect events were evaluated by Pearson's chi-squared test or Fisher exact test according to the appropriated condition. Pain scores were evaluated by Mann-Whitney U test. The statistical significance was set at a p-value less than 0.05.

Results

From August 2022 to January 2023, A total of 120 women with abnormal cervical screening indicated colposcopy were enrolled. Patients with a history of allergies to NSAIDs (five participants), anticoagulant drug usage (three participants), and pregnancy (two participants) were excluded. Therefore, one hundred and ten participants were randomly divided into two groups (55 participants in each group) as shown in Figure 1.

Summarized demographic and colposcopic data are demonstrated in Table 1. The mean age of overall participants was 42.6 years old. Two-thirds of the participants were multiparity. Premenopausal status, body mass index, history of dysmenorrhea, and previous colposcopy were comparable between groups. There was no statistical difference in cervical cytology results, high-risk human papillomavirus status, and high-grade

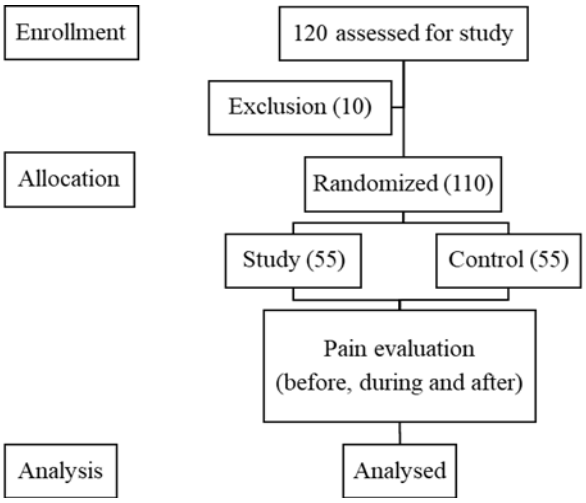

Figure 1. Flow Chart of Study. Exclusion, fit for exclusion criteria; before, pain score before colposcopy; during, each pain score at speculum insertion, 3% acetic acid application, cervical biopsy, endocervical curettage; after, pain score after colposcopy at 10 minutes and 24 hours

Table 1. Demographic Characters among Abnormal Cervical Cancer Screening Cases (55 Cases per Group)

	Study*	Control*	p-value
Age (years)**	43.9 ± 11.5	41.4 ± 10	0.243
BMI (kg/m2)**	23.3 ± 3.6	23.7 ± 4.7	0.644
Multiparity	39 (70.9)	30 (54.5)	0.076
Premenopausal	38 (69.1)	46 (83.6)	0.073
Dysmenorrhea	20 (36.4)	22 (40)	0.695
Previous colposcopy	11 (20)	17 (30.9)	0.189
CDB	50 (90.9)	53 (96.4)	0.241
ECC	42 (76.4)	41 (74.5)	0.825
LGC	34 (61.8)	36 (65.5)	0.55
hrHPV +	35 (63.6)	37 (67.3)	0.462
CIN2+ histology	15 (27.3)	14 (25.5)	0.829

*n (%), **mean ± standard deviation (SD); BMI, body mass index; CDB, colposcopic directed biopsy; ECC, endocervical curettage; LGC, low grade cervical cytology; hrHPV +, positive high risk Human papillomavirus test; CIN2+, cervical intraepithelial neoplasia grade 2, grade 3, invasive carcinoma

cervical intraepithelial neoplasia.

Assessment of pain intensity

The data analysis included all subjects from the originally assigned groups, as there was no subject dropout. The median NRS pain score at baseline was 0 for both groups (p = 0.682). At the time of speculum insertion, the median pain score was 3 for both groups (p = 0.537). Similarly, during 3% acetic acid application, the median pain score was 2 and 3 in the study and control group, respectively (p = 0.414). There were no statistically significant differences.

The median NRS pain score during and after the procedure was shown in Figure 2. This boxplot exhibited that pain scores at CDB, ECC, 10 minutes, and 24 hours after colposcopy of the study group were significantly lower than the control group. At 10 minutes after the procedure, the pain decrement of the study group was significantly higher than that of the control group.

Assessment of side effects

The side effects of etoricoxib were evaluated 24 hours post-procedure. Nausea and vomiting were reported in one and two cases in the study and control group, respectively. Dizziness was reported at the percentage of 12.7 (7/55) and 14.5 (8/55) in the study and control groups, respectively. No colposcopy-related complication was reported in any of the participants. There was no significant difference in side effects between the study and control group.

Discussion

Colposcopic procedure causes pelvic discomfort and moderate pain (Darweesh et al., 2020). Since year 2001, Church et al reported that oral ibuprofen 30 minutes before colposcopy could not relieve pain. Subjects in Church's study were mostly multiparity and Caucasian ethnicity. Meanwhile, half of the subjects in the current study were

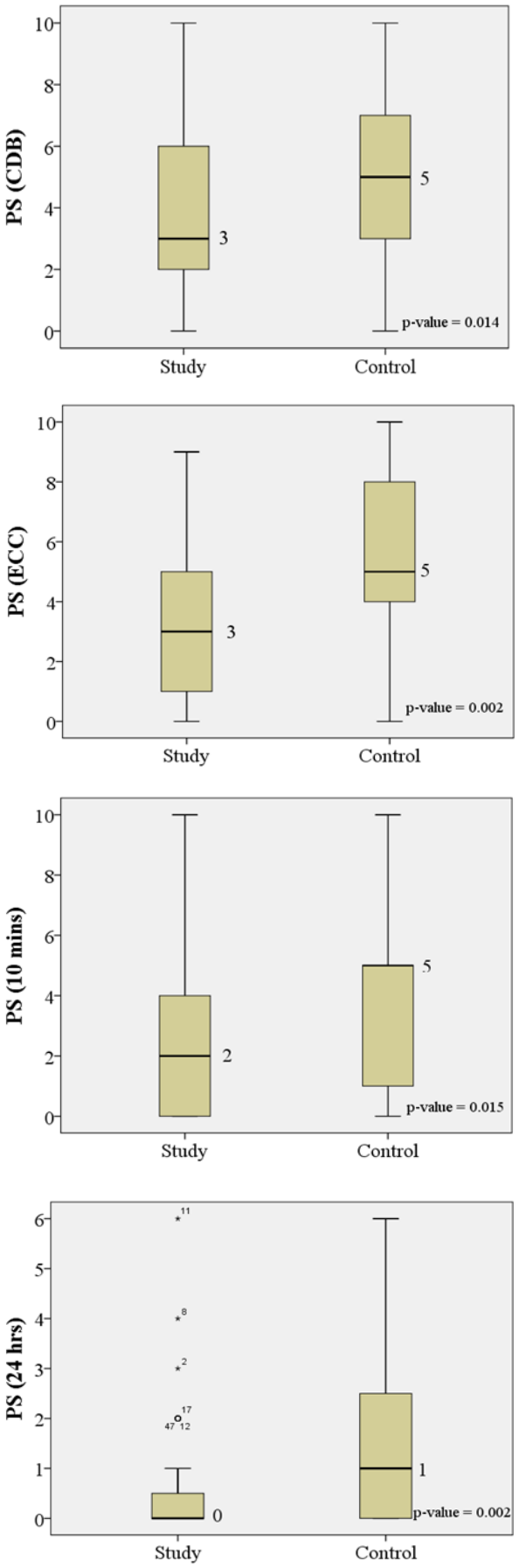

Figure 2. Median Pain Scores among Study and Control Group. PS, median pain score; CDB, colposcopic directed biopsy; ECC, endocervical curettage; 10 mins, post procedure 10 minutes; 24 hrs, post procedure 24 hours

Table 2. Comparison of Pain Score

	Church	Bogani	Karaman	Darweesh	Pradit	Sivapornpan
Years	2001	2014	2019	2020	2022	2023
Country	USA	Italy	Turkey	Egypt	Thailand	Thailand
Comparison	Ibu/Pl	LA/FC	LS/FC	Tra/Pl	LM/Pl	Eto/Pl
Cases (n)	50	100	86	150	240	110
PS-Spec	0.63/0.75	17.7/16.5	1.4/1.2	2.16/2.24	2.83/2.94	3-Mar
PS-Acetic	N/A	N/A	N/A	2.53/2.33	N/A	3-Feb
PS-Biopsy	2.25/3.0	11.9/13.2	3.25/4.4*	1.43/4.39*	4.21/4.3	3/5*
PS-ECC	3.75/3.5	N/A	N/A	4.08/5.99*	N/A	3/5*
PS-5 mins	N/A	1.4/0.8	1.9/2.1	N/A	N/A	N/A
PS-10 mins	N/A	N/A	N/A	1.61/4.19*	2.34/2.25	2/5*

PS, pain score; 5 mins, after procedure 5 minutes; 10 mins, after procedure 10 minutes; Ibu, ibuprofen; Pl, placebo; LA, lidocaine injection at cervix; FC, forced coughing; LS, lidocaine spray; Tra, tramadol; LM, listening to music; Eto, etoricoxib; *, statistic significant: p-value <0.05

nulliparous and Asian ethnic. Subjects in the control group of Church's study reported minimal pain from the procedure (pain score of 3/10) while the present study reported a pain score of around 5/10 in the control group. The subject in Church's study had no benefit from 800 mg ibuprofen (Church et al., 2001). Despite of non-selective COX inhibitor in Church's study and the selective COX-2 inhibitor in the current study were used as a single dose, the GI side effects were comparable.

Another study from Egypt (Darweesh et al., 2020) reported that a 50-mg of oral tramadol administration at 30 minutes before the procedure resulted in excellent pain reduction in all processes of colposcopy. However, nausea and vomiting in Darweesh's and the current study were 11 (8/75) and 2 (1/55) percent, respectively. Only oral etoricoxib could relieve pain in colposcopic procedures with minimal nausea and vomiting. Tramadol was a high-potency analgesia that might be inappropriate for mild to moderate pain procedures.

Some studies reported that pain relief during CDB and ECC by either using local lidocaine intracervical injection or force coughing or listening to music were inconclusive result. (Bogani et al., 2014; Hecken JM et al., 2022; Pradit et al., 2022). The average pain of subjects in both groups in Bogani's study was around 1-2/10 score during the procedure. Therefore, analgesia might not be recommended in subjects who had minimal pain from the procedure, according to Church's and Bogani's studies (Church et al., 2001; Bogani et al., 2014).

A Turkish study in year 2019 presented that local lidocaine spray at the cervix before CDB could relieve pain only at the time of cervical biopsy. It was inefficient to reduce pain after procedure (Karaman et al., 2019). The short-acting property of lidocaine spray explains the result of Karaman's study. The current study showed that single oral etoricoxib could relieve pain until 24 hours post-procedure. Thus, oral analgesia administration might be the drug of choice for pain relief in the colposcopic procedure. A comparison of the current study to previous literature was summarized and presented in Table 2.

Etoricoxib could be administrated via the oral route. A single dose of etoricoxib was enough for pain control until 24 hours post-procedure. It had benefits for mild to moderate pain procedure control with minimal side effects. The authors recommended a single dose of oral etoricoxib before colposcopy to improve women's health during the procedure.

The strength of our study was a randomized controlled trial. The demographic data were comparable between study and control groups. The pain level was evaluated at each step of colposcopy until 24 hours post-procedure. However, one-fifth of subjects had prior colposcopy which might be a limitation of the study. Future studies should compare the efficacy of the other types of oral NSAIDs.

In conclusion, 90- mg etoricoxib can improve pain relief during CDB, ECC, 10-minute and 24 hours post-procedure with a low side effect.

Author Contribution Statement

Sarunya Sivapornpan designed the research, collected, summarized, analyzed clinical data and wrote the paper. Awassada Punyashthira designed the research, analyzed clinical data, wrote the paper; gave critical comment and was the corresponding author. Komsun Suwannarurk analyzed clinical data and gave critical comments. Nopwaree Chantawong, Pattra Wisarnsirirak, Karicha Maireang, Yuthadej Thaweekul and Yenrudee Poomtavorn gave critical comments. All authors approved the final version for publication. Junya Pattaraarchachai designed and responsibility to statistical analysis.

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Ethical Approval

This study was approved by the human research ethics committee of Thammasat University (MTU-EC-

OB-1-342/64) and registered at the Thai Clinical Trials Registry (TCTR20220712004).

Data Availability Statement

The dataset generated and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors had no conflict of interest to report.

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