Naproxen for Pain Relief during Endometrial Biopsy: A Randomized Controlled Trial

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Objective: *To evaluate the effectiveness of naproxen 500 mg taken orally 30 minutes before endometrial biopsy for pain relief during the procedure.*
Material and Method: *A double blind, randomized, placebo-controlled trial was conducted in 80 patients with indication for endometrial biopsy at Ramathibodi Hospital between April 2013 and January 2014. The patients were randomly allocated into two groups to receive naproxen 500 mg (n = 40) or placebo (n = 40), 30 minutes before endometrial biopsy. Pain score was assessed using Visual Analogue Scale during and 10 minutes after the procedure. Adverse events were observed.*
Results: *The mean pain score during endometrial biopsy in the treatment group was significantly lower compared to the placebo group (5.11±0.18 vs. 6.49±0.17, respectively, p-value <0.001). However, the mean pain score at 10 minutes after endometrial sampling were minimal and had non-statistical significance in both groups. (0.60±0.56 vs. 0.59±0.64, p-value 0.971).*
Conclusion: *Naproxen 500 mg taken orally 30 minutes before endometrial biopsy significantly reduce pain score during the procedure.*

Keywords: *Endometrial biopsy, Naproxen, Pain score, Randomized controlled trial*

J Med Assoc Thai 2015; 98 (7): 631-5
Full text. e-Journal: *http://www.jmatonline.com*

Abnormal uterine bleeding is one of the most common gynecologic problems in women[1]. The majority resulted from pathology of the endometrium such as endometrial polyps, hyperplasia, and cancer[2]. The pathological results of endometrial tissue are the gold standard for the diagnosis of abnormal uterine bleeding caused by endometrial pathology[3]. Endometrial biopsy is a procedure to sample endometrial tissue. It has no difference in sensitivity and specificity as compared to fractional curettage[4,5]. Moreover, it is a minimally invasive procedure, available at outpatient department, take a few seconds (about 5 to 20 seconds) to complete, and no serious complications, such as uterine perforation or anesthetic complications, have been reported[6].

Although endometrial biopsy is the less aggressive procedure, it still causes pain[7]. Nowadays, there is no guideline for preoperative analgesia to control pain during the procedure. Naproxen is a non-steroidal anti-inflammatory drug that inhibits prostaglandin synthesis, which causes uterine cramping. Therefore, naproxen is widely used as analgesia in gynecological procedure such as fractional curettage, dilatation and curettage and IUD insertion, because of its effectiveness, low cost, safety and rapid onset (30 to 60 minutes after ingestion)[8]. The drug is also listed in the Thai National List of Essential Medicines. With these properties, preoperative ingestion of naproxen may play an important role for pain relief during endometrial sampling. Therefore, the main purpose of the present study was to assess the effect of preoperative ingestion of naproxen 500 mg on pain relief during endometrial sampling.

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Material and Method

This double blind, randomized, placebo-controlled trial was conducted among women who attended the Gynecology Outpatient Clinic, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand between March 2013 and January 2014. The inclusion criteria were non-pregnant women

who had painless abnormal vaginal bleeding with the indications for endometrial biopsy. The patients who had any underlying conditions contraindicating naproxen usage including peptic ulcer, asthma, bleeding disorders, impaired renal or hepatic function, and hypersensitivity to naproxen as well as patients without history of sexual intercourse were excluded from this study. Informed consent was obtained from all patients prior to the procedure.

After the approval of the Institutional Ethics Committee, all participants were randomly allocation and concealment conducted into one of the two groups by block-of-four randomization. The treatment group received naproxen 500 mg orally 30 minutes before procedure, while the control group received placebo (Vitamin B complex), which has similar size and color. The patients, doctors, and the assessors were all blinded to the allocation.

Before the procedure, all patients were instructed how to assess pain using Visual Analogue Scale (VAS) ranging from 0 (no pain) to 10 (worst possible pain). The doctors' endometrial biopsy techniques were standardized including speculum placement, antiseptic preparation, endometrial biopsy instrument insertion and suction. All patients underwent endometrial biopsy using Endosampler®. Cervical manipulation with Allis or Tenaculum would be performed only when the operator could not pass the instrument after the first attempt. Pain score was assessed by measuring the distance from 0 to the point where the patient indicated and recorded in centimeter with one decimal point during and at 10 minutes after the procedure.

The sample size was calculated from the result of the study by Guzel et al[9] with a 5% level of significance and power of 80%. A sample size of 32 women per group was required. Considering a 10% drop-out rate, 40 women per group were recruited.

Statistical analysis was performed by an independent statistician who also blinded to randomize and allocation process by using STATA software version 13 (College Station, TX, USA). Continuous variables were presented as mean and standard deviation (SD); whereas categorical variables were presented as count number and percentage (n, %). Differences between outcomes of the two groups were evaluated by using Chi-square test or unpaired t-test as appropriate. All outcomes were considered significant only if the *p*-value was lower than 0.05 (*p*-value <0.05).

Results

Eighty patients who fulfilled the inclusion criteria were recruited to the study. Of the 40 women in the study group, the procedure was abandoned in three cases due to unable to pass the instrument through cervical os, thus 37 completed the study. Among the 40 women in control group, the procedure was abandoned in one case due to unable to pass the instrument through cervical os, thus 39 completed the study (Fig. 1). History of route of delivery, previous dilatation and curettage, previous endometrial sampling, and indication for endometrial sampling were comparable in both groups. The uses of Allis or Tenaculum forceps to grasp and manipulate the cervix when the operator initially failed to pass the instrument were also comparable between both groups. The baseline characteristics were demonstrated in Table 1.

The mean pain score from VAS during endometrial sampling in the treatment group was significantly lower than in the control group (5.11±0.18 vs. 6.49±0.17, *p*-value <0.001). The mean pain score at 10 minutes after endometrial sampling in the treatment group was slightly higher than in the control group without statistical significance (0.60±0.56 vs. 0.59±0.64, *p*-value 0.971) (Table 2).

The adverse effects were reported in the present study including nausea in control group was slightly higher than the treatment group without statistical significance. No severe complication such as anaphylaxis occurred.

Discussion

Endometrial biopsy is widely used to sample endometrial tissue in patients with abnormal uterine bleeding. Previous studies demonstrated that the accuracy of endometrial sampling is not statistical different from dilatation and curettage[10], even higher

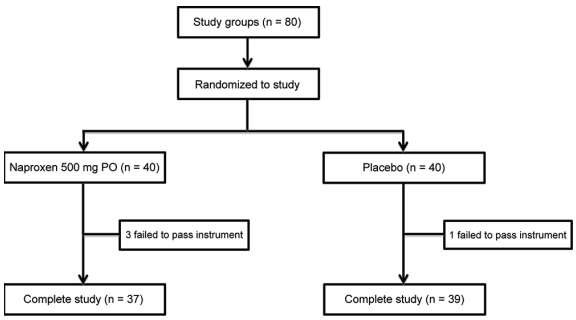

Fig. 1 Study flow chart.

Table 1. Baseline demographic data

Demographic data	Treatment group (n = 40)	Placebo group (n = 40)	*p*-value
Age (years), mean ± SD (range)	50.125±1.19 (35-66)	48.525±1.31 (35-64)	0.843
Route of delivery, n (%)			
Vaginal delivery	10 (25.0)	9 (22.5)	0.793
Cesarean section	30 (75.0)	31 (77.5)	
History of dilatation and curettage, n (%)			
Yes	27 (67.5)	27 (67.5)	1.000
No	13 (32.5)	13 (32.5)	
History of endometrial biopsy, n (%)			
Yes	28 (70.0)	27 (67.5)	0.809
No	12 (30.0)	13 (32.5)	
Indication, n (%)			
Postmenopausal bleeding	10 (25.0)	13 (32.5)	0.862
Menometrorrhagia	14 (35.0)	14 (35.0)	
Endometrial hyperplasia	10 (25.0)	9 (22.5)	
Others	6 (15.0)	4 (10.0)	
Use of Allis or Tenaculum forceps, n (%)			
Yes	11 (27.5)	13 (32.5)	0.626
No	29 (72.5)	27 (67.5)	

Table 2. Pain scores during endometrial sampling and 10 minutes after endometrial sampling and adverse effects

Results	Treatment group (n = 37)	Placebo group (n = 39)	*p*-value
Pain score during ES, mean ± SD	5.11±0.18	6.49±0.17	<0.001
Pain score 10 minutes after ES, mean ± SD	0.60±0.56	0.59±0.64	0.971
Adverse effect, n (%)			
Nausea	4 (10)	6 (15.0)	0.955
Headache	6 (15)	3 (7.5)	0.876
Rash	0 (0)	1 (2.5)	0.998

ES = endometrial sampling

accuracy in diagnosing endometrial cancer when an adequate specimen is obtained[11]. Even though this procedure is easy to performed, minimally invasive and availability to do at an outpatient department in a short period of time, pain is inevitable during endometrial biopsy.

Leclair et al reported that pain score by VAS during endometrial biopsy was estimated to be 6.21[7]. Endosampler® was selected for endometrial sampling in the present study because data from previous study showed that more endometrial tissue could be obtained from Explora® sampling device compared with Pipelle®, but pain score during procedure was higher using Explora®[7]. Endosampler® and Explora® were similar that they had to be connected to a locking syringe to create suction effect.

Currently, there is no guideline to relieve pain during endometrial biopsy. Previous studies suggested different analgesic techniques before uterine curettage such as oral mefenemic acid, intravenous morphine, or paracervical block; all had comparable effectiveness in pain reduction during the procedure[12,13].

For endometrial biopsy, one study reported that patients who received intrauterine 2% lidocaine with naproxen sodium 550 mg taken orally before endometrial biopsy had significantly lower pain score during the procedure[14], but the application of this technique is not practical to be done at an outpatient setting.

Other medication, such as etoricoxib was reported to be used as an oral drug for reduction of pain during endometrial biopsy. Although it did not decrease the pain score during endometrial biopsy, the pain score at 30 minutes after the procedure was significantly lower as compare with placebo group[15]. Eight mg of lornoxicam taken orally at 30 minutes before endometrial sampling was also reported to reduce the pain score significantly at 0, 30,

and 60 minutes after the procedure[9], however, the drug is not available in Thailand.

In the present study, naproxen was chosen because its effectiveness, easy to use and low cost. As the drug is listed in the Thai National List of Essential Medicines, it is available nationwide and covered by all health policies.

The results demonstrated significantly lower pain score by VAS during endometrial biopsy in the naproxen group, yet the difference of the mean pain score was merely 1.38, which might not be clinically significant. Further studies should be conducted with measures for clinical significance or patient satisfaction. Pain should be less if a softer device such as Pipelle® or Endocell® is used.

The mean pain score at the 10-minute time point after the procedure was 0.59 in the treatment group and 0.60 in the control group, which was not statistically significant, implying that most of the patients had negligible pain at 10 minutes after endometrial biopsy regardless of analgesic use. This finding can be used to counsel the patients before the procedure.

The adverse effects such as nausea, headache and rash were comparable in both groups, which was not statistical significant. No women in the present study reported serious adverse effect.

This is the first study to determine the effectiveness of naproxen 500 mg orally before endometrial biopsy proven by a randomized control trial with planned allocation concealment. The authors accept that the limitation of this study is small sample size and inability to identify the relationship between pain scores during endometrial biopsy and age, parity, history of vaginal delivery, history of curettage or endometrial biopsy, and the use of Allis or Tenaculum forceps. Hence, further studies with larger sample size are required to assure the result.

Conclusion

Naproxen 500 mg taken orally 30 minutes before endometrial biopsy significantly decreased the pain score during endometrial biopsy as compared to placebo. The authors found no serious adverse effect of this drug throughout the entire procedure.

What is already known on this topic?

Endometrial biopsy is replacing conventional dilatation and curettage in the retrieval of endometrial specimen for pathological evaluation of abnormal uterine bleeding. Currently, there has been no guideline regarding the analgesia for the procedure. The methods that demonstrate good efficacies such as lornoxicam or intrauterine lidocaine are either expensive, cumbersome, or not available in Thailand.

What this study adds?

The administration of naproxen 500 mg orally 30 minutes before endometrial biopsy reduced pain score during the procedure without serious side effects. This regimen might be included in the standard protocol for endometrial sampling.

Potential conflicts of interest

None.

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การใช้ยานาพรอกเซนรับประทานก่อนการเก็บเยื่อบุโพรงมดลูกส่งตรวจเพื่อระงับความเจ็บปวดขณะทำหัตถการ: การศึกษาแบบสุ่ม

วีรภัทร สมชิต, อาบอรุณ เลิศขจรสุข, ศักดา อาจองค์ วัลลิภากร

วัตถุประสงค์: *เพื่อศึกษาประสิทธิผลของการให้ยานาพรอกเซน 500 มิลลิกรัม รับประทาน 30 นาที ก่อนการเก็บเยื่อบุโพรงมดลูกส่งตรวจในการระงับความเจ็บปวดระหว่างการทำหัตถการ*

วัสดุและวิธีการ: *เป็นการศึกษาแบบสุ่มโดยเปรียบเทียบกับยาหลอกในผู้ป่วยทั้งหมด 80 ราย ที่มีข้อบ่งชี้ในการเก็บเยื่อบุโพรงมดลูกส่งตรวจ ณ โรงพยาบาลรามาธิบดี ตั้งแต่เดือนเมษายน พ.ศ. 2556 ถึง มกราคม พ.ศ. 2557 โดยสุ่มผู้ป่วยออกเป็น 2 กลุ่ม กลุ่มหนึ่งได้รับยานาพรอกเซน 500 มิลลิกรัม (40 ราย) หรือ ยาหลอก (40 ราย) 30 นาที ก่อนการเก็บเยื่อบุโพรงมดลูกเพื่อส่งตรวจทางพยาธิวิทยา ประเมินคะแนนความเจ็บปวดทำโดยใช้ visual analogue scale ระหว่าง และ 10 นาที หลังการทำหัตถการ รวมถึงสังเกตภาวะแทรกซ้อนและอาการข้างเคียง*

ผลการศึกษา: *ค่าเฉลี่ยของคะแนนความเจ็บปวดระหว่างเก็บเยื่อบุโพรงมดลูกส่งตรวจในกลุ่มที่ได้รับยานาพรอกเซนต่ำกว่ากลุ่มที่ได้รับยาหลอกอย่างมีนัยสำคัญทางสถิติ (5.11±0.18 เทียบกับ 6.49±0.17 ตามลำดับ, p-value <0.001) อย่างไรก็ตามค่าเฉลี่ยของคะแนนความเจ็บปวดที่ 10 นาที หลังเก็บเยื่อบุโพรงมดลูกส่งตรวจ มีความเจ็บปวดน้อยมากในทั้งสองกลุ่มโดยไม่มีนัยสำคัญทางสถิติ (0.60±0.56 เทียบกับ 0.59±0.64, p-value 0.971)*

สรุป: *การรับประทานยานาพรอกเซน 500 มิลลิกรัม 30 นาที ก่อนการเก็บเยื่อบุโพรงมดลูกส่งตรวจ สามารถลดระดับคะแนนความเจ็บปวดระหว่างการทำหัตถการดังกล่าวอย่างมีนัยสำคัญ*