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Effectiveness of Preoperative Oral Diazepam for Reducing Anxiety during Loop Electrosurgical Excision Procedure: A double-blind randomized controlled trial

Sattawat Charoenwong, M.D.*,
Saowanee Tangmanowuttikul, M.D.*,
Metha Songthamwat, M.D., Ph.D.*
Srisuda songthamwat, M.D.**,
Ueamporn Summart, DrPH.***

** Department of Obstetrics and Gynecology, Udonthani Hospital, Udon Thani, Thailand*
*** Phetchabun Hospital, Phetchabun, Thailand*
**** Faculty of Nursing, Roi Et Rajabhat University, Roi Et, Thailand*

ABSTRACT

Objectives: To compare the pre- and postoperative anxiety score by State-Trait Anxiety Inventory (STAI) and visual analogue scale of anxiety (VAS-A) of the patients who received preoperative oral diazepam with those who received a placebo during loop electrosurgical excision procedure (LEEP).

Materials and Methods: This study is a double-blind, randomized controlled trial. There were 156 patients enrolled and allocated; group 1 received an oral diazepam 10 mg (n = 78) and group 2 received a placebo (n = 78) 1 hour before the operation. Both groups had received the same local anesthesia and standard care. Pre- and postoperative anxiety were measured by STAI and VAS-A immediately before the operation and, again, one hour after the operation. Pain score was measured by visual analogue scale of pain 30 minutes after the operation. All anxiety and pain scores were compared for both groups using an unpaired t test.

Results: The baseline characteristics were similar between groups. The preoperative diazepam and placebo group had STAI scores of 45.60 versus 44.02, respectively with the mean difference -1.57 (95% confidence interval -4.36,1.20) without a significant difference. Also, the postoperative anxiety score, pain score, heart rate and mean arterial pressure were not significantly different.

Conclusion: Preoperative oral diazepam 10 mg administered one hour before operation did not decrease the pre- and postoperative anxiety or pain levels in LEEP. Other treatments are required and should be the subject of further studies.

Keywords: diazepam, anxiety, loop electrosurgical excision procedure, State-Trait Anxiety Inventory, visual analogue scale of anxiety.

Correspondence to: *Metha Songthamwat, M.D., Department of Obstetrics and Gynecology, Udonthani Hospital, Udon Thani 41000, Thailand. Email: Udonhome@yahoo.com*

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ประสิทธิผลของการใช้ยาไดอะซิแพมในรูปแบบกินก่อนทำหัตถการเพื่อลดความกังวลขณะทำการผ่าตัดปากมดลูกด้วยห่วงลวดไฟฟ้า: การศึกษาเชิงทดลองแบบสุ่มปกปิดสองทาง

ศตวรรษ เจริญวงศ์, เสาวณีย์ ตั้งมโนวุฒิกุล, เมธา ทรงธรรมวัฒน์, ศรีสุดา ทรงธรรมวัฒน์, เอื้อมพร สุ่มมาตย์

บทคัดย่อ

วัตถุประสงค์: *เปรียบเทียบระดับค่าคะแนนความกังวลของผู้ป่วยที่ได้รับยาไดอะซิแพมในรูปแบบกินก่อนผ่าตัดและยาหลอกขณะผ่าตัดปากมดลูกด้วยห่วงลวดไฟฟ้า*

วัสดุและวิธีการ: *การศึกษาทดลองแบบสุ่ม โดยผู้ป่วยที่มารับการผ่าตัดปากมดลูกด้วยห่วงลวดไฟฟ้าจำนวน 156 คนเข้าร่วมการศึกษา และได้รับการจัดสรรให้อยู่ในกลุ่มหนึ่งในสองกลุ่ม กลุ่มที่ 1 ได้รับยาไดอะซีแพมในรูปแบบรับประทาน ขนาด 10 มิลลิกรัม (n = 78), กลุ่มที่ 2 รับยาหลอกซึ่งลักษณะเม็ดคล้ายกัน (n = 78) ก่อนทำหัตถการ 1 ชั่วโมง โดยทั้ง 2 กลุ่มได้รับยาชาเฉพาะที่และการรักษาตามมาตรฐานที่เหมือนกัน ทำการวัดค่าความวิตกกังวลก่อนเริ่ม และหลังการทำหัตถการ 1 ชั่วโมงด้วย State-Trait anxiety inventory (STAI) และ Visual Analogue Scale of Anxiety และวัดคะแนนความเจ็บปวดที่ 30 นาทีหลังทำหัตถการ ด้วย Visual Analogue Scale of Pain เปรียบเทียบค่าคะแนนความกังวลระหว่างกลุ่มโดย unpaired t test*

ผลการศึกษา: *ไม่มีความแตกต่างของลักษณะทางคลินิกพื้นฐานก่อนการผ่าตัดระหว่างทั้งสองกลุ่ม ค่าเฉลี่ย STAI ก่อนเริ่มการผ่าตัดระหว่าง 2 กลุ่มเท่ากับ 45.60 และ 44.02 โดยค่าเฉลี่ยความแตกต่างเท่ากับ -1.57 (ช่วงความเชื่อมั่น 95% -4.36,1.20) ซึ่งไม่มีความแตกต่างกันทางสถิติ และค่าคะแนนความกังวลหลังทำหัตถการ 1 ชั่วโมง คะแนนความปวด อัตราการเต้นของหัวใจและความดันเลือดเฉลี่ย ไม่พบมีความแตกต่างกันอย่างมีนัยยะสำคัญทางสถิติระหว่างกลุ่ม*

สรุป: *การรับประทานยาไดอะซิแพม 10 มิลลิกรัม 1 ชั่วโมงก่อนผ่าตัด ไม่สามารถลดความวิตกกังวลหรือความเจ็บปวดในการทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้า การรักษาด้วยวิธีอื่นเพื่อลดความกังวลยังคงจำเป็นและต้องมีการศึกษาเพิ่มเติมต่อไป*

คำสำคัญ: *ไดอะซิแพม, ความกังวล, การตัดปากมดลูกด้วยห่วงลวดไฟฟ้า, State-Trait Anxiety Inventory, visual analogue scale of anxiety*

Introduction

Cervical cancer is the third most common cause of death for cancer patients especially in the developing countries[1]. Precancerous finding is the aim of worldwide screening program to eliminate cervical cancer around the world. Loop electrosurgical excision procedure (LEEP) is the most popular method for the diagnosis and treatment of cervical intraepithelial neoplasia (CIN) lesion. The World Health Organization (WHO) recommends LEEP for women who have histologically CIN2+ disease[2].

Receiving bad news about abnormal cervical cytology and fear of treatment procedures such as colposcopy and LEEP can cause significant anxiety and psychological distress, mostly due to fear of having cancer and an unclear understanding of the treatment process[3-5]. Some patients feel nervous and tend to have insomnia[6-7] and it is well established that the increase of anxiety levels is associated with worse pain during operation[5]. Several methods, both pharmacological and non-pharmacological, have been used for decreasing anxiety levels which aim to reduce hemodynamic instability due to stress induced during surgery. Diazepam is a common anxiolytic drug that has been used to decrease tension before and during surgery[8], Diazepam is a long-acting benzodiazepine. This drug affects the central nervous system, which can help with sedation and hypnosis. However, its effectiveness in the preoperative stages of a LEEP procedure has not been studied. Therefore, the aim of the present research was to compare the anxiety scores of the patients who received preoperative oral diazepam with patients who were given a placebo before undergoing a LEEP.

Materials and Methods

This study was a randomized controlled trial conducted at a tertiary care hospital. The study protocol was approved by Udonthani Hospital Ethical Committee on human research (number 123/2566) and was registered in Thaiclinicaltrials.org (TCTR20240630006). The study period was from January 2024 to August 2024. The inclusion criteria were women aged 18 years or older, who have abnormal cervical cytology with an indication for LEEP according to the American Society for Colposcopy and Cervical Pathology (ASCCP) guideline (2019)[9] for abnormal cervical cancer screening tests and cancer precursors. The exclusion criteria were as follows: (1) diazepam allergy; (2) pregnancy; (3) cervical and vaginal infection; (4) taking diazepam or benzodiazepine drug less than 24 hours before the procedure; (5) cirrhosis (6) chronic kidney disease stage 3 or higher; (7) unstable blood pressure; (8) depression, central nervous system depression, or other mental disease; (9) myasthenia gravis, attention deficit, hyperactivity disorder, or chronic obstructive pulmonary disease; (10) cardiovascular events such as stroke, cerebral ischemia, or myocardial infarction before 6 month (11) visual impairment.

The primary outcome was to compare both pre- and postoperative anxiety score by State- Trait Anxiety Inventory (STAI)[10] and visual analogue scale of anxiety (VAS-A)[11] immediately before the operation (1 hour after taking the intervention) between treatment and placebo groups. The secondary outcomes were to compare 1) anxiety scale at 30 minutes post-operation 2) visual analogue scale of pain (VAS-P) at 30 minutes postoperation and 3) the mean arterial pressure and heart rate at preoperative, intraoperative and postoperative times between groups.

All participants were informed about the disease and surgical procedure before their participation in this study. After enrollment, the participants were allocated sequentially into one of two groups by research assistants using the computer generated randomization number in opaque sealed envelopes. Group 1 received an oral diazepam 10 mg; group 2 received the placebo in similar packaging one hour before the procedure. Both intervention packages were prepared by a pharmacist who was not involved with the data

collection process. The questionnaires were answered by the participants before LEEP (1 hour after intervention). The questionnaire was composed of baseline characteristics, STAI, VAS-A, VAS-P, heart rate, and mean arterial blood pressure. STAI designed by Spielberger[10] in 1989, was translated to a Thai version, validated and tested, by Kotchapakdee et al[12]. It consists of 20 questions, 10 positive questions and 10 negative questions. The participants were required to complete the questionnaires by themselves, the possible scores range from 20 to 80. A high score indicates a high level of anxiety. The anxiety score was divided into 3 groups: mild anxiety (20-40 points), moderate anxiety (41- 60 points) and severe anxiety (61-80 points)[12]. The VAS-A and VAS-P were both comprised of a 10 cm line where the participant marked her degree of pain and anxiety, 0 cm indicates "no pain or no anxiety", 10 cm indicates "maximum pain or anxiety". We used separate scales of pain and anxiety. The VAS-P scale for pain was rated 0 to 4 mm was classified as no pain; 5 to 44 mm was mild pain; 45 to 74 mm was moderate pain; and 75 to 100 mm was severe pain[13-14]. The anxiety levels of the participants were measured before intervention, and again at 30 minutes after the operation. The pain score during the operation was retrospectively measured at 30 minutes after operation. Heart rate and mean arterial blood pressure were recorded at 1 hour before operation, during the operation and again 30 minutes after operation.

LEEP was performed by medical residents and staff of Obstetrics and Gynecology, Udonthani Hospital. All LEEP was performed in operative room. The participant was placed in the lithotomy position. Preoperative vaginal cleansing was done using povidone iodine. The LEEP machine was a monopolar electrosurgery machine. The operators chose the size of loop depending on the cervical size. All participants were anesthetized by paracervical block using 10% lidocaine without adrenaline. Cervical tissue was excised by cutting mode and bleeding was stopped by coagulation mode, then Monsel's solution was applied. Tampon packing was used in cases that minimal bleeding remained. After LEEP, the participants were observed for 1 hour in the postoperative room.

The sample size was calculated based on Levandoski et al study data[15]. The N4studies application was used for the calculation using the formula of a randomized controlled study[16]. The mean STAI of the treatment group was 38.13 and the standard deviation was 6.94 and the control group was 41.91 with a standard deviation of 8.88[14] with the 0.05 alpha error and 0.2 beta error. The calculated sample size was 70 patients in each group. Assuming a 10% dropout rate, 78 patients per group were included in this study.

Statistical analyses were performed using STATA statistical program version 13. Continuous data was reported as the mean and standard deviation. The comparison of the continuous data from both groups was examined by the unpaired t-test. Categorical data shown as the number and percentage. The comparison of the categorical data between groups was examined by Pearson chi-square test or Fisher exact test. P values < 0.05 was used for statistically significant level.

Results

There were 157 patients who were enrolled in this study, one patient was excluded due to taking diazepam within 24 hours before the procedure. After receiving their written consent, 78 patients were randomly assigned to the diazepam group and 78 patients to the placebo group. All 156 patients completed the intervention process and were included in the statistical analysis. The consort diagram is shown in Fig. 1. The baseline characteristics, including age, body weight, Height, BMI, underlying diseases, smoking, alcohol drinking, history of abortion, LEEP indication, and operative time were not significantly different between groups. The details of both group's characteristics are shown in Table 1.

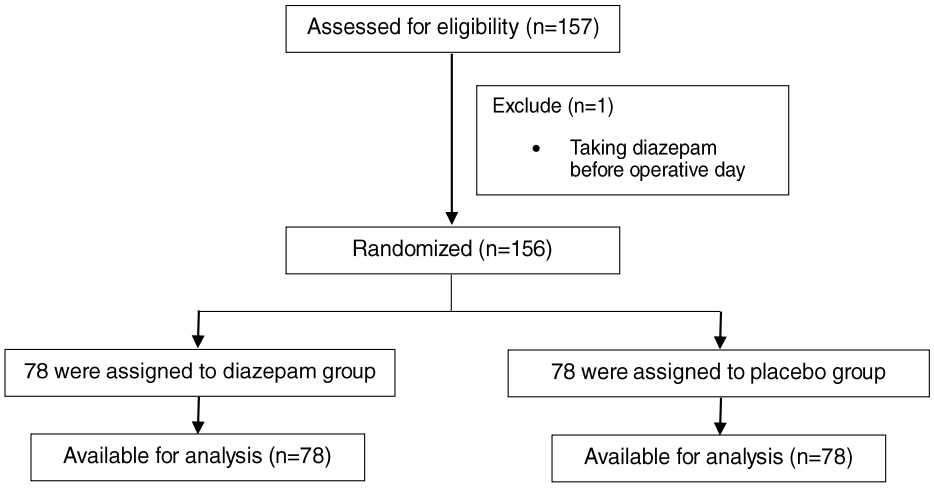

Fig. 1. The percentage of endometrial carcinoma and endometrial intraepithelial neoplasia in each age group.

Table 1. Baseline characteristics.

Characteristic	Group		p value*
	Diazepam (n = 78)	Placebo (n = 78)	
Age (years), mean ± SD	39.41 ± 9.15	41.47 ± 9.03	0.158
Body weight (kg), mean ± SD	58.70 ± 10.47	61.60 ± 12.47	0.118
Height (cm), mean ± SD	157.42 ± 5.31	156.97 ± 5.97	0.620
BMI (kg), mean ± SD	23.71 ± 4.29	24.91 ± 4.33	0.086
Underlying diseases			
Diabetic mellitus, n (%)	1 (1.28%)	5 (6.41%)	0.210
Hypertension	3 (3.85%)	2 (2.56%)	1.000
Asthma	1 (1.28%)	2 (2.56%)	1.000
Smoking	4 (5.13%)	1 (1.28%)	0.367
Alcohol drinking	18 (23.07%)	14 (17.95%)	0.428
History of abortion	14 (17.95%)	23 (29.49%)	0.090
LEEP indication			
HSIL	75 (96.15%)	74 (93.59%)	0.369
Cervical cancer	1 (1.28%)	3 (3.85%)	
Other	2 (2.56%)	1 (1.28%)	
Operative time (min)	13. 07 ± 4.57	14.19 ± 7.18	0.249

SD: standard deviation, min: minutes, kg: kilogram, cm: centimeter, BMI: body mass index, LEEP: loop electrosurgical excision procedure, HSIL: high-grade squamous intraepithelial lesion

* p value was calculated by unpaired t-test, Pearson chi square or Fisher's exact test

Preoperative STAI and VAS-A were not significantly different between oral diazepam and placebo groups (mean difference -1.57, 95% CI -4.36,1.20 by STAI and 1.79, 95% CI -4.36,1.20 by VAS-A). The mean preoperative anxiety scores of both groups were in the moderate anxiety level.

Postoperative STAI and VAS-A were not significantly different between oral diazepam and placebo groups (mean difference -1.89, 95% CI -5.26,1.46 by STAI and 0.38, 95% CI -4.36,1.20 by VAS-A). The mean postoperative anxiety scores of both groups were in the mild anxiety level and markedly decreased from the preoperative anxiety level.

The mean pain score with VAS-P in each group was not significantly different (mean difference -0.25, 95% CI -6.83,6.32). Both postoperative pain levels in each group were mild pain. Both heart rate and mean arterial pressure at any time of operation were not significantly different between groups (Table 2).

Table 2. Study outcomes.

Result	Group		mean difference (95%CI) p value*
	Diazepam (n = 78) (mean ± SD)	Placebo (n = 78) (mean ± SD)	
Pre-operative outcomes			
Anxiety score with STAI	45.60 ± 8.80	44.02 ± 8.74	-1.57 (-4.36, 1.20) 0.264
Anxiety score with VAS-A (mm)	57.94 ± 18.73	59.74 ± 21.01	1.79 (-4.50, 8.09) 0.574
Heart rate (bpm)	83.24 ± 14.61	83.46 ± 14.58	0.27 (-4.39, 4.83) 0.925
Mean arterial blood pressure (mmHg)	94.59 ± 13.99	95.28 ± 14.18	0.68 (-3.79, 5.17) 0.762
Intra-operative outcomes			
Heart rate (bpm)	77.96 ± 11.56	78.74 ± 12.24	0.78 (-2.98, 4.54) 0.682
Mean arterial blood pressure (mmHg)	90.94 ± 10.99	91.76 ± 12.55	0.82 (-2.91, 4.55) 0.664
Post-operative outcomes			
Anxiety score with STAI	35.37 ± 11.48	33.47 ± 9.70	-1.89 (-5.26,1.46) 0.266
Anxiety score with VAS-A	23.33 ± 22.19	23.71 ± 20.13	0.38 (-6.31, 7.08) 0.909
Pain score with VAS-P (mm)	22.56 ± 22.70	22.30 ± 18.72	-0.25 (-6.83,6.32) 0.938
Heart rate (bpm)	77.34 ± 9.91	78.30 ± 10.80	0.96 (-2.31, 4.24) 0.563
Mean arterial blood pressure (mmHg)	89.37 ± 14.21	90.93 ± 10.91	(-2.46, 5.57) 0.444

CI: confidence interval, SD: standard deviation, STAI: The state trait anxiety inventory, VAS-A: visual analogue scale of

Discussion

The present study showed that preoperative 10 mg oral diazepam at one hour before operation did not significantly reduce the pre and postoperative STAI and VAS-A and VAS-P score. The mean anxiety scores in this study were moderate anxiety in preoperative time and mild anxiety in postoperative time. The mean VAS-P was mild.

The result of this study was compatible with Nimmaanrat et al study[17] at Prince Songkla University Hospital which reported that 5-10 mg of diazepam at two hours before elective surgery under general anesthesia did not significantly reduce the preoperative anxiety in comparison to a placebo. A study by Dyck et al in Toronto Hospital also reported that no difference of STAI anxiety level among the anxiolytic properties between diazepam 10 mg at 1-1.5 hour before operation, and placebo in the outpatient dilatation and curettage for therapeutic abortion[18]. These results were incompatible with Jakobsen et al [19], a double-blind study which showed that orally administered diazepam given early in the morning within 6 hours before operation resulted in significantly decreased preoperative discomfort in minor surgical operations such as hernia repair, treatment of varicose veins, excision of benign breast tumors, dilatation and curettage, laparoscopic sterilization, endoscopy and minor orthopedic operations. A randomized control study by Salami et al which reported that oral diazepam 5 mg was effective for VAS-P score pain reducing in the impacted mandibular third molar surgery[20]. The reason for this difference might be the difference of type of operation. Because, the LEEP patients had been diagnosed with intraepithelial cervical dysplasia or cervical cancer which had a higher concern than other types of surgery. Another explanation of non-significant difference between groups was the limitation of sample size, some trends of the reduction of anxiety score such as preoperative VAS-A score in the treatment group was seen, even its statistical significance weren't achieved. This could be explored in future studies with larger sample sizes. A higher dose of diazepam or another type of benzodiazepine such as triazolam, lorazepam or midazolam has been shown to reduce anxiety in other studies[15, 21-26]. However, it needs a longer period of postoperative observation due to the greater sedative effects of a higher dose. There were some studies reported that diazepam was less effective for anxiety reduction when compared with other anxiolytic drugs[17, 25]. However, diazepam has a lower cost and is more readily available than the other benzodiazepines in Thailand and other low- and middle-income countries. The impact of this study to clinical practice is that the administering preoperatively of 10 mg of oral diazepam is not effective for anxiety reduction and further studies which examine the proper dosage of diazepam for LEEP should be conducted. The other anxiolytic drugs such as non-benzodiazepine drug (nitrous oxide, melatonin, buspirone, barbiturates and beta-blocker) should be evaluated[27-31]. Multimodality medications using the combination of pharmacological and non-pharmacological is also interesting for future studies.

The strength of the present study was that it was a double-blind, placebo controlled, randomized trial study. However, the limitation was the context of the inpatient, intraoperative room and only in the LEEP which might affect the generalization of the application. Some variables such as education level and occupation were not included in this study and also the postoperative complication such as postoperative infection was not recorded. The limited sample size might influence the study outcome; therefore, the cost-effectiveness of diazepam needs further larger studies to determine its benefit in future clinical practice especially in the low resource setting.

Conclusion

Preoperative 10 mg oral diazepam at 1 hour before LEEP was not effective in the reduction of anxiety levels. The proper methods to reduce anxiety in this procedure still need further studies.

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Potential conflicts of interest

The author declares no conflicts of interest.

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