Thai Journal of Obstetrics and Gynaecology
May 2024, Vol. 32, No. 3, pp. 196-204.

GYNAECOLOGY

Intravenous Dexamethasone for Preventing Postoperative Nausea and/or Vomiting in Total Abdominal Hysterectomy: A randomized double-blinded, placebo-controlled trial

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ABSTRACT

Objectives: To assess the efficacy of postoperative dexamethasone compared to placebo in reducing the incidence of postoperative nausea and/or vomiting (PONV) in women undergoing benign total abdominal hysterectomy (TAH).

Materials and Methods: Participants who were scheduled for TAH with or without adnexal surgery between August 2022 and April 2023 were included. The participants were randomly divided into two groups: the dexamethasone group (n = 43), who received 2 ml (8 mg) of intravenous dexamethasone injection, and the control group (n = 43) received 2 ml of normal saline at 2 hours after surgery.

Results: There was no significant difference in the incidence of PONV within 24 hours between the dexamethasone group and control group (32.6% vs 48.8%, relative risk 0.67(95% confidence interval 0.39 to 1.13), p = 0.09). The need for antiemetic drugs was not statistically different between groups (0% vs 9.3%, p = 0.05), and without serious adverse events in both groups. The dexamethasone group experienced a lesser pain score than the control group at 24 hours (4.7 ± 1.5 vs 5.8 ± 2.2, p = 0.01) after surgery. There was no difference in additional analgesic requirements.

Conclusion: The administration of 8 mg of intravenous dexamethasone postoperatively did not result in a significant reduction in PONV within the first 24 hours following benign TAH.

Keywords: postoperative nausea and vomiting, PONV, dexamethasone, hysterectomy.

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Received: 29 September 2023, **Revised:** 6 December 2023, **Accepted:** 20 December 2023

ผลของการการฉีดยาเดกซ่าเมทาโซนในการป้องกันภาวะคลื่นไส้ และหรือ อาเจียนหลังผ่าตัดมดลูก: การศึกษาแบบสุ่ม

กันยาวีร์ สุหงษา, เจษฎา วุฒิธรรมสุข, ทุมวดี ตั้งศิริวัฒนา

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลของการฉีดยาเดกซ่าเมทาโซนในการลดภาวะคลื่นไส้และหรืออาเจียนหลังผ่าตัดมดลูกทางหน้าท้องที่ไม่ใช่มะเร็ง*

วัสดุและวิธีการ: *ผู้เข้าร่วมวิจัยที่ได้รับกำหนดการผ่าตัดมดลูกทางหน้าท้องและหรือปีกมดลูกและรังไข่ ระหว่างเดือนสิงหาคม พ.ศ.2565 ถึงเมษายน พ.ศ.2566 ได้รับการสุ่มแบ่งอาสาสมัครเป็นสองกลุ่ม กลุ่มละ 43 คน กลุ่มได้รับยาเดกซ่าเมทาโซนฉีดทางเส้นเลือดดำ ปริมาณ 2 มิลลิลิตร (ขนาด 8 มิลลิกรัม) และกลุ่มควบคุม ได้รับนอร์มอลซาไลน์ปริมาณ 2 มิลลิลิตร แบบฉีดทางเส้นเลือดดำ ที่สองชั่วโมงหลังผ่าตัด*

ผลการศึกษา: *ไม่พบความแตกต่างอย่างมีนัยสำคัญของอุบัติการณ์การเกิดคลื่นไส้อาเจียนภายใน 24 ชั่วโมงหลังผ่าตัดของกลุ่มที่ได้ยาเดกซ่าเมทาโซนและกลุ่มควบคุม (32.6% vs 48.8%, relative risk 0.67(95% confidence interval 0.39 to 1.13), p = 0.09) ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติในการขอยาต้านอาเจียนเพิ่ม (0% vs 9.3%, p = 0.05) ไม่มีผลข้างเคียงที่รุนแรงเกิดขึ้นในผู้ร่วมวิจัยทั้งสองกลุ่ม กลุ่มเดกซ่าเมทาโซนมีคะแนนความปวดหลังผ่าตัด 24 ชั่วโมง (4.7 ± 1.5 vs 5.8 ± 2.2, p = 0.01) ไม่พบว่ามีความแตกต่างในการขอรับยาแก้ปวดเพิ่มเติมในทั้งสองกลุ่ม*

สรุป: *การได้รับยาเดกซ่าเมทาโซน 8 มิลลิกรัมแบบฉีดทางเส้นเลือดดำหลังผ่าตัดไม่ช่วยลดภาวะคลื่นไส้อาเจียนอย่างมีนัยสำคัญทางสถิติในช่วง 24 ชั่วโมงหลังการผ่าตัดมดลูกทางนรีเวชที่ไม่ใช่มะเร็ง*

คำสำคัญ: *ยาเดกซ่าเมทาโซน, ภาวะคลื่นไส้อาเจียนหลังการผ่าตัด, ผ่าตัดมดลูก*

Introduction

postoperative nausea and/or vomiting (PONV) is a common symptom complained in early postoperative patients. PONV can be uncomfortable owing to substantial medical complications such as aspiration of stomach contents and wound dehiscence. Participants with severe PONV symptoms may be unable to walk, necessitating an extended hospital stay[1].

The Apfel simplified risk score is used to assess the risk of PONV for participants undergoing surgery under general inhaled anesthesia considering a) female sex, b) nonsmoking status, c) history of nausea and or vomiting, motion sickness, and d) postoperative intravenous opioids that each parameter was worth 1 point, for a total of 4 points. The respective risk of PONV was around 10%, 20%, 40%, 60%, and 80% when the total scores were 0, 1, 2, 3, and 4[1]. Our gynecologic participants got at least 2 points on the Apfel simplified risk assessment.

PONV has been demonstrably reduced by dexamethasone when used as a premedication for preventing chemotherapy-induced vomiting[2]. Notwithstanding, dexamethasone is not widely used to prevent PONV among participants undergoing benign total abdominal hysterectomy (TAH)[1].

The intravenous route of dexamethasone is an effective antiemetic mechanism explained by the central suppression of the brainstem[3]. Dexamethasone also inhibits multiple inflammatory cytokines, suppressing inflammation and decreasing pain[4].

Eight milligrams of intravenous dexamethasone significantly reduced PONV with no adverse events, including hypersensitivity, pruritus, dyspepsia, infected wound, and increased blood sugar level. The safety of a single dosage of dexamethasone has been established[5].

TAH is the most frequent procedure in benign uterine tumor[6]. Although the meta-analysis showed dexamethasone could reduce PONV incidence in participants who underwent abdominal surgery, their study included various operations and populations but the study included only a few participants who underwent TAH[7]. The benefit of dexamethasone to reduce PONV in gynecologic surgery especially TAH had limited data[7].

The difference in time administering intravenous dexamethasone before and after induction reported a significant reduction in PONV compared with placebo especially in 24 hours[8]. However, there is no evidence of dexamethasone used in the postoperative period to prevent PONV. The advantages of using 8 mg of intravenous dexamethasone included a reduction in the incidence of PONV; early ambulation, especially within the first 24 hours after surgery; reduced postoperative pain, increased satisfaction, and improved postoperative care[9]. Therefore, the authors conducted the randomized controlled trial (RCT) to assess the efficacy of postoperative dexamethasone compared to placebo in reducing the incidence of PONV in women undergoing benign TAH.

Materials and Methods

This was a randomized, double-blinded, placebo-controlled trial approved by the Khon Kaen Hospital Institute Review Board in Human Research. Recruited participants were diagnosed with benign gynecologic conditions and scheduled for TAH with or without adnexal surgery. Participants were excluded if they (a) had a known hypersensitivity to dexamethasone; (b) had conditions that might influence gastrointestinal motility (including previous bowel surgery, previous abdominal irradiation, chronic constipation, pancreatitis, peritonitis, hypothyroidism, and chronic use of drugs that impact intestinal peristalsis; (c) had underlying diabetes mellitus who got poor glycemic control; (d) were immunocompromised (tuberculosis, human immunodeficiency virus Infection); and/or, (e) experienced an intraoperative blood loss of more than 1,000 ml or blood loss that required blood transfusion. The participants were informed about the study at the gynecology ward before the surgery. The participants were required to sign the letter of consent before enrollment. Postoperative hysterectomy and/or adnexal surgery who met the eligibility criteria were randomly assigned into two groups using a computer-generated

block of four and allocation concealment using sequentially opaque envelopes.

Baseline characteristics were recorded, including age, body mass index (BMI), comorbid diseases, indications for surgery, previous abdominal surgery, operation, operative time, anesthetic time, anesthetic gas inhaler, intraoperative antiemetic drug, intraoperative dexamethasone, intraoperative opioids, total doses of morphine injection, and estimated blood loss. Before the operation, all participants received the same standard preoperative care, anesthetic protocol, and intravenous antibiotic prophylaxis after induction of anesthesia. The surgical procedures were performed by staff.

Two hours after the operation refers to the time participants transferred from the post-anesthesia care unit (PACU) to inpatient department (IPD), and the ward nurse opened the randomization list, which contained 2 ml of dexamethasone or normal saline, identical in appearance. The dexamethasone group received 2 ml (8 mg) of intravenous dexamethasone, while the control group received 2 ml of intravenous normal saline two hours after surgery. The surgeon and research assistant were blinded to the investigation. The research assistant asked the participants to assess the pain level using a 10-cm visual analog scale (VAS) after arriving at the IPD and gaining full consciousness before receiving intravenous drugs. After that, the participants were informed about various outcomes that might be observed (feelings of nausea and/or vomiting). While participants were asleep, research assistants observed the PONV symptoms every four hours until 24 hours after surgery. A digital clock was set up as the standard time for recording the outcomes. If they had any symptoms of PONV described as just nausea with or without vomiting, they could request the antiemetic drug metoclopramide 10 mg intravenously every 6 hours. Dipstick blood sugar was checked every 6 hours. If hyperglycemia (250 mg/dl or more) was detected, insulin was administered per standard protocol. At 24 hours postoperatively, the participants were asked to assess the pain scores by VAS. The postoperative care protocol was intravenous administration of an opioid agent (2 mg of morphine for weight < 50 kg or 3 mg for weight ≥ 50 kg) every 4 hours for 24 hours. Participants who complained of severe pain over 8 on the VAS score could request additional morphine injections to relieve the breakthrough pain. Prophylactic antibiotics (2 g of cefazolin) were given before surgery and continued for 24 hours after surgery. Ambulation was promoted the day after surgery. The postoperative feeding step was standardized as a liquid and soft diet on the first postoperative day and a regular diet for the next 24 hours.

Additional analgesics were provided according to the level of pain. Standard pain relief was based on the World Health Organization (WHO) analgesic ladder. For example, oral paracetamol 500 mg or ibuprofen 400 mg were given when the pain score was 4-7 out of 10, while intravenous morphine was provided when the pain was ≥ 8 out of 10.

Primary and secondary outcomes were assessed. The primary outcome was the incidence of PONV after a benign TAH within 24 hours. The secondary outcomes were additional antiemetic requirements, additional analgesic requirements, side effects of dexamethasone, pain score measured by VAS (0-10), and the duration of hospital stay.

Participants could be discharged when they could tolerate a regular diet, had no postoperative complications, including abnormal bleeding per vagina, fever, and wound complications, and could ambulate without assistance. Before discharge, the length of hospital stays, satisfaction, and adverse events were recorded.

The sample size was calculated by using the incidence of PONV from the pilot study (Pintervention = 0.4, Pcontrol = 0.73) with a power of 80%, an α level of 0.05, and a dropout rate of 5%. Eighty-six participants (43 per group) were required. Data were statistically analyzed based on an intention-to-treat analysis using STATA version 14. The student's t-test was used to analyze continuous data. Chi-squared and Fisher's exact test were used to analyze continuous and categorical data. A p value < 0.05 was considered statistically significant.

Results

Between August 2022 and April 2023, 89 eligible participants scheduled for benign TAH, with or without adnexal surgery, were enrolled in the study. One was excluded due to intraoperative estimated blood loss of more than 1,000 ml and received blood transfusion; two were excluded due to incidental intraoperative findings of malignancy. Eighty-six participants were randomly assigned to the dexamethasone and control groups (Fig. 1).

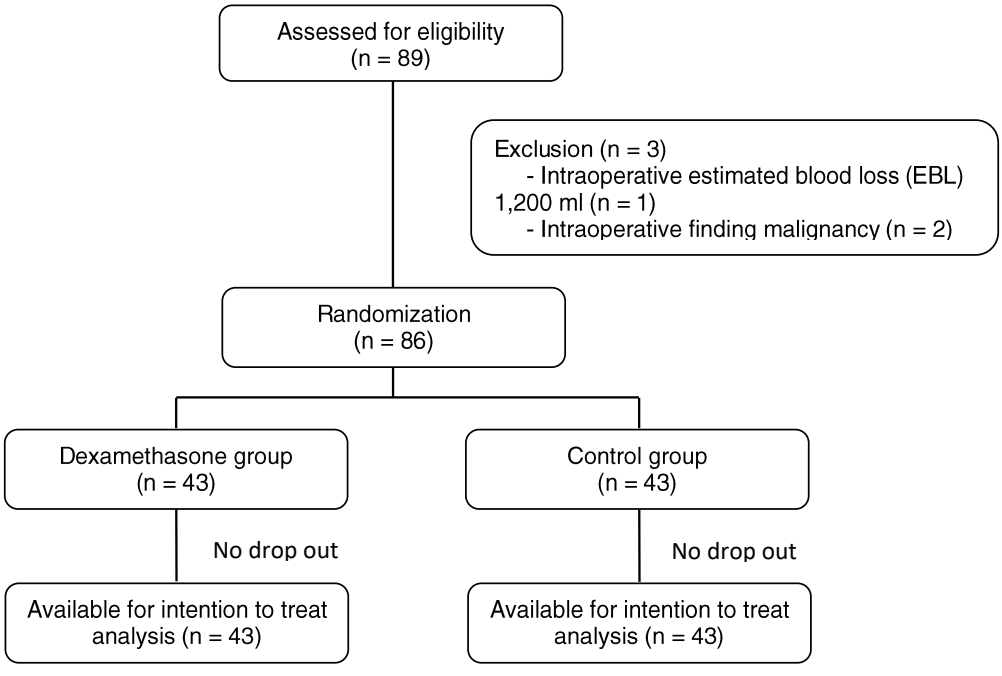

Fig. 1. Research study flow

Baseline characteristics were similar between groups, except hypertension in co-morbid diseases was found in the intervention group more than in the control group (Table 1).

The incidence of PONV within 24 hours of the dexamethasone group was 14 (32.6%), and the control group was 21 (48.8%), relative risk (RR) 0.67 (95% confidence interval (CI) 0.39-1.13), p = 0.09. After subgroup analysis, the incidence of PONV at 4, 8, 12, 16, 20, and 24 hours after surgery was not statistically significant (Table 2).

The additional antiemetic drugs were not significantly different among groups (0% vs 9.3%, p = 0.05) as well as additional analgesic drugs.

There were no serious adverse events found in this study. The incidence of dyspepsia and dizziness in the dexamethasone group was not statistically significant compared to the control group (14% vs 9.3%, p = 0.39 and 4.7% vs 0%, p = 0.24). Neither hyperglycemia nor insulin treatment were found (Table 3).

Pain scores measured by VAS (0-10) at 24 hours after surgery were lower in the dexamethasone group than in the control group. At 2 hours postoperatively, the scores were 7.7 ± 2.3 vs 8.6 ± 1.8 (mean difference 0.93 (95%CI 0.03-1.83), p = 0.04) and at 24 hours postoperatively, they were 4.7 ± 1.5 vs 5.8 ± 2.2 (mean difference 1.09 (95%CI 0.26-1.92), p = 0.01). The length of hospital stay was not different among groups (mean difference = 0.09 (95%CI 0.09-0.28), p = 0.32) (Table 3).

Table 1. Baseline characteristics.

	Dexamethasone group (n = 43)	Control group (n = 43)	p value
Age (yrs), mean ± SD	48.0 ± 8.1	49.4 ± 8.2	0.44 [a]
BMI (kg/m^2), mean ± SD	23.9 ± 3.4	25.7 ± 4.8	0.05 [a]
Co-morbid diseases, n (%)	11 (25.6)	18 (41.9)	0.11 [c]
Diabetes mellitus	1 (2.3)	5 (11.6)	0.20 [b]
Hypertension	4 (9.3)	15 (34.9)	< 0.001 [c]
Dyslipidemia	0 (0.0)	5 (11.6)	0.05 [b]
Thyroid	3 (7.0)	0 (0.0)	0.24 [b]
others	4 (9.3)	6 (14.0)	0.50 [c]
Indication for surgery, n (%)			
Leiomyoma	32 (74.4)	31 (72.1)	0.80 [c]
Adenomyosis	8 (18.6)	5 (11.6)	0.36 [c]
Adnexal disease	2 (4.7)	6 (14.0)	0.26 [b]
HSIL	1 (2.3)	1 (2.3)	1.00 [b]
Previous abdominal surgery, n (%)	23 (53.5)	27 (62.8)	0.38 [c]
Major abdominal surgery	12 (27.9)	12 (27.9)	1.00 [c]
Minor abdominal surgery	11 (25.6)	15 (34.9)	0.34 [c]
Operation, n (%)			
TAH c BS	30 (69.7)	29 (67.4)	0.82 [c]
TAH c unilateral SO	6 (14.0)	8 (18.6)	0.55 [c]
TAH c BSO	7 (16.3)	6 (14.0)	0.76 [c]
Operative time (min), mean ± SD	99.8 ± 29.0	101.8 ± 26.5	0.73 [a]
Anesthetic time (min), mean ± SD	132.9 ± 31.8	139.4 ± 30.5	0.33 [a]
Anesthetic substance for induction, n (%)			
Nitrous oxide	22 (51.2)	15 (34.9)	0.12 [c]
Propofol	43 (100.0)	43 (100.0)	1.00 [c]
Intraoperative drug, n (%)			
Ondansetron	22 (51.2)	27 (62.8)	0.26 [c]
Dexamethasone	19 (44.2)	23 (53.5)	0.38 [c]
Intraoperative opioid, n (%)			
Morphine	40 (93.0)	38 (88.4)	0.46 [c]
Fentanyl	3 (7.0)	5 (11.6)	0.43 [c]
Total dose of Morphine injection ± SD	22.7 ± 2.1	23.3 ± 2.7	0.22 [a]
Estimated blood loss (ml), mean ± SD	216.2 ± 28.0	168.3 ± 16.5	0.14 [a]

[a] student t-test, [b] Fisher's exact test, [c] chi-square test, significant $p < 0.05$*

BMI: body mass index, SD: standard deviation, HSIL: high grade squamous intraepithelial lesion, TAH: total abdominal hysterectomy, BS: bilateral salpingectomy, SO: salpingo-oophorectomy, BSO: bilateral salpingo-oophorectomy

Table 2. Incidence of PONV within 24 hours.

Primary Outcome	Dexamethasone group (n = 43)	Control group (n = 43)	RR (95%CI)	p value
Incidence of PONV, n (%)				
within 24 hours	14 (32.6)	21 (48.8)	0.67 (0.39-1.13)	0.09 [a]
4 hours	5 (11.6)	6 (14.0)	0.83 (0.27-2.53)	0.50 [c]
8 hours	2 (4.7)	4 (9.3)	0.50 (0.10-2.59)	0.40 [b]
12 hours	1 (2.3)	3 (7.0)	0.33 (0.04-3.08)	0.30 [b]
16 hours	0 (0.0)	4 (9.3)	0	0.58 [b]
20 hours	3 (7.0)	4 (9.3)	0.75 (0.18-3.15)	0.50 [c]
24 hours	3 (7.0)	4 (9.3)	0.75 (0.18-3.15)	0.50 [c]

[b] Fisher's exact test, [c] chi-square test, significant $p < 0.05$*
CI: confidence interval, PONV: postoperative nausea and/or vomiting, RR: relative risk

Table 3. Secondary outcomes: additional drug requirements, side effects, pain score, and length of hospital stay.

	Dexamethasone group (n = 43)	Control group (n = 43)	RR (95%CI)	p value
Additional drug requirements, n (%)				
Metoclopramide	0 (0.0)	4 (9.3)	0	0.50 [b]
Morphine	0 (0.0)	0 (0.0)	-	-
Side effects of dexamethasone, n (%)				
Dyspepsia	6 (14.0)	4 (9.3)	1.50 (0.46-4.94)	0.39 [c]
Dizziness	2 (4.7)	0 (0.0)	0	0.24 [b]
Postoperative pain score, mean ± SD				
24 hours	7.7 ± 2.3	8.6 ± 1.8	0.93 (0.03-1.83)	0.04 [a*]
24 hours	4.7 ± 1.5	5.8 ± 2.2	1.09 (0.26-1.92)	0.01 [a*]
Length of hospital stay (days), mean ± SD	3.0 ± 0.6	3.0 ± 0.0	0.09 (0.09-0.28)	0.32 [a]

[a] student t-test, significant $p<0.05$*, [b] Fisher's exact test, c chi-square test, significant $p < 0.05$*
CI: confidence interval, SD: standard deviation

Discussion

The incidence of PONV was about 32% in participants who underwent benign TAH who received 8 mg of dexamethasone postoperatively, which was lower than the study by Selzer et al[9] who used 8 mg of dexamethasone intravenously for women who underwent cesarean delivery with intrathecal morphine and reported an incidence of PONV of more than 80%. Their results might be explained by intrathecal morphine-induced PONV symptoms, which are typically more common than the intravenous route[1]. However, when compared with placebo, our study also showed no statistically significant difference, which was similar to the study by Selzer[9].

According to the difference of time administering intravenous dexamethasone before and after induction

reported the same effect, the intervention groups had lesser PONV incidence, especially in 24 hours[8]. However, dexamethasone was not given in all patients at induction period. Our study administered dexamethasone two hours after the operation refers to the time participants transferred from PACU to IPD, gained full consciousness, and complained suffering from PONV symptoms due to anesthetics gas inhaler or intraoperative opioids. Dexamethasone might have benefit in PONV and postoperative pain within 24 hours[9]. Weibo S et al reviewed 43 clinical trials that used 8 mg of intravenous dexamethasone to prevent vomiting in participants who underwent operation under general anesthesia. They recommended that a high dose of intravenous dexamethasone be used to prevent vomiting in participants who underwent an operation under general anesthesia[7], which contradicted our findings. The different results may be explained by the participants in this study who received standard treatment by an anesthesiologist using a gas inhaler, which affects PONV, which might explain the differences in findings. They assessed each participant individually using the Apfel simplified risk score and rating participants as at high or low risk of PONV. Anesthesiologists delivered intraoperative dexamethasone and antiemetic drugs to more than half of the participants, which could have contributed to the low incidence of PONV in both groups of this study.

The inflammatory process of surgery can cause pain. The dexamethasone group had considerably lower postoperative pain scores than the control group. This finding supported the concept that dexamethasone has anti-inflammatory properties and can minimize postoperative discomfort. According to Parthasarathy[10], intravenous dexamethasone 8 mg considerably reduced postoperative pain compared to placebo in surgical patients.

Our study participants reported dyspepsia and dizziness, and dizziness was reported in both groups without significant differences. None of the participants reported other complications, such as pruritus, high blood sugar levels that required insulin treatment, wound infections, and wound dehiscence.

The strengths of the study included a power of 80%, its prospective, double-blind, placebo-controlled design, adequate sample size, and absence of dropouts. Limitations of this study included the prophylactic PONV therapy during intra-operative administration of dexamethasone and antiemetic drugs would impact the incidence of PONV within 24 hours.

Conclusion

Postoperative administration of 8 mg of intravenous dexamethasone did not significantly reduce the incidence PONV in women undergoing benign TAH.

Acknowledgments

We thank (a) the Obstetric-Gynecologists, residents, and the ward nursing staff for their support throughout the research, and (b) Mr. Bryan Roderick Hamman for assistance with the English-language presentation of the manuscript under the aegis of the Publication Clinic, Research Affairs, Khon Kaen University.

Potential conflicts of interest

The authors declare no conflicts of interest.

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