Thai Journal of Obstetrics and Gynaecology
July 2023, Vol. 31, No. 4, pp. 265-272.

GYNAECOLOGY

Effects of Caffeine Dose on Bowel Function Recovery Following Gynecologic Cancer Surgery: A randomized double-blind controlled trial

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ABSTRACT

Objectives: To compare the effects of different caffeine doses on bowel function recovery following abdominal gynecological cancer surgery.

Materials and Methods: A randomized double-blind controlled trial was undertaken. 92 patients were enrolled and allocated to one of two groups: with group 1, 50 mg caffeine (n = 46) or group 2, 100 mg caffeine (n = 46). Both groups being prescribed three times a day in the postoperative period. Surgical staging had been performed on patients who were diagnosed with endometrial, ovarian, and cervical cancer. The primary outcome was to compare the time to first flatus after surgery between patients of each group. The secondary outcomes were to determine the time to first defecation, time to normal bowel movement and time to tolerate a solid diet.

Results: The mean time to first flatus was 36.54 vs 38.39 hours (p = 0.53), time to first defecation was 66.65 vs 67.08 hours (p = 0.92) and time to normal bowel sound was 26.61 vs 29.41 hours (p = 0.16). All of the results in both groups were not significantly shorter in the 100 mg caffeine group than in the 50 mg caffeine group. Furthermore, 15.22% in the 100 mg caffeine group experienced insomnia compared to 2.17% in 50 mg caffeine group (p = 0.03).

Conclusion: Drinking coffee with 50 mg of caffeine after abdominal gynecological cancer surgery did not affect bowel function recovery than 100 mg caffeine. However, it caused fewer adverse effects that could be used as additional treatment in postoperative care.

Keywords: coffee, ileus, gynecologic cancer, postoperative.

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Received: 30 September 2022, **Revised:** 14 November 2022, **Accepted:** 28 November 2022

ผลของปริมาณคาเฟอีนต่อการฟื้นตัวของการทำงานของลำไส้หลังการผ่าตัดมะเร็งทางนรีเวช: การศึกษาทดลองแบบสุ่มปกปิดสองทาง

เยาวพา จิระวงศ์ประภา, โชคชัย โชติบูรณ์, ศรีสุดา ทรงธรรมวัฒน์, เอื้อมพร สุ่มมาตย์, เมธา ทรงธรรมวัฒน์

บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบผลของปริมาณคาเฟอีนที่แตกต่างกันต่อการฟื้นตัวของการทำงานของลำไส้หลังผ่าตัดมะเร็งนรีเวชทางหน้าท้อง*

วัสดุและวิธีการ: *การศึกษาทดลองแบบสุ่มปกปิดสองทาง โดยผู้ป่วย 92 รายได้รับการลงทะเบียนและถูกจัดสรรให้อยู่ในกลุ่มหนึ่งในสองกลุ่ม ได้แก่กลุ่ม 1 ได้รับคาเฟอีน 50 มิลลิกรัม (n = 46) หรือกลุ่ม 2 ได้รับคาเฟอีน 100 มิลลิกรัม (n = 46) ทั้งสองกลุ่มถูกกำหนดให้ดื่มกาแฟสามครั้งต่อวันหลังผ่าตัด ใน ผู้ป่วยที่ได้รับการผ่าตัดเพื่อกำหนดระยะโรคของมะเร็งเยื่อบุโพรงมดลูก รังไข่ และปากมดลูก ผลลัพธ์หลักคือการเปรียบเทียบเวลาที่ผายลมครั้งแรกหลังผ่าตัดระหว่างผู้ป่วยแต่ละกลุ่ม ผลลัพธ์รองคือเวลาที่ถ่ายอุจจาระครั้งแรก เวลาที่ลำไส้คลื่นไหวปกติและเวลาที่ทนต่อการรับประทานอาหารที่เป็นของแข็ง*

ผลการศึกษา: *เวลาเฉลี่ยของการผายลมครั้งแรกคือ 36.54 ชั่วโมงเทียบกับ 38.39 ชั่วโมง (p = 0.53) เวลาในการถ่ายอุจจาระครั้งแรกคือ 66.65 ชั่งโมงเทียบกับ 67.08 ชั่วโมง (p = 0.92) เวลาที่ได้ยินเสียงลำไส้ปกติคือ 26.61 ชั่วโมงเทียบกับ 29.41 ชั่วโมง (p = 0.16) ผลลัพธ์ทั้งหมดในทั้งสองกลุ่ม ในกลุ่มคาเฟอีน 100 มิลลิกรัมไม่ลดลงอย่างมีนัยสำคัญเมื่อเทียบกับกลุ่มคาเฟอีน 50 มิลลิกรัม นอกจากนี้ ร้อยละ 15.22 ในกลุ่มคาเฟอีน 100 มิลลิกรัมมีอาการนอนไม่หลับเทียบกับร้อยละ 2.17 ในกลุ่มคาเฟอีน 50 มิลลิกรัม (p = 0.03)*

สรุป: *การดื่มกาแฟที่มีคาเฟอีน 50 มิลลิกรัมหลังการผ่าตัดมะเร็งทางนรีเวชทางช่องท้องส่งผลต่อการฟื้นตัวของการทำงานของลำไส้ไม่แตกต่างอย่างมีนัยสำคัญจากการดื่มกาแฟที่มีคาเฟอีน 100 มิลลิกรัม แต่มีผลข้างเคียงน้อยกว่าและสามารถใช้เป็นการรักษาเพิ่มเติมในการดูแลหลังผ่าตัดได้*

คำสำคัญ: *กาแฟ, ลำไส้หยุดทำงาน, มะเร็งทางนรีเวช, หลังผ่าตัด*

Introduction

Postoperative ileus (POI) is defined as a temporary cessation of coordinated bowel motility, which causes the obstruction and intolerance of oral intake following nonabdominal or abdominal surgery, especially after laparotomy for any cancers[1]. The incidence of POI in patients who have undergone hysterectomy and radical hysterectomy with pelvic lymph node dissection for treatment of gynecologic malignancy is 10.5-15.5% and 7.9-20.0%, respectively[2].

Postoperative gastrointestinal dysmotility causes abdominal distension, abdominal pain, nausea, vomiting, and abdominal cramps. Gastrointestinal dysfunction is usually self-resolved[3]. However, when POI is prolonged, it leads to patient discomfort, dissatisfaction, prolonged hospital stays, and other postoperative complications, that impact on health care costs[4,5].

Therefore, to reduce the incidence of POI, several methods are used to prevent and restore intestinal function after surgery such as minimal invasive surgery[6], epidural anesthesia[7], multimodal analgesia[8], other pharmacological drugs, chewing gum[9], and coffee. Coffee is a popular beverage worldwide and has multiple systemic effects on the neuropsychiatric[10], cardiovascular[11], and gastrointestinal system[12]. For most adults, consumption of up to 400 mg of caffeine a day appears to be safe[13].

There have been several studies which have shown the beneficial effects of caffeinated coffee consumption on POI[14-17]. However, from previous studies, it is clear that many different doses of caffeine have been used. Some studies have used moderate amounts of caffeine up to high doses (100 mg to 100 g for consumption three times a day) which may present a risk of serious adverse effects when compared with normal daily coffee that has about 27 to 173 mg per drink. Therefore, we conducted this study to compare the effects of caffeine dose that has been used in normal daily life (instant coffee, 50 mg) on bowel function recovery to determine that the low dose caffeine coffee was effective and safer for improving intestinal function and reducing the incidence of POI after gynecological cancer surgery

Materials and Methods

This was a randomized double-blind controlled trial, conducted in the Gynecological Cancer Unit, Department of Obstetrics and Gynecology, UdonThani Hospital, UdonThani, Thailand, during January to July 2022. The study protocol was approved by UdonThani Hospital Ethical Committee on human research (number 90/2564).

The inclusion criteria were that the patients were aged between 18 and 75 years old who were diagnosed with cervical cancer, endometrial cancer, ovarian cancer, and other cancer (such as uterine sarcoma) and planned for surgical staging (abdominal hysterectomy, salpingo-oophorectomy, pelvic lymph node dissection, omentectomy, peritoneal washing, appendectomy, and other surgical procedure). The exclusion criteria were hypersensitivity or allergy to caffeine, thyrotoxicosis, cardiac arrhythmia, liver disease, chronic kidney disease, irritable bowel disease, chronic constipation (defined as defecation less than or equal to 2 time a week), history of previous bowel surgery, bowel anastomosis, a need for intensive care for more than 24 hours postoperatively, and a need for nasogastric tube drainage postoperative. The study details were explained to all patients and their written informed consent was obtained prior to the patients' participation in this study. The randomization was performed when the patients came to the gynecological oncology unit. Eligible patients were randomly assigned to one of two groups by investigator who consecutively opened sequentially numbered, opaque, sealed envelopes. The randomization was performed using computer

generated numbers with a blocked randomization protocol. Group 1 drank three cups of caffeinated coffee in hot water 100 mL (100 mg caffeine per cup) in one day, Group 2 drank three cups of caffeinated coffee in hot water 100 mL (50 mg caffeine per cup) in one day, beginning on the morning after surgery at 7:00, 12:00, 17:00 o'clock within 30 minutes under the supervision of a nurse or a doctor. The same coffee package in both groups was prepared using conventional coffee (Nescafe® red cup).

A standard protocol for pre-operation was implemented for all participants. All operations were performed by the gynecological oncologist's team. During the postoperative period, nonsteroidal analgesia and antiemetic agents were provided according to the patients' request protocol. Early ambulation was encouraged. Postoperative feeding regimen was standardized, liquid diet was begun on the first postoperative day in the morning and stepped up to a regular diet in 24 hours as the individual patients could tolerate.

The primary outcome measurement was the time to first pass of flatus after surgery. The secondary outcomes were the time to first defecation, time to normal bowel movement after surgery, time to tolerate solid diet, POI symptoms, side effects of postoperative coffee intake, additional antiemetics and analgesics used in postoperative care and the length of hospital stay. The time of first flatus and defecation were recorded based on the patient's own statements. The time to normal bowel movement after surgery was defined as the time to audible bowel sound 5 times in 2 minutes[18]. The time to tolerate solid diet was defined as the patients tolerance to intake solid food without nausea or vomiting within 4 hours after meal. POI symptoms and signs were evaluated 3 times daily. The hospital discharge criteria were stable vital signs for at least 24 hours, ability to ambulation, ability to tolerate a solid diet without nausea and vomiting, normal urination, and the absence of any complication after surgery. All data was collected by investigators who were blinded to the study allocation.

Sample size calculation

The number of samples was calculated based on a Güngördük et al' s study. The formula of non-inferior trial by N4studies application was used. The mean time of the first flatus was 33.28 hours in 100 mg caffeine group (control) with the standard deviation was 10.90. The mean difference was 8 hours with the margin of 2. Considering the power of 80% with and α level 0.01. The calculated sample size was 41 patients in each group. Assuming a 10% dropout rate, 92 patients were included.

Statistical analysis

Statistical analyses were performed using STATA statistical program version 13. Continuous data were reported as the mean and standard deviation. Categorical data were shown as the number and percentage. A t-test for comparison of continuous data, and Pearson chi-square test for categorical data. P values < 0.05 was considered statistically significant.

Results

In this study, 94 patients were enrolled; 47 patients were randomly assigned to the 50 mg caffeine coffee group and 47 patients were randomly assigned to the 100 mg caffeine coffee group. Two patients (one in each group) were excluded after surgery because of an intestinal injury during surgery. Ultimately, 46 patients in the 50 mg caffeine group and 46 patients in the 100 mg caffeine group were analyzed. The reason for exclusion is shown in Fig. 1.

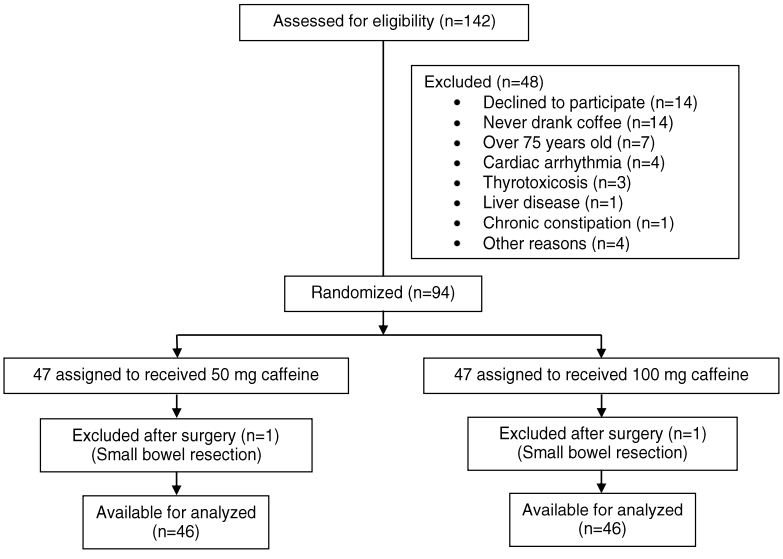

Fig. 1. Consort diagram

The demographic characteristics of the subject are presented in Table 1. In the 50 mg caffeine group, endometrial cancer (43.48%) was the most common indication for surgery than ovarian cancer (39.13%) and cervical cancer (15.22%), respectively. In the 100 mg caffeine group, the most common indication for surgery was ovarian cancer (56.52%) followed by endometrial cancer (32.61%) and cervical cancer (10.87%). There was no statistically significant difference in age, body mass index (BMI), gravida, history of alcohol drinking, and previous abdominal surgery. The surgical characteristics of both caffeine groups are shown in Table 2. The type of operative procedure, duration of operation, duration of anesthesia, estimated blood loss, and blood transfusion showed no significant differences.

Table 1. Baseline characteristics of the patients.

	Coffee 50 gm Group (n = 46)	Coffee 100 gm Group (n = 46)	p value
Age (year)	54.48 ± 9.21	51.35 ± 11.49	0.16
Body mass index (kg/m^2)	25.46 ± 4.97	24.56 ± 4.95	0.39
Gravida	1.61 ± 1.24	1.80 ± 1.45	0.49
Alcohol drinking	1 (2.17)	1 (2.17)	1.00
Hypertension	12 (26.09)	8 (17.39)	0.31
Diabetes mellitus	10 (21.74)	3 (6.52)	0.036
Other disease	21 (45.65)	9 (19.57)	0.008
Indication for surgery			
Endometrial cancer	20 (43.48)	15 (32.61)	0.28
Ovarian cancer	18 (39.13)	26 (56.52)	0.10
Cervical cancer	7 (15.22)	5 (10.87)	0.54
Other cancer	1 (2.17)	0 (0)	0.36
Previous abdominal surgery	23 (50.00)	23 (50.00)	1.00

Data are presented as mean ± standard deviation or number (%)

Table 2. Surgical characteristics of the patients.

	Coffee 50 gm Group (n = 46)	Coffee 100 gm Group (n = 46)	p value
Hysterectomy	43 (93.48)	40 (86.96)	0.29
Salpingectomy and/or oophorectomy	45 (97.83)	43 (93.48)	0.307
Pelvic LN dissection	19 (41.30)	16 (34.78)	0.52
Omentectomy	35 (76.09)	34 (73.91)	0.81
Appendectomy	1 (2.17)	4 (8.7)	0.17
Peritoneal washing	20 (43.48)	22 (47.83)	0.68
Lysis adhesion	36 (78.26)	39 (84.78)	0.42
Other procedure	5 (10.87)	4 (8.70)	0.73
Duration of operation (min)	94.24 ± 26.96	92.41 ± 29.92	0.76
Duration of anesthesia (min)	112.07 ± 28.78	108.70 ± 30.16	0.58
Blood transfusion	3 (6.52)	4 (8.7)	0.69
Estimated blood loss (mL)	95 ± 85.08	128.80 ± 171.14	0.23

Data are presented as mean ± standard deviation or number (%)
min: minutes, LN: lymph node

The primary outcomes and secondary outcomes of the study are shown in Table 3. The mean time to first flatus, the time to first defecation, and time to normal bowel sound in 100 mg caffeine group were all insignificantly shorter than in the 50 mg caffeine group (36.54 vs 38.39 hours, p = 0.53, 66.65 vs 67.08 hours, p = 0.92, 26.61 vs 29.41 hours, p = 0.16, respectively). The mean time to tolerate a solid diet and the length of hospital stay in the 50 mg caffeine group were not significantly shorter than in the 100 mg caffeine group. In the postoperative period, 73.91% of patients in the 100 mg caffeine group and 63.04% in the 50 mg caffeine group required additional analgesic drugs (p = 0.26), 23.91% in the 100 mg caffeine group and 15.22% in the 50 mg caffeine group required additional antiemetic drugs (p = 0.29).

Table 3. Study outcomes.

	Coffee 50 gm Group (n = 46)	Coffee 100 gm Group (n = 46)	p value
Mean time of first flatus (hours)	38.39 ± 14.41	36.54 ± 13.36	0.53
Mean time of first bowel movement (hours)	29.41 ± 11.70	26.61 ± 6.69	0.16
Mean time of first defecation (hours)	67.08 ± 20.18	66.65 ± 20.10	0.92
Additional analgesic	29 (63.04)	34 (73.91)	0.26
Additional antiemetic	7 (15.22)	11 (23.91)	0.29
Postoperative ileus	0 (0)	1 (2.17)	0.32
Side effect of caffeine			
Palpitation	1 (2.17)	2 (4.35)	0.56
Insomnia	1 (2.17)	7 (15.22)	0.03
Time to tolerate diet (days)	2.52 (0.51)	2.54 (0.50)	0.84
Length of hospital stay (days)	4.5 (1.22)	4.89 (1.66)	0.20

Data are presented as mean ± standard deviation or number (%)

In both caffeine consumption groups, 2 patients in the 100 mg caffeine group and 1 patient in the 50 mg caffeine group had palpitation (4.35% vs 2.17%, p = 0.56). Furthermore, 7 patients in the 100 mg caffeine group and 1 patient in the 50 mg caffeine group experienced insomnia (15.22% vs 2.17%, p = 0.03), this was statistically significant. Only one patient in the 100 mg caffeine group had postoperative ileus symptoms. However, no patients required re-admission or re-operation after hospital discharge.

Discussion

This study demonstrated that patients who drank 100 mg caffeine in the postoperative period after abdominal gynecological surgery experienced a shorter; mean time to first flatus, mean time to first defecation and time to normal bowel sound than patients who drank 50 mg caffeinate after surgery, but this was not significantly different. However, in the 50 mg caffeinated coffee group the time to tolerate solid food and length of hospital stay were insignificantly shortened. Furthermore, the need for additional analgesia and/or antiemetics was lower in the 50 mg caffeine group and adverse effects after coffee consumption during the postoperative period were significantly more common in the 100 mg caffeine group than in the 50 mg caffeine group. In this present study, only one patient in the 100 mg caffeine group had POI symptoms.

From the literature review, several studies found that coffee consumption could encourage bowel function recovery and may reduce POI[14-17]. A systematic review and meta-analysis by Gkegkes et al[14] reviewed about the effect of caffeinated coffee intake on postoperative ileus, four randomized studies were enrolled to this meta-analysis (3 studies referred to colorectal procedure and 1 study referred to gynecological procedure). The postoperative administration of caffeinated coffee significantly reduced the time to first bowel movement, the time to first flatus, the time to defecation and time to tolerance of a solid diet. Güngördük et al[16] randomly assigned 114 patients to receive either 100 g caffeinate three times a day or no treatment after abdominal gynecological cancer surgery. The coffee drinkers experienced significantly shorter mean time to flatus, mean time to defecation and mean time to ability to tolerate solid food. Likewise, Koseoglu et al[17] studied patients that had undergone elective cesarean section, randomly assigned 108 patients to receive either 100 mg caffeinate three times a day and no intervention after cesarean section. The mean time to passage of first flatus, the time to defecation and time to tolerate a solid diet were significantly shorter in the coffee group.

This randomized trial tried to demonstrate that 50 mg caffeinated, which is a normal commercial coffee dose, had the similar effect with the 100 mg caffeinate, which is usually in the fresh coffee, in the postoperative period after abdominal surgery. Thus, we suggested that patients diagnosed with gynecological cancer who undergo abdominal surgery should drink coffee with 50 mg of caffeine during the postoperative period, which was effective in restoring intestinal function after surgery. This was not significantly different from drinking coffee with a large amount of caffeine and significantly fewer adverse effects with lower cost.

The strength of this study was a prospective randomized trial that the investigators and patients were blinded. The participants were randomly assigned by computer generated numbers for allocation of two caffeinated coffee groups. Moreover, the two groups had similar demographic and surgical profiles. The limitations of this study were that (1) it did not have a placebo group, (2) the time of flatus and defecation were retrieved from patients and might, in some cases, be inaccurate and (3) many data collectors were employed (doctors or a nurse), which can cause discrepancies in the evaluation such as bowel sound examination. (4) Also, we avoided disturbing the postoperative patients at the night or during sleeping time, therefore some examinations were postponed. (5) Normally, surgical time in oncologic surgery was not less than 150-180 min and blood loss was not less than 500 cc. However, this study was conducted in a single center with only two highly experienced gynecological oncologists, the short duration of operation and less amount of intraoperative blood loss could affect the postoperative bowel function recovery.

Conclusion

Drinking coffee with 50 mg of caffeine after abdominal gynecological cancer surgery could

accelerate bowel function recovery and had statistically significant fewer adverse effects, that could be used as an additional treatment in postoperative care.

Acknowledgments

We gratefully acknowledge gynecological oncologists, gynecological cancer clinic UdonThani Hospital team, the investigators and patients who participated in this trial.

Potential conflicts of interest

The authors declare no conflicts of interest.

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