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# Role Of Caffeine As A Bowel Stimulant After Major Gynecological Surgeries

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# **Abstract**

**Objective:** To investigate the role of caffeine as a bowel stimulant after major gynecological surgeries. Coffee is a low-cost strategy to accelerate postoperative recovery of intestinal function/motility after colorectal and gynecological surgery. Postoperative ileus or bowel paralysis is quite common in the postoperative period after abdominal surgery, such as elective colectomy, colorectal resection, caesarean section, or gynecological surgery. The occurrence of postoperative ileus leads to prolonged patient hospital stay.

**Methods:** This randomized control study was single-centered, conducted in Obstetrics and Gynecology department of Liaquat National Hospital Karachi after approval from Research and Ethical review committee of hospital (Ref#:0416-2019-LNH-ERC ). The duration of study was one year from 20<sup>th</sup> February 2019 to 20<sup>th</sup> February 2020. In this randomized controlled trial, 120 patients were randomly assigned before major gynecological surgery into control and intervention groups.

**Results**: A total of 120 women who met the inclusion and exclusion criteria were included in the study. Descriptive statistics of the demographic data were similar between the two groups.

Statistical significant difference (p= 0.001) was found between the mean time ( $23\pm6.9$  vs.  $30\pm9.4$  hours) for the passage of first flatus between the intervention group and the control group. Mean time to first bowel movement ( $37\pm6.8$  vs.  $30\pm4.8$  hours), mean time to first defecation ( $42\pm8.3$  vs. $32\pm6.6$  hours) and mean length of hospital stay after surgery ( $101\pm7.8$  vs. $72\pm5.6$  hours) showed statistical significant difference between the two groups with p-value<0.05.

**Conclusion:** Coffee consumption (caffeine) after major gynecological surgery played an important role as a bowel stimulant. Drinking coffee reduced the mean time for first passage of flatus, First bowel sound, first defecation, and hours of hospital stay after surgery.

Keywords: Bowel, Caffeine, Gynecology, Flatulence.

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## Introduction

Major gynecological surgeries are defined as surgical procedures done on the female reproductive system aimed at treating female genital patho-

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Email: kanwalmasroor95@gmail.com Date of Submission: 8<sup>th</sup> March 2024 Date of 1 st Revision: 16<sup>th</sup> May 2024 Date of Acceptance: 23<sup>th</sup> May 2024 pathologies and involve either removal or treatment of organs that are included in the aforesaid classification - commonly performed and encompass hysterectomy, dilation and curettage biopsies and laparoscopic surgeries. Among all gynecological surgeries, hysterectomy is the most performed procedure and is usually indicated for removal of fibroid uterus, dysfunctional uterine bleeding, leiomyoma, chronic pelvic disease prolapses and malignancy<sup>1</sup>.

Laparoscopic surgeries are next in line and are done to remove ovarian cysts, polycystic ovaries, and treatment of infertility<sup>2</sup>, whereas hysteroscopic procedures are performed for removing adnexal mass, post-menopausal and perimenopausal bleeding<sup>3</sup>.

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Although bowel function is a vital concern in post-operative care and delayed bowel recovery, the most encountered challenge in major gynecological surgeries, still there has been no significant progress in understanding or treating it. The definition of post-operative ileus varies in different reports and is determined commonly by the recovery of bowel sounds and passage of exhaust gas. This leads to abdominal discomfort and distension, pain, nausea, vomiting and delayed passage of stools. The said factors lead to complications like prolonged length of stay in the hospital and pneumonia<sup>4</sup>.

Caffeine, the most studied and utilized substance in the world, has various effects on the human body. It has been found that it has a profound effect on physical and mental performance, neuroprotection, and pregnancy. Caffeine has been observed to also have a significant effect on bowel activity leading to less time for first bowel movement and early defecation after surgery. It is found to be a colonic stimulant and increases colonic motility<sup>5</sup>.

It is present naturally in coffee, black tea, chocolate, green tea and artificially in energy drinks, soft drinks, and some types of milk beverages. Among these, coffee has widely been used as a source of caffeine and has been consumed in traditional medicines of Asian countries for biological activities related to aging, infectious diseases, and cardioprotective effects<sup>6</sup>.

Coffee has been studied widely for its potential benefits in post-operative bowel recovery. Several trials have found that coffee administration can reduce postoperative ileus. In a study done by Hasler in 2019 on patients undergoing laparoscopic colorectal elective surgery, coffee was found to decrease the time to nasogastric tube removal and hospital stay<sup>7</sup>.

Additionally, Zaman Abadi in 2021 in a study on women undergoing C-section found that coffee intake led to shorter postoperative bowel movement and defecation times<sup>8</sup>.

The objective of the study is to investigate the effect of coffee consumption on acceleration of the recovery of bowel function after major gynecological surgeries. Thus, consumption of coffee can be used as an adjunct to minimize the development of post-surgical complications such as paralytic ileus after gynecological surgeries.

# Methodology

This randomized control study was single-centered, conducted in Obstetrics and Gynecology department of Liaquat National Hospital Karachi after approval from Research and Ethical review committee of hospital (Ref#:0416-2019-LNH-ERC). The duration of study was one year from 20<sup>th</sup> February 2019 to 20<sup>th</sup> February 2020. Sample size was calculated using the openepi sample size calculator with N=120 (Two-sided significance level (1-alpha):95; Power (1-beta, % chance of detecting):80; Percent of Exposed with Outcome: 25<sup>11</sup>).

In this experimental study, 120 preoperative female subjects were randomly assigned and were divided into two groups (control & intervention group). Control group (n=60) included patients who were not given coffee postoperatively. However, the intervention group(n=60) included patients who were given coffee three times daily at intervals of 8 hours, 12 hours and 20 hours postoperatively.

Admitted female patients with an age range of 45-75 years, undergoing either of the major gynecological surgeries such as abdominal hysterectomy, bilateral salpingo-oophorectomy, laparotomy/myomectomy or as part of staging surgery for endometrial, ovarian, cervical or tubal cancers. Patients who underwent minor gynecological procedures, patients with cesarean sections and those who had surgeries under spinal or epidural anesthesia were excluded from study.

The data collection was started after taking ethical committee approval. An informed consent was obtained from each participant. A demographic profile, complete medical history, gynecological history of each subject was gathered on a questionnaire.

The variable to be measured primarily included the average time to pass the first flatus post-operatively. Secondary outcome measures were the time to first bowel movement, time to first defecation and length of hospital stay after surgery. All this information was collected on a predesigned questionnaire.

Statistical Analysis was done on SPSS Version 22. Quantitative variables (Age in years, BMI in kg/m2 & Gravidity) were measured as Mean± Standard Deviation and qualitative variables (type of gynecological surgery) were represented as frequency and percentages. Student's t-test was used to compare the means of both the primary and the secondary outcome measures among the control and intervention groups. A p-value < 0.05 was considered as statistically significant.

#### Results

A total of 120 women who met the inclusion criteria were included in the study. Descriptive statistics of the demographic data including age in years, body mass index in kg/m² and parity were calculated for both the control and the intervention group. Mean age in the control group was 58± 8.7 and in the group which consumed coffee after the gynecological surgery had a mean age of 59± 2.3. Student t-test showed no statistical mean differences between the age in both the groups. Similarly, no statistical differences were observed among mean BMI and parity in both the groups. (Table-1)

Among the gynecological surgeries, most common surgical indication reported in both the groups was total abdominal hysterectomy and bilateral salpingo-oophorectomy followed by laparotomy/myomectomy, endometrial, ovarian, cervical, or tubal cancer as in Table-2.

The variable to be measured primarily in our study included the average time to pass the first flatus post-operatively. Results of the primary outcome of the study are shown in Table-3. Statistical significant difference was found between the mean time (23  $\pm$  6.9 vs. 30  $\pm$  9.4 hours) for the passage of first flatus between the intervention group (consumed coffee early during the postoperative period)

and the control group (without the coffee consumption) postoperatively.

Moreover, secondary outcomes measures including mean time to first bowel movement (37 $\pm$ 6.8 vs. 30 $\pm$ 4.8 hours), mean time to first defecation (42 $\pm$ 8.3 vs.32 $\pm$ 6.6 hours) and mean length of hospital stay after surgery (101 $\pm$ 7.8 vs.72 $\pm$ 5.6 hours) showed to be statistically significant between the two groups with p-value<0.05.

Comparison of frequency of postoperative abdominal symptoms in both the coffee and control group was found to be statistically significant. In control group, twenty nine patients (48.3%) complaint of abdominal pain compared to only nine patients (15%) in the coffee group and significant difference was reported among the two groups. Similarly, Increased frequency of abdominal distention( 26.6% vs 8.3%) with additional use of analgesics(20% vs 3.3%) after surgery was reported in control group compared with the intervention coffee group. Drinking coffee after the surgery was well tolerated by all patients, and no adverse events were reported in the intervention group based on coffee intake.

Table 1. Descriptive statistics of quantitative variables

Study Variables	Control group (n=60) Mean ± SD	Intervention group (n=56)	p-value
Age (years)	58 ± 8.7	59 ± 2.3	0.44
BMI (kg/m²)	27 ± 2.3	28 ± 3.1	0.23
Gravidity	2 ± 1.2	2 ± 1.5	0.48

Table 2. Frequency & percentages of type of gynecological surgery in both groups

Type of gynecological surgery	Control group N=60	Coffee group N=56	
Total abdominal hysterectomy	24(40%)	22 (36.6%)	
Bilateral salpingo-oophorectomy	12(20%)	08(13.3%)	
Laparotomy/myomectomy	10(16.6%)	12(20%)	
Endometrial cancer	04(6.6%)	02 (3.3%)	
Ovarian cancer	05 (8.3%)	07(11.6%)	
Cervical cancer	02 (3.3%)	03 (5%)	
Tubal cancer	03(5%)	02(3.3%)	

**Table 3.** Comparison of means of primary and secondary outcome measures between the two groups.

Study outcome	Control group (n=60)	Coffee group (n=56)	p-value
Mean time of first flatus (hours)	30 ± 9.4	23 ± 6.9	0.001
Mean time of first bowel movement (hours)	37 ± 6.83	0 ± 4.8	0.02
Mean time of first defection (hours)	42 ± 8.3	32 ± 6.6	0.03
Mean length of Hospital stay post-surgery (hours)	101 ± 7.8	72 ± 5.6	0.001

# **Discussion**

Postoperative ileus is explained as slow or absent gastrointestinal motility after surgical procedures. Clinically, it is established by intolerance of oral intake and abdominal distention due to inhibition of the gastrointestinal motility without signs of mechanical obstruction. Generally, patients who went through abdominal surgical procedure do develop some degree of temporary impairment of gastrointestinal motility. Often, this is an uncomplicated sequel with mild effect on results. Some surgeons consider it as a normal physiologic response of the intestine to surgery<sup>12</sup>. Prolonged gastrointestinal impairment, however, can lead to several difficulties including patient discomfort, prolonged hospital stays and increased healthcare costs <sup>13</sup>.

As ileus is a common sequel after abdominal surgeries, various protocols regarding post-surgical quick recovery of the patients can decrease their stay in the hospital and cause improvement in the outcome of the patients. Recent studies on coffee consumption after colorectal and gynecological surgeries have proven to reduce the gastrointestinal impairment. In a study conducted by Holland et al, post-operative coffee consumption was found to be safe and inexpensive and it reduced the length of hospital stay in patients having resection of their small intestines (intervention coffee group had a hospital stay of 6.7 median days and the group who was given only water post-operatively had a median hospital stay of 7.7 days)<sup>14</sup>.

Descriptive statistics in our study did not show any significant differences among age, body mass index and parity in both the groups. This was in agreement with the findings of Gungorduk et al, in which the participant characteristics were similar between the two groups<sup>15</sup>.

In our study, most common operative procedure reported in both the groups was total abdominal hysterectomy followed by bilateral salpingo-oophorectomy. These findings were not in agreement with the results of Gungorduk et al. He found endometrial cancer to be the most common surgical indication, followed by endometrial hyperplasia in both groups<sup>15</sup>.

The results of our study showed that coffee consumption after gynecological surgeries reduced the mean time for passage of first flatus to seven hours in the intervention group compared to control group (30±9.4 versus 23±6.9).

This was consistent with the meta-analysis of randomized control study conducted by Eamudomkarn N et al. In his meta-analysis, he included the study characteristics of Gungorduk K et al on effects of coffee consumption on gut recovery after surgery of gynecological cancer patients and the findings of his primary outcome measure i.e; mean time to passage of flatus after surgery (30.2±8.0 vs 40.2±12.1 hours) were in agreement with the results of our study<sup>16,17</sup>.

In our study, secondary outcome measures were analyzed in both the groups which included; mean time to first bowel movement (37±6.8 vs. 30±4.8 hours), mean time to first defecation (42±8.3 vs.32±6.6 hours) and mean length of hospital stay after surgery (101±7.8 vs.72±5.6 hours).

Among the findings of the secondary outcome measures in our study, mean time to first bowel movement (37±6.8 vs. 30±4.8 hours) showed significant differences between the two groups. These findings were in agreement with a study conducted by Zamanabadi et al who found that coffee intake led to shorter postoperative bowel movement in women undergoing C-section<sup>8</sup>. Similar findings were

also reported by Parnasa et al and Gkegkes et al. Their results concluded that postoperative caffeine consumption led to a significantly shorter time to first bowel movement<sup>18,19</sup>.

However, an interventional study conducted by Rabieipour et al investigating the effect of coffee on bowel movements after surgery, found that the time of onset of bowel movements was not statistically different between the coffee and the control groups which was contradictory to the findings of our study<sup>20</sup>.

Another concordant study conducted by Güngördük k et al, noticed that, in the postoperative period, the number of intestinal movements heard by auscultation method, time of passage of first gas and first defecation in patients who consume coffee are shorter than patients who do not have it. They had shorter stays in the hospital, also<sup>15</sup>.

Moreover, we found significant difference of the mean time of first defecation (hours) between the coffee and the control groups (42±8.3vs32±6.6). This was consistent with the study conducted by Watanabe J et al. In his meta-analysis, he included thirteen randomized control trials. Of the 13 trials, two were on gynecological surgery in which, he observed that intake of coffee after surgeries significantly decreased mean hours of first defecation (10.1hours).He also observed that coffee decreased patients stay in the hospital after gynecological surgery (mean difference; 1.5 days) which was also concurrent with the results of our study ((101±7.8 vs.72±5.6 hours).<sup>21</sup>

Another meta-analysis conducted by Yang et al was in agreement with the findings of the secondary outcome measures of our study. He included four randomized control trials with 312 subjects who underwent colon surgeries. He concluded, that postoperative coffee use, reduced the patient stay in the hospital by 0.95 days; and the appearance of first bowel sounds by a mean difference of 10.36 hours<sup>22</sup>.

In another study done by Kane et al, coffee shortened the time to the passage of first stool after surgery with a mean difference of 9.38 with significant p-value. Moreover, patient stay in the hospital was also shortened in the coffee intervention group along with their better tolerance to food post-operatively in comparison to those who did not use coffee after surgery<sup>23</sup>.

On the contrary, Hayashi K et al conducted a single-centered RCT, to study efficacy of coffee on post-surgical intestinal motility. In his study, there was no significant mean time differences to the passage of first stool (55.1 vs 69.7; p/ d" 0.13) and first flatus (9.3 vs 12.6; p/ d" 0.35) after the surgery among the coffee and control group<sup>24</sup>.

Our results also showed increased frequency of abdominal symptoms in control group compared to group with coffee consumption. This could be explained by the study conducted by Tajik N et al who mentioned the beneficial effects of chlorogenic acid present in coffee on various inflammatory factors. It produces it's action against inflammation by blocking the formation of multiple inflammatory markers( TNF-alpha & IL-6). Moreover, it also reduces the formation of edema and thus improving the pain. All these factors play an important role in preventing post-operative ileus and shortens duration of hospital stay<sup>25</sup>.

Strength of our study was that both groups had familiar demographic data and gynecological surgery data. In our study, blinding was not done which is one of the limitations. Moreover, increased mean age of the participants in both the groups could be one of the confounding factors affecting the results of the study. Future Recommendations include more randomized control studies which should be triple blinded.

## Conclusion

The current randomized control trial suggests that coffee plays a major role as a bowel stimulant after major gynecological surgeries by decreasing the mean time for passage of first flatus, first bowel sound, first passage of stools, and patient stay in the hospital post-operatively.

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## References

- Bhat S, Bhat N, Niyaz I, Wani R. A 2-year histopathological audit for non-oncological hysterectomies in a tertiary care hospital. International Journal of Reproduction, Contraception, Obstetrics and Gynecology 2017;6(8):3261. [DOI: 10.18203/2320-1770.ijrcog20173145].
- Chisty S, Chowdhury L. Laparoscopic Management of Benign Ovarian Cysts: Three Years Experience in Combined Military Hospital, Dhaka. Journal of Armed Forces Medical College, Bangladesh 2019;15(2):209-12. [DOI: 10.3329/jafmc.v15i2.50840].
- Sarvi F, Alleyassin A, Aghahosseini M, Ghasemi M, Gity S. Hysteroscopy: A necessary method for detecting uterine pathologies in post-menopausal women with abnormal uterine bleeding or increased endometrial thickness. Turk J Obstet Gynecol 2016;13(4):183. [DOI: 10.4274/tjod.66 674].
- Su'a B, Hill AG. Opiates in Enhanced Recovery After Surgery: still not convinced. ANZ J Surg 2015 Nov 1;85(11):795. [DOI: 10.1111/ans.13289].
- Gkegkes ID, Minis EE, Iavazzo C. Effect of caffeine intake on postoperative ileus: a systematic review and meta-analysis. Dig Surg 2020;37(1):22-31. [DOI: 10.1159/000496431].
- Rodak K, Kokot I, Kratz EM. Caffeine as a factor influencing the functioning of the human body— Friend or foe? Nutrients 2021;13(9):3088. [DOI: 10.3390/nu13093088].
- Hasler-Gehrer S, Linecker M, Keerl A, Slieker J, Descloux A, Rosenberg R, Seifert B, Nocito A. Does coffee intake reduce postoperative ileus after laparoscopic elective colorectal surgery? A prospective, randomized controlled study: the coffee study. Diseases of the Colon & Rectum 2019;62(8):997-1004. [DOI: 10.1097/DCR.000000 0000001405].
- Zamanabadi MN, Alizadeh R, Gholami F, Aryafar M. Effect of caffeine on postoperative bowel movement and defecation after cesarean section. Ann Med Surg (Lond). 2021;68:102674. [DOI: 10.1016/ j.amsu.2021.102674].
- Nehlig A. Effects of Coffee on the Gastro-Intestinal Tract: A Narrative Review and Literature Update. Nutrients 2022;14(2):399. [DOI: 10.3390/nu14020 399].
- Cornwall HL, Edwards BA, Curran JF, Boyce S. Coffee to go? The effect of coffee on resolution of ileus following abdominal surgery: A systematic review and meta-analysis of randomised contro lled trials. Clin Nutr 2020;39(5):1385-94. [DOI: 10.

- 1016/j.clnu.2019.06.003].
- Trukhan DI, Degovtsov EN, Degovtsova EA, Karasev VE. Postoperative ileus in obstetric and gynecological practice: a prospective solution to the problem: A review. Gynecology 2023;25( 3):301–306. [DOI: 10.26442/20795696.2023.3. 202288].
- Buchanan L, Tuma F. Postoperative Ileus. 2023 Jul 31. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://pubmed.ncbi.nlm.nih.gov/32809615/. Accessed on 19<sup>th</sup> May 2024.
- 13. Stakenborg N, Gomez-Pinilla PJ, Boeckxstaens GE. Postoperative Ileus: Pathophysiology, Current Therapeutic Approaches. Handb Exp Pharmacol 2017;239:39-57. [DOI: 10.1007/164 2016 108].
- Holland C, Shaffer L, Dobkin E, Hall J. Coffee administration to promote return of bowel function after small bowel resection: A randomized, controlled trial. Am J Surg 2023; 226(2):156-160. [DOI: 10.1016/j.amjsurg.2023.03.026].
- Güngördük K, Gülseren V, Özdemir ÝA. The use of coffee for the prevention of ileus following abdominal surgery: A review of the current evidence. Pelviperineology 2022;41(3):189-193. [DOI: 10.34 057/PPj.2022.41.03.2022-3-2].
- Eamudomkarn N, Kietpeerakool C, Kaewrudee S, Jampathong N, Ngamjarus C, Lumbiganon P. Effect of postoperative coffee consumption on gastrointestinal function after abdominal surgery: A systematic review and meta-analysis of randomized controlled trials. Sci Rep 2018;8(1):17349. [DOI: 10.1038/s41598-018-35752-2].
- Gungorduk K, Ozdemir IA, Gungorduk O, Gulseren V, Gokcu M, Sanci M. Source: Am J Obstet Gynecol 2017;216(2):145 e1- e7. [DOI: 10.1016/j.ajog.2016.10.019].
- Parnasa SY, Marom G, Bdolah-Abram T, Gefen R, Luques L, Michael S et al. Does caffeine enhance bowel recovery after elective colorectal resection? A prospective double-blinded randomized clinical trial. Tech Coloproctol 2021;25(7):831-839. [DOI: 10.1007/s10151-021-02450-7].
- Gkegkes ID, Minis EE, Iavazzo C. Effect of caffeine intake on postoperative ileus: a systematic review and meta-analysis. Dig. Surg. 2020; 37(1):22–31. [DOI: 10.1159/000496431].
- Alizadeh R. Effects of prehospital traige and diagnosis of ST segment elevation myocardial infarction on mortality rate. Int. J. Gen. Med. 2020; 13:569. [DOI: 10.2147/IJGM.S260828].

- Watanabe J, Miki A, Koizumi M, Kotani K, Sata N. Effect of Postoperative Coffee Consumption on Postoperative Ileus after Abdominal Surgery: An Updated Systematic Review and Meta-Ana lysis. Nutrients. 2021; 13(12):4394. [DOI: 10.3390/ nu13124394].
- Yang TW, Wang CC, Sung WW, Ting WC, Lin CC, Tsai MC. The effect of coffee/caffeine on postoperative ileus following elective colorectal surgery: a meta-analysis of randomized controlled trials. Int J Colorectal Dis. 2022 Mar;37(3):623-630. [DOI:10.1007/s00384-021-04086-3].
- Kane TD, Tubog TD, Schmidt JR. The Use of Coffee to Decrease the Incidence of Postoperative Ileus: A Systematic Review and Meta-Analysis. J Perianesth Nurs 2020;35(2):171-177. [DOI: 10.10 16/j.jopan.2019.07.004].
- Hayashi K, Tsunoda A, Shiraishi A. Kusanagi H. Quantification of the effects of coffee on postoperative ileus after laparoscopic ventral rectopexy: a randomized controlled trial. Eur Surg 51, 325–332 (2019). [DOI: 10.1007/s10353-019-0605].
- Tajik N, Tajik M, Mack I. et al. The potential effects of chlorogenic acid, the main phenolic components in coffee, on health: a comprehensive review of the literature. Eur J Nutr 2017;56:2215-44. [DOI:10.1007/s00394-017-1379-1].



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