Title: Effect of postoperative coffee consumption on postoperative ileus after abdominal surgery: An updated systematic review and meta-analysis (protocol)

Jun Watanabe*, MD, PhD[1,2], Atsushi Miki, MD, PhD[1], Kazuhiko Kotani, MD, PhD[2], Naohiro Sata, MD, PhD[1]

[1]Department of Surgery, Division of Gastroenterological, General and Transplant Surgery, Jichi Medical University, Shimotsuke-City, Tochigi, Japan

[2]Division of Community and Family Medicine, Jichi Medical University, Shimotsuke-City, Tochigi, Japan.

Running title; Coffee and ileus after abdominal surgery

Corresponding author: Jun Watanabe, MD, PhD;

Department of Surgery, Division of Gastroenterological, General and Transplant Surgery, Jichi Medical University, Shimotsuke-City, Tochigi, Japan, 329-0498, Japan,

Tel: +81-285-58-7371, Fax: +81-285-44-3234, E-mail: m06105jw@jichi.ac.jp

Abstract

Introduction: Coffee, a popular and cheap beverage worldwide, may have an important effect on postoperative ileus (POI). However, previous systematic reviews have not clarified whether the effect is due to caffeine or coffee itself, or shortening hospital stay. We will aim to assess the effect of postoperative coffee consumption on POI.

Methods: Studies evaluating the effect of postoperative coffee consumption will be searched using the electronic databases and the trial registries. Meta-analyses will be performed using random-effects models. The Grading of Recommendations, Assessment, Development, and Evaluation approach will be used to assess the certainty of evidence.

Keyword: abdominal surgery; caffeine; coffee; ileus; length of stay; meta-analysis; systematic review

1.Introduction

Postoperative ileus (POI), defined as the transient cessation of coordinated bowel motility, is a common cause of delay in return to normal bowel function after abdominal surgery (e.g. colorectal and gynecologic surgery), with a rate of 10 to 15% [1,2]. Delayed defecation associated with POI develop vomiting, bloating, and intolerance to food, and POI often leads to invasive interventions such as nasogastric tube insertion [3]. POI increases postoperative length of stay (LOS) and treatment-related costs [4,5].

Coffee is the most widely consumed pharmacological substance in the world. Caffeine exerts anti-inflammatory effects on the gastrointestinal system as well as the cardiovascular system, mediated by its antagonistic effects on A2A receptors on immune cells such as T and B cells and macrophages [6-8]. Since the implementation of enhanced recovery protocols (ERPs), multimodal strategies have been used to improve the return of gastrointestinal function after surgery [9,10]. Recommendations regarding the use of coffee vary in various international ERPs [9,10] and previous systematic reviews demonstrated that more clinically useful and pragmatic endpoints, such as length of stay and POI, are not statistically significantly reduced [11-14]. In addition, it

is unclear whether caffeinated coffee or decaffeinated coffee is effective in treating POI [11].

Therefore, the present updated systematic review and meta-analysis will aim to assess the effect of postoperative coffee consumption on postoperative ileus after abdominal surgery.

2.Research question

P: participants of any age after abdominal surgery

I: postoperative coffee or caffeine consumption immediately after surgery within 24 hours, regardless of dose or time

C: a comparative control group (tea, water, or no treatment)

O: primary outcomes were time from surgery to first defecation (hours), lengths of hospital stay (days), and postoperative ileus. Secondary outcomes were time from surgery to first bowel movement (hours), time from surgery to first flatus (hours), time from surgery to tolerance of solid food (hours), and all adverse events.

3.Method

3.1 Protocol

We followed the Preferred reporting items for systematic review and meta-analysis 2020 (PRISMA-2020) for preparing this protocol [15]. We will publish this protocol in protocols.io (https://www.protocols.io/).

3.2 Inclusion criteria of the articles for the review

3.2.1 Type of studies

We will include randomized controlled trials that assess the effect of postoperative coffee consumption after abdominal surgery. We will not apply language, country, observation period, or publication year restrictions. We will include all papers including published, unpublished articles, abstract of conference and letter. We will exclude review articles, and case serious and reports.

3.2.2 Study participants

Inclusion criteria will be patients underwent abdominal surgery.

Exclusion criteria will be patients who have not undergone surgery.

3.2.3 Intervention

Intervention will be defined as postoperative coffee or caffeine consumption immediately after surgery within 24 hours, regardless of any dose or time.

3.2.4 Control

Control will be defined as tea, water, or no treatment.

3.3 Type of outcomes

3.3.1 Primary outcomes

1. time to first defecation

Definition: time from surgery to first defecation (hours)

Period: from surgery to first defecation

2. lengths of hospital stay

Definition: lengths of hospital stay (days)

Period: from hospitalization to discharge

3. Postoperative ileus

Definition: Postoperative ileus was defined as the number of patients who had postoperative ileus described as a narrow mindedness to oral nourishment without clinical or radiological indications of obstruction, that either a) requires nasogastric tube insertion; or b) was related with two of the accompanying: nausea/vomiting, stomach distension, and the nonattendance of flatus hours on or after postoperative day two, divided by total patients in each group.

Period: from hospitalization to discharge

3.3.2 Secondary outcomes

1. time to first bowel movement (hours)

Definition: time from surgery to first bowel movement (hours)

Period: from surgery to first bowel movement

2. time from surgery to first flatus (hours)

Definition: time from surgery to first flatus (hours)

Period: from surgery to first flatus

3. time from surgery to tolerance of solid food (hours)

Definition: time from surgery to tolerance of solid food (hours)

Period: from surgery to tolerance of solid food

4. All adverse events and/or complications

Definition: definitions of adverse events and/or complications are set by original authors.

Period: during follow up period

3.4 Search method

3.4.1 Electronic search

We will search the following databases: MEDLINE (PubMed), the Cochrane Central Register of Controlled Trials (Cochrane Library), and EMBASE (Dialog) (Appendix 1).

3.4.2 Other resources

We will also search the following databases for ongoing or unpublished trials: the World Health Organization International Clinical Trials Platform Search Portal (ICTRP), and ClinicalTrials.gov (Appendix 2).

We will check the reference lists of studies, including international guidelines [9,10] as

well as the reference lists of eligible studies and articles citing eligible studies. We will ask the authors of original studies for unpublished or additional data.

3.5 Data collection and analysis

3.5.1 Selection of the studies

Two independent reviewers (JW and AM) will screen titles and abstracts, followed by the assessment of the eligibility based on the full texts. We will contact original authors if relevant data is missing. Disagreements between the two reviewers will be resolved by discussion, and if this fails, a third reviewer will act as an arbiter (KK).

3.5.2 Data extraction and management

Two reviewers (JW and AM) will perform independent data extraction of the included studies using standardized data collection form. We will use a pre-checked form using 10 randomly selected studies. The form will include the information on study population, interventions and outcomes. Any disagreements will be resolved by discussion, and if this fails, a third reviewer will act as an arbiter (KK).

3.6 Assessment of risk of bias in included studies

Two reviewers (JW and AM) will evaluate the risk of bias independently using the Risk of Bias 2 [16]. Disagreements between the two reviewers will be discussed, and if this fails, a third reviewer (KK) will be acting as an arbiter, if necessary.

3.7 Measures of treatment effects

We will pool the relative risk ratios and the 95% confidence intervals (CIs) for the following binary variables: postoperative ileus and all adverse events and/or complications.

We will pool the mean differences and the 95% CIs for the following continuous variables: lengths of hospital stay (days), and time to first defecation (hours), first bowel movement (hours), first flatus (hours), and tolerance of solid food (hours). If several different scales have been used in the included studies, we will pool the effect estimates using standard mean differences (SMDs).

3.8 Unit of analysis issues

Clustering at the level of the enrolled units in cluster randomized studies. In dealing with cluster-RCTs, for dichotomous data, we will apply the design effect and calculate effective sample size and number of events using the intra-cluster correlation coefficient (ICC) among each unit and the average cluster size, as described in Chapter 16.3.5 of the Cochrane Handbook [17]. If the ICC has not been reported, we will use the ICC of a similar study as a substitute. For continuous data, only the sample size will be reduced; means and standard deviation will remain unchanged [17].

In dealing with randomized cross-over studies, we will consider only data from the first period.

In dealing with multiple comparisons, all intervention groups that are relevant to this review will be included.

3.9 Handling of missing data

We will ask not-presented data to the original authors.

3.9.1 Missing outcomes

We will perform the intention-to-treat (ITT) analysis for all dichotomous data as much as possible.

For continuous data, we will not impute missing data based on the recommendation by Cochrane handbook [17]. We will perform meta-analysis about the available data in the original study.

3.9.2 Missing statistics

When original studies only report standard error or p-value, we will calculate the standard deviation based on the method by Altman [18]. If we don't know these values when we contact the authors, standard deviation will be calculated by confidence interval and t-value based on the method by Cochrane handbook [17], or validated method [19]. Validity of these methods will be analyzed by sensitivity analysis.

3.10 Assessment of heterogeneity

We will evaluate the statistical heterogeneity by visual inspection of the forest plots and

calculating the I^2 statistic (I^2 values of 0% to 40%: might not be important; 30%to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity) [17]. When there is substantial heterogeneity (I^2> 50%), we will assess the reason of the heterogeneity. Cochrane Chi2test (Q-test) will be performed for I^2 statistic, and P value less than 0.10 will be defined as statistically significant.

3.11 Assessment of reporting bias

We will search the clinical trial registry system (ClinicalTrials.gov and ICTRP) and will perform extensive literature search for unpublished trials. To assess outcome reporting bias, we will compare the outcomes defined in trial protocols with the outcomes reported in the publications. We will assess the potential publication bias by visual inspection of the funnel plot. We will conduct Egger test to assess the publication bias. We will not conduct the test when we find less than 10 trials [17]. We will also assess the potential publication bias by visual inspection of the funnel plot.

3.12 Meta-analysis

Meta-analysis will be performed using Review Manager software (RevMan 5.4.2). We will use a random-effects model.

3.13 Subgroup analysis

To elucidate the influence of effect modifiers on results, we will evaluate the subgroup analyses of the primary outcomes on the following factors when sufficient data are available.

1. (For participants) surgery types (colorectal resection, caesarean section, or gynecological resection)

2. (For intervention) coffee types (caffeinated or decaffeinated coffee)

3.14 Sensitivity analysis

We will undertake the following sensitivity analyses for the primary outcomes to assess whether the results of the review are robust to the decisions made during the review process.

1. Exclusion of studies using imputed statistics.

4. Summary of findings table

Two reviewers (JW and AM) will evaluate the certainty of evidence based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach [20]. Disagreements between the two reviewers will be discussed, and if this fails, a third reviewer (KK) will be acting as an arbiter, if necessary. Summary of findings table will be made for the following outcome based on the Cochrane handbook [17]: time to first defecation (hours), lengths of hospital stay (days), postoperative ileus, and time from surgery to first bowel movement (hours), first flatus (hours), and tolerance of solid food (hours).

5. Conflict of Interest

The authors declare no conflicts of interests.

6. Support

Self-funding.

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Appendix 1: MEDLINE (PubMed) search strategy

#1. ("coffee"[Mesh] OR "coffee"[tiab]) OR ("caffeine"[Mesh] OR "caffeine"[tiab])

#2. ("abdomen"[Mesh] OR "abdomen"[tiab] OR "abdominal"[tiab]) OR ("surgical procedures, operative"[Mesh] OR "surgical" OR "producer" OR "operation" OR "operative")

#3. #1 AND #2

#4. (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR drug therapy[sh] OR placebo [tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals [mh] NOT humans [mh])

#5. #3 AND #4

Appendix 2: CENTRAL (Cochrane Library) search strategy

([mh coffee] OR coffee:ti,ab OR ([mh caffeine] OR caffeine:ti,ab)) AND ([mh abdomen] OR abdomen:ti,ab OR abdominal:ti,ab OR ([mh "surgical procedures, operative"] OR surgical OR producer OR operation OR operative))

Appendix 3: EMBASE (Dialog) search strategy

S1 (EMB.EXACT.EXPLODE("coffee") OR (ab("coffee") OR ti("coffee")) OR EMB.EXACT.EXPLODE("caffeine") OR (ab("caffeine") OR ti("caffeine")))

S2 EMB.EXACT.EXPLODE("abdomen") OR (ab("abdomen") OR ti("abdomen")) OR (ab("abdominal") OR ti("abdominal")) OR (EMB.EXACT.EXPLODE("abdominal surgery")) OR (ab("surgical") OR ti("surgical")) OR (ab("producer") OR ti("producer")) OR (ab("operation") OR ti("operation")) OR (ab("operative") OR ti("operative"))

S3 S1 AND S2

S4 (ab(random*) OR ti(random*)) OR (ab(placebo*) OR ti(placebo*)) OR (ab(double NEAR/1 blind*) OR ti(double NEAR/1 blind*))

S5 S3 AND S4

Appendix 4: ICTRP search strategy

(Coffee OR Caffeine) AND (abdomen OR abdominal OR surgical OR producer OR operation OR operative)

Appendix 5: ClinicalTrials.gov search strategy

Condition or disease: (abdomen OR abdominal OR surgical OR producer OR operation OR operative)

Intervention: Coffee OR Caffeine