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Dietary interventions to reduce postoperative ileus: coffee and chewing gum

Abstract

Background and aims

Background and aims: Postoperative ileus (POI) is a common complication after gastrointestinal (GI) surgery requiring parenteral nutrition (PN), with an average length of hospital stay (LHS) of 8.5days per patient at Brighton and Sussex University Hospital (BSUH). Chewing gum (CG) and coffee are cheap and easily accessible and could be used in postoperative care to reduce the rates of POI. The use of CG as a postoperative treatment is also advocated in the Enhanced Recovery after Surgery (ERAS) guidelines. This review aims to determine the efficacy of coffee and CG on reducing POI and investigate their impact upon: LHS, the need for PN, financial outcomes, and safety/efficacy in postoperative management.

Methods: A literature search of randomised controlled trials (RCTs) was performed to identify studies concerning POI, and coffee and CG respectively. Studies dated between January 2008 to December 2018 were obtained from MEDLINE, EMBASE, NICE evidence and TRIP; grey literature sources were also reviewed. Primary outcomes included: time to first flatus, time to first defecation and LHS. Safety, cost effectiveness and the development of complications were also examined.

Results: CG studies (n=10) and coffee studies (n=3) were identified and showed an overall reduction in the development of POI as shown by significant reductions in the time to first flatus and time to first defecation ($p<0.05$). For LHS, almost half of the included CG studies (n=3) found this to be significantly lower than the control arm ($p<0.05$), whilst one coffee study found LHS to be significantly lower when compared to tea ($p<0.01$). Complications were not common or serious and occurred mainly as a result of the surgical intervention rather than from CG or coffee.

Conclusions: This novel review showed CG and coffee to be safe, inexpensive interventions that decrease the incidence of POI and LHS. These findings strengthen the evidence base advocating for the use of CG postoperative –as per the ERAS guideline recommendations. Limitations include the number of studies included, their heterogeneity and their overall quality. However, despite these limitations, this review indicates that further, robust clinical evaluation of this topic would be warranted to clearly establish whether these cheap, conservative measures could be utilised to improve current clinical practices and enable better outcomes for patients.

Keywords: coffee, chewing gum, POI, GI surgery, LHS, systematic review, ERAS

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Abbreviations: BSUH, brighton and sussex university hospital; CASP, critical appraisal skills programme; CG, chewing gum; CRBT, cochrane risk of bias tool; CRP, C-reactive protein; ERAS, enhanced recovery After Surgery; ESPEN, european society for clinical nutrition and metabolism; GI, gastrointestinal; LHS, length of stay; MeSH, medical subject headings; PN, parenteral nutrition; POI, postoperative ileus; RCT, randomised control trial; SC, standard care; TTFD, time to first defecation; TTFF, time to first flatus

Introduction

Chewing gum and coffee

Coffee, a brewed beverage derived from roasted beans of the Coffea species, was archaically used for its energising effect.[1] Chewing gum (CG), a non-edible substance, was historically designed for mastication, breath freshening properties, antiseptic capabilities, and sustenance of oral health.[2] Each have since assumed different cultural and social significance, however neither are widely regarded as potential therapeutic agents within modern-Western medical practice. However, recent studies have explored whether either agent could be employed in a medically beneficial way. Specifically, CG and coffee have been investigated for their potential value in reducing postoperative ileus (POI), and whether this may impact upon length of hospital stay (LHS) as well as other clinically relevant outcomes.[3,4]

Ileus

Ileus is a common postoperative complication of lower gastrointestinal (GI) surgery, occurring in 10-30% of GI postoperative patients. Ileus is characterised by abdominal distention, nausea and emesis without a mechanical obstruction. These impacts elongate total post-operative recovery, thereby increasing LHS and subsequently the overall healthcare costs financially.[3–5] The average costs when managing a patient postoperatively in 2018,[6] is the following:

a. Average cost of hospital stay per day – £400
b. Average LHS after abdominal surgery – 8.5 days.
c. Total cost of hospital stay following abdominal surgery – £3400
d. Cost of parenteral nutritional (PN) per day – £54.60

e. Food budget per patient per day – £4.50.

The cost of managing POI can be high. The average LHS after abdominal surgery is 8.5days, and while the bowel remains in a paralytic state, patients require intravenous hydration and nutrition – including by parenteral means, dose and route modifications to be made to medications and nasogastric decompression. Such factor also influence LHS, which subsequently impacts staffing and bed availability at the hospital.[5,7] As such, the value of identifying cheap agents that reduce an individual's propensity to develop POI – or to reduce the time it takes them to recover from it – is considerable both financially and for the overall quality of care provided.

Guidelines and existing studies

Enhanced recovery after surgery (ERAS) for colorectal surgery is a multimodal and multidisciplinary set of evidence-based protocols which can be applied to both inpatient and outpatient day surgeries. These include recommendations on perioperative, intraoperative and postoperative optimisation of care to benefit both patients and healthcare systems.[8] Current treatments for POI include nasogastric tube decompression, and analgesia.[5] These measures are limited in their useful; incidence of POI remains high, and evidence exists that indicates nasogastric tubes do not help the return of GI functionality. Nasogastric tube are, however, associated with increased patient morbidity.[9] Additionally prolonged use of opioid analgesia can cause, or may lengthen POI.[10]

CG appears to be the most cost-effective and the researched of the proposed interventions; it is also advocated by ERAS alongside standard postoperative care[8]. Sugar free gum chewed for greater than ten minutes three to four times a day after colorectal surgery appears safe and is associated with improved post-operative recovery[11] and a decreased LHS.[11,12] However, the capacity to make meaningful comments regarding the usefulness of CG is limited when derived from single studies – particularly when other studies exist that contract the previously stated findings.[13] As such, a comprehensive review of current, existing data is indicated and would allow for clarity regarding the subject that may subsequently inform further research or clinical practice.

ESPEN guidelines for clinical nutrition in surgery[14] emphasise the nutritional aspects of ERAS,[8] focusing on the prevention of malnutrition and underfeeding. Both protocols emphasise the introduction of early feeding to decrease LHS. Reintroduction of nutrition is also important to prevent refeeding syndrome. However this increases the risk of emesis, predisposing patients to complications, meaning PN is often required[15] which can be an expensive alternative. Furthermore, the evidence base supporting the introduction of early nutrition is derived from studies that lack sufficient quality to influence clinical guidelines.[16,17]

Effects of coffee on the GI system are poorly documented. It is thought that compounds including caffeine and polyphenols found in coffee may be pharmacologically active in relation to the GI tract[4]. Caffeinated coffee has previously been demonstrated to induce greater colonic motor stimulation when compared with water and decaffeinated coffee.[18] However, further investigation of this potential link is undeniably necessary before meaningful assertions can be made regarding its potential clinical efficacy.

ERAS and ESPEN too, have limitations. They exclusive focus on the reduction of LHS;[8,14] as such, a review that accounts for the cost-benefit of an intervention is vitally needed – particularly if such interventions were to be considered as viable agents in a nationally funded healthcare model, such as the National Health Service (NHS) operating in the United Kingdom. Furthermore, neither aims to evaluate coffee as an intervention. This is the first review comparatively exploring the efficacy of both, relatively inexpensive, safe and widely available methods of reducing POI in an attempt to decrease LHS and subsequently reduce overall healthcare costs.

Aims and objectives

To conduct a review of the literature concerning the effects of CG and coffee on POI and to investigate the potential for using these interventions in clinical practice.

Primary objectives

a. Determine the effects of CG and coffee on the rates POI through time to first flatus (TTFF) and time to first defecation (TTFD).

b. Investigate whether these interventions have an effect on LHS.

Secondary objectives

a. Determine the safety of using CG and coffee in postoperative care.

b. Determine the potential cost-benefit of these interventions.

Methods

Literature search

Comprehensive literature searching was carried out in line with the PRISMA guidelines.[19] The following databases were searched: MEDLINE, EMBASE, NICE Evidence, and TRIP. The combinations of Medical Subject Headings (MeSH) that were used included: "chewing gum", "coffee", 'gastrointestinal motility", "intestinal obstruction", "ileus", "postoperative", "gastrointestinal transit", "peristalsis". These terms were also searched as key words. Relevant grey literature sources were identified through advanced Google searching with the advent of search-specific domains being employed. Domains included 'nhs.net' and 'gov.uk'. Relevant web searching was also conducted and included examining of the National Institute of Clinical Excellent (NICE) evidence search tool and NICE guidelines. Searches were conducted separately for coffee and CG respectively. Studies considered suitable for inclusion were published between 2008-2018. The search was not limited by language or country.

Inclusion and exclusion criteria

All studies were searched and selected with an unblinded approach against predetermined inclusion/exclusion criteria. Studies were selected for further analysis if they aimed to investigate the use of CG and/or coffee on POI following GI surgery, met inclusion criteria and did not demonstrate characteristics outlined in the exclusion criteria. Studies were included if they satisfied the following conditions: [(i)]Study design must be randomised control trial (RCT) and be presenting primary data (i.e. not a review articles, systematic reviews or metanalyses), [(ii)]all patients included were adults (18+ years), [(iii)] patients had developed POI after GI surgery, [(iv)]surgeries indicated were lower GI surgeries, [(v)]studies specifically defined coffee and CG, [(vi)]study designs were considered robust and included a control variable, [(vii)]studies reported all outcomes for POI from coffee or CG

use. Studies were disregarded for the following reasons: [(i)]paper was not yet published or not available as a full text, [(ii)]paediatric studies, [(iii)] inadequate raw data presented.

Data extraction

Information obtained from each study included: surname of first author, year of publication, country, type and indication of surgery, patient demographics for both treatment and control groups, regime of CG or coffee intervention, rate of complications, quality indicators, and the overall effect. This information is shown in Tables 2 & 3.

Quality assessment

The risk of bias and the quality of each study were examined using the Cochrane Risk of Bias Tool (CRBT).[20] This tool consists of the subsequent dimensions: sequence generation, blinding, and outcome data covered by seven items. These domains were then categorised into 'low risk of bias', 'high risk of bias', or 'unclear' for each study. Articles were appraised further by evaluation against the Critical Appraisal Skills Programme (CASP) checklist.[21]

Table 1 Summary of the characteristics for the included RCTs for CG

CG						
First author (Year)	**Country**	**Jadad score**	**Type of surgery**	**CG type/regime**	**Number of patients**	**Overall result**
Atkinson (2016)	United Kingdom	3	Elective colorectal resection	Wrigley's CG. 5-10 min, 4 times a day for 5 consecutive days or until discharge, if less than 5 days from the first postoperative morning	412	CG had no effect on the return of bowel function or LHS
Byrne (2018)	United Kingdom	2	Elective open or laparoscopic bowel surgery	Wrigley Extra. 15 min, 4 times a day, for up to 14 days following their operation or until a normal bowel motion had occurred	162	CG aided earlier return of bowel function but no effect LHS
Hwang (2013)	South Korea	0	Laparoscopic colorectal surgery	Brand not specified. 3 times a day, 10-20 minutes, until normal feeding was resumed from first postoperative day	132	No significant effect on bowel function. LHS was shorter in the gum group
Marwah (2012)	India	0	Relaparotomy for ileostomy closure	Orbit, 3 times a day for 1h each time starting from 6 h after the surgery until the passage of first flatus	100	CG aided earlier return of gut function
Ngowe (2010)	Cameroon	-1	Open appendectomy	Brand not specified. 3 times a day, for 30 minutes after surgery	46	CG aided earlier return of gut function. LHS was shorter in the gum group
Shum (2016)	China	3	Elective laparoscopic colorectal resection	Wrigley's Airwaves, honey and lemon. 3 times a day for 30 min, from the first day after surgery to the day of discharge	86	CG aided earlier return of gut function but no effect on LHS
Topcu (2016)	Turkey	1	Elective open colorectal surgery	Brand not specified. 3 times a day after meals for 15 min from the first morning after the operation until discharge	60	CG aided earlier return of gut function. LHS was shorter in the gum group
Van den Heijkant (2015)	Amsterdam	2	Elective open colorectal surgery	Stimorol®. Two packs, each including 12 pieces. The frequency and duration of gum chewing was not standardized	158	CG aided earlier return of gut function but no effect on LHS
Vergara-Fernandez (2016)	Mexico	-1	Elective colorectal surgery	Not specified	64	CG aided earlier return of gut function but no effect on LHS
Yang (2018)	China	3	Elective open proctectomy	Wrigley Sugar Co., Ltd. 3 times a day for 30 min, 2 pieces of gum during three intervals	110	CG aided earlier return of gut function

Table 2 Summary of the characteristics for the included RCTs for coffee

Coffee							
First author (year)	**Country**	**Jadad score**	**Type of surgery**	**Comparator**	**Regimes**	**Number of patients**	**Overall result**
Dulskas (2015)	Lithuania	2	Elective laparoscopic colonic resection	De-caffeinated coffee Water	Caffeinated coffee: Lavazza Qualita Oro 8 g of coffee per capsule, 100 ml, 3 times a day within 10 min De-caffeinated coffee: Lavazza Caffe Decaffeinato, 8 g of coffee per capsule, 100 ml, 3 times a day within 10 min	48	Both caffeinated and de-caffeinated coffee aided earlier return of bowel function
Muller (2012)	Germany	2	Elective open or laparoscopic colorectal resection	Water	Lavazza Blue Espresso Dolce 100 per cent Arabica coffee, 8g coffee per capsule, 100 ml, 3 times a day, within 10 min served at 50–60°C. No supplements allowed	80	Coffee consumption aided earlier return of bowel function. No effect on LHS
Piric (2015)	Croatia	1	Elective colorectal resection	Tea	Coffee: Instant coffee NES, 100 ml, 3 times a day in 10 minutes. Served at 50-60°C. No supplements allowed. Tea: Three portions of 100 ml of tea	60	Coffee consumption aided earlier return of bowel function. LHS was shorter in the coffee group

Table 3 Secondary outcomes for CG studies included time to first bowel sounds, time to first feeling of hunger, time to first oral feed and gastric emptying rate following the first meal. Significant findings are highlighted.

Author	**Variable investigated**	**Chewing Gum**	**Standard care**	**p value**
Atkinson (2016)	Time to first bowel sounds (hours)	48.00	48.00	0.619
Marwah (2012)	Time to first feeling of hunger (hours)	65.84	92.85	**0.004**
Shum (2016)	Time to first feeling of hunger (hours)	16.00	25.00	**0.001**
Topcu (2016)	Time to first oral feed (hours)	73.68	104.88	**0.005**
Van den Heijkant (2015)	Gastric emptying following first meal (%)	25.00	10.00	**0.004**
Vergara-Fernandez (2016)	Number of patients who had an oral feed before 72 hours	27 (of 32)	21(of 32)	0.080

Analyses

The Jadad score[22] was employed to support the CRBT[20] and CASP[21] assessments and to produce a quantitatively evident evaluation of the articles of the dataset. The primary outcome was the effect of CG or coffee on POI. POI was assessed by TTFF and TTFD; LHS was also noted. Secondary outcomes included safety of CG and coffee as postoperative agents; this was assessed by observing the development of any complications. Different articles employed different units of measurement in their assessment of their data. To enable uniform comparison, all recordings were converted to use 'hour(s)' as a unit of measurement. The exception to this is in our analysis of LHS, in which 'day(s)' was favoured. Where primary and secondary objectives were analysed, a p-value of 0.05 or less was considered to be statistically significant.

Results

Study selection

MEDLINE, EMBASE, TRIP and NICE Evidence literature searching identified a total of 209 studies (CG: n=180, coffee: n=29). A further seven (CG: n=6, coffee: n=1) were identified from grey literature (Figure 1). After duplicates had been removed, 162 articles were considered potentially relevant and so were scrutinised for quality and relevance. A total of 126 references were excluded as they failed to meet the inclusion criteria (49 studies focused on gynaecological surgery patients, two focused on spinal surgery patients, 20 studies were systematic reviews or meta-analyses, three were synopses or summaries and 37 studies were non-surgical). A further 15 studies were excluded because a full transcript was unavailable at the time of searching. This resulted in 36 articles (CG: n=33, coffee: n=3) which were appraised and assessed for eligibility for inclusion in this review. Of these 36, 18 further articles were dismissed due to their focus being on upper GI surgeries; three were published ten or more years ago and thus dismissed; one was removed as the design did have include a control group for comparison purposes. 13 RCTs: CG (n=10),[23–32] coffee (n=3)[33–35] were therefore included.

Study characteristics

The characteristics of the included studies are summarised in Tables 1 & 2. All studies were published between 2008-2018. Studies across the world were included. All of the GI surgeries conducted that comprise the data set of four studies[27,29,30,32] were performed using open surgical techniques. Two studies employed only laparoscopic techniques[24,33]. Three studies[25,28,33] used both open and laparoscopic techniques. Three studies[23,31,35] did not clearly state the surgical technique that was utilised. In studies where CG was tested as an intervention, there was some variety in the surgeries that patient underwent. Eight concerned patients who underwent colorectal resections,[23–25,28–32] one concerned appendicectomy patients,[27] and one patients who had undergone an ileostomy closure.[26] In all the coffee studies patients had undergone colorectal resections. In all studies, the primary outcome was the effect on POI as measured by TTFF and TTFD. Other outcome variables measured included: LHS, time to first solid food, return of appetite, inflammatory makers, and safety (by observing the incidence of complications). All patients in every study received standard postoperative care. All the included CG studies compared a CG regime with standard care (SC) only. In all the coffee studies, caffeinated coffee was used. One study investigated the effects of coffee against tea,[35] another against water only[34] and the last study evaluated caffeinated coffee against decaffeinated coffee against water.[33]

Validity

Quality assessment was conducted by using the Jadad scoring system[22] (Tables 1 & 2). This was also supported by the CRBT[20] (Figure 2). The CG studies were generally of poor to medium quality with Jadad scores ranging from -1 to 3. The coffee studies were also of similar quality with Jadad scores ranging from 1 to 2.

Chewing gum or coffee regime

Five of the CG studies used commercially available sugar-free gum[23,24,26,28,30] while one study utilised xylitol gum[32] for their treatment arm. Four studies did not specify the type of CG used.[25,27,29,31] Six studies told their patients to chew a piece of gum three times a day, three of which executed this for a period of 30 minutes,[27,28,32] two for a period of 10-20minutes,[25,29] and one study governed that patients did this for one hour.[26] Two studies investigated patients chewing gum four times a day for a period of time ranging from five to 15 minutes.[23,24] Another study investigated patient chewing CG by the hour; these participants could chew any number of pieces of CG during the allotted time periods.[30] One study did not detail the CG regime[31] (Tables 1 & 2).

All three of studies investigating coffee required their treatment arms to drink 100ml of coffee three times a day within ten minutes. Two of these studies used eight grams of the brand Lavazza coffee; one allowed their patients to add any supplements (milk and sugar)[33] and one did not allow this.[24] The final study used a small spoon of NES instant coffee with no additional supplements[35] (Tables 1 & 2).

TTFF

Eight of the ten studies investigated the effect of CG on the TTFF[23–29,32] (Figure 3). The remaining two studies[30,31] set a cut off at 48 hours and instead investigated the number of patients who achieved flatus at 48 hours (Appendix 1). Five of these studies found CG significantly reduced the TTFF[26–29,32] Byrne et al.[24] noted the CG group took longer to achieve first flatus than the SC group (83.4 vs 79.2 hours); however finding was not considered statistically significant (p=0.554). Atkinson et al.[23] found the CG and SC groups both achieved flatus within 48 hours, without demonstrating statistical significance(p=0.586). Van den Heijkant et al.[30] found 65% of the CG group (34 of 52 patients) achieved flatus in 48 hours compared to 50% (30 of 60 patients) in the SC group (p=0.004). Vergara-Fernandez et al.[31] found flatus within 48 hours occurred in 94% of the test subjects (30 of 32 patients) vs 63% in controls (20 of 32), p=0.002.

Two of three studies assessing coffee considered TTFF.[33,34] Both observed that coffee reduced the TTFF compared to water (Figure 4). Muller et al.[34] maintained this was not statistically significant (p=0.214). Dulskas et al.[33] however, saw that both caffeinated and decaffeinated coffee had significantly lower TTFFs compared to water. Decaffeinated coffee had the lowest time for patients to achieve TTFF (caffeinated = 38.8 vs decaffeinated = 34.56 vs water = 46.08 hours, $p<0.05$).

TTFD

For investigating the TTFD, seven studies[23,24,26–29,32] were included (Figure 3B). An additional study was considered that specifically investigated the number of patients who had defecated within 4 days of surgery[30] (Appendix 2). *All* studies found that TTFD was reduced in the CG group compared to the SC group and that that this observation can be considered statistically significant (with the exception of Atkinson et al.,[23] who found their result lacked statistical significance, p=0.153). Van den Heijkant et al.[30] noted that 85% of the test group achieved defecation within four days of surgery, compared with 57% in the control group (44 of 52 vs 34 of 60) – a finding that was seen to be statistically significant (p=0.006).

All coffee studies included assessments of TTFD. Coffee was seen to reduce TTFD to a statistically significant extent compared with control groups in all studies (Figure 4B). Piric et al.[35] found tea produced a longer TTFD compared to coffee (96.2 vs 80.93 hours, $p<0.05$). Dulskas et al.[33] noted that patients who drank coffee defecated sooner than those who drank water; however those who drank decaffeinated coffee achieved the lowest TTFD (77.52 vs 87.36 vs 93.6hours, respectively, $p<0.05$). Muller et al.[24] compared coffee to water and similarly found coffee patients defecated sooner (60.4 vs 74 hours, p=0.006).

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LHS

To assess the effect of CG on LHS, eight studies were considered.[23–28,30,31] Of these, only 3 studies[25,27,29] found CG to significantly lower LHS, ranging from a difference of 0.5-1.8 days (p=0.018, p=0.0001, p=0.008, respectively, Figure 3C). Marwah et al.[26] and Yang et al.[32] did not include assessments of LHS.

Two of the coffee studies were included for the assessment of coffee on LHS[34,35] however only one[35] demonstrated statistically significant findings (Figure 4C). Piric et al.[35] noted that those who had been drinking tea had double the LHS compared to those who had been drinking coffee (8.61 vs 16.17 days, p<0.01). Muller et al.[34] found that LHS in the coffee drinking group was less by an average of 0.5 days compared with those drinking water, though this result was deemed statistically insignificant (p=0.497).

Secondary outcomes

The studies also investigated the effect of CG on various other factors (Table 2). When considered, time to first bowel sounds, was not significantly different between groups (p=0.619).[23] Two studies which investigated the time it took patients to feel the first sensation of hunger postoperatively found this to be significantly lower in the CG group (p= 0.004, p=0.001, respectively).[26,28] Shum et al.[28] also carried out a sub analysis of the primary and secondary outcomes to see whether having a stoma had any impact; no statistically significant difference was noted between subjects who did or did not have a stoma (p>0.05). The time taken for patients to have their first oral feed was found to be significantly lower in the CG group (p=0.005).[29] Vergara-Fernandez et al.[31] concentrated on the number of patients who achieved an oral feed before 72 hours, though no statistically significantly difference was observed between test and control groups (p=0.08). Van den Heijkant et al.[30] investigated gastric emptying rates following the first meal and noted gastric emptying to be significantly more in the CG group vs control (p=0.004).

The coffee studies also assessed other variables; many of these were not statistically significant (Table 4). Both Dulskas et al.[33] and Muller et al.[34] observed the time it took until patients ate their first solid food. Only Dulskas et al.[33] found this to be significantly lower in the treatment arm (p<0.05). Both Muller et al.[34] and Piric et al.[35] commented on laxative use and nasogastric tube use however there were no significant differences between groups (p>0.05). Piric et al.[35] did however find a correlation between the postoperative stool and C-reactive protein (CRP) levels: CRP levels were higher if the postoperative stool occurred later, and was noted to be high in stool from tea consumers compared to coffee consumers (p<0.05).

The strength of the evidence base for each outcome measure is summarised collectively for CG and coffee in Appendix 3.

Table 4 Secondary outcomes for coffee studies included time to first solid food, number of patients who used laxatives, number of patients who had a reinsertion of a nasogastric tube, and CRP. X indicates the study arm was not used for the respective study. Significant findings are highlighted

Author (year)	Variable investigated	Caffeinated coffee	Decaffeinated coffee	Tea	Water	p value
Dulskas (2015)	Time to first solid food (hours)	58.08	39.12	X	68.40	**<0.05**
Muller (2012)	Time to first solid food (hours)	49·20	X	X	55·80	0.276
	Number of people who used any laxatives	13 (of 40)	X	X	21 (of 39)	0·055
	Number of patients who had reinsertion of nasogastric tube	6 (of 40)	X	X	10 (of 39)	0·239
Piric (2015)	CRP	64.49	X	115.40	X	**<0.01**
	Number of patients who had reinsertion of nasogastric tube	1(of 1)	X	0	X	> 0.05
	Number of people who used any laxatives	13 (of 25)	X	12 (of 25)	X	> 0.05

In all the studies postoperative complications were infrequent and the majority reported were not statistically significant (Table 4, p>0.05). Eight CG studies noted any complications that developed.[23,24,26–28,30–32] Marwah et al.[26] found that nausea and vomiting were significantly lower in the CG group (p=0.020). Additionally, more people developed a POI in the control arm according to both Vergara-Fernandez et al.[31] and Yang et al.[32] (p=0.006, p=0.028, respectively). Furthermore, regarding post-operative pain management, Byrne et al.[224] underlined that after the second postoperative day, the treatment arm required significantly less analgesia (p=0.019); this was reflected in the pain scores, which were significantly lower from day three in the CG group (p=0.014). Topcu et al.[29] also found significantly lower pain levels in the CG groups on the third and fifth postoperative days (p<0.05). Furthermore, Yang et al.[32] discovered their CG group had significantly lower pain levels than the SC group (p=0.005).

Similarly, in the coffee studies, there were very few complications, none of which were found to be statistically significant (Table 4). The complications cited included anastomic leakage and wound infection. Dulskas et al.[33] reported that their patients did not develop any complications.

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Table 5 Complications noted for CG and coffee studies. Overall complication rates were very few in number and not statistically significant. X indicates studies where complications were not investigated. Significant findings are highlighted.

	Author (year)	Complications listed	Significant findings
CG	Atkinson (2016)	Nausea, vomiting, ileus	No Significant findings
	Byrne (2018)	Pyrexia, ileus, urinary retention, wound infection	CG group required less analgesia from second postoperative day (11.18mg vs 16.0mg, **p=0.019**). CG group pain scores lower from third postoperative day (on a scale of 1-10 with 10 being the worst pain: 2.7/10 vs 3.7/10, **p=0.014**)
	Hwang (2103)	X	X
	Marwah (2012)	Nausea, vomiting, wound discharge, pyrexia	Nausea and vomiting lower in CG group (14/50 cases vs 25/50 cases, **p=0.020**)
	Ngowe (2010)	Parietal sepsis	No Significant findings
	Shum (2016)	Urinary retention	No Significant findings
	Topcu (2016)	X	CG group had lower pain levels on third and fifth postoperative days **(p<0.05)**
	Van den Heijkant (2015)	Anastomic leak	No Significant findings
	Vergara-Fernandez (2016)	Nausea, vomiting, surgical site infection, pneumonia, ileus	Overall POI rates lower in CG group (2/32 patients vs 7/32 patients, **p=0.006**)
	Yang (2018)	Abdominal bloating, nausea, vomiting, ileus	Overall POI rates lower in CG group (3/43 patients vs 11/46 patients **p=0.028**). Pain levels lower in CG group **p=0.005**
	Dulskas (2015)	No complications	No Significant findings
	Muller (2012)	Anastomic leakage	No Significant findings
Coffee	Piric (2015)	Wound infection, abscess, partial dehiscence of the surgical wound	No Significant findings

Discussion

This review aimed to investigate the impact of both CG and coffee on POI after lower GI surgery. The data collated and analysed from 2008-2018 indicates that each of these interventions can decrease rates of POI as measured through TTFF and TTFD. Resultantly, each can also be seen to lower LHS. While previous systematic reviews and meta-analyses have established the efficacy and safety of CG for POI after colorectal surgery,[12,34] there have been no review articles assessing the safety and efficacy of coffee. As such, our study is both novel and presently the most up to date regarding this topic. Our findings serve to add to the body of knowledge for CG and further emphasise its safety and efficacy in treating POI, whilst also highlighting the potential applications that exists for coffee in this regard. These findings offer a valuable insight into the data existing regarding this topic presently and would therefore be a suitable source of information to guide further research efforts in the future. Furthermore, our summary and analysis also demonstrate the cost-benefit impacts that such interventions could offer – information that is of course important, but would be of even greater value in healthcare systems such as the NHS, where cost-benefit is a crucial underlying concept within the model. To explore the dataset we have presented further, we will now offer an in-depth analysis of our findings and their potential applications and significance.

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Mechanisms underlying CG and coffee impacts on POI

It is thought that gum chewing mimics food consumption (sham feeding) by neurohormonal mechanisms – such as vagal cholinergic stimulation, for example – resulting in increased gastric emptying and the return of small and large bowel motility. The majority of the CG studies tested sugar-free CG that contained sorbitol and mannitol. These are known for being non-stimulant gut laxatives.[35] As such, there is some evidence to support that claim that the observed impact of CG on gut motility and subsequently POI may be independent of mechanisms that are inherently GI-stimulant derived.

Offering meaningful postulations as to the observed effects in coffee studies is more difficult than with CG due to the smaller number of studies. One theory is that the stimulant properties of caffeine may mean it is the active ingredient driving the effects seen on GI motility.[19] However, one of our included studies showed that decaffeinated coffee enhanced colonic activity more than caffeinated coffee.[33] Decaffeinated coffee contains *some* caffeine, though less than conventional coffee. As such one must question a number of things, including: is caffeine the active ingredient in coffee; do certain quantities of caffeine elicit a great effect on GI motility than others; are there other active ingredients in coffee; and, if caffeine is the active ingredient, are the effects it is seen to exert grounded in its pharmacodynamics as a stimulant or due to some other property?

Assessing the barometers employed to measure the effects of CG and coffee

Two widely utilised barometers for measuring the gastro-motility impact of CG and coffee on POI is TTFF and TTFD. All but two studies noted a significant decrease in the TTFF and TTFD.[23,24] However, it is vital to note that TTFF and TTFD are subjective surrogate endpoints that rely upon patient reporting and are fundamentally not objective, reliable measurements. Other variables have been utilised to measure POI. For CG studies, time to first feeling of hunger was employed by Marwah et al.[26] and Shum et al.[28] with each finding this to be significantly lower in the CG group. Once again, subjectivity and potential for bias cloud the validity of this as a measurement option, however. Furthermore, the spectrum of hunger is likely even less objective than assessing TTFF or TTFD would be.

Studies have shown that the introduction of an early diet may reduce POI[17,18] and this is also promoted in ERAS[8] and ESPEN[14] guidelines. However this may precipitate vomiting and associated complications such as aspiration pneumonia, as bowel motility is weaker straight after GI surgery.[16] Our study has shown that the use of CG and coffee lowers the time to the first oral feed and was associated with only minimal, non-significant complications. Interestingly, Van den Heijkant et al.[30] measured gastric emptying rates with ultrasonographic antral observations and found it to be significantly higher compared to the control group. This appears to be a very effective, quantitative method for measuring POI.

Another striking finding was that there was decreased systemic inflammation as shown by significantly decreased levels of inflammation-associated compounds TNFRSF1A (transmembrane receptor for tumour necrosis factor 1 (TNF-1)) and IL-8 (a pro-inflammatory chemokine).[30] Consequently, a reduced inflammatory response was observed in the CG group due to a decrease in leucocytes migration into the intestinal mucosa; this may contribute to the improved intestinal motility observed. One coffee study also investigated the impact upon inflammatory markers and found CRP to be significantly lower in coffee consumers compared to tea consumers. Positive correlation was observed between higher levels of CRP and increased TTFD; this observations persisted even when the populous was stratified by type of surgery.[35] CRP is a widely recognised and utilised biochemical indicator of postoperative complications and we feel having surveyed existing datasets and methodological approaches that it would be a beneficial variable to assess in addition to TTFF and TTFD for study groups aiming to comment upon POI, LHS and subsequently on cost-benefit and outcomes.

CG and coffee on LHS

POI lengthens the recovery and therefore increasing hospital costs, meaning that ultimately, the function of these interventions is to achieve a shorter LHS. Only 3/8 CG articles investigating LHS noted a statistically significant decrease in test groups; 1/2 coffee studies noted this. One explanation for this is heterogeneity in the types of surgeries patients underwent. Different surgeries have different average-LHS – appendicectomies, for example, are typically simpler and require smaller incisions than extensive rectal surgeries and resultantly have shorter average-LHS. Furthermore, it is difficult to comment on LHS being increased due to POI as surgery is associated with other complications that may lengthen LHS and that may or may not have been included in an article's analysis or measured variables. However, what can be observed from the findings of this review is the impact of CG and coffee on POI. Irrespective of other complications, POI alone can be seen to increase LHS and therefore interventions that oppose should be considered at least worthy of robust analysis to ascertain more clearly their effect on LHS, provided they are not seen to promote harmful complications, which they do not appear to.

Interestingly the only coffee study that found LHS to be significant reduced compared coffee to tea, which also contains caffeine. As discussed in 5.2, the impact of coffee on GI motility may not be wholly attributable to the stimulant effect of caffeine in coffee. This notion is supported by Dulskas et al.,[13] who noted subjects receiving decaffeinated coffee had a significantly faster restoration of normal bowel function. Fundamentally, it remains difficult to assert that coffee significantly reduce LHS presently, even though it appears coffee does result in the earlier return of bowel motility.[12,17] However, given the low cost of coffee and the observations of the impact of coffee on POI, it is reasonable to highlight the potential benefit that larger scale exploration of this topic may present.

Health economics

In section 1.2, we have highlighted the potentially high financial cost of POI management. Most of the CG studies used commercially available gum; Atkinson et al.[23] indicated the cost per patient for a five-day course was £1.39. Muller et al.[34] indicated that the cost of coffee per patient was around £2.15. Implementing these cheap methods can improve LHS as shown by various studies, thereby decreasing additional costs patients may require as a result of POI. More importantly, most studies found a positive effect for CG and coffee in the faster return of bowel function, indicating that it can improve quality of life as POI can be uncomfortable for patients.

Safety

Complications were minimal in both treatment and control arms in the reviewed articles. Furthermore, complications that did occur were attributable to the surgical intervention rather than the test variable. However, there additional factors impacting safety in any surgical study that warrant consideration.

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Firstly, there are case-specific variables that affect a patient's likelihood of developing POI and subsequent complications that would impact upon the perceived safety of any intervention – for example, larger surgical sites. Larger sites involve more tissue damage, causing the product of more pro-inflammatory compounds, which may in turn cause POI as explored in 5.2. Assessment of each article's characteristics showed there to be an even distribution between treatments arms of laparoscopic vs open techniques in studies that did not specifically investigate either approach exclusively. Investigating these surgical techniques separately and comparatively in conjunction with CG and coffee would be a beneficial approach for future research.

Secondly, POI can *independently* predispose patients to other complications. For example, POI may raise intraabdominal pressure, which can increase the incidence of abdominal wall dehiscence and anastomic leakage.[15] Complications were rare in study groups and no significant difference could be demonstrated between test and control groups in any article. However, most studies were underpowered, suggestive of a type 2 error, which may mean complication rates were unrepresentative of the wider population. Van den Heijkant et al.[30] and Piric et al.[34] highlighted that inflammatory markers (IL-8, TNFRSF1A, and CRP) that may be implicated in the development of postoperative complications were significantly lower in the treatment arms. As such, it is difficult to confidently suggest that either intervention would not reduce complications and improve safety in a larger test cohort.

Finally, analysis of the long-term safety benefits of the interventions has not been provided – such as whether complications occurred post discharge leading to re-admission and, essentially, longer LHS. Analysis of a longer period of time – including post discharge – would be helpful in ascertaining the overall safety impact of CG or coffee.

Limitations

This review has a number of limitations. Firstly, the cohort of articles identified for inclusion is reasonably small, which impacts upon the potential to extrapolate our findings to the wider population. One contributing factor to the small sample size is our limiting the search to articles published within a ten-year window. Despite resulting in the identification of fewer articles, this approach accounts for the fact that surgical technique and approaches are continually evolving, which may otherwise have been a source of potential heterogeneity between articles. Assessing contemporary articles ensures findings have greater potential for application in current postoperative care as there is a greater chance the investigated technique may still be an employed approach; however, the compromise of this approach is that the overall power of the data is reduced. We have also limited our focus to POI after lower GI surgeries. Lower GI operations have a high incidence of POI as a complication and, given that CG and coffee have considerable supporting evidence for preventing POI after other abdominal surgeries, there is great potential for examining their potential value as interventions when applied to this context. Once again, however, this reduces the cohort of articles in the review, which itself is fundamentally a limitation for strength of data (albeit that more specific information is yielded).

Included studies were of poor to medium quality. As is often true with nutritional/surgical variable, blinding of participants and personnel is not possible. Consequently, all the articles are subject to performance bias. Generally, the included studies accounted for selection bias by random sequence generation, and allocation concealment, allowing treatment groups to be regarded as comparable in terms of known and unknown confounding factors. There was a low risk of detection bias in most studies; the outcome assessors were blinded and even if they were not, the outcome measures were unlikely to be influenced by lack of blinding. Additionally, many studies included an objective outcome measure alongside subjective ones. Studies generally avoided attrition bias by reporting the reasons for any missing data[23,24,28–30,32–35]. All studies may have been a risk of reporting bias as TTFF and TTFD relied solely on the patient conveying these outcomes. However, despite being subject, these are commonly utilised outcomes in clinical practice, are considered reliable measures of POI and have been widely employed in the existing literature to date. As such, the overall risk of selective reporting bias is low.

A final limitation was the heterogeneity in the studies concerning the use of pain killers. Postoperative opiates usage is widely confirmed to prolong colonic transit time due to their effect on the peripheral mu-opioid receptors. Not all studies reported the pain killer regime, and of the studies that did[23,24,26–28,32–34] different painkillers and different regimes were administered. This was also similar for laxative use. This is reflective of the variety of approaches employed within different institutions and individuals, however – for strength of data – consistency of these variables would have been optimal.

Future implications

This review functions as a contemporary contributor to the evidence base suggesting CG can have a valuable role within postoperative care. Our findings support ERAS guidelines[8] and thereby validate clinical guidelines and approaches that advocate for CG use as a therapeutic intervention to combat POI. Importantly, this study also demonstrates the value of coffee as a therapeutic agent against POI. Our findings indicate that further clinical evaluation is both indicated and of potential value. Effort to clarify and validate coffee's clinical value would benefit from incorporating elements of our analysis into their design, namely: investigation of coffee with a variety of caffeine concentrations to ascertain if this is the active ingredient in coffee; investigating larger cohorts of individuals; and investigating individuals undergoing the same procedure with the same proposed technical approach. Additionally, we have highlighted the possible cost-benefit potential of these economical interventions, however robust financial analysis would undeniably be of value and should be incorporated more intrinsically in future research.

Conclusion

This is the only review investigating and comparing CG and coffee respectively on POI. We have established that these are safe, inexpensive interventions that reduce the rates of POI and reduce patient morbidity. Furthermore, they lower LHS, thereby adding to their cost effectiveness and strengthening the claim for their utilisation in postoperative management of POI. We have offered suggestions that might improve future research of these interventions. These include the creation of study designs that serve to ascertain whether caffeine is the active ingredient in coffee as well as how to confirm if there is an optimal concentration of caffeine in relation to POI. We have also included analysis that showed demonstrated the reduction of proinflammatory chemokines through the use of CG and postulated how this may improve safety in relation to postoperative

complications including, but not limited to, POI. This functions as both a useful pathophysiological explanation for our observations and as well as serving to highlight the importance that biochemical assay analysis is in relation to investigation POI interventions. As such, we would advocate for future studies to be design in a way that facilitates such analysis.

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Ethical considerations

No ethical considerations were required. Local approval for this work was obtained from Brighton and Sussex Medical School and Brighton and Sussex University Hospital.

Conflict of interests

No author or co-author has any conflict of interest that would compromise their contributions to or involvement with this project.

Author contributions

Dr Nahima Miah: First author of paper and chief reviewer.

Dr Sanjay Noonan: Second author, reviewer and provided edits for paper.

Emma Copeland: Supervisor and involved with scoping research.

Elaine Macaninch: Senior supervisor and involved with scoping research.

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