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An unblinded randomised controlled trial of preoperative oral supplements in colorectal cancer patients

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Abstract

Background: Perioperative oral supplementation has been shown to reduce post-operative complications. However, the use of preoperative standard oral supplements in a cohort of colorectal cancer patients has not been evaluated. The present study examined whether preoperative supplements are beneficial in this group.
Methods: In a randomised controlled trial, patients were assigned to receive 400 mL of oral supplement and dietary advice or dietary advice alone. Primary outcome was the number of post-operative complications. One hundred and twenty-five patients were recruited (59 randomised to the intervention group and 66 to the control group) and nine were excluded.
Results: In the intervention group, 24 (44%) patients had a complication compared to 26 (42%) in the control group ($P = 0.780$). In the intervention and control groups, there were eight (15%) and 16 (25%) surgical site infections, respectively ($P = 0.140$) and seven (13%) and 11 (17%) chest infections, respectively ($P = 0.470$). Subgroup analysis for hypothesis generation included 83 (71%) weight-losing patients, where there was a significant reduction in surgical site infections using the Buzby definition ($P = 0.034$), although this was not the case for the Centre for Disease Control definition ($P = 0.052$).
Conclusions: There was no evidence that preoperative supplements were beneficial in reducing the number of complications, although there may be some benefit for surgical site infections in selected weight-losing preoperative patients.

Introduction

Obesity is often associated with colorectal cancer (CRC) and, in a recent review, increasing body mass index was found to be associated with a moderate increase in the risk of developing colon and rectal cancers (Harriss *et al.*, 2009). However, during surgical management of CRC, it was reported from a series of 578 CRC patients that 260 (45%) had lost more than 3 kg in the preoperative period, although the duration of this was not specified (Brown *et al.*, 1991). More recently, 66% of preoperative CRC patients were found to have lost weight, and weight loss >10% was reported in 20% of this patient group (Burden *et al.*, 2010).

In a cross-sectional study of CRC patients, the median weight loss for stage three and four disease was 18 kg over the previous 6 months (Ravasco *et al.*, 2003) and, in a larger nutritional survey of gastrointestinal cancers, 48% of patients had lost weight (Khalid *et al.*, 2007). The literature highlights that weight loss is a problem in gastrointestinal cancer patients and that those with weight loss have poorer outcomes (Andreyev *et al.*, 1998).

Clinical benefits of parenteral and enteral nutrition in gastrointestinal surgery patients include reduced complication rates and length of stay, as well as improved patient outcomes (Smith *et al.*, 1985; Schroeder *et al.*, 1991; Veterans Affairs 1991, Carr *et al.*, 1996; Stratton *et al.*, 2003). These forms of nutritional support are expensive and invasive, requiring hospital admission during the preoperative period or significant logistics to facilitate home nutritional support. It is therefore logical to examine whether the administration of oral nutritional supplements, which are easy to administer, is of any benefit clinically, as well as acceptable to the patient.

Nutritional support intervention in the perioperative period has been evaluated using standard oral nutritional supplements in mixed patient populations (Keele *et al.*, 1997; Beattie *et al.*, 2000; Macfie *et al.*, 2000; Smedley *et al.*, 2004). In these trials, oral nutritional intervention positively influenced the clinical course by reducing post-operative complications. There is evidence, however, to support the integration of nutrition into the care pathway for CRC patients. The use of preoperative immune-enhancing oral supplementation has been shown to reduce complication rates in CRC patients (Waitzberg *et al.*, 2006). Immune-enhancing supplementation is an expensive alternative to standard formula products. Although a benefit has been demonstrated, their cost is currently prohibiting large-scale implementation into routine practice in the preoperative period for elective CRC patients.

Nutritional intervention in the form of oral supplements costs the National Health Service £150 million annually (Elia *et al.*, 2006). This is a large enough area of expenditure to justify investigation to allow nutritional supplements to be targeted to specific patient groups. The use of standard oral supplements has not previously been evaluated in a fully powered trial recruiting only CRC patients in the preoperative period. It is therefore justifiable to evaluate standard oral supplements in this targeted group of patients. Many of the trials evaluating novel substrates compare the intervention with standard supplements in the control (Waitzberg *et al.*, 2006) and thus do not evaluate whether there is any benefit with standard supplements compared to routine care with no nutrition support. Furthermore, standard supplements have not been evaluated in a single CRC cohort from the time that patients first present for surgery, whereas immune-enhancing nutrition is usually administered 5–7 days pre-operatively. Accordingly, this trial is evaluating the administration of standard supplements for a longer time period.

The present study aimed to determine whether preoperative oral supplementation using a standard formulation reduces the number of post-operative complications.

Materials and methods

Patients presenting for elective curative surgery for CRC were asked to participate. The inclusion criteria were patients with CRC where surgery was their planned treatment option, those aged >18 years and informed consent. Patients were only included if there was a minimum period of 10 days before surgery (minimum period of oral supplementation). Patients were excluded if they were pregnant, enrolled in another trial, could not give informed consent or had an inoperable tumour.

Intervention

Patients randomised to the intervention group received 400 mL of an oral supplementary drink daily and dietary advice: the control group received dietary advice only. Milk-based supplements (630 kJ and 6 g protein per 100 mL; Fortisip® Nutricia Clinical Care; Nutricia Ltd, Wilts, UK) were offered in the first instance and, if these were not tolerated, a fruit juice (630 kJ and 4 g protein per 100 mL; Fortijuce® Nutricia Clinical Care; Nutricia Ltd) was given. Patients were instructed to consume two cartons totalling 400 mL daily between meals. Neither group could be blinded to the intervention; however, ward staff were unaware of the randomisation. Patients started the supplements at the time of enrolment and continued until surgery. Supplements were stopped at surgery and not continued post-operatively. Dietary advice consisted of increasing energy and protein from food based on an information leaflet. To determine compliance, patients were asked to keep a diary of how many drinks they consumed daily and how much of the carton they consumed.

Patients were asked to enrol in the trial when it was considered that surgery was appropriate by a consultant surgeon. An information sheet was given to patients at the clinic by the doctor seeing the patient, or posted to the patient at a later date. All patients were visited at home by a dietitian where consent was obtained. Baseline data for all patients enrolled in the trial were recorded to determine sample characteristics. This was a pragmatic trial designed to determine effectiveness in the real-world clinical environment.

Randomisation

Block randomisation was used to try to ensure that there were similar numbers in each group. Weight loss was considered to be a prognostic variable at baseline so that patients were stratified according to percentage weight loss in the previous 3–6 months. Patients were weighed before randomisation and divided into two strata for randomisation: a weight loss from 0% to 9% and weight

loss ≥10% in the previous 3–6 months. Patients were randomised using a numerical sequence of random blocks generated by an independent statistician. Brown opaque envelopes were used and an independent volunteer set up the procedure. Each envelope was sequentially numbered, allowing an audit trail. Patients were allocated to groups by the dietitian when the patient was visited at home.

Post-operative complications

The primary outcome measure was total post-operative complications recorded by applying two definitions of complications: Centre for Disease Control (CDC) (Ayliffe *et al.*, 1993) and Buzby (Buzby *et al.*, 1988). Data were collected post-operatively from the medical notes and complications were clarified with the clinical team as a result of the practicalities of data collection over three hospital sites. Secondary outcomes were infectious complications, surgical site infections (SSI), chest infections and urinary tract infections (UTI).

Antibiotics and length of stay

Antibiotics prescribed to treat infections post-operatively were recorded. Date of admission, operation and discharge were recorded, and length of stay was calculated. The type of operation was recorded, along with cancer staging information.

Nutrition measurements

All patients were assessed using subjective global assessment (Detsky *et al.*, 1984). The anthropometry undertaken included weight, measured to the nearest 0.1 kg using portable scales (model 1618; Tanita, Tokyo, Japan). Height was measured to the nearest 0.5 cm using the Harpenden pocket Stediometer (Practical Metrology, Lancing, UK) and, where patients could not stand, self-reported height was used for the body mass index calculation. Grip strength was measured using a handgrip dynamometer (British Indicators, Burgess Hill, UK). The nondominant hand was used and the average of three measures were recorded (Klidjian *et al.*, 1982).

Grip strength is a functional assessment of nutritional status and values <85% of an age- and gender-specific reference range were taken as an indication of malnutrition and predictive of post-operative morbidity (Klidjian *et al.*, 1980). Oral intake was recorded using a standard dietary assessment technique, which comprised of unstructured 24-h recalls (Bingham *et al.*, 1994) at enrolment and preoperatively to determine energy and protein intake from food. Preoperative dietary recalls were undertaken 48 h before surgery. Diet histories were analysed using COMP EAT 4 Nutritional Analysis Software (Nutrition Systems, Banbury, UK). Co-morbidity was recorded, including all past medical problems. The questionnaires completed at baseline were the Hospital Anxiety and Depression Scale (Snaith & Zigmond, 1983), Karnofsky Performance Index (KPI) (Karnofsky, 1948).

Based on a reduction of complications in previous studies (Beattie *et al.*, 2000; Smedley *et al.*, 2004), it was calculated using nQuery Advisor 6 (Statcon, Witzenhausen, Germany) that a total of 116 patients would be required to give the study a power of 80% to detect (by chi-squared test with 5% two-sided significance) a difference in the primary outcome of total post-operative complications (50% versus 25% for the control and intervention groups).

Analysis was performed according to the intention-to-treat principle all patients enrolled who had surgery for CRC were included. Patients were analysed in the groups that they were randomly assigned to, irrespective of whether or not they adhered to the intervention. The primary outcome was analysed using an adjusted and unadjusted analysis. The adjusted analysis used logistic regression with odds ratios and 95% confidence intervals. The unadjusted analysis used Pearson's chi-squared test for the categorical data. The secondary outcomes were analysed using *t*-tests for normally distributed interval data and Mann–Whitney *U*-tests for skewed data. Subgroup analysis was planned on patients who were weight-losing. The data were analysed using SPSS, version 11.5 (SPSS Inc., Chicago, IL, USA).

Central Manchester Ethics Committee approved the study and local ethical approval was obtained to collect data at two other hospital sites. Honorary contracts were obtained where appropriate and management approval was obtained.

Results

Sample characteristics

There were 125 patients enrolled in the study over a 2-year period and patients were followed up until 3 months after their operation date; nine were excluded because they did not go on to have surgery (CONSORT diagram; Fig. 1). Of these nine patients, six had metastatic disease and three patients died. These patients were excluded because they did not go on to have surgical treatment and supportive nutritional intervention could not be evaluated post-operatively. Patient characteristics are shown in Table 1. Data were missing for some patients for staging and type of operation. Three patients did not complete the questionnaires at the end of the enrolment session because they were limited for time, which led to missing data for Hospital Anxiety and Depression Score, subjective global

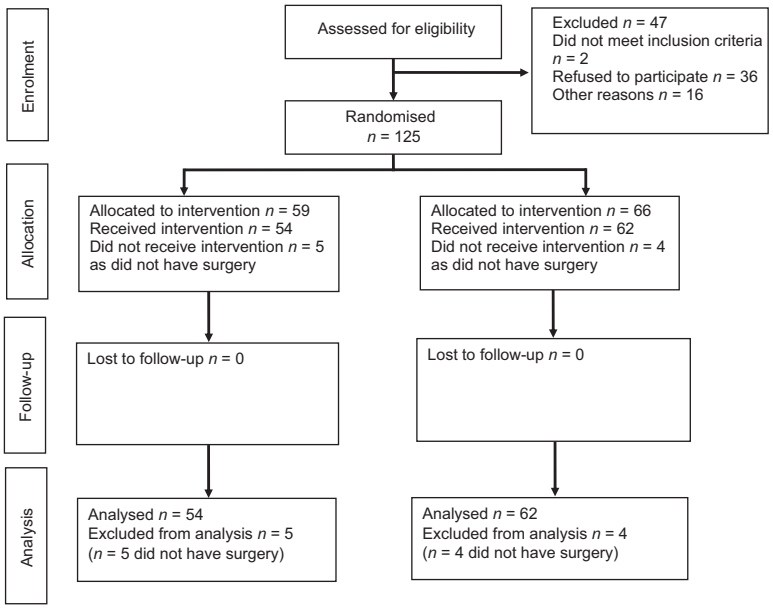

Figure 1 CONSORT diagram showing patients enrolled, recruited, followed up and analysed.

Table 1 Demographics including nutritional, clinical and patients reported questionnaire

	Intervention (*n* = 54)	Control (*n* = 62)
Age, mean (SD)	64.5 (13.9)	65.3 (2.7)
Sex ratio (male : female)	34 : 20	38 : 24
Number of smokers	10	13
BMI (kg/m^2), mean (SD)	25.0 (4.8)	26.8 (4.7)
% Weight loss, mean (SD)*	6.2 (6.8)	3.9 (4.8)
SGA-C and B: malnutrition	30	23
SGA-A: well nourished	23	37
Handgrip (kg), mean (SD)	26.6 (10.4)	27.7 (9.9)
KPI, mean (SD)	82.0 (12.0)	84.0 (14.8)
HADS, mean (SD)	12.1 (9.0)	10.7 (7.2)
Anterior resection	21	24
APR	7	11
Right and left hemicolectomy	15	12
Hartmann's procedure	2	1
Total colectomy	1	2
Sigmoid colectomy	3	3
Laparotomy	2	2
Total pelvic clearance	2	3
Proctocolectomy	0	2
TNM stage 1	4	6
TNM stage 2	14	22
TNM stage 3	20	14
TNM stage 4	3	3
Other	2	11

SGA, subjective global assessment; KPI, Karnofsky Performance Index; HADS, Hospital Anxiety and Depression Score; TNM, tumour, nodal, metastatic; APR, abdominoperineal resection; BMI, body mass index. *Over the previous 6 months, unless otherwise stated, cell entries are the number of patients.

assessment and KPI. There were 83 (71%) patients who had lost weight in 3–6 months preceding surgery. The percentage of usual body weight lost was in the range 1–31% [mean (SD), 5.8% (6.5%)].

The mean (range, SD) time to surgery was 37 (7–371, 54.7) days. Those who were randomised to the intervention group received supplements for a minimum of 10 days to a maximum of 252 days [mean (SD) 37.6 (42.8) days]. The intervention was only given in the preoperative period. Surgery was delayed in nine patients as a result of investigations and treatment of co-morbidities.

Compliance

Of the 54 patients randomised to the treatment group, 50 completed a diary to record compliance to the intervention. It was reported that 36 (72%) of patients managed 100% of the intervention which was two full cartons daily, eight (16%) managed 50%, which was at least one carton daily and six (12%) managed <25% of the intervention. Nausea and vomiting were reported by four patients and exacerbation of diarrhoea was reported in two cases. In four cases, data were missing because three patients died post-operatively and one was transferred out of area.

Nutritional intake data from enrolment and preoperative time points using 24-h unstructured dietary recall are summarised in Table 2. There was a significant difference between the energy intake from enrolment to the preoperative time point. However, a significant difference was not demonstrated for protein.

Table 2 Dietary intake from 24-h recalls including calories and protein from sip feeds

	Intervention, mean (SD)	Control, mean (SD)
Enrolment		
MJ	5.5 (1.8)	5.9 (2.1)
kcal	1338.0 (431.0)	1421.0 (517.0)
Preoperative		
MJ	7.2 (2.6)*	3.1 (1.5)*
kcal	1722.6 (488.7)*	745.0 (366.0)*
Enrolment protein	63.2 (28.6)	62.0 (22.0)
Preoperative protein	51.8 (33.6)**	33.0 (16.0)**

*P = 0.001, **P = 0.157.

Complications

This was a pragmatic trial so the effect of any differences in variables at baseline on the outcome were evaluated with an adjusted analysis. An adjusted analysis was performed to determine whether the difference in nutritional status, using weight loss, at baseline, which was cited as a prognostic variable affected the primary outcome measure. This is reported in Table 3 and demonstrates that the prognostic variables at baseline did not significantly affect the outcome. Post-operative complications are shown in Tables 4 and 5. A summary of the complication rates for Buzby definitions are divided into four categories. Total complications comprise of infectious and non-infectious complications, SSI, chest and UTIs (Table 4). A total is given for the number of patients who suffered a post-operative infection defined by the CDC definitions (Table 5).

Table 3 Adjusted analysis using logistic regression of cancer staging and percentage weight loss using Buzby definitions as the dependent variable

		95% confidence intervals		
	Odds ratio	Lower	Upper	Significance
Randomisation	1.07	0.43	2.66	0.875
% Weight loss	0.97	0.90	1.05	0.588
Staging	0.85	0.35	2.05	0.730

Table 4 Total numbers of patients with one or more complications using Buzby definitions for infectious and non-infectious complications

	Intervention (n = 54) n (%)	Control (n = 62) n (%)	χ^2	P
Non-infectious and infectious	24 (44)	26 (42)	0.07	0.785
Wound infection	8 (15)	16 (25)	2.12	0.145
Chest infection	7 (13)	11 (17)	0.50	0.478
Urinary tract infection	8 (15)	6 (9)	0.12	0.724
Total number of patients with an infection	20 (37)	20 (37)	0.22	0.589

Table 5 Total number of patients with one or more complications using the Centre for Disease Control definitions for infectious complications

	Intervention (n = 54) n (%)	Control (n = 62) n (%)	χ^2	P
Wound	9 (16)	17 (27)	2.12	0.145
Chest	8 (15)	14 (22)	1.54	0.125
Urinary tract	8 (15)	6 (9)	0.12	0.724
Total patients with an infection	20 (37)	27 (43)	1.21	0.271

Antibiotics

The number of patients in the control group who received post-operative antibiotics was 28 (45%) compared to the intervention group, which was 20 (37%; P = 0.290).

Subgroup analysis

A subgroup analysis was undertaken on weight-losing patients comparing SSI and chest infections by group. This analysis included patients with a weight loss between 1% and 31% of their usual body weight. SSI and chest infections were analysed for this group of patients. Table 6 shows that there was a statistically significant difference between the intervention and the control groups for SSI defined by the Buzby definition.

The length of stay (LOS) in hospital for this group of patients was in the range 5–99 days. The median LOS in the intervention group was 13.5 days, whereas it was 14 days for the control group.

Discussion

The present study aimed to evaluate the use of preoperative nutritional supplementation in an elective cohort of

Table 6 Number of weight-losing patients with a wound or chest infection

	Intervention (n = 46)	Control (n = 37)	χ^2	P
CDC wound	5	10	3.61	0.052
CDC chest	7	10	1.93	0.166
Buzby wound	5	10	8.41	0.034*
Buzby chest	6	8	1.92	0.377

*Significant $P \leq 0.05$. CDC, Centre for Disease Control.

CRC patients. This RCT evaluated preoperative oral supplements for CRC patients using post-operative complications as the primary outcome.

The intention-to-treat analysis identified no statistically significant difference between the intervention and control groups for the primary outcome (i.e. total post-operative complications) using two definitions: (i) Buzby, which is popular in the nutritional literature (Buzby *et al.*, 1988), and (ii) that is recommended by the CDC (Ayliffe *et al.*, 1993). In this study, 71% elective surgical patients with CRC were weight-losing preoperatively. Oral nutritional supplements were beneficial at reducing wound infections in this subgroup, although this was only using the definition from Buzby *et al.* (1988) and not the definition from CDC (Ayliffe *et al.*, 1993).

In the present study, patients had to be contacted at least 10 days preoperatively; therefore, those with rectal tumours were more likely to be enrolled because they had the longest preoperative lead in time. The differences in the sample reflected the practicalities of patient recruitment. The clinical population was obtained from outpatient clinics over three hospital sites involving patients referred to nine colorectal surgeons. The use of three centres for recruitment increased the generalisability. Only 16% of patients did not give consent in this study, which is comparable to 21% in a similar trial (Smedley *et al.*, 2004).

At baseline, the percentage weight loss was higher in the intervention group compared to the control group. Weight loss has been shown to influence the incidence of post-operative complications in previous studies (Brown *et al.*, 1991; Burden *et al.*, 2010). This difference introduces the possibility of bias into the trial. The randomisation was stratified on weight loss <9% and ≥10% in the previous 6 months, although the data showed that six patients in the intervention group had a weight loss >15% compared to one in the control group. It is possible that this has affected the primary outcome measures. An adjusted analysis was performed to evaluate chance bias in predicting variables at baseline. The absolute size of the imbalance decreases as the number of recruits increases in a trial. Increasing the sample size can reduce sampling error (Roberts & Torgerson, 1999) and a reasonable number were recruited to help minimise the effect of randomisation imbalance at baseline.

Preoperatively, the mean energy intake of the patients was significantly different in the control group compared to the intervention group. This was not seen for protein; however, in the present study, 24-h recalls were used that only give an indication of dietary intake over a short period of time. Assessing dietary intake for a longer period of time may have affected the results and given more insight into within person variation in dietary intake.

Patients in the present study randomised to the intervention group received the oral supplements for different lengths of time and not all patients were compliant with the intervention. This could have affected the outcome of the nutritional status measurements, although improvements in physiological measurements from nutritional interventions have been reported in the absence of improvements in nutritional status (Haydock & Hill, 1986). Collagen deposition after surgery was affected by recent nutritional intake in the absence of any change in anthropometric measurements (Haydock & Hill, 1986). Collagen deposition and production are directly related to wound healing. There was no difference in weight gain between the two groups.

This trial has highlighted the effect on outcomes when using different definitions for complications. There were fewer complications according to the definitions from Buzby compared to CDC. The main reason for this is that the Buzby criteria for chest infections specify a requirement for radiological confirmation and documentation of pathological organisms in sputum. The CDC definition for chest infection specifies new or increased purulent sputum and/or a temperature >38 °C with appropriate chest signs. For the Buzby definitions, there were fewer wound infections recorded. For wound infections, the definitions are very similar; however, the CDC definition included more detail, such as an increase in temperature and the isolation of an organism.

The LOS reported in the present study was before the introduction of any enhanced recovery after surgery (ERAS) which, has been demonstrated to decrease hospital stay (Nygren *et al.*, 2009). The reported LOS in a similar trial without ERAS was 13.2 days for the control group and 10.8 days for the intervention group (Keele *et al.*, 1997). The present trial was also conducted over three hospital sites involving a number of surgical teams, which enhances the effectiveness and the pragmatic nature of the trial, albeit with the converse affect of decreasing the efficacy.

Post-operative complications were recorded for this trial from patients' medical notes when they were in hospital and discussed with the clinical team. All complications identified at clinic visits for 3 months after surgery were recorded. The method of collecting data thus relied on the documentation of the complication and discussion with the clinical teams managing the patients across three different sites, which may have introduced bias into the data collection.

The identification of preoperative CRC patients who are weight-losing would be advantageous to allow the early instigation of oral nutritional supplements. This hypothesis is based on a subgroup analysis and should be investigated further.

In conclusion, the present study adds to the perioperative literature in gastrointestinal surgical patients by evaluating oral supplements preoperatively. The time over which supplements were given in the present study was longer then in other trials (Waitzberg *et al.*, 2006). Supplements were instigated at the point that patients were identified as outpatients as candidates for surgery. The evidence for oral supplementation in gastrointestinal surgery is expanding and this trial did not detect any evidence of an advantage in administering oral supplements to all patients with CRC preoperatively, although there may be some advantage in weight-losing patients. Also, because of the patients' trajectory preoperatively and radiotherapy in rectal cancer, it may be necessary to investigate subgroups of these patients based on site of tumour and nutritional status. Post-operative feeding is now included in ERAS protocols that are established in clinical practice, although there may still be a role for early preoperative feeding in selected patients.

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Conflicts of interests, source of funding and authorship

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SB carried out the study, data analysis and drafted the manuscript. JH assisted with the identification of sample, study design, interpretation of analysis and manuscript preparation. JS participated in study design and contributed to the manuscript. MC undertook some of data analysis and interpretation and assisted with the manuscript. CT assisted with study design, interpretation of analysis and the manuscript. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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