

## CLINICAL INVESTIGATION

# Does Early Enteral Feeding Affect Clinical Outcome Or Cytokine Profiles After Elective Surgery For Colorectal Cancer?

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**Abstract:** Patients who have intestinal cancer are prone to malnutrition, which can result in deterioration of physiological function, poor wound healing, increased risk of infection and prolonged hospital stay. These complications are particularly relevant after colorectal surgery. Early enteral feeding, to enhance nutritional status, has been reported to reduce post-operative complications, length of hospital stay and morbidity and mortality after upper gastro-intestinal cancer surgery.

Inflammatory cytokines (IL-6, TNF- $\alpha$ ), clinical outcomes and postoperative complications were measured in 147 patients undergoing elective surgery for colorectal cancer (84 standard care; 64 patients had early enteral feeding in addition).

There were no significant differences in age, length of operation, complication rate or days to discharge between the two groups.

IL-6 levels peaked on POD-1 in both groups. TNF- $\alpha$  levels gradually increased from the pre-operative sample to POD-7.

In both groups cytokine levels correlated significantly with complications ( $P < 0.05$ , Spearman's correlation).

Post-operative plasma levels of the inflammatory cytokines correlated with the occurrence and severity of surgical complications after elective colorectal surgery. Early enteral nutrition was not associated with increased post-operative complications nor was it related to any change in cytokine profiles.

**Key Words:** Colorectal cancer, immunonutrition, cytokines

## Introduction

Operative interventions for diseases of the colon and rectum are often major and are undertaken in older patients, many of whom have co-morbidities. There is a considerable risk of complications following colonic surgery, even when planned electively, partly due to impairment in immune defence mechanisms and an altered inflammatory response (1). Post-operative complications have been reported in up to 50% of patients following colonic resection (2, 3).

Up to 40% of patients admitted to hospital are malnourished, and many continue to deteriorate during their hospital stay (4). The consequences of malnutrition can be dire, leading to deterioration of physiological function, poor wound healing, increased risk of infection, depressed immune system, prolonged length of hospital stay and an increase in morbidity and mortality (5,6).

It has been reported that early nutritional support starting on the first post-operative day, significantly reduces both infections and non-infectious complications (7, 8) particularly if given via the enteral route as this gives protection to the gut mucosal cells and enhances gut associated immunity (9). Lack of gastrointestinal feeding is associated with gut mucosal atrophy, colonisation and subsequent translocation of bacteria through the gut barrier wall to the mesenteric lymph and systemic organs (10) with the release of endotoxin, a cytokine response and increased risk of systemic inflammatory response (SIRS), sepsis and organ dysfunction (11). Total parenteral nutrition (TPN), the traditional choice for early post-operative feeding, does not offer this benefit and has many complications (7,8). It is also expensive and has not been proven to be effective in improving patient outcome (12).

Therefore, the aims of the study were to determine the effect of early enteral nutrition on clinical outcome i.e. post-operative complications, hospital length of stay and inflammatory cytokine profiles following elective surgery for colorectal cancer.

## Materials and Methods

### Patients

148 patients undergoing elective surgery for colorectal cancer were recruited for the study; of these patients, the first 84 had standard postoperative care in which feeding was left to the consultant surgeon in charge. The standard regimen was 30ml hourly for the first 24 to 48 hours then increase of fluids through to full feeding depending on bowel sounds, passage of flatus and bowel action, usually achieved by 4 to 5 days. However, no patients achieved full diet level until at least the third post-operative day. The subsequent 64 patients were given early enteral nutrition which was either immune-enhanced nutritional support (Impact) or a control isocaloric (101 kcal/100 ml) isonitrogenous (5.6g protein, 3.8g lipids and 13.4g carbohydrate per 100ml) conventional feed administered orally in the pre-operative period (for 5 days); both regimens gave 2000 calories per day. During the post-operative period, the same feeds were administered nasogastrically starting on the first post-operative day and increased to 1litre per day of the enteral feeds based on bowel function. This was in addition to balanced intravenous fluids of normal saline or 5% dextrose (i.e. 2.5 to 3 litres of fluid in total per day depending on urine output and gastric aspirates if excessive). The feeding regimen in use in the hospital intensive care unit (ICU) was followed to achieve maximal nutritional support of 25 mls/kg in each 24 hour period within 36 to 48 hours of surgery. Hospital policies on feed administration and infection control were also followed.

All patients had pain control with a pain team approach with epidural or patient controlled analgesia (PCA).

The study was approved by the University Hospital of North Tees and Hartlepool NHS Trust Local Research Ethics Committee and informed consent was obtained from all participants.

### Enzyme Linked Immunosorbent Assays

Four plasma samples were taken from each patient with consent pre-operatively and on post-operative days 1, 3 and 7.

Plasma levels of the cytokines IL-6 and TNF- $\alpha$  were determined by ELISA (R & D Systems, Abingdon, UK) following the assay protocol. The optical density of each well was determined using a microplate reader set at 450nm with a correction wavelength set at 540 nm for IL-6 and for TNF- $\alpha$ , 490 nm with a correction wavelength set at 650nm.

The microplate reader was linked to Revelation software to determine antigen concentrations (Dynatech Laboratories, Billingham, UK) and results were expressed as picograms per millilitre (pg/ml).

### Statistical Analysis

For comparisons between the levels of cytokines in the plasma samples on different post-operative days, the Mann Whitney U test for non-parametric data, with 95% confidence intervals, was performed. Spearman's correlation coefficient was used to determine whether a correlation existed between cytokine levels on each post-operative day with various clinical parameters including length of the operation and estimated blood loss during the operation, whether there were any post-operative complications and number of days to discharge. Differences were considered significant at the  $P < 0.05$  level.

## Results

### Patient Information

#### Demographics

Plasma samples were analysed from 148 patients undergoing elective surgery for colorectal cancer. 84 patients had standard nutrition and 64 patients had early enteral nutrition. The overall male to female ratio of the patients was 96:52 and their median age was 67.5 with a range of 40 to 86 years old, the demographics based on patient group are summarised in Table 1.

#### Clinical Parameters

Patients were followed up daily as in-patients and then at 2 and 6 weeks post-operatively for mortality and morbidity, particularly the infectious complications of pneumonia, surgical site infection and urinary tract infection. The type and length of operation, whether

Table 1. Patient Demographics: Standard versus Fed groups.

Demographics	Standard	'Fed'
Sex (Male:Female)	52 : 31	43 : 21
Age (median (range))	68 (25 – 93)	64 (40 – 88)
Operation Time (minutes)	150 (52 – 325)	165 (60 – 465)
Post-operative Complications	29	27
Days to Discharge	10 (6 – 60)	11 (7 – 65)

there were any post-operative complications and the number of days until the patients were discharged are summarised in Table 1.

There was no significant difference in age, length of operation, complication rate or days to discharge between the two groups.

Approximately 50% of the fed group reached the full post-operative regimen. The reasons for discontinuation of enteral feeding included early oral diet, tube removal, abdominal bloating and aspiration.

#### Daily Profiles of Inflammatory Cytokines

The daily profiles of IL-6 and TNF- $\alpha$  are summarised in Table 2. In brief, pre-operative plasma IL-6 levels were low in both groups with peak levels observed on post-operative day 1, levels then decreasing down to post-operative day 7. TNF- $\alpha$  plasma levels in the standard

group increased from the pre-operative sample up to post-operative day 3 and remained constant up to post-operative day 7. Similarly, TNF- $\alpha$  levels in the 'fed' groups peaked on post-operative day 3 but then levels decreased slightly by day 7.

There was no significant difference between IL-6 levels on each day between the two groups. TNF- $\alpha$  levels were significantly greater in the fed group in the pre-operative and post-operative day 3 samples ( $P < 0.05$ , Mann Whitney U).

#### Cytokine Levels and Clinical Outcome

In the 'fed' group, IL-6 levels on post-operative day 1 correlated significantly with the length of the operation.

A significant positive correlation was found between cytokine levels and post-operative complications in both groups. IL-6 levels in both groups on each post-operative day correlated significantly with post-operative complications and also the severity of the complication. That is, patients who did not have post-operative complications had lower IL-6 plasma levels than those that did, and IL-6 levels were greater in patients with 'major' complications than those with 'minor' (Figure 1; Spearman's correlation  $P < 0.05$ ).

IL-6 plasma levels on each post-operative day also correlated significantly with the number of days that a patient was discharged (Spearman's correlation  $P < 0.05$ ).

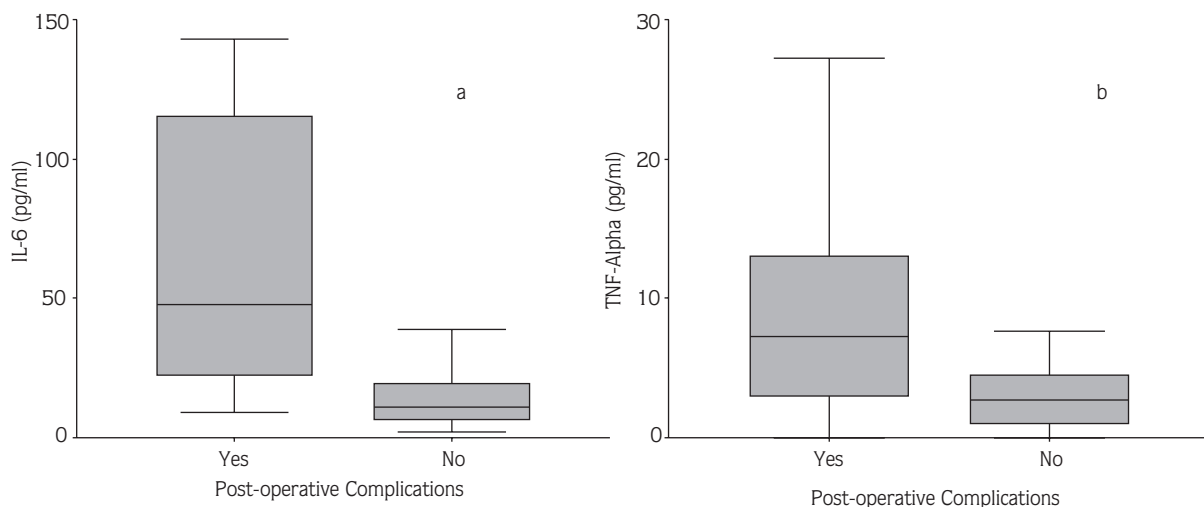


Figure 1. Box plots illustrating the significant correlation between cytokine levels and whether there were postoperative complications. a) IL-6 and b) TNF- $\alpha$  levels on postoperative day 7 plasma samples from patients given standard nutrition ( $P < 0.05$  Spearman's correlation coefficient). The horizontal bold line within the box corresponds to the median value and the whiskers to the interquartile ranges.

Table 2. Daily profiles of IL-6 and TNF-a (median (range) pg/ml) in standard versus 'fed' patients.

	Pre-operative	POD-1	POD-3	POD-7
IL-6 (Standard)	5 (0–500)	178 (0–600)	36 (0–412)	21 (2–591)
IL-6 (Fed)	5 (0–321)	168 (22–1,333)	27 (3–461)	14 (0–1,143)
TNF-α (Standard)	1.6 (0–7.0)	2.5 (0–10.0)	3.0 (0–15.0)	3.0 (0–36.7)
TNF-α (Fed)	2.9 (0.3–24.5)*	2.6 (0.5–20.7)	4.2 (0.6–33.0)*	3.8 (0.2–67.4)

POD – Post-operative day

\* P < 0.05 Mann Whitney U, Standard versus enteral nutrition (fed)

### Discussion

Exaggerated cytokine production and development of SIRS is the most common result of infectious complications which leads to organ failure and death following major abdominal surgery (11).

A complication can be defined as any deviation from an expected recovery after a surgical operation. In general, surgical complications relate to technique in the operating theatre, the general health of the patient and/or the magnitude of the operation. Some complications may be unavoidable particularly after emergency operations. However, in the elective situation where planning and preparation can be maximised, good peri-operative care of these surgical patients can minimise incidence and severity of complications.

Following gastrointestinal surgery, post-operative complications occur more frequently and the mortality rate is higher than in most surgical specialities (13,14). Post-operative morbidity leads to prolonged hospital stay, increased consumption of resources and often prolonged disability or permanent incapacity.

Early post-operative nutrition has been shown to significantly reduce both infectious and non-infectious complications (7, 8) especially if given via the enteral route, as this protects gut mucosal cells. Enteral feeding has been shown to improve the outcome following surgery, however the benefits depend on timing, route (enteral versus parenteral) (15) and nutrient composition (16). In a study involving patients with colorectal disease, differential cytokine levels were observed depending on the preoperative nutritional status of the patient (17).

The current study has determined the effect of early enteral feeding in elective colorectal surgery on

inflammatory cytokine profiles and clinical outcomes i.e. postoperative complications and length of hospital stay and to our knowledge this is the first study to do so. The study investigated whether early enteral nutrition affected the systemic production of the inflammatory cytokines IL-6 and TNF-α in patients undergoing elective colorectal surgery. In the standard and the 'fed' groups, the daily profiles and the range in plasma levels of IL-6 plasma were similar. However, TNF-α levels in the pre-operative sample and on the third post-operative day were significantly greater in the fed group. This is in contrast to previous studies that have reported lower levels of both cytokines in patients given a supplemented diet (18,19), but may represent a type I error. Previous studies have contrasting results: one study has demonstrated significantly greater systemic IL-6 and IL-8 levels following TPN than enterally fed patients (20) and another found patients given TPN had lower postoperative IL-6 and IL-8 levels than those with standard nutrition (21). However the number of patients recruited in these studies were small (n=12 (20), n=22 (21)).

Possible explanations for differences between studies could be the number of patients recruited in the study, the assays used to determine cytokine levels may have different sensitivities and specificities, the type of nutrition, route of administration and feeding regimes and the nutritional status of the patient preoperatively and the surgical procedure performed.

The levels of the studied inflammatory cytokines demonstrated several significant correlations with the clinical outcome. Post-operative IL-6 levels correlated with post-operative complications in particular and the severity of the complication.

Early enteral feeding did not decrease the number of post-operative complications or the length of hospital stay and this is in agreement with a previous study in upper gastrointestinal cancer patients (21).

Previous studies suggest that enterally administered immunonutrition is effective in reducing incidences of post-operative complications and hospital length of stay in comparison to those receiving TPN. However the immune and control groups do not differ significantly enough to warrant a change in nutritional dietary supplementation (18). The majority of studies focus on upper gastrointestinal surgery (15, 22) with very little on lower GI surgery. Two separate studies by Stewart (23,24) did show that it was possible to feed colorectal patients early but their studies were very small.

In patients undergoing surgery for colorectal disease there appears to be no difference in postoperative cytokine response following standard postoperative care or the introduction of early enteral feeding. However, this group of patients do not have the severe nutritional depletion seen in patients having upper gastrointestinal disease (15,18,21).

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