

## Pre-operative intravenous feeding—a controlled trial

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### Summary

Seventy-four patients with a pre-operative diagnosis of stomach or oesophageal cancer were entered into a randomized, controlled clinical trial to assess the value of a short course of pre-operative intravenous nutrition. The effectiveness of this treatment was assessed by the clinical course and monitored by means of immune and biochemical profiles.

Pre-operative parenteral nutrition given over a 7-10-day period resulted in a significant reduction in the incidence of postoperative wound infections. Clinical benefit was confined to those patients who had a low serum albumin on admission to hospital. It is doubtful whether this limited benefit justifies the routine use of intravenous feeding, with its attendant hazards, in the pre-operative preparation of patients with upper gastrointestinal cancer.

### Introduction

Intravenous feeding has gained wide acceptance in the nutritional management of seriously ill or starving patients. Although many studies have confirmed that this form of treatment confers biochemical improvement in patients with a variety of deranged metabolic states, there is little evidence from properly controlled trials to confirm that intravenous nutritional support is of clinical benefit.

In this study the clinical response of patients undergoing a short intensive course of intravenous feeding has been studied in a randomized, controlled trial. The aim of the study was to determine whether a short course of parenteral feeding, using a technique applicable to the routine situation of a general hospital, could decrease the morbidity associated with surgery. A secondary aim was to determine whether the immune depression known to exist in cancer patients could be partially or completely reversed, with possible strengthening of the host side of the host-tumour relationship.

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Patients undergoing surgical treatment for suspected cancer of the stomach or oesophagus were chosen because of the malnutrition commonly present in this group and the difficulties of complete correction by oral supplementation. Patients were randomized into groups to receive either intensive oral supplementary feeding, or a combination of intensive oral feeding together with a course of intravenous pre-operative feeding. The clinical response to nutritional therapy was assessed by means of standard parameters of morbidity, and correlated with the patient's immune and biochemical profiles. A parenteral feeding regime was chosen which gave reasonably comprehensive nutrition and was applicable to the routine use of a non-specialized surgical unit.

### Patients and methods

Seventy-four patients with a pre-operative diagnosis of stomach or oesophageal cancer were admitted to hospital before surgery and randomly allocated into one of 2 groups according to odd or even year of birth.

#### Group 1

Patients were encouraged to eat and drink as much as possible of a standard ward diet consisting of 3000 cal (12.6 mJ) and 15 g of nitrogen, supplemented with oral multivitamins. The diet was available in a liquid form where dysphagia prevented or limited solid food intake.

#### Group 2

Patients had oral feeding as in Group 1, together with an intravenous feeding solution (Aminoplex 5) in a dose of 40 cal/kg body weight. This solution contains 5 g nitrogen and 1000 cal (4.2 mJ) per litre in the form of synthetic L-amino acids, ethanol and sorbitol, together with electrolytes, minerals, and vitamins. The solution was given for 7-10 days immediately before surgery.

Intravenous feeding solutions were given by continuous infusion throughout the 24-hr period by means of a central venous cannula introduced by percutaneous puncture of the median cubital vein, and positioned in the superior vena cava. The cannulae were inserted by one of 3 clinicians experienced in this technique, and only one type of cannula was used throughout the study (Drum-Cartridge, Abbott). The position of the catheter tip was checked on a chest radiograph, and a free backflow of blood was obtained from the catheter.

Patients who underwent an oesophageal anastomosis received intravenous feeding from the second postoperative day, until oral intake was recommenced, following a satisfactory gastrograftin swallow on the fifth postoperative day. Other patients did not receive postoperative intravenous feeding.

#### *Clinical assessment*

Patients were weighed on admission to hospital and daily thereafter until the day of operation, and also at discharge from hospital. Measurements were made on the same set of scales and by the same observer for each patient. The length of stay in hospital was recorded before and after operation. Wounds were inspected on the second, fifth, seventh and tenth postoperative days by one observer unfamiliar with the treatment each patient had received before operation for evidence of purulent discharge or surrounding erythema and induration. The development of infections at other sites, particularly the chest, and the point of insertion of the intravenous cannula were also noted.

#### *Immune testing*

Tests of immune function were performed on admission to the trial, at intervals throughout the hospital course, both pre- and postoperatively, and at the out-patient follow-up for periods of up to one year. Blood samples for peripheral lymphocyte count, immunoglobulin levels, and lymphocyte response to phytohaemagglutinin (PHA) were taken at initial presentation of the patient in the out-patient clinic, on admission to hospital and on alternate days throughout the period in hospital. Serum IgG, IgA, and IgM levels were measured by radioimmunoassay using Behringwerke AG Tri-Partigen plates, allowing the diffusion to go to completion (Mancini, Carbonara and Heremans, 1965). Lymphocyte responsiveness to PHA was measured by a micromethod (Whitehead, Bolton and Newcombe, 1974).

#### *Biochemistry*

Blood was taken on alternate days throughout the study for the measurement of haemoglobin, urea,

electrolytes, calcium, phosphate, osmolality, serum proteins, and liver function tests. Twenty-four hour urine collections were maintained continuously throughout the study in the first 20 patients admitted to each treatment group and measurements were made of the daily urinary urea excretion and amino acid nitrogen content.

#### **Results**

Thirty-eight patients were randomized to receive pre-operative intravenous feeding and 36 patients were entered into the control group (Table 1). In the treated group, 3 patients had palliative bypass procedures, 6 had a radial partial gastrectomy and 10 patients a total gastrectomy. In the control group, 2 patients underwent oesophagectomy, 2 had palliative bypass procedures, 9 had a radical partial gastrectomy and 9 a total gastrectomy. Three surgeons performed the operations. Five patients who developed anastomotic leakage following total gastrectomy died despite continued intravenous nutritional support in the postoperative period. One of the 2 patients undergoing oesophagectomy in the control group also experienced an anastomotic leak, which closed spontaneously after 15 days of postoperative intravenous feeding.

TABLE 1. The clinical details of patients admitted to the trial

	Treated group	Control group
No.	<i>n</i> = 38	<i>n</i> = 36
Age (years)	65.6 ± 11.2	66.4 ± 9.8
Male : female ratio	26 : 12	20 : 16
Pathology at operation		
Negative laparotomy	2	2
Benign pathology	5	5
Operable cancer	19	22
Inoperable cancer	12	7

#### *Clinical assessment*

Mortality and 3 measurements of morbidity were each decreased in the treated group, but only in the case of wound infections did this reach statistical significance (Table 2). Retrospective review of the antibiotic prescribing in these patients showed no differences between the 2 groups. There were no significant differences in the total length of time the patients were in hospital or in the overall changes in body weight between the 2 groups of patients.

#### *Immune tests*

There were no significant differences in the tests of immune function performed on patients in the 2 groups, either during the pre- or postoperative periods. Neither group showed significant variation

in immune parameters before operation. Both groups of patients showed evidence of depressed PHA responses in the first 4 days after surgery and also with recurrence of tumour or general deterioration of the clinical state during postoperative follow-up. The reduction in postoperative wound infections in the treated group was not associated with any measurable differences in immune parameters when compared to the patients in the control group.

TABLE 2. The operative mortality and morbidity observed in the treated and control groups of patients. The figures in parenthesis indicate the number of patients in each group

Morbidity	Treated group (n=39)	Control group (n=36)
Deaths	6 n.s.	8
Anastomotic leakage (Total gastrectomy with oesophago-jejunal anastomosis)	2 (10) n.s.	3 (9)
Wound infection	3 $P < 0.05$	11
Other infections	9 n.s.	16

### Biochemistry

A fall in the serum proteins was observed in all patients when the initial values were compared with those at the time of discharge from hospital post-operatively. In the treated group of patients the mean fall in total protein fraction was  $3.4 \pm 7.2$  g/l and the control group  $3.9 \pm 8.0$  g/l. The mean serum albumin in the treated group fell by  $3.8 \pm 4.7$  g/l and in the control group  $3.0 \pm 4.2$  g/l. There was no significant difference in the fall between the groups. A significantly greater number of patients with low serum albumin levels on admission to hospital (less than 35 g/l) developed wound infections in the control group than in the treated group (Table 3).

TABLE 3. The operative complications occurring in treated and control patients with low serum albumin levels on admission to hospital ( $< 35$  g/l)

	Treated group (8)	Control group (9)
Deaths	1 n.s.	1
Anastomotic leakage	0 n.s.	0
Wound infection	0 $P < 0.05^*$	5

\* By Fischer's exact test.

Patients receiving intravenous feeding had a mean daily urinary urea excretion of 22 g (range 16.0–28.6 g) compared to a mean daily excretion in the control group of 12.5 g (range 6.0–17.3 g) before operation. In the immediate postoperative period, the mean daily urinary urea in the control group

rose to 17.7 g (range 8.5–35.3 g) whereas in the treated group the mean value was 20.4 g (range 11.0–35.4 g) excluding those patients receiving post-operative intravenous feeding.

The mean daily urinary amino acid nitrogen output was less than 800 mg in all patients, and there was no significant difference between the 2 groups of patients either before or after operation.

### Complications

Tolerance of the intravenous solution was variable, but patients not infrequently complained of feeling unwell when the solution was infused faster than the recommended rate. This form of treatment was found to be associated with a risk of the development of acute folate deficiency (Wardrop *et al.*, 1975) and of venous thrombo-embolism (Heatley *et al.*, 1976).

Complications arising from the intravenous cannulae were common but not in general serious. It was necessary to re-site the cannula on 25 occasions in 17 patients because of cannula occlusion, arm swelling, or infection, each cannula being left *in situ* for an average of 7 days. On 9 occasions a swollen arm was noted which settled spontaneously in all except 2 patients on removal of the cannula. These 2 patients were subsequently demonstrated by venography to have a thrombosis of the respective subclavian vein. Review of the chest radiographs taken at the time of insertion of the cannulae in these patients demonstrated that the cannulae had been incorrectly positioned, the tips lying in the subclavian vein rather than in the superior vena cava. There was one proved case of septicaemia and on 2 occasions patients experienced rigors which settled on removing the cannulae.

### Discussion

This study has demonstrated that some patients with upper gastrointestinal cancer may experience limited clinical benefit from a short course of intravenous nutrition before operative treatment. Although intravenous feeding is now widely used in patients with a variety of metabolic disturbances, there is little evidence currently available to show that this form of treatment confers clinical improvement to patients. The use of intravenous feeding to prepare patients with oesophageal cancer for surgery has been described previously and reported to be associated with diminished morbidity (Hadfield, 1965). However, these patients were not randomized and retrospective controls were used. Intravenous feeding has been shown to be of clinical value in patients with acute renal failure. In a strictly controlled study, intravenous feeding has been shown to hasten recovery of renal insufficiency, and

subsequently significantly to reduce the morbidity and mortality of the condition (Abel *et al.*, 1973).

In the present study, only wound sepsis was significantly improved by intravenous feeding. This clinical benefit was not associated with measurable improvement in immune parameters, and this is contrary to previous studies in which intravenous feeding has been claimed to improve measurements of cell-mediated immunity (Law, Dudrick and Abdou, 1973; Copeland, MacFadyen and Dudrick, 1976).

Biochemical measurements in this study suggest that the amino acids present in the intravenous preparation used were adequately utilized and not wasted significantly by urinary excretion. However, the increase in urinary urea excretion in patients receiving intravenous feeding must, in the absence of an increase in catabolic rate, suggest that much of the amino acid was converted directly to urea, rather than into new protein. It is possible, therefore, that similar clinical benefit could be achieved with a reduced daily nitrogen intake, perhaps to 10 g for each 24-hr period. It is also possible that utilization of the infused nitrogen could be enhanced by increasing the ratio of calories to nitrogen (Woolfson, Heatley and Allison, 1977).

In this study, the 3 main complications were those associated with the intravenous cannula, folate deficiency and deep vein thrombosis. Some of the complications of central venous cannulae might be reduced with intensive nursing care or intravenous infusion pumps, but a significant improvement is unlikely to be achieved in general ward usage. The occurrence of folate deficiency in a clinically dangerous form is most probably a direct effect of the intravenous nutrient solutions (Wardrop *et al.*, 1975), possibly the methionine content (Connor *et al.*, 1978), and may be rectified by the provision of parenteral folate supplements (Wardrop *et al.*, 1977).

The development of deep vein thrombosis in association with intravenous nutrition has not been previously noted, and there may be many predisposing factors present in the patients in this study. Pre-operative deep vein thrombosis is not uncommon in patients admitted to hospital for some days with this degree of illness (Heatley and Hughes, 1977). In the early part of this study, isotopic evidence of venous thrombosis was found in 5 of the first 22 patients between the fourth and tenth day of parenteral feeding. Four of these developed clinical venous thrombosis and one of these patients subsequently died postoperatively from a pulmonary embolus. Following this experience, the authors added 500 ml of dextran 70 to the intravenous regime on alternate days. Only one subclinical isotopic deep vein thrombosis was demonstrated in 16 patients receiving

intravenous nutrition. This treatment, therefore, appears to reduce the risk of venous thromboembolism in association with intravenous feeding.

In this study, pre-operative intravenous nutritional support given for 7–10 days to patients with malignant disease of the upper gastrointestinal tract resulted in a significant reduction in the incidence of postoperative wound infection. This improvement was seen despite the administration of maximum tolerated oral nutrition to the control group of patients. This small benefit has to be set against the morbidity associated with intravenous nutrition and the costly and time-consuming nature of the therapy. It is doubtful that the limited benefit achieved justifies the routine use of this type of regime, even in patients whose nutritional status has been impaired by upper gastrointestinal malignancy. The one measure of clinical benefit, decreased wound infection, was seen particularly in that group of patients who appeared to be most malnourished as reflected by a low serum albumin level.

It seems likely that this approach to treatment in the future will be developed along the lines of defining those patients who are most likely to benefit from therapy and subjecting these patients to a longer course of nutrition, perhaps for 3 weeks, to influence more adequately their state of malnutrition. The benefits of parenteral nutrition in such a selected situation should again be subjected to the rigour of a randomized controlled clinical study. However, the present trial has shown that such randomized studies are formidable, both in obtaining numbers which are likely to lead to statistically significant results, and because of the large number of patients with inoperable disease who will be subjected unnecessarily to a prolonged course of intravenous nutrition with inevitable increase in morbidity and loss of some of their remaining life.

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