Randomized trial

Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care

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Background: **Postoperative oral nutritional supplementation has been shown to be of clinical benefit. This study examined the clinical effects and cost of administration of oral supplements both before and after surgery.**

Methods: **This was a randomized clinical trial conducted in three centres. Patients undergoing lower gastrointestinal tract surgery were randomized to one of four groups: group CC received no nutritional supplements, group SS took supplements both before and after surgery, group CS received postoperative supplements only, and group SC were given supplements only before surgery. Preoperative supplements were given from the time it was decided to operate to 1 day before surgery. Postoperative supplements were started when the patient was able to take free fluids and continued for 4 weeks after discharge from hospital. Data collected included weight change, complications, length of stay, nutritional intake, anthropometrics, quality of life and detailed costings covering all aspects of care.**

Results: **Some 179 patients were randomized, of whom 27 were withdrawn and 152 analysed (CC 44, SS 32, CS 35, SC 41). Dietary intake was similar in all four groups throughout the study. Mean energy intake from preoperative supplements was 536 and 542 kcal/day in the SS and SC groups respectively; that 2 weeks after discharge from hospital was 274 and 361 kcal/day in the SS and CS groups respectively. There was significantly less postoperative weight loss in the SS group than in the CC and CS groups ($P < 0{\cdot}050$), and significantly fewer minor complications in the SS and CS groups than the CC group ($P < 0{\cdot}050$). There were no differences in the rate of major complications, anthropometrics and quality of life. Mean overall costs were greatest in the CC group, although differences between groups were not significant.**

Conclusion: **Perioperative oral nutritional supplementation started before hospital admission for lower gastrointestinal tract surgery significantly diminished the degree of weight loss and incidence of minor complications, and was cost-effective.**

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Introduction

Gastrointestinal surgery is associated with postoperative morbidity such as wound infection, anastomotic dehiscence, intra-abdominal sepsis and other extraintestinal complications[1]. Pre-existing malnutrition increases postoperative morbidity and mortality rates, and duration and cost of hospital stay[2,3], prompting the question of whether perioperative nutritional support might improve clinical outcome[4].

The Editors have satisfied themselves that all authors have contributed significantly to this publication

There is considerable debate over the role of parenteral and enteral feeding before and after surgery. Many studies have been carried out, but with wide variation in case mix, pre-existing nutritional status, route of feeding, and amount and type of feed used[5–17]. Furthermore, such nutritional support is labour intensive, carries a risk of complications and can be relatively expensive. The exact place of artificial nutritional support in the management of surgical patients is therefore far from clear.

Use of oral nutritional supplementation (ONS), together with voluntary food intake, as a means of providing nutritional support to surgical patients is more straightforward; these products are easy to administer, comparatively cheap, free from complication and, with the range of flavours now available, palatable[18–23]. Importantly, postoperative ONS has been shown to have a beneficial effect on outcome after surgery[18–22].

The primary aim of the present study was to investigate the clinical efficacy of ONS administered to surgical patients over an extended period before hospital admission, during the hospital stay and after discharge. Entry was restricted to patients undergoing elective major to moderate lower gastrointestinal surgery, as previous analysis[4] suggests that these patients are most likely to benefit from perioperative oral nutritional support. There are few prospective data available on the cost-effectiveness of perioperative enteral nutrition support[16,20,24]. This aspect was also addressed in the present study, although a detailed economic evaluation will be presented elsewhere.

Patients and methods

The study was conducted at three UK centres – The North West London Hospitals National Health Service (NHS) Trust (Central Middlesex Hospital), London, University Hospital of North Staffordshire NHS Trust, Stoke-on-Trent, and Chelsea and Westminster Hospitals NHS Trust, London. Ethics committee approval was given in all centres.

This was a two-phase, randomized clinical trial involving patients undergoing elective moderate to major lower gastrointestinal surgery. Phase I commenced before operation, when the decision to operate electively was made in the outpatient setting, and ended 24 h before surgery. Phase II commenced on the first day that the patient was able to take free fluids or a light diet after operation, and ended 4 weeks after discharge from hospital. The primary outcome was postoperative change in bodyweight. Secondary outcomes were clinical complications, length of hospital stay, nutritional status, quality of life and cost of care.

Exclusion criteria were age under 18 years, pregnancy, overt dementia, emergency or laparoscopic surgery, receipt of other forms of preoperative nutritional support, and inability to take ONS for a minimum of 7 days before operation. Patients were withdrawn from the study if they did not proceed to a qualifying operation, if enteral or parenteral feeding was given after surgery, or if they were unwilling to continue with the study. Those who were randomized to receive ONS but could not or would not take them, and those who were randomized not to receive supplements but were nevertheless prescribed them by the clinician, continued in the trial, and their data were included in the analysis.

Patients were randomized to one of four groups by means of sealed envelopes (*Table 1*). They were stratified according to nutritional status before randomization using a combination of body mass index, history of weight loss and age, according to previously validated criteria, to ensure even distribution of poorly nourished individuals[25].

Fortisip (Nutricia, Wageningen, The Netherlands), a drink containing 1·5 kcal and 0·05 g protein per ml, was used for oral nutritional supplementation. Patients were encouraged to drink this *ad libitum* in small, frequent quantities between meals. The volume consumed was recorded in terms of whole or half cartons taken.

All patients received standard postoperative care from clinical and nursing staff with commencement of free fluids and reintroduction of normal diet without interference by the study team or protocol. The postoperative course, both inpatient and outpatient, was carefully monitored. Complications were noted as major or minor using validated criteria[26].

A single dietitian at each centre collected the data to minimize interobserver variation. Anthropometric measurements including bodyweight, body mass index, mid-arm circumference, triceps skinfold thickness, mid-arm muscle circumference and hand-grip dynamometry were made using standard techniques at recruitment, on admission to hospital, on the day of resumption of free fluids or

Table 1 Randomization

Group	Phase I	Phase II
Group 1 (SS)	Supplements	Supplements
Group 2 (SC)	Supplements	No supplements
Group 3 (CS)	No supplements	Supplements
Group 4 (CC)	No supplements	No supplements

light diet, at hospital discharge, and 2 and 4 weeks after discharge.

Nutritional intake was assessed with 4-day food diaries for outpatients and food record charts for inpatients. The diaries were completed before admission and at 2 and 4 weeks after discharge. The inpatient charts were kept from the day of resumption of free fluids to day 7 or discharge, whichever occurred earlier. Energy and protein intake were calculated using validated software packages[27].

Quality of life was assessed using the Short Form 36 and EuroQol instruments. These were completed on recruitment, admission, at the time of discharge and 4 weeks later. They were self-completed where possible to minimize bias. In addition a well-being index for surgical patients[28] and a ten-point visual analogue scale for fatigue[29] were applied at the same time points.

Health service costs were measured by identifying all resource elements in both primary and secondary care, including use of consumables, staff time, ward costs and specific ward-based tasks such as wound dressing and urinary catheterization. Further details of the methodology will be presented elsewhere. Resource use was determined from the beginning of the hospital stay until 28 days after discharge, but also included the ONS taken before admission. The cost of the surgery was common to all groups and therefore excluded. Detailed unitary costs were obtained from the University Hospital of North Staffordshire. Where this was not possible, national sources were used[30–32]. Costs were aggregated per group and a mean cost per patient derived. Bootstrapping was used to obtain confidence intervals for the mean costs in each group[33].

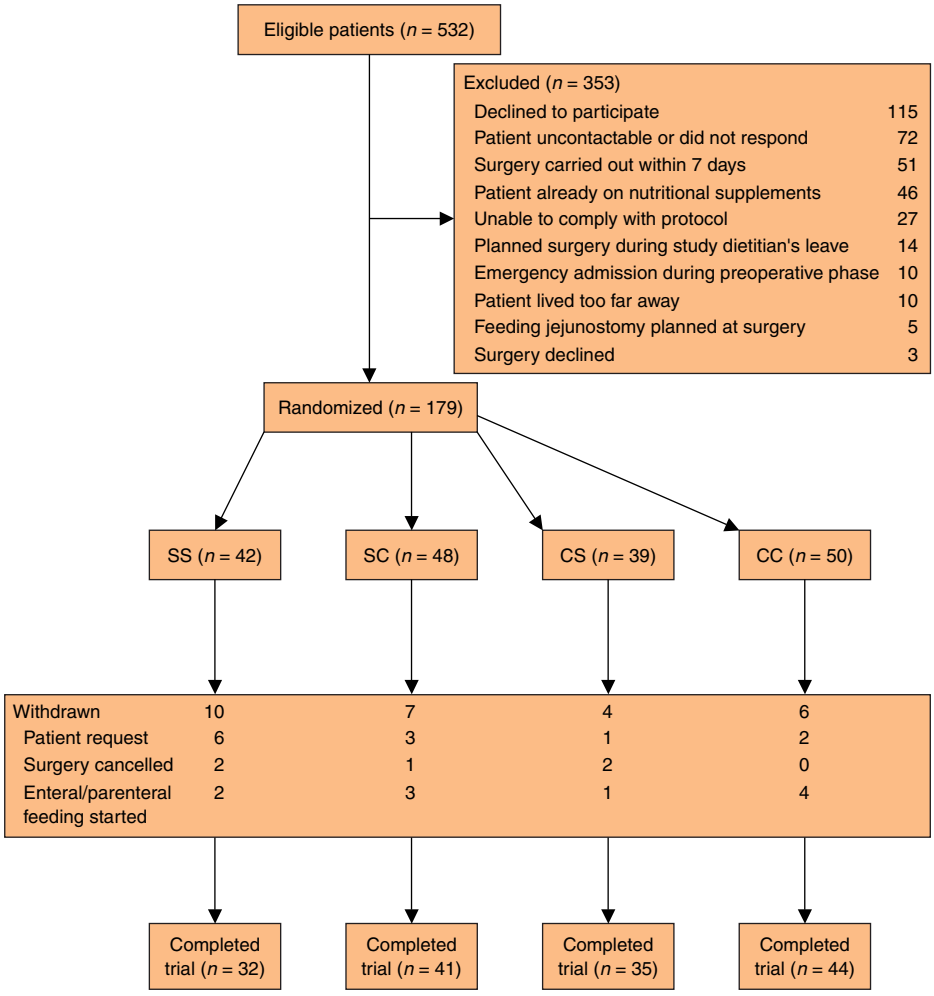

Fig. 1 Trial profile. SS, supplements before and after surgery; SC, supplements only before surgery; CS, postoperative supplementation only; CC, no nutritional supplement

Table 2 Patient demographics at baseline

	SS ($n = 42$)	SC ($n = 48$)	CS ($n = 39$)	CC ($n = 50$)
Contribution from each site‡				
1	2	4	5	6
2	25	34	22	29
3	15	10	12	15
Age (years)*	55 (26–81)	61 (23–84)	62 (22–83)	63 (25–88)
Sex ratio (M : F)	19 : 23	33 : 15	20 : 19	28 : 22
BMI (kg/m^2)†	24·9(4·5)§	26·9(4·9)	25·5(4·5)	27·8(5·6)
Mean grip strength (kPa)†	74·6(20·5)	74·1(23·1)	74·6(19·9)	71·5(20·7)
Fatigue score†	4·5(2·3)	4·1(2·1)	4·6(2·4)	4·2(2·1)
Stratification				
At risk	14	16	14	17
Not at risk	28	32	25	33
Diagnosis				
Colonic or rectal cancer	21	31	25	35
Colitis	12	7	7	6
Diverticulosis	6	5	3	3
Other	3	5	4	6

Values are *mean (range) or †mean(s.d.). ‡1, North West London Hospitals NHS Trust (Central Middlesex Hospital); 2, University of North Staffordshire Hospital NHS Trust; 3, Chelsea and Westminster Hospitals NHS Trust. BMI, body mass index. §$P < 0{\cdot}050$ *versus* CC (Bonferroni adjusted analysis).
SS, supplements before and after surgery; SC, supplements only before surgery; CS, postoperative supplementation only; CC, no nutritional supplement.

Table 3 Daily energy intake

	SS ($n = 32$)	SC ($n = 41$)	CS ($n = 35$)	CC ($n = 44$)
Phase I: preoperative				
Duration of ONS (days)*	14·5 (7–36)	15·1 (7–61)		
ONS (kcal/day)	536(231)	542(268)	0	0
Diet (kcal/day)	1946(544)	1993(548)	1953(630)	1923(475)
Total (kcal/day)	2478(688)†	2528(606)†	1953(630)	1923(475)
Phase II: postoperative (inpatient)				
Time from surgery to free fluids or light diet (days)*	4·7 (1–11)	5·8 (2–14)	4·7 (1–8)	5·4 (2–12)
ONS (kcal/day)	300(245)	0	258(201)	0
Diet (kcal/day)	1040(473)	996(567)	1033(579)	927(458)
Total (kcal/day)	1343(478)‡	996(567)	1296(640)‡	927(458)
Phase II: postoperative (outpatient); 2 weeks				
ONS (kcal/day)	274(163)	0	361(284)	0
Diet (kcal/day)	2110(514)	1990(609)	1761(648)	1791(360)
Total (kcal/day)	2390(503)‡	1990(609)	2133(792)§	1791(360)
Phase II: postoperative (outpatient); 4 weeks				
ONS (kcal/day)	340(160)	0	259(221)	0
Diet (kcal/day)	1981(517)	2068(555)	1946(621)	1919(447)
Total (kcal/day)	2253(590)	2068(555)	2209(688)	1919(447)

Values are mean(s.d.) unless indicated otherwise; *values are mean(range). ONS, oral nutritional supplementation. †$P < 0{\cdot}050$ *versus* CS and CC, ‡$P < 0{\cdot}050$ *versus* CC and SC, §$P < 0{\cdot}050$ *versus* CC (Bonferroni adjusted analysis).
SS, supplements before and after surgery; SC, supplements only before surgery; CS, postoperative supplementation only; CC, no nutritional supplement.

Statistical analysis

The primary outcome measure was differences in bodyweight change at discharge between the treated and the control groups. In a previous study, comparison of weight loss in patients receiving postoperative ONS with diet *versus* diet alone indicated an estimated variance of 6·63. The study observed a difference of 2·4 kg between the two groups, which represents a large effect size[34]. Assuming a large effect size in the present study, analysis by ANOVA and a 5 per cent significance level, 31 patients in each of four groups would be sufficient to achieve 95 per cent power. Measurements in the four groups were compared

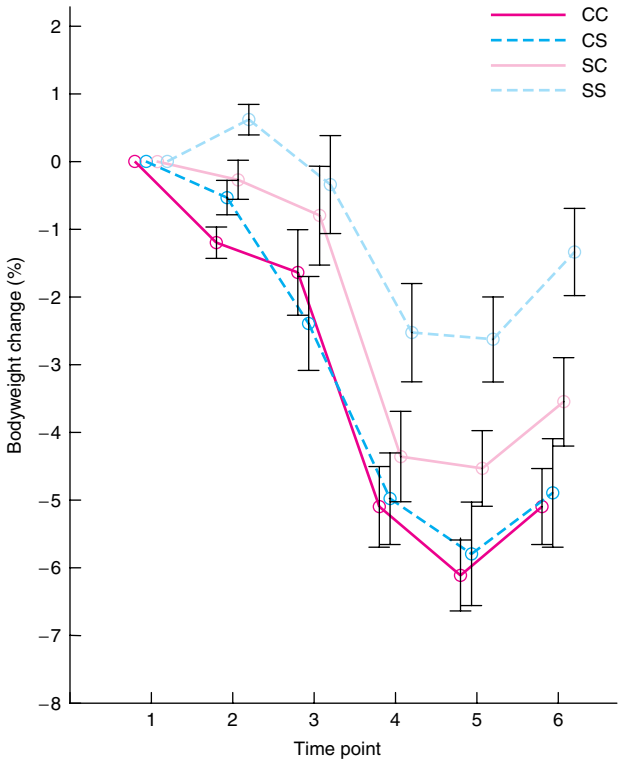

Fig. 2 Changes in bodyweight expressed as a percentage of weight at recruitment. Time points: 1, recruitment; 2, admission; 3, day 1 of free fluids or diet; 4, discharge from hospital; 5, 2 weeks after discharge; 4 weeks after discharge. $P < 0{\cdot}050$ (SS *versus* CC and CS, ANOVA followed by Bonferroni adjusted tests on pairs). SS, supplements before and after surgery; SC, supplements only before surgery; CS, postoperative supplementation only; CC, no nutritional supplement.

by ANOVA for approximately normally distributed data, followed by tests on pairs of groups using the Bonferroni adjustment. Non-normal data were compared by the Kruskal–Wallis test followed by Mann–Whitney *U* tests with *P* values adjusted for multiple testing.

Results

One hundred and seventy-nine patients were recruited between October 1998 and March 2001 (*Fig. 1*). They were well matched for age, sex, nutritional status and risk, diagnosis (*Table 2*) and operation performed (data not shown), apart from a difference in body mass index between the SS and CC groups. Twenty-seven patients were withdrawn (*Fig. 1*), leaving 152 patients for analysis.

Energy intake in the various phases of the study is shown in *Table 3*. Preoperative ONS was given for a mean of 15 days, with a mean energy intake of 536 and 542 kcal/day in the SS and SC groups respectively. Postoperative ONS was given once free fluids or a light diet could be tolerated, between 4·7 and 5·8 days after surgery. ONS was then continued until 4 weeks following discharge. There were no significant differences in mean intake of ONS at the inpatient phase and at 2 and 4 weeks after discharge from hospital between two supplemented groups (SS: 300, 274, 340 kcal/day respectively; CS: 258, 361 and 259 kcal/day respectively). There were no significant differences in dietary intake, in terms of energy consumed, between groups at any time point.

Only patients in the SS group gained weight before surgery; these patients also lost significantly less weight over the course of the study than those in the CC or CS groups ($P < 0{\cdot}050$, Bonferroni adjusted test[35]) (*Fig. 2*). There were no differences between groups in any other anthropometric variable measured, or in fatigue and quality of life scores (data not shown).

The rate of major complications was similar in the four groups, but there were significantly fewer minor complications in the SS and CS groups than in the CC group ($P < 0{\cdot}050$) (*Table 4*).

The overall costs in all three supplemented groups were less than those in patients who received no ONS by approximately £300 or 15 per cent per patient episode, although the difference was not significant (*Table 5*).

Table 4 Duration of postoperative hospital stay and complications

	SS ($n = 32$)	SC ($n = 41$)	CS ($n = 35$)	CC ($n = 44$)
Postoperative hospital stay (days)*	11·7(5·1)	12·8(4·5)	13·4(7·5)	14·1(6·6)
Complications				
Minor	10†	17	13†	30
Major	5	3	2	4
Mean no. per patient	0·31	0·41	0·37	0·68
Total	15	20	15	34

*Values are mean(s.d.). †$P < 0{\cdot}050$ *versus* CC (Kruskal–Wallis followed by adjusted Mann–Whitney *U* test).
SS, supplements before and after surgery; SC, supplements only before surgery; CS, postoperative supplementation only; CC, no nutritional supplement.

Table 5 Mean cost per patient

	SS ($n = 32$)	SC ($n = 41$)	CS ($n = 35$)	CC ($n = 44$)
Before admission (ONS only) (£)	40	37	0	0
Inpatient (£)	1827	1967	2005	2276
After discharge (£)	422	282	319	342
Total cost (£)	2289 (2034, 2717)	2286 (2050, 2566)	2324 (2018, 2661)	2618 (2272, 3181)

Values in parentheses are 95 per cent confidence intervals. ONS, oral nutritional supplementation.
SS, supplements before and after surgery; SC, supplements only before surgery; CS, postoperative supplementation only; CC, no nutritional supplement.

Discussion

Patients receiving ONS over an extended perioperative period lost significantly less weight than those who received no supplements or postoperative supplements only. The incidence of minor complications was significantly lower in patients receiving ONS throughout or after surgery than in those receiving no supplements or preoperative supplements only. Use of ONS led to cost savings per patient, irrespective of when supplements were administered.

The few studies that have investigated preoperative and perioperative enteral tube feeding have produced conflicting results, some showing benefit[12–14,16] and others none[15]. However, comparisons are difficult because of differences in study design, diets, method and amount of feeding, case mix and nutritional status. Although most authorities accept that any perioperative nutritional support required should be enteral (unless contraindicated) rather than parenteral, there is still no consensus on the optimal enteral support strategy.

Administration of ONS is easier and cheaper than parenteral or enteral tube feeding and is without complication. Six studies have critically examined the benefits of ONS in surgical patients, five of which showed clinical benefit from postoperative supplementation[18–22]. The present study explored in more detail the value of use of standard ONS in surgical patients, both in clinical and economic terms, and examined the effect of timing of administration.

The original intention was to administer ONS for up to 4 weeks before surgery. However, shortly after planning the trial, political imperatives in the UK led to a more efficient streamlining of patient care and treatment of this cohort of patients, most of whom had malignant disease. As a result the preoperative supplementation period was curtailed to a mean of 15 days.

Provision of ONS before surgery alone conferred no benefit on postoperative morbidity or quality of life. Although both preoperative and postoperative administration of ONS resulted in a significant reduction in weight loss compared with the provision of postoperative ONS alone, this was not associated with a decreased incidence of postoperative complications. Nutritional supplementation both before and after surgery probably failed to confer added clinical benefit in the present study because the preoperative nutritional intake from food in all four groups was surprisingly good (mean more than 1900 kcal/day), as was the overall nutritional status (as indicated by body mass index). It is also possible that the duration of preoperative feeding may have been insufficient for a significant effect to be evident.

Use of postoperative ONS resulted in a significant reduction in postoperative morbidity and weight loss, regardless of body mass index; this finding is in full agreement with other similar studies[18–22] and was confirmed in a recent meta-analysis[36].

The only other trial that evaluated the clinical effects of administering ONS both before and after surgery produced results that are apparently at variance with the present data. MacFie *et al.*[23] suggested that the routine use of perioperative ONS in patients undergoing major gastrointestinal surgery does not confer any clinical or functional benefit. Their study, in which the majority of patients also underwent elective lower gastrointestinal surgery, employed different postoperative management protocols, including oral nutritional supplementation and voluntary food intake on the first postoperative day. Moreover, different criteria were used to define complications: those described by Buzby *et al.*[26] in the present study and those of Copeland *et al.*[37] in that of MacFie and colleagues. Such important differences in experimental design make it difficult to compare results directly.

Following discharge from hospital, patients taking ONS maintained enhanced nutritional intake at 2 weeks, but by 4 weeks the total intake was similar in the four groups. These increases in the early discharge phase were not, however, accompanied by any apparent clinical benefit nor, importantly, were there any positive influences on quality of life. These findings are similar to those of a previous study in which ONS was administered for 4 months after discharge[19], and suggest that routine nutritional supplementation following hospital discharge is

not indicated as long as voluntary food intake is satisfactory (in the present study approximately 2000 kcal/day).

An important finding of the present study is that the benefit of postoperative ONS on clinical outcome occurred independently of nutritional status, and was not restricted to malnourished patients. This is in agreement with the conclusions from previous studies[12,18,19]. In terms of explanation for the benefits seen, it is interesting to speculate whether ONS and better nutritional state may influence insulin resistance after surgery, as is seen with preoperative glucose loads[38]. Taken together, the authors believe that these findings question the veracity of recently published guidelines recommending that elective surgical patients should receive artificial nutritional support only if a preoperative weight loss of 10 per cent or more is detected, or if adequate oral food intake is expected later than 10 days after surgery[39–43].

Only three studies have examined the costs associated with use of ONS in surgical patients. Two of these involved patients fed with either an immune-modulating or a control diet for 5 days before and 10 days after surgery for upper gastrointestinal tract cancer[16,24]. Both showed non-significant cost savings, although in one[24] these reached significance when patients with anastomotic leaks were included in the analysis. The third study demonstrated savings for orthopaedic patients receiving postoperative ONS compared with hospital diet alone[20].

The present study is very different in design from these previous cost analyses. It is unique in its detailed acquisition of cost data, and includes quantification of staff time, as well as more easily identifiable costs of consumables, to give a more accurate picture of overall resource usage. Regardless of the timing of administration, use of ONS produced a cost saving of approximately £300 – about 15 per cent – per patient compared with the cost of treatment without ONS. Although differences in cost were not statistically significant, this represents considerable savings taken the number of surgical patients in each hospital.

This study joins a growing body of literature on the impact of use of ONS in surgical patients. Although comparison between studies is difficult, the overall impression is that use of perioperative ONS has no disadvantages, leads to clinical benefit and is cost-effective in patients undergoing moderate to major lower gastrointestinal tract surgery. ONS should therefore be offered to all such patients irrespective of nutritional status. Whether supplements should be given for longer periods before operation, and whether there are specific patient groups that might gain greater benefit from ONS, are questions that still need to be resolved.

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