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Conference on 'Malnutrition matters'

Symposium 3: Nutrition is the cutting edge in surgery: peri-operative feeding
Peri-operative nutritional management

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The metabolic response to surgical trauma is mainly characterised by an increase in BMR, a negative N balance, increased gluconeogenesis and increased synthesis of acute-phase proteins. These reactions aim at ensuring the availability of endogenous substrates for healing wounds while the synthesis of acute-phase proteins enhances the scavenging process and helps repair. However, if this process is excessive or continues for too long, it leads to a progressive depletion of body compartment with a consequent adverse outcome. Obviously, the severity of such depletion is magnified if the patient is starving or is already malnourished and the consumption of lean body mass is not compensated by an exogenous supply of nutrients. The nutritional control of this metabolic reaction represents the traditional rationale for nutritional support of surgical patients. Subsequent data have shown that the negative effects of starvation are not simply due to the starvation *per se* but due to the starving gut, and peri-operative enteral nutrition has proven successful in blunting the metabolic response after injury and improving protein kinetics, net balance and amino acid flux across peripheral tissue and consequently in decreasing the complications. Finally, further clinical research has shown that many post-operative infections may result from immune suppression and that such state might be reversed to some degree by modulation of the immune response through specialised nutritional support in surgical patients, regardless of their nutritional status. This paper will focus on the updated evidence-based research on peri-operative nutrition (parenteral, enteral and immune-enhancing) in patients undergoing major surgery.

Peri-operative parenteral nutrition: Peri-operative enteral nutrition: Peri-operative immunonutrition

The metabolic response to surgical trauma is mainly characterised by an increase in BMR, a negative N balance, increased gluconeogenesis and increased synthesis of acute-phase proteins. These reactions aim at ensuring the availability of endogenous substrates for healing wounds while the synthesis of acute-phase proteins enhances the scavenging process and helps repair.

However, if this process is excessive or continues for too long, it leads to a progressive depletion of body compartments with a consequent adverse outcome. Obviously, the severity of such depletion is magnified if the patient is starving or is already malnourished and the consumption of lean body mass is not compensated by an exogenous supply of nutrients.

The nutritional control of this metabolic reaction has represented the traditional rationale for nutritional support of surgical patients because it is understood that severe weight loss ($\geq 10\%$ of the usual body weight) is associated with an increased risk of surgical complications[1]. This increased risk of complications due to the presence of malnutrition (evaluated as severity of the weight loss or with the use of more complex scores including anthropometric, biologic or immunologic parameters) has been replicated in several prospective investigations (see a

Abbreviations: EN, enteral nutrition; IEEN, immune-enriched enteral nutrition; PN, parenteral nutrition; RCT, randomized clinical trial.
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Table 1. Pre-operative parenteral nutrition *v.* no nutritional support

	Pre-operative		Post-operative	
Author	No. of studies	Patients (*n*)	No. of studies	Patients (*n*)
Klein *et al.*[16]	13	(1358)	9	(754)
Torosian[17]	14	(1245)	8	(710)
Braunschweig *et al.*[18]			2	(181)
Heyland *et al.*[19]	11	(1165)	16	(1742)
Koretz *et al.*[20]	25	(2164)	18	(482)

Adapted from Howard and Ashley[21].

comprehensive review in Stratton *et al.*[2]) and is well recognised by the scientific community.

The first randomized clinical trial (RCT) that compared parenteral nutrition (PN) with standard intravenous infusion was published in 1977[3]. This study, performed at the Massachusetts General Hospital in Boston, compared two groups of patients having lost at least 5 kg body weight to receive parenteral 'hyperalimentation' (thirty patients) or not (twenty-six patients). Even if nowadays we would consider this study obsolete because of its limited statistical power, the marginal malnutrition of the patients' population and the short time period of the pre-operative treatment (72 h), nevertheless the authors have to be recognized as the first to focus their research on the area of peri-operative nutrition and to apply the methodology of the RCT to investigate this issue. Their approach will be widely followed in the subsequent decades by a generation of surgeons.

In subsequent years it became clear that the negative effects of starvation are not simply due to the starvation *per se* but due to the starving gut.

The physiologic (and beneficial) changes induced by delivery of enteral nutrition (EN) have been recently summarised in an excellent review by McClave and Heyland[4].

The provision of oral nutrition or via the gastric or the jejunal route (EN) supports the functional and structural integrity of the intestinal epithelium. In addition, this approach stimulates the bowel contractility and the release of bile salts, and other agents that have a trophic effect for the intestine as gastrin, motilin and bombesin[5].

A good contractility, sweeping the bacteria downstream, may reduce the total number of bacteria within the proximal gut and may promote the role of commensal bacteria[6]. These degrade the bacterial toxins, inhibiting colonisation by pathogenic micro-organisms as well as fermenting pre-biotic fibres, resulting in the production of SCFA. These SCFA can stimulate the butyrate receptors in the colon and consequently down regulate the inflammatory response as well as oxidative stress[7].

In addition, EN stimulates blood flow to the bowel and supports the immune system because IgA-producing immunocytes proliferate and then migrate out to distant sites such as lung, kidney and liver[5,8,9]. Similarly, the proliferating T-helper 2 CD4 helper lymphocytes spill out in the systemic circulation and create an anti-inflammatory effect that opposes any T-helper 1 response present in the circulatory system[10,11]. In the absence of food antigen and in the presence of pathogenic bacteria overgrowth there is a predominance of T-helper cell 1 cells that generates a pro-inflammatory effect and this spills over into the systemic circulation raising a systemic inflammatory response through the production of pro-inflammatory cytokines (IL-2, interferon-γ, and TNF-β)[8,12,13].

Following these premises, EN entered in the nutritional management of surgical patients and in effect peri-operative EN has proven successful in blunting the metabolic response after injury and improving protein kinetics, net balance and amino acid flux across peripheral tissues and consequently in decreasing the post-operative complications.

The first RCT comparing PN and EN in surgical patients was published in 1986[14].

Finally, further clinical research has shown that many post-operative infections may result from immune suppression, of whatever origin, and that such a state might be reversed to some degree by modulation of the immune response through specialised nutritional support in surgical patients, regardless of their nutritional status.

The first RCT comparing immune-enriched enteral nutrition (IEEN) to standard EN appeared in 1992[15].

This paper focuses on the updated evidence-based research on peri-operative nutrition (parenteral, enteral and immune-enhancing) in patients undergoing major surgery.

Pre-operative parenteral nutrition

This can be only considered in patients who do not require urgent surgical intervention.

PN starts in the pre-operative period and is usually continued post-operatively, and in several RCT the control arm also receives post-operative PN.

There are five meta-analyses[16–20] that include RCT on patients with moderate or severe malnutrition (Table 1). The two first meta-analyses analysed pre- and post-operative RCT separately, whereas the last three analysed them together and included RCT using hypoenergetic PN (protein sparing nutrition).

The pooled results from all five meta-analyses showed no effect on post-operative mortality, but three of them[16,17,19] found a reduction in post-operative complications: the major complications declining from 40% in the control arm to 30% in the treated arm. It is worthy of note that in no study was there benefit seen if pre-operative PN lasted less than 5 d. In severely malnourished patients only PN for 7 d or more proved to be clinically beneficial. According to the largest trial of pre-operative PN including 395 patients[22], the benefit was confined to severely malnourished patients but this group accounted for 5% of all elective surgical patients. Hence, the indication for a pre-operative PN appears limited, but when considering selected pathologies (gastrointestinal cancer patients, for instance), the percentage of weight-losing patients could be substantially higher.

Post-operative parenteral nutrition

Post-operative PN usually does not refer to nutritional support started before surgery and continued post-operatively

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but refers to an intravenous nutrition started just after the surgical procedure. In contrast with the pre-operative PN that may be recommended only in malnourished patients, post-operative PN was mainly performed in non-malnourished patients.

There are nine RCT involving more than 700 patients and three meta-analyses[18–20].

The conclusions of these studies were that post-operative PN increased morbidity by 10%, mostly due to an increase in septic complications.

Pre-operative standard enteral nutrition

There have been few pre-operative standard EN RCT[23–26] because this approach became rapidly obsolete and, like PN, it can be only considered in patients who do not require urgent surgical intervention.

When compared with standard hospital regimen (usually isotonic infusions or routine hospital diet), these studies demonstrated a reduction of surgical complications. In the study of Shukla *et al.*[23] the patients who received the tube feedings showed a reduction in post-operative mortality by 50% (6·0% enteral nutrition group, 11·7% controls) and wound infections were reduced 75% (10·4% enteral nutrition group, 37·2% controls). Foschi *et al.*[24] randomized pre-operative patients with obstructive jaundice undergoing *trans*-hepatic biliary drainage to 20 d of 'hyperalimentation' (86% by the enteral route) or the routine hospital diet. They reported a reduction in post-operative mortality by 75% in the treated group (3·5% enteral nutrition group *v.* 12·5% in controls). Flynn and Leightty[25] randomized outpatients with squamous cell carcinoma of the head and neck to routine diet with a nocturnal supplement for 10–20 d prior to surgery or the routine diet alone and reported that post-operative complications were reduced 50% in the supplemented group (32% enteral nutrition group *v.* 59% controls). Finally, Von Meyenfeldt *et al.*[26] randomized 151 patients with gastric or colorectal cancer to 10 d of either pre-operative PN (*n* 51) or pre-operative EN (*n* 50). Control patients (*n* 50) went to surgery without delay. A *post-hoc* analysis showed that only in the severely depleted patients there was a significant decrease of intra-abdominal abscesses in both intervention groups compared with the depleted controls.

Post-operative standard enteral nutrition

This type of nutritional support is usually started in the first post-operative day and the feeding is administered through a small catheter with the tip preferably placed in the post-pyloric area and often in the proximal jejunum.

There are two meta-analyses. The first by Koretz *et al.*[27] involved thirteen RCT and 1032 patients and reported that EN, when compared with standard isotonic fluids, was associated with fewer infections. The second[28], considered thirteen RCT (EN consisted in tube feeding in seven studies and oral nutritional support in six studies), and involved 1173 patients. This demonstrated that early EN (within 24 h from the operation) was able to lower mortality and decrease the length of stay. This was achieved despite an increase in episodes of vomiting, especially in patients receiving oral nutritional supplements.

Comparing parenteral with enteral nutrition

Three meta-analyses[18–20] have considered this issue: these analysed twenty RCT involving 1033 patients and demonstrated that standard EN was superior to PN with fewer post-operative complications and shorter hospital stay. These findings were confirmed in a more recent meta-analysis of RCT in cancer patients by Elia *et al.*[29].

A further recent meta-analysis compared post-operative (standard or immune-enriched) EN *v.* PN[30]: twenty-nine trials, which included 2552 patients undergoing surgery for gastrointestinal cancer, were analysed. EN was beneficial in the reduction of any complication (relative risk, 0·85; 95% CI 0·74, 0·99; $P = 0·04$), any infectious complication (relative risk, 0·69; 95% CI 0·56, 0·86; $P = 0·001$), anastomotic leak (relative risk, 0·67; 95% CI 0·47, 0·95; $P = 0·03$), intra-abdominal abscess (relative risk, 0·63; 95% CI, 0·41, 0·95; $P = 0·03$) and duration of hospital stay (weighted mean difference, −0·81; 95% CI −1·25, 0·38; $P = 0·02$). There were no clear benefits in any of the other complications. A subgroup analysis that stratified standard enteral (eleven RCT) *v.* immune-enriched (two RCT) showed that the benefit was not due to the patients receiving immune-enhancing enteral nutrition.

Immune-enhancing *v.* standard enteral nutrition

Several reviews and meta-analyses have been published on this topic[31–34]. The most recent and complete was published by Cerantola *et al.* in 2001[35].

This paper[35] included twenty-one RCT enrolling a total of 2730 patients.

IEEN formulas included arginine, *n*-3 fatty acids, RNA (but two studies used glutamine and *n*-3 fatty acids).

The regimen of the control arm was isoenergetic and isonitrogenous in nine studies and only isocaloric in four studies.

The conclusions were that IEEN, regardless of the time of administration (pre-operative, post-operative or both) was able to reduce the complication rates (OR: 0·48, 95% CI 0·54, 0·39), and the infections (OR: 0·36, 95% CI 0·53, 0·41).

In addition, IEEN reduced hospital stay by 2 d (95% CI −2·9, −1·2, $P = 0·001$) but there was no difference in mortality.

Three RCT[36–38] have investigated the costs involved and reported a mean saving of 52, 13 and 18% from IEEN, respectively.

The Milan experience

Recently, Bozzetti *et al.*[39] pooled the databases of their previous RCT[40–46] on peri-operative nutrition with the purpose of investigating the potential joint prognostic role of different variables on the occurrence of post-operative

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Table 2. Multivariate analysis of risk factors in relation to major complications

	OR	95% CI	*P**
Nutrition			0·002
TPN *v.* SIF	0·39	0·19, 0·80	
EN *v.* SIF	0·27	0·13, 0·57	
IEEN *v.* SIF	0·32	0·16, 0·63	
Age (years)			0·050
56–65 *v.* ≤55	1·48	0·72, 3·05	
66–75 *v.* ≤55	1·55	0·77, 3·12	
75 *v.* ≤55	3·05	1·35, 6·86	
Tumour site			0·004
Stomach *v.* colon-rectum	2·82	1·48, 5·37	
Pancreas *v.* colon-rectum	2·87	1·38, 5·98	
Weight loss†	–	–	0·029

*Wald's *P* for testing the overall association between the occurrence of complications and main series characteristics.
†OR and CI estimates are given only for categorical factors.
IEEN, immune-enriched enteral nutrition; SIF, standard intravenous fluid; TPN, total parenteral nutrition.

complications after gastrointestinal cancer surgery. They considered baseline demographic, clinical and nutritional parameters, type of nutritional support and intra-operative factors.

They reanalysed databases of 1410 patients with cancer who were divided into the following groups: standard intravenous fluid (*n* 149); total PN (*n* 368); enteral nutrition (*n* 399); and IEEN (*n* 500). The daily nutritional regimen was as follows: standard intravenous fluid: 1673·6–3765·6 kJ (400–900 kcal); total PN: 104·6–142·25 kJ (25–34 kcal/kg) + 0·25 g N/kg and EN or IEEN: 104·6–117·15 kJ (25–28 kcal/kg) + 0·25 g N/kg.

The occurrence of all complications in-hospital was reported with a special focus on the major complications (lethal complications or those that required a relaparotomy or admission to intensive care unit). Major and minor complications occurred in 101 (7·2%) and 446 (31·6%) patients, respectively. Factors that correlated with post-operative complications on multivariate analysis were pancreatic surgery ($P<0·001$), advanced age ($P=0·002$), weight loss ($P=0·019$), low-serum albumin ($P=0·019$) and nutritional support ($P=0·001$). The major clinical benefit was observed, in the order, with IEEN, EN, total PN and standard intravenous fluid (Table 2; Fig. 1).

Owing to the large number of patients it was possible to calculate the probability of complications by the severity of weight loss considered as a continuous variable and we demonstrated that the higher the percentage of weight loss, the higher was the risk of complications. Fig. 1 shows the probability of complications *v.* the percentage weight loss and depending of the type of nutritional support different risks are estimated. The lower curves report the percentage of complications for a low-risk population (young patients, colorectal resection, normal albumin serum level), the upper curves for high-risk patients (elderly patients, pancreatic resections low albumin serum level). Depending on the different combination of risk factors (age, type of surgery, albumin serum level) present in a patient, we have different intermediate curves which are always correlated with the severity of weight loss and type of perioperative nutritional support.

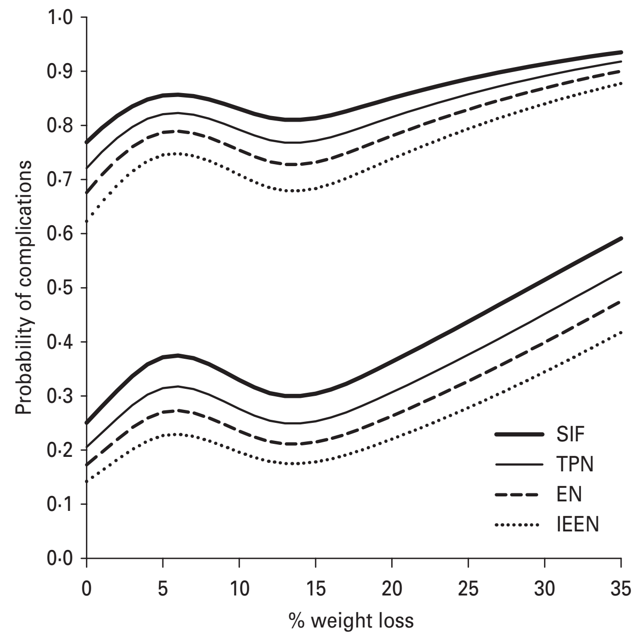

Fig. 1. The probability of complications *v.* the percentage weight loss and depending of the type of nutritional support different risks are estimated. The lower curves show the percentage of complications for a low-risk population (young patients, colo-rectal resection, normal albumin serum level) and the upper curves with regard to high-risk patients (elderly patients, pancreatic resections, low albumin serum level). SIF, standard intravenous fluid; TPN, total parenteral nutrition; EN, enteral nutrition; IEEN, immune-enriched enteral nutrition.

Conclusion

A pre-operative PN (that usually continues in the post-operative period) is nowadays rarely recommended because the benefit is seen limited to severely malnourished patients who represent a minority of those candidates for the elective surgery. Moreover, the enteral approach is more efficient and has the advantage that patients can receive the treatment prior to their admission to the hospital.

In some situations, especially in cancer patients undergoing gastrointestinal surgery, a pre-operative course of PN of at least 1 week, can be given while the patients undergo any diagnostic tests during their hospital stay.

It may be that the benefit of pre-operative PN is not due to an improvement of malnutrition because many experts feel unlikely that a chronic condition of underfeeding lasting for several weeks or months be reversed by few days of nutritional support. In addition, the nutritional status of malnourished patients on pre-operative PN who will not present post-operative complications cannot be differentiated from that of patients who will develop complications despite PN[41]. Pre-operative PN might work through a reduction of post-operative insulin insensitivity with a mechanism similar to the pre-operative carbohydrate load

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that was pioneered and popularised by Ljungqvist *et al.*[47]. The metabolic and clinical, previously unrecognised, benefits of the pre-operative carbohydrate administration, are now widely acknowledged and are incorporated in the so-called 'fast track' approach[48].

For the same reasons, a pure post-operative PN (without a pre-operative induction) is not recommended unless there are post-operative complications in patients who cannot be totally fed through the enteral route, an event that is not rare.

A pre-operative standard EN (which was reported beneficial in malnourished patients) has become obsolete in view of the better results with IEEN that is efficient regardless of the nutritional status of the patient, and hence represents the first nutritional option.

These recommendations are also reported in the recent Guidelines of the European Society for Parenteral and Enteral Nutrition and Clinical Metabolism[49,50].

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