Review Article

Clinical trials of immunonutrition in surgical cancer patients

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ABSTRACT: In the last years adding specific nutrients, such as arginine, omega-3 fatty acids and nucleotides, has modified standard enteral diets. These substrates have been shown to up-regulate host immune response, control inflammatory response, and improve nitrogen balance and protein synthesis after injury.
Most randomized trials focused on clinical outcome have been carried out in gastrointestinal (GI) cancer patients undergoing elective surgery. When immunonutrition was limited to the postoperative period the results were conflicting, probably because the amount of substrates given in the first days after surgery was not sufficient to reach adequate tissue and plasma concentration quickly enough to be active. Better results on outcome were obtained when the immunoenhancing diet was administered before surgery. This enabled to reduce significantly the postoperative infection rate in either malnourished or well-nourished patients.
Cost-benefit analyses showed that immunonutrition is cost-effective when compared to the standard treatment. (Nutritional Therapy & Metabolism 2006; 24: 115-9)

KEY WORDS: Immunonutrition, Surgery, Postoperative morbidity, Postoperative infections, Costs

INTRODUCTION

Despite significant changes in elective surgical care and the latest antimicrobial agents, postoperative infectious complications remain common and result in increased length of hospital stay (LOS), healthcare costs and potential excess mortality. Furthermore, the rates of nosocomial infections are rising in surgical and intensive care units, and the apparent increase in both Gram-positive and Gram-negative resistant bacteria is of particular concern, making the prevention of infection a major surgical issue (1). The causes of infectious surgical complications are multi-factorial and somewhat dependent on the underlying surgical disease, and the type and magnitude of the operation. Nevertheless, there is growing evidence that trauma and surgical insult is associated with a period of relative immune suppression, which may expose patients to subsequent risk of infection.

In addition, surgeons are increasingly under pressure to reduce healthcare costs. In many countries healthcare payers and providers encourage medical and surgical staff to reduce patient LOS, particularly for elective surgery. It is therefore imperative to reduce the potential for postoperative infectious complications (2).

Among the proposed strategies to reduce post-operative morbidity and its related costs, artificial nutrition is recognized as an important aspect of patient care, particularly for patients undergoing major surgery for cancer of the GI tract. In recent years, major advances have been made in the field of clinical nutrition. Improvements in patients outcome have been obtained with early enteral nutrition in both malnourished cancer patients undergoing elective major surgery and intensive care unit patients (3, 4). A further interesting field of research is the likely modulation of post-injury metabolic response by using new formulas supplemented with specific nutrients (immunonutrition).

IMMUNONUTRITION - RESULTS OF CLINICAL TRIALS

Recently, the main focus of clinical nutrition has moved from the issue of energy and nitrogen requirements to the pharmacological effects of specific key nutrients. Adding specific substrates such as arginine, glutamine, omega-3 fatty acids, nucleotides, symbiotics, and others has modified standard nutritional feeds. The main goal of these new diets is not only to provide energy and nitrogen, but also to modulate inflammatory post-injury response and counteract postoperative immune impairment, which may per se raise patient susceptibility to infectious complications. Most of the randomized controlled trials performed so far in GI cancer patients undergoing elective surgery have tested a combination of arginine, omega-3 fatty acids and nucleotides.

When the administration was limited to the postoperative period, immunonutrition enhanced the host defense mechanisms and helped to overcome the post surgical immune depression more rapidly than the standard diet. However, this improvement occurred with some delay (5). In fact, in the first days after surgery, the impairment of phagocytosis and lymphocyte mitogenesis, the alteration of cytokine profiles, the reduction in immunoglobulin levels and number of activated T and B cells were similar in patients fed with either supplemented or standard diet.

The delayed recovery in immune response might explain why supplemented diets given solely in the postoperative course led to variable improvements in outcome (5-9). Heslin et al, who studied 195 patients undergoing elective cancer surgery, did not find any difference in postoperative infectious and noninfectious complications when comparing groups treated with either an early postoperative immunoenhancing diet or simple crystalloid fluid replacement (6). However, in the immunonutrition group the average postoperative energy intake was 60% of the nutritional goal and only 30% was given with the immunoenhancing diet. When the amount of immunonutrients given early after surgery was higher, a significant reduction in postoperative infections was reported by Daly et al. (7), whereas a not statistically significant reduction of overall postoperative complications by immunonutrition was found in a multicentre study from Germany (5) and in a large single-centre study from Italy (8). These contrasting results supported the hypothesis that the amount of substrates given in the first days after surgery was not sufficient to reach adequate tissue and plasma concentration promptly enough to be active. In fact, it takes approximately five days for immune-enhancing nutrients to be incorporated into host tissues and thus modulate inflammatory mediators and fatty acid profiles. Since the impairment of the host defense mechanisms occurs immediately after surgery, immunonutrients should be given prior to surgery to obtain adequate levels at the time of surgical stress.

TABLE I - POSTOPERATIVE METABOLIC EFFECTS OF IMMUNONUTRITION IN GI CANCER PATIENTS

Improvement of PMN phagocytosis ability
Improvement of lymphocyte mitogenesis
Improvement of cell-mediated immune response
Reduction in proinflammatory cytokine synthesis
Improvement of gut microperfusion /oxygenation
Improvement of short half-life protein synthesis

When immunonutrition was given orally for seven days before surgery, better metabolic effects were obtained in comparison with standard diets (Tab. I). In particular, modulation of inflammatory response, enhancement of cell-mediated immune response, and up-regulation of gut microperfusion and oxygenation have been found early after surgery (10, 11). These results suggested the idea that the key point in elective surgery cancer patients is to provide immunonutrients before surgery.

A first negative clinical trial on preoperative immunonutrition was published by McCarter et al. who tested the effect of preoperative arginine and omega-3 fatty acids alone or in combination in a population of patients with upper GI cancer. The Authors could not show any significant modification in several immunometabolic parameters and the rate of postoperative complications was similar among groups (12). Yet, the sample size was small and the oral preoperative intake of immunonutrients was quite limited, thus making the conclusions inconclusive.

Two prospective, randomized, double-blind clinical trials demonstrated that cancer patients fed before and after surgery with a diet supplemented with arginine, omega-3 fatty acids, and RNA had a significant reduction of both postoperative infections and LOS when compared to patients fed with a standard enteral formula (13, 14). It could be speculated that the reduction of postoperative infections found in the supplemented group in both studies is the translation of the immunologic and metabolic advantages previously reported in patients receiving perioperative supplementation with immunonutrition (10, 11). It has been also reported that perioperative immunonutrition is effective regardless of the baseline nutritional status of the patients (Tab. II). In fact, preoperative administration

TABLE II - EFFECTS OF PREOPERATIVE IMMUNONUTRITION ON INFECTION RATE IN GI CANCER PATIENTS

Author	Blinding	Control group	Pts #	Nutritional status treatment vs. control	Infection rate	P
Braga (13)	yes	standard EN	206	mixed	13% vs. 29%	0.02
Senkal (14)	yes	standard EN	154	mixed	13% vs. 24%	0.08
Gianotti (15)	no	fluids	305	welln.	14% vs. 30%	0.006
Braga (16)	no	fluids	200	welln.	12% vs. 30%	0.04
Braga (17)	no	standard EN	150	maln.	10% vs. 24%	0.06

of immunoenhancing diets reduced postoperative infection rate not only in malnourished patients, but also in the subgroup of well-nourished patients in whom an impairment of the host defence mechanisms has been reported after surgery (13).

A post-hoc analysis showed that clinical outcome was improved also in a subgroup of patients who received only the preoperative supplementation because they did not tolerate early postoperative jejunal infusion. This is the reason why we designed a randomized clinical trial in well-nourished patients with GI cancer comparing oral administration of immunonutrition for five days before surgery, perioperative immunonutrition and conventional treatment (no feeding). Preoperative supplementation was as effective as the perioperative treatment in reducing postoperative morbidity and both approaches were significantly superior when compared with conventional treatment (15). In other words, prolonging infusion of immunonutrients via the jejunal route postoperatively did not further improve the clinical outcome. Another randomized clinical trial showed the same result by preoperative supplementation of key nutrients in well-nourished patients undergoing elective colorectal resection for neoplasm (16). This further supported the concept that the mechanism of action of these key substrates is more pharmacological than nutritional. A post-hoc analysis suggested that in the general cohort of the so-called well-nourished patients the risk of developing postoperative complications was progressively higher with increasing body mass index (BMI). In particular, postoperative morbidity rate was significantly higher in obese patients (55%) compared to patients with normal BMI value (p=0.04). Preoperative administration of immunonutrition reduced post-operative infection rate in all three subgroups (normal, overweight and obese) with a similar pattern (15). These results fully confirmed that obesity is a major negative predictive variable on surgical outcome and recommended obese patients as potential target in future randomized clinical trials to evaluate the possibility of reducing postoperative morbidity rate by using immune-enhancing substrates.

Different results were obtained in malnourished patients in whom perioperative immunonutrition was superior to the simple preoperative approach. In fact, prolonging immunonutrition in the postoperative period allowed a further reduction in postoperative infection rate (17). This could be explained by the fact that malnourished patients have both greater impairment of immune response and higher energy and nitrogen requirements compared to well-nourished patients.

IMMUNONUTRITION - COST BENEFIT ANALYSIS

Despite promising results from randomized clinical trials, the high cost of these new nutritional products could be considered a major drawback for their routine use. In view of the worldwide increasing concerns over exploding costs in medical care, the decision process for adopting the use of new products for routine treatments should not only weigh the clinical benefits and risks, but also consider whether these benefits are worth the health care resources used. This decision making process should be informed by cost-effectiveness analyses of clinical trials in which the following costs have to be calculated: the mean in-hospital-related costs of routine surgical care per patient, the costs of treating postoperative infectious and non-infectious complications, the costs of nutrition, and the overall costs for all patients.

From a methodological point of view a blind economic analysis should be performed by an economist on data gathered from a prospective randomised clinical trial. For resource assessment, a specific electronic record form should be used to enable a detailed assessment of the amount of health care goods and resources that each patient with postoperative complication received for the treatment of the same complication. To simplify and standardize the recording,

TABLE III - COST-EFFECTIVENESS ANALYSIS OF PREOPERATIVE IMMUNONUTRITION

Author	Cost of nutrition*		Cost of complication*		Cost -effectiveness*	
	treatment	control	treatment	control	treatment	control
Senkal (14)	347	49	964	2,688	1,504	3,587
Gianotti (18)	347	103	768	2,345	1,339	3,725
Braga (19)	144	33	1,728	3,089	2,985	6,244

* per randomized patient. Costs reported in Euro.

resources have to be defined in advance to include the following items: complication type and duration in days; laboratory and microbiology analyses; medical, technical and diagnostic services; surgical and therapeutic interventions; medications; and outpatient follow-up consultations. For patients who developed more than one complication, resources used should be separately recorded for each complication. The additional LOS due to postoperative morbidity has to be valued at a daily rate, which covers the cost of board, lodging, routine medical supervision, and nursing.

Three cost-effectiveness analyses evaluated whether the use of preoperative immunonutrition led to a saving in health care resources consumed (Tab. III). The cost of nutritional formula was approximately three-fold higher in the group receiving the supplemented diet compared to the control group receiving a standard diet. In all three studies it was found that the savings due to significant reduction in postoperative morbidity by preoperative immunonutrition offset the higher cost of the supplemented diet (14, 18, 19). This translated into substantial cost saving and in positive cost-effectiveness when compared to a standard diet. Looking in detail, this overall net saving in the cost-effectiveness ratio is largely due to the differences observed for infectious complications, whereas a much smaller or no effect was observed for non-infectious complications or anastomotic leaks. Moreover, the mean cost to treat an infectious complication was significantly lower in the supplemented group, because of the shorter time needed to recover from the complication and a lesser amount of resources used. Although speculative, this could be due to a more efficient immune response observed in the patients who received immunonutrition.

Interesting findings were obtained by correlating the actual costs to DRG reimbursement rates (19). In patients without complications, the specific DRG reimbursement rate covered the costs in both groups. When postoperative complications occurred, only the preoperative approach demonstrated consistent profitability in all three types of operation. In fact, the percentages of DRG reimbursement consumed by costs of complications were 71% in colorectal surgery, 69% in GI surgery, and 97% in pancreatic surgery. Conversely, DRG reimbursement did not cover the costs of complications for gastroesophageal and pancreatic surgeries in the conventional group, despite the higher DRG reimbursement rates applicable to complicated cases.

These results could stimulate the transition to preoperative oral immunonutrition into routine practice. In fact, patients can be easily prepared for surgery at home in a short period of time (five days) and no postoperative prolongation of immunonutrition is required in well-nourished subjects, thus avoiding any potential side effects of early jejunal feeding.

Some general limitations of economic analyses should be noticed on the transferability of the present clinical and economic data, which may also influence their reproducibility. Comparable cost saving by the routine use of preoperative immunonutrition might be achieved in hospitals where the same type of operations is performed on a similar volume and complication rate. Moreover, the economic parameters may differ from country to country based on the type of health care system and reimbursement rates.

The cost-benefit analyses are usually based only on calculation of hospital resources spent. The assessment of community associated costs, including sick leave, rehabilitation, full recovery of physical and social performance would probably magnify the advantage of immunonutrition even more.

CONCLUSION

Administration of immune-enhancing diets before surgery seems to be the key point for improving outcome in GI cancer patients undergoing elective surgery. In these subjects, preoperative immunonutrition

improved metabolic postoperative response and significantly reduced postoperative infection rate and length of hospital stay.

Cost-benefit analyses suggested that preoperative immunonutrition could be the dominant nutritional support strategy in patients who are candidate for major GI cancer surgery.

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