The Role of Immune-Enhancing Diets in the Management of Perioperative Patients

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ABSTRACT

Objective: *To review the effects of immunonutrients in the perioperative patient.*

Data sources: *Articles and published peer-review abstracts of studies reported on immune enhancing diets in patients during the perioperative period.*

Summary of review: *Enteral nutrition is the method of choice for substrate supplementation in patients with a normal gastrointestinal tract but who are otherwise unable to eat normally. It is also a safer, more practical and less expensive alternative to the parenteral route and is now being used successfully in previously contraindicated conditions including pancreatitis and major abdominal trauma.*

Advances in enteral nutrition include the development of immunonutrients which have been used to attenuate the adverse effects of starvation, illness and surgery on the architecture and function of the gastrointestinal tract, implicated in the development of multiple organ dysfunction syndrome. These agents stimulate immune function and are potentially an effective strategy in improving the outcome in the peri-operative period by reducing post-operative infections and length of hospital stay.

Conclusions: *Immunonutrition confers an additive benefit when compared with standard enteral and parenteral nutrient preparations in the management of perioperative malnourished patients. What is less clear is at what severity of illness this benefit begins, whether there is a significant reduction in mortality and at what point the cost benefit in the reduction in complications no longer occurs.* (**Critical Care and Resuscitation 2003; 5: 277-283**)

Key words: Nutrition, enteral nutrition, immunonutrition, perioperative patient, critically ill, metabolism

Malnourished patients commonly present for major surgery,[2] and can be easily identified from the history and physical examination.[3] The clinical review is important since such patients suffer from a generalised reduction in cellular and humoral immunity with a greater incidence of complications following elective surgery.[4] This effect may be attenuated by peri-operative nutrition.[5] The last decade has seen the emergence of enteral nutrition as a safer,[6] more practical and less expensive[7] alternative to the parenteral route, particularly in situations where enteral nutrition has been traditionally contraindicated such as pancreatitis[8] and major abdominal trauma.[9]

Immunonutrients work in a variety of ways to attenuate the effects of starvation, illness and surgery on the architecture and function of the gastrointestinal tract leading to the multiple organ dysfunction syndrome.[1] This review will address the question of whether there is a proven benefit in the use of immune enhancing diets in the peri-operative period and consider the composition and mechanisms of action of these diets.

What is immunonutrition?

Immunonutrition is the supply of specialised nutrients to critically ill patients in an attempt to modulate the inflammatory response and reduce morbidity and mortality. Most studies have addressed the incidence of infection in the perioperative, post-traumatic or critically ill period and the influence of immunonutrition on mortality, length of stay in hospital and cost. This review will be confined to those issues, although it is important to note that the beneficial

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effects of immune enhancing diets may be more profound. For example, the earlier recovery of natural killer cell counts demonstrated by Braga *et al*,[10] may have an impact on rates of tumour recurrence in cancer surgery and the provision of omega-3 (ω3) fatty acids with cyclosporine may lead to the improvement of graft survival in the setting of renal transplantation.[11] While there are many immunomodulatory therapies, the nutrients most studied, and consequently included in commercial preparations, are the nucleotides, ω3 fatty acids and the amino acids of arginine and glutamine.

Amino acids

Arginine. Arginine is well known as a precursor of nitric oxide, which is involved in a wide variety of processes including regulating microcirculatory blood flow, gastrointestinal permeability and motility, and cytotoxicity of immune cells. Arginine is also known to stimulate several hormones such as growth hormone, prolactin, insulin-like growth factor, somatostatin and norepinephrine[12] and has been shown to stimulate thymic cellularity and responsiveness and to enhance immune cell release and function. In humans, Daly et al,[13] found that peri-operative arginine supplementation improved peripheral lymphocyte responsiveness after major gastrointestinal surgery and Kirk *et al*,[14] demonstrated improved wound healing.

Glutamine. Although glutamine is the most abundant amino acid in humans, it is considered to be "conditionally essential" in catabolic states where demand may exceed supply, particularly in the presence of starvation. Glutamine is a primary fuel source for enterocytes but is not readily synthesised in the human gastrointestinal tract.[15] It is a precursor of glutathione, an important anti-oxidant, and is required for lymphocyte and macrophage function. Glutamine is also important for nucleotide synthesis.

The supplementation of standard parenteral nutrition with glutamine attenuates the increased gut permeability found with standard enteral preparations in both experimental and clinical models and leads to the preservation of normal gut mucosa longer in the presence of starvation. Ziegler *et al*,[16] demonstrated a reduction in infections and length of hospital stay in bone marrow transplant patients fed with a parenteral glutamine preparation compared with a control group. Griffiths *et al*,[17] also recorded a significant reduction in mortality in critically ill patients at six months following parenteral glutamine supplementation.

Nucleotides

Nucleotides are crucial for the synthesis of RNA and DNA and for the components of the mitochondrial energy transfer system. Nucleotide supplementation leads to improved survival in animal models of bacterial[18] and fungal[19] sepsis and to a more rapid recovery of immune function.[20] This benefit has been confirmed in human studies when nucleotides are administered as part of a broader immunomodulatory strategy (table 1).

Omega-3 (ω3) fatty acids

Substitution of ω3 fatty acids from fish oil, with predominantly eicosapentanoic acid and docosahexaenoic acid, for omega-6 (ω6) fatty acids such as linoleic acid, reduces the constituents of cell membranes derived from arachidonic acid (thereby influencing cell signalling and surface enzyme activity). This results in a reduced production of dienoic prostaglandins, thromboxane and tetraenoic leukotrienes in favour of the less immunosuppressive trienoic prostaglandins, thromboxane A_2 and pentaenoic leukotrienes. There is also a reduction in platelet aggregation and clotting inhibition as well as an improvement in delayed hypersensitivity responses, all of which may be beneficial, although high doses of ω3 fatty acids may be immunodepressive.

Kenler and co-workers,[21] compared the effects of an enteral feed enriched with ω3 fatty acids with a standard feed in patients undergoing surgery for upper gastrointestinal malignancy and reported a 50% reduction in the infection rate. However, this effect did not reach statistical significance.

Mechanism of action

The most likely mechanism by which enteral immunonutrients and, to a lesser extent, parenteral immunonutrients confer a benefit is by a structural and functional preservation of the lymphoid tissue within the gastrointestinal tract (i.e. gut-associated lymphoid tissue). Gut-Associated Lymphoid Tissue (GALT) has four main anatomic units: Peyer's patches, mesenteric lymph nodes, lamina propria beneath the mucosa and intra-epithelial lymphocytes.

IgA is produced by GALT and secreted by the gastrointestinal mucosa, preventing bacterial adherence to mucosal surfaces and producing a primary epithelial defence against intraluminal bacterial invasion. Naïve T and B lymphocytes are sensitised to antigens from the gut lumen, they proliferate in the mesenteric lymph nodes and migrate to the lamina propria via the thoracic duct and circulate to provide a local source of specific immunity. T and B cells released into the circulation also migrate to extraintestinal mucosal surfaces such as the respiratory tract, genitourinary tract, the salivary and mammary glands, functioning as a source of IgA production for these surfaces. These extraintestinal cell populations are called Mucosal Associated Lymphoid Tissues (MALT) and confer protection against viral and bacterial pathogens and passive immunity to neonates

Table 1. A summary of studies using immune enhancing diets

Investigators	*Study population*	*Preparation*	*Effects*	*Comments*
Cerra *et al* 1990[36]	Surgical n = 22	Imp. vs Osm.	NS ↓ LOS mortality, infections	Included in a meta-analysis[24]
Gottschilch *et al* 1990[37]	Burns n = 50	Shriner's vs Osm. vs Traum.	Significant ↓ LOS/ wound infections	
Daly *et al*, 1992[38]	Surgical n = 85	Imp. vs Osm.	Significant ↓ LOS /wound complication	Included in a meta-analysis
Moore *et al*, 1994[6]	Trauma n = 114	ImmunA. vs Viv.	Significant ↓ abdominal abscess / MOF	Included in a meta-analysis
Brown *et al*, 1994[39]	Trauma n=98	Experimental diet	Significant ↓ in infections	
Daly *et al*, 1995[40]	Surgical n=60	Imp. vs Traum.	Significant ↓ in infections, LOS complications	Included in a meta-analysis
Bower *et al*, 1995[41]	Medical/Surgical/ Trauma n = 36/12/248	Imp. vs Osm.	Significant ↓ in infections & LOS *	*In successful feeders & septic groups
Kudsk *et al*, 1996[42]	Trauma n = 35	ImmunA. vs Prom.	Significant ↓ in infections/LOS	Included in a meta-analysis
Schilling, *et al*, 1996[43]	Surgical n = 30	Imp. vs Fres.	NS ↓ in LOS & infections	Included in a meta-analysis
Senkal *et al*, 1997[31]	Surgical n = 164	Imp. vs IC, IN diet	Significant ↓ in late infections	Included in a meta-analysis
Mendez, *et al*, 1997[44]	Trauma n = 43	Experimental vs Osm.	↑ ventilator days in treatment group.	
Hasselmann *et al*, 1997[45]	Mixed ICU n =?	Imp. vs IC, IN diet	↓ infection	Groups not comparable at recruitment
Saffle *et al*, 1997[46]	Burns n = 50	Imp. vs Repl.	No effect	
Heslin *et al*, 1997[29]	Surgical n = 195	Imp. vs 5% dextrose	No effect	Inadequate dose of feed
Weimann *et al*, 1998[47]	Trauma n = 32	Imp. vs IC, IN diet	NS ↓ LOS & ventilator days	Included in a meta-analysis
Braga *et al*, 1998[27]	Surgical n = 110	Imp. vs IC, IN diet	Significant ↓ in severity of infection	Included in a meta-analysis
Atkinson *et al*, 1998[30]	Medical/Surgical/ Trauma n = 222/732/36	Imp. vs IC, IN diet	Significant ↓ in LOS and ventilator days	Included in meta-analysis
Galban, *et al*, 1998[48]	Septic medical n = 181	Imp. vs PH.	Significant ↓ in mortality	Included in meta-analysis

LOS = length of stay, MOF = multiple organ failure, IC = isocalorific, IN = isonitrogenous, Imp = Impact™, Osm = Osmolite™, Traum = TraumaCal™, ImmunA = ImmunAid™, Prom = Promote™, Fres = Fresubin™, Repl = Replete™, PH = Precitene Hiperproteico™, Viv = Vivonex™

via IgA secreted in breast milk.[22]

IgA production and GALT function are reduced in animals fed parenterally compared with animals fed complex enteral diets[23] and is associated with increased mucosal permeability, aerobic bacterial overgrowth and translocation as well as reduced respiratory tract IgA levels.[24] These studies provide a persuasive argument that the reduction in infection conferred by these diets is achieved by immune enhancement, particularly with respect to infections of the respiratory tract in ventilated patients where colonisation with enteric gram negative bacteria is common.

Therapy with immunoenhancing diets

Table 1 summarises the results of the available clinical trials of immune-enhancing nutrients. Two of the commercially available preparations (Impact™, Novartis Nutrition, Bern, Switzerland and Immun-Aid™, McGaw, Irvine, CA, USA) contain the nutrients discussed and have been subjected to randomised controlled outcome studies in hospitalised patients.

Many of these trials have been included in a meta-analysis by Beale and colleagues,[25] who review whether immune enhancing diets should be prescribed to critically ill patients. They analysed 1482 patients from 12 studies and found no effect of immunonutrition on mortality (relative risk [RR] 1.05, 95% confidence interval [CI] = 0.78 - 1.41, p = 0.76) but in the immuno-nutrition group there were significant reductions in infection rate (RR = 0.67, CI = 0.05 - 0.89, p = 0.006,) ventilator days (2.6 days, CI = 0.1 - 5.1, p = 0.04) and length of hospital stay (2.9 days, CI = 1.4 - 4.4, p = 0.0002). This benefit appeared to be most marked the surgical subgroup.

Recent studies in the peri-operative period

Braga and co-workers, have contributed greatly to our current understanding of the role of immunonutrition in the peri-operative period with a series of studies.[10,26-28] Initially this group demonstrated the improvement in immunological markers in patients given an immuno-enhancing diets before major surgery versus controls.[10] They randomised 40 patients undergoing surgery for gastrointestinal malignancy to receive for 7 days, 1 litre per day of an arginine/glutamine/nucleotide/ω3 fatty acid enriched formula (Impact™) or a standard enteral preparation. The same feeds were continued post-operatively for 1 week via a jejunostomy feeding tube placed at the time of surgery. In the immunonutrition group phagocytosis and respiratory burst were signific-antly higher and C-reactive protein was significantly lower. In the treatment group, small and large bowel gastrointestinal blood flows, as measured by gastric tonometry and intra-operative point laser Doppler, were significantly better. Postoperative levels of nitric oxide were significantly higher and intestinal isoenzyme alkaline phosphatase, a marker of gut damage, significantly lower in the immunonutrition group.

In a follow up study of 171 patients undergoing surgery for gastrointestinal malignancy they demonstr-ated a significant reduction in infection rate (10.5% vs 24%, $p < 0.05$) and length of stay (11.1 ± 4.4 days vs 12.9 ± 4.6 days) in the patients who received immuno-nutrition.[26] Nevertheless, this group was unable to reproduce this benefit (e.g. a significant reduction in infection rate and length of stay in those patients who were malnourished or had homologous blood trans-fusions) in a prospective randomised control trial (n = 166) of a similar cohort of patients with a group randomised to total parenteral nutrition where feeding was not commenced until 6 hours post-operatively.[27]

Braga *et al*, further evaluated the potential advant-ages of perioperative versus postoperative administrat-ion of an enteral immune enhancing diet on host defence and protein metabolism. Thirty subjects who underwent gastrectomy for cancer were allocated into two groups. Fifteen received Impact™ for 7 days before and after surgery; the second 15 received the same diet but only for 7 days following surgery. Perioperative immuno-nutrition prevented the early postoperative impairment of phagocytosis, delayed hypersensitivity response, total number of lymphocytes and CD_4/CD_8 ratio ($p < 0.05$ vs postoperative group.) The interleukin-2 receptor levels, a marker of polymorphonuclear cell phagocytic activity, were significantly higher in the perioperative group compared with the postoperative group on postoperative days 4 and 8, ($p < 0.05$). The perioperative group also had lower levels of interleukin-6 ($p < 0.05$) on post operative days 1, 4, and 8 and higher levels of prealbumin ($p = 0.04$) on postoperative day 8. The perioperative administration of immunonutrition appeared to ameliorate the host defence mechanisms, control the inflammatory response and improve the synthesis of short half-life constitutive proteins.[28]

Heslin and colleagues,[29] studied 195 patients with upper gastrointestinal malignancy undergoing resection, comparing an enriched enteral preparation with intra-venous crystalloid infusion. There was no difference in any outcome measure between the two groups and the authors concluded that early enteral nutrition with an immune enhancing feed was not beneficial compared with routine crystalloid therapy. However, the treatment group only received 10 - 35% of their scheduled feeding target by day 10 so it is doubtful that a sufficient dose of immune-enhancing feed was delivered to enable the hypothesis to be tested fairly. This premise is supported by the largest single study by Atkinson and colleagues,[30] where a reduction in length of stay and ventilator days was only seen in those patients who received greater than 2500 mL of feed in the first 72 hours (i.e. "successful feeders").

Is immunonutrition cost-effective?

Senkal and colleagues,[31] studied 154 patients admitted to intensive care following upper gastro-intestinal surgery for cancer. Patients were randomised to receive an immune enhancing diet or an isocaloric isonitrogenous diet initiated 12 - 24 hr post surgery at 20 mL/hr advanced to 80 mL/hr by day 5. Complication

events were prospectively divided into early (before day 5) and late (after day 5). There was no significant difference between the two groups except for complications occurring after day 5, (5 vs 13, $p < 0.05$.) When the cost of treating the complications was calculated there was a cost reduction of DM 38 867 in the immunonutrition group at the end of the study period.

New immunonutritional strategies

There are an enormous number of immunonutritional strategies currently under investigation in what is becoming an exciting new area of research. For example, a recent randomised controlled trial of enteral ornithine *a*-ketoglutarate in patients with burns ranging from 20 - 50% body surface area, found improved nitrogen balance in the treatment group and established a dosage range for further investigation.[32] The administration of dietary fibre has been found to reduce bacterial adherence to mucosal surfaces and improve the digestion of fats by enhancing their conversion to short chain fatty acids, a primary fuel source of enterocytes. Probiotic bacteria such as *Lactobacillus plantarum*, which competes with potentially pathogenic organisms to recondition the gastrointestinal mucosa, in addition to immunonutrients are reviewed by Bengmark.[33] Enteric nervous system neuropeptides influence the intestinal mucosa and IgA production by GALT. Bombesin is a tetradecapeptide analogous to gastrin releasing peptide in humans which stimulates neuropeptide release resulting in increased IgA production within the rat intestine and reverses the increase in bacterial translocation associated with intravenous total parenteral nutrition. Kudsk and co-workers, using a murine model of GALT histology, IgA mediated antiviral defences and bacterial pneumonia, demonstrated that bombesin prevents almost all deleterious effects of iv total parenteral nutrition.[34]

Conclusion

With the exception of specific autoimmune conditions immunosuppressive therapies have not been effective in reducing mortality in patients at risk of or suffering from significant infection[35]. This has lead to investigation of immune-enhancing therapies such as granulocyte colony stimulating factor and immunonutrition. There is no doubt that immunonutrition confers an additive benefit when compared with standard enteral and parenteral nutrient preparations in patients who are malnourished, septic or have endured an immunosuppressive insult such as homologous blood transfusion. It is also clear that this benefit is only seen in those patients who receive an adequate dose of immunonutrients, which may only be achieved by starting therapy pre-operatively. What is less clear is at what severity of illness this benefit begins and at what point the cost benefit in the reduction in complications no longer occurs.

Received: 22 August 2003
Accepted: 4 November 2003

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