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Revisión

Modulation by enteral nutrition of the acute phase response and immune functions

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Abstract

To use nutrition in order to limit the negative consequences of physical and mental stress is not new. Recent advances in immunology and particularly in the understanding of the chemical language used to communicate both by eukarytic and prokarotic cells has made it easier to objectively evaluate effects of various immunomodulating efforts including the use of nutrients, vitamins and antioxidants in preventing or limiting the development of disease and its late consequences.

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Key words: *Acute phase response. Enteral nutrition. Immune system.*

REGULACIÓN DE LA RESPUESTA DE FASE AGUDA Y DE LAS FUNCIONES INMUNITARIAS MEDIANTE NUTRICIÓN ENTERAL

Resumen

El empleo de la nutrición para limitar las consecuencias negativas del estrés físico y mental no es nuevo. Los últimos avances introducidos en la inmunología y, en especial, el conocimiento del lenguaje químico empleado por las células eucariotas y procariotas para comunicarse han permitido evaluar con objetividad los distintos esfuerzos de regulación inmunitaria, incluido el empleo de nutrientes, vitaminas y antioxidantes para prevenir o limitar la aparición de enfermedades y sus consecuencias.

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Palabras clave: *Nutrición enteral. Respuesta de fase aguda. Sistema inmunitario.*

The acute phase response (APR)

Numerous different mediators regulate the alarm reaction, which more or less immediately occurs in stress situations. Central to this reaction, given the name of acute phase response, is release of various pro- and anti-inflammatory cytokines, released and activated by various immune cells, especially monocytes, but also most other cells. Also mucosa cells and commensal flora have been shown to be very active in producing messenger molecules such as cytokines or bacteriokines, if produced by microbial cells. Important are also various other potent chemical messengers like nitric oxide (NO), enzymes and hormones, and a large number of liver-produced peptides, called acute phase proteins (APRs). The functions of different Iymphocytic cells, especially the so-called T-cells seem to be crucial to outcome. A balance between Thl response, mainly consisting in cellular immunity and production of disease-promoting cytokines (TNF-α, IL-1, IFN-γ), and Th2 response mainly consisting in humoral response and production of host-protective cytokines (IL-4, IL-5, IL-6, IL-10), has been attributed great importance.

The gut immune system (GALT, MALT)

The gut is an often-neglected part of the immune system, despite the fact that about 75 of the immune system is localised to the gut. About 80% of the production of the immunoglobulins of the body occur in the gut. At least 50% of the body's lymphocytes are to be found in the gut. Thus, it is increasingly evident the functionality of the Gut Associated Lymphoid Tissue (GALT) or the Mucosa Associated Lymphoid Tissue (MALT) is of the greatest importance to outcome. If not well functioning, if immuno-paralysis has developed, the mortality and morbidity is steeply rising.

It is an obvious fact that a fast increasing numbers of diseases, with in the past an unknown aetiology, are today known to be infectious. An even larger

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group of diseases, in the past classified as degenerative, are with increasing knowledge in molecular biology reclassified as inflammatory. Even if the word "Chronic Phase Reaction" is not yet fully accepted, it is a documented fact that those who develop symptoms of chronic diseases almost always show increased levels of acute phase proteins and cytokines long before they show manifest disease.

Complications and sequalae

The acute phase reaction is aimed to regulate the defence mechanisms of the body and prevent sepsis, bleeding and other unwanted consequences of trauma, inflammation and infection. However, due to "overreaction" negative consequences will sometimes occur. It is reasonable to assume that complications in trauma, surgery, and to disease are due to an exaggerated "over-expressed" acute phase response. Much evidence support that this is the case for the three major complications/sequelae of surgery; sepsis, thrombosis and adhesion formation.

Infections

Nosocomial infections remain despite extensive use of antibiotics an unsolved problem. It is calculated that in the US only does 6% of the population (2 millions) suffer hospital-related infections and the main victims are neutropenic patients, elderly and those being the object of more extensive surgery. Sepsis is reported to occur in every second organ transplantation, every third patient having major surgery such as hepatic or pancreatic resection, every fifth patient having larger gastrointestinal or neurosurgical procedure and every tenth patient after coronary bypass. The negative consequences of antibiotics are increasingly becoming obvious; induction of antibiotic resistance and also depression of the immune functions are increasingly reported, and there is much to indicate that we are approaching the end of the antibiotic era, And eagerly looking for a substitute of antibiotics.

Thrombosis

Although we with modern anticoagulation therapy are successful in suppressing the clinical manifestations of hypercoagulabity, subclinical thrombosis can still be documented by contrast phlebography to occur in 40-70% of the patients receiving parenteral nutrition (PN). An interesting recent study compared the modulating effects of enteral (EN) and PN on coagulation and fibrinolysis in human volunteers with induced endotoxemia. They reported profound changes in the activation of coagulation with no differences in fibrinolysis, and suggested that "one common complication (bacterial infection) may facilitate the occurrence of another common complication (venous thrombosis) by synergistic stimulation of the coagulation system".

Adhesions

Varying degree of adhesions occur in about 95% of all patients being the object to intraperitoneal or intrathoracic surgery. It is likely that the development of adhesions, which almost always occurs within the first 48 hours is also facilitated by the same mechanisms. Al so here does increased production of fibrinogen and inhibited fibrinolysis play a crucial role. Experimental studies support that if these mechanisms can be controlled for about 48 hours there will be no adhesion formation. It is likely that all these changes should be possible to modulate nutritionally. Much support that the extent of adhesion formation is related to the environment of the gut. Germ-free animals do not develop adhesions. It has been shown that significantly longer coagulation time and softer jelly-like clots occur in persons living in rural areas and consuming large quantities of live lactobacilli and vegetable fibres than in those living in urban areas. It has also been suggested, that feeding high fibre diet reduces the incidence of venous thrombosis.

Enteral nutrition not new

Prominent American research groups demonstrated already during World War II definite advantages of oral or gastric feeding or needle jejunostomy over parenteral nutrition. However, during the next 50 years not much attention was paid to these observations; the interest of both science and industry was in creating the perfect total parenteral nutrition formula. Observations in the 1980's such as that intestinal mucosa is unable to nourish itself from blood, enteral nutrition increases visceral circulation, enteral nutrition stimulates an earlier positive balance, and enteral nutrition with high protein content increases survival in burn patients passed almost unnoticed. Several clinical and experimental studies performed during the 1980's showed distinct advantages of EN over PN, the most pronounced being a significant reduction in the sepsis rate.

Routine TPN or EN?

A milestone is the controlled study by Kudsk et al, performed in patients with abdominal trauma, which showed a 76% lower rate of infection in the group receiving early EN compared to the group on PN. A metanalysis evaluating the results of 18 different controlled trials on the effects of perioperative parenteral nutrition (TPN) concluded: *"the routine use of perioperative total parenteral nutrition in unselected patients having major surgery is not justified; however, this intervention may he helpful in subgroups of these patients, who are at high risk."*

The failure of TPN to meet the nutritional demands in the postoperative and post trauma situation, the frequent complications with TPN, the cost of TPN, but also the failure of antibiotics in general, the increasing awareness of the dangers of using antibiotics in combination with the promising experience with early applied EN make it a noteworthy alternative for routine nutrient supply and morbidity prevention in postoperative and post trauma patients.

Several studies reported in the literature during the last ten years do not all support beneficial effects of EN. An important and well-controlled study could not find any influence by EN on the normalisation of the permeability defect always observed following upper gastrointestinal surgery. This does, however, not exclude that it would not be able to limit the permeability defect if instituted early enough, e.g. before the defect has developed. A subsequent study by the same group and performed in patients with acute pancreatitis did clearly demonstrate a significant modulation of the acute phase response by EN, when compared to PN, paralleled by significant improvements in immune parameters, disease severity and clinical outcome. Others have reported similar immune enhancing and morbidity reducing effects from studying patients after larger surgery such as liver resection.

Early acute phase reactions

Studies suggest that the most important reactions in enzymes, cytokines, acute phase proteins etc occur within minutes after infliction of trauma. If the narrow therapeutic window to modulate the APR available during the first 12 to 24 hours is not effectively used, all subsequent treatment efforts will at the best limit, but not prevent late development of complications. Much support that most efforts made at this stage are met with little or no success.

Conditions for optimal effects of EN

One can, based on the knowledge available in the literature, assume that a treatment aimed to modulate the APR should for optimal outcome meet some important requirements, including the following:

1. Be instituted immediately as the acute phase reactions occur during the first minutes and hours after trauma or onset of disease.
2. Should contain substrate (fibre) to be fermented by the commensal flora in order to produce locally the needed immunoregulatory nutrients (SCFAs, polyamins, amino acids, antioxidants, vitamins etc). It should be remembered that the dominant part of the immune system is localised to the large intestine, where flora, mucosal cells and GALT cells are activated and produce APR-modulating cytokines.
3. Saturated fat should be avoided due to its immunodepressive effects. Fat in the diet has been shown to significantly influence outcome after surgery, in burns, and in pancreatitios.
4. Attempts should be made to preserve the essential flora by providing nutrients for the flora, avoid use of flora-reducing antibiotics and if necessary resupply flora if lost.

It is obvious from studying the literature that few if any studies have so far met these requests. Common to most of the studies, including those discussed above, is that EN is regularly instituted too late (early EN is often defined as within 72 hours), fibre is usually not an ingredient of the feeding formula given, the feeding does often contain up to 35% in saturated fat, and no attempts are made to consider the flora and its nutritional needs. In addition, most often prophylactic antibiotics are supplied to these patients. Based on a rather extensive documentation from animal experiments pronounced modulatory effects on the APR and significant reduction is morbidity and mortality could be expected, if attempts were made to meet these biological requirements also in humans.

Preoperative enteral starvation - a relict?

It is increasingly accepted that the traditional praxis to withheld enteral nutritional support until bowel sounds return should be abandoned. Instead it is suggested that efforts should be made to administer EN uninterruptedly e.g. immediately before, during, and immediately after surgery, whenever possible.

Uninterrupted peri- and intraoperative EN was introduced as a treatment in burn patients, who frequently have multiple operations, and in whom interruption of EN can cause significant caloric deficit and increase the risk of infections. A controlled study in burn patients published in 1994 confirms that uninterrupted EN (UEN) is safe, but also efficient when given throughout the whole operative procedure. In this particular study 40 patients received EN during 161 surgical procedures and 40 had enteral support as traditionally practised withheld during 129 procedures. The traditionally fed group showed a significant caloric deficit ($P < 0.006$), increased incidence of wound infections ($P < 0.02$), and a significant necessity of higher albumin supplementation ($P < 0.04$) compared with the uninterruptedly fed group.

Need of more efficient feeding tubes

The main obstacle to global routine use of EN during the peri- and intraoperative period has so far been the lack of simple and reliable feeding tubes. A prerequisite for universal acceptance of UEN as a standard of feeding surgical patients is availability of feeding tubes that are easy to introduce into the upper intestine, tubes that will not obstruct the GI tract, and that will not be regurgitated prematurely. Under ideal circumstances, such tubes should within minutes or a few hours position themselves in the region of the li-

gament of Treitz, and, if possible, without support of expensive techniques such as radiology or endoscopy.

A selfpropelling, selfanchoring tube

This was the reason why I developed a tube with a coil and a light weight tip made to maximally absorb and use the motility of the stomach and the duodenum in order to be transported through the pylorus and down to the Treitz region (fig. 1). The intension when constructing the tube was to introduce it in the evening before surgery and, if ever possible, use it more or less immediately. It is normally in place after about one hour, but feeding can start when the tube has been placed in the stomach. In addition to being self-propelling, the tube has also proved, when in place to be self-anchoring. Unintentional removal, otherwise a great problem, is rarely seen. The tube can without problem be used during the entire perioperative period.

Early studies have shown a rate of spontaneous transpyloric passage (STP) close to 100%, and this without any pharmaceutical stimulation of motility. The motility is on introduction stimulated by either a light meal such as a sandwich or a pizza or just by eating fruits/vegetables such as an orange or rhubarb. Especially rhubarb has been shown to stimulate motility.

No verification of location of the tube is necessary, but if wanted, simple pH measurements of aspirated content are enough to verify location of the tip below pylorus. The tupe is marketed in Europe by the Nutricia/Royal Numico group under the name of the Bengmark flocare tube.

Effective also in reduced GI motility?

Although the tube was originally constructed only for patients with normal peristalsis, e.g. elective surgery, it has recently been shown also to be effective in patients who already are in intensive care and have reduced GI motility. A study performed in Verona in more than fifty patients demonstrated that the tip also in this group of patients, even if with some delay, will reach the region of the ligament of Treitz. The intubation success rate was in this study 100%. The mean time from introduction to definite placement was 5.2 hours, and the range one minute to 24 hours. There was in no instance a need to support the introduction by endoscopy or x-ray.

Final conclusions

It is important that the nutrition solutions always contain nutrients destined to the large intestine e.g. fibres. The fibres are, however, ineffective in absence of an effective flora. Supply of specific lactic acid bacteria offers a strong tool to modulate the acute phase response and limit the induced superinflammation. There strong indications that lactic acid bacteria act in consortia and potentiate each other's effects. One can thus anticipate that stronger clinical effects can be obtained by combining several lactic acid bacteria and several fibres. One promising composition is Synbiotic 2000 (Medipharm, Kågeröd, Sweden), build on four lactic acid bacteria and four fibres, which is presently tried around the world. The LAB and fibres in this composition are especially chosen for their high bioactivity; including abilities such as mucus adherence, ability to ferment, antioxidant index, transcription NF-$_{K}$B NF, influence on cytokine release etc.

The combination of LAB (probiotics) and fibre (prebiotics) can be expected to have the most pronounced effects if supplied with the uninterrupted enteral nutrition and for at least 14 days after surgery, or as long as the patient does not eat normal food properly. Some experience indicates also that patients, who have undergone transplantation may benefit from long-term postoperative supply of LAB and fibre, often to be stretched over months and years.

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