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Immunonutrition

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Summary
Based on a grade A level of evidence, immunonutrition should be given to all patients operated on for a digestive cancer 5 to 7 days prior to surgery whatever could be the patient nutritional status. Immunonutrition should be continued in the postoperative phase in malnourished patients for 5 to 7 days or until patients are able to recover oral feeding covering at least 60% of their needs.

Rationale

Cancer surgery is associated with defective immune function and an increase in both postoperative mortality and morbidity, particularly infections. Strengthening the patient's immune defences is a useful approach to help to reduce these complications. In recent years alongside the standard artificial nutrition products, solutions which are enriched in nutrients with the aim of stimulating the host immune response, improving control of the inflammatory response and increasing nitrogen balance and protein synthesis after major surgery have developed. These immunonutrients are glutamine, arginine, polyunsaturated fatty acids (omega-3), nucleotides, taurine, vitamins A, E and C, beta-carotene and trace elements such as zinc and selenium. Their combination in the nutritional formula is called immunonutrition (IN).

The aim of this chapter is to provide a summary of published information from randomised trials and meta-analyses on IN, guidelines for its use and practical details for its prescription.

Products

IN in the nutritional solution containing a, usually high protein, high energy mixture supplemented with specific nutrients which are, mostly arginine, omega 3 fatty acids and nucleotides. At present this nutrient mixture only exists as an enteral form for oral administration or through a tube.

The oral product which has most often been assessed is Oral Impact®, a ready to drink liquid in the form of 237 ml cartons each containing 18g of protein and an energy value of 334 kcal, i.e. a calorie to nitrogen ratio of 1/91. Three flavours are available: vanilla, tropical and coffee. The cartons are sold in packs of 3.

The product most frequently assessed amongst the enteral forms is Impact Entéral®, 500 ml enteral nutrition bag containing 28g of protein and an energy value of 505 kcal, i.e. a calorie to nitrogen ratio of 1/91.

Apart from solutions which are supplemented, usually with glutamine, none or available for parenteral use.

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Results of clinical trials and meta-analyses

The use of perioperative IN has been studied in more than 28 randomised controlled trials. Most of these trials found IN to be beneficial and associated with a significant reduction in an infectious complication rate, length of hospital stay and costs compared to a standard isocaloric, isoenergy nutritional solution [1,2]. Most of these studies, however suffer from considerable heterogeneity in terms of the state of malnutrition of patients at inclusion, the variety of products used, the inclusion of various gastrointestinal cancers, various prescribing periods (pre- post or perioperatively), type of control used (enteral or parenteral nutrition or no nutritional support), and occasionally from small patient numbers.

As a result, in order to have a more general robust view of results from the literature, many meta-analyses have been published assessing the utility of IN by aggregating findings from the published studies. The conclusions of the 4 most recent meta-analyses [3-6] are consistent and show that prescription of an IN during the perioperative period is associated with a reduction in infectious complications and in length of hospital stay compared to standard enteral nutrition although has no demonstrated effect on mortality (level of evidence 1).

A key factor appears to be starting IN in the preoperative phase which significantly improves the postoperative course as a result of better metabolic impact. Administration in the preoperative period achieves sufficient plasma concentrations of immuno-nutrients in the early postoperative period to promote modulation of the inflammatory response, increase the cellular immune response and improve intestinal micro-perfusion and oxygenation [1].

Preoperative IN alone is less effective in malnourished patients that perioperative IN although is invariably more effective than standard nutrition (level of evidence 1). Preoperative IN also appears to be effective in non-malnourished patients [7] (level of evidence 1).

Guidelines

Many learned societies have produced guidelines on the nutritional management of patients undergoing surgery for gastrointestinal cancer, particularly the Société Française de Chirurgie Digestive (SFCD) [8], the Société Francophone de Nutrition Clinique et Métabolisme (SFNEP), the Société Française d'Anesthésie Réanimation (SFAR) [9,10], the European Society for Parenteral and Enteral Nutrition (ESPEN) [11] and the American Society for Parenteral and Enteral Nutrition (ASPEN) [12]. In addition, the French National Health Authority published a framework memorandum in July 2014 on rapid rehabilitation programmes in surgery which incorporated IN into the programme [13].

All of these publications are consistent in recommending (grade A):

- Enteral IN (oral or through a tube) for 5 to 7 days preoperatively in all, malnourished and non-malnourished patients due to undergo gastrointestinal cancer surgery.
- Continuing IN postoperatively in patients who were malnourished preoperatively (i) for 5 to 7 days in the absence of complications or (ii) until oral feeding has been restored providing at least 60% of nutritional requirements.
- Ideally combining IN with physical activity to be more effective, to increase muscle blood flow, increase protein assimilation and reduce patient's inflammatory state [14].

How to prescribe it?

Prescription support

The prescription must only be written on a CERFA no 12708*1 prescription for exception drugs products and services which can be requested from the Caisse Primaire d'Assurance Maladie (main French National Health Insurance Funds). The prescription exists as 4 carbon copies, the first to be kept by the prescriber, the second and third to be sent to the Health Insurance organisation by the patient and the fourth to be held by the pharmacist or sent directly to the contract organisation, which will deliver the product within 24 hours.

Who can prescribe it?

By decree, the prescription must be written by a gastrointestinal surgeon, intensive care anaesthetist, gastroenterologist or oncologist.

The surgeon is a key person in the prescription as he/she sees the patient in the initial consultation, assesses the patient's nutritional state, informs the patient about the methods and risks of surgery and follows up the patient perioperatively, particularly in nutritional terms.

Duration of prescription

Preoperatively the prescription is for 5 to 7 days.

Postoperatively the prescription must not be for less than 7 days and should be continued until oral intake has returned, providing at least 60% of nutritional requirements.

Amount to prescribe

An average intake of 1000 kcal/d is recommended postoperatively in addition to normal diet, i.e. 3 cartons orally per day or failing this, 2 enteral nutrition bags.

Postoperatively average intake of 1500 kcal/d is recommended, i.e. 4 to 5 oral cartons or 3 enteral nutrition bags.

Which patients to prescribe preoperative immunonutrition to?

Preoperatively, IN should not be prescribed to all patients due to undergo planned gastrointestinal cancer surgery regardless of their nutritional state, whether or not they are malnourished. Non-malnourished overweight patients also benefit from prescription of an IN in order to improve their postoperative course. The decision algorithm shown in Figure 1 may assist prescribing.

Should immunonutrition be continued postoperatively?

IN should only be continued postoperatively in patients who are malnourished preoperatively (i) for one week in the absence of complications or (ii) until oral dietary intake has returned providing at least 60% of nutritional requirements, i.e. in practice over half of the meals served. The decision algorithm shown in Figure 1 may assist with prescribing.