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Review Article

CIENT PERIODIQUE

Impact of Perioperative Immunonutrition in Colorectal Surgery

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Abstract

The association between malnutrition and digestive pathology due to surgical treatment is well known and causes an increase in postoperative complications.

In recent years, standard nutritional formulas have been modified by the addition of specific components such as arginine, ω-3 fatty acids, and glutamine, among others, in what has been termed immunonutrition. Immunonutrition results in an elevated immune response by modulating the inflammatory response and enhancing protein synthesis after surgery. However, few publications have focused on the use of immunonutrition in patients scheduled to undergo surgery for colorectal cancer.

In the present review, enteral supplements enriched with immunonutrients appeared to decrease the overall rate of infections in patients with colon cancer scheduled to undergo colorectal surgery, reducing the duration of hospital stay.

The association between malnutrition and digestive pathology associated with surgical treatment is well known. Malnourished patients undergoing surgery have a higher incidence of infectious complications and an increased mortality than patients who are well nourished [1]. Consequently, there has been a special interest in the adequate nourishment of surgical patients.

Nutritional support has evolved significantly since Stefen and Randall [2] described its application with excellent results in 1969 in critical surgical patients. Since then, numerous studies have demonstrated its effectiveness, and evaluations of elemental diets, polymer standards and endless formulas have revealed that certain nutrients facilitate the nutritive effect by providing a therapeutic effect on some organs or systems of the individual. Studies of immunonutrition have shown that some nutrients, such as ω-3 fatty acids, some amino acids such as glutamine and arginine and nucleotides are able to enhance and modulate the immune response of patients [3].

The ω-3 fatty acids, as precursors in the synthesis of prostaglandin, have anti-inflammatory properties [4].

Glutamine, a conditionally essential amino acid, is the main source of energy for enterocytes, macrophages and lymphocytes. It also participates in cell signaling and antioxidant functions and increases the expression of heat shock proteins. Glutamine deficiency causes a dysfunction in the immune system and alters the barrier function of the intestinal epithelium [4,5].

Arginine is a conditionally essential amino acid that is involved in the production of polyamines, which are important for cell growth and differentiation. An increase in the formation of anabolic hormones stimulates T cell functions and provides precursors for the synthesis of nitric oxide. Arginine deficiency causes alterations in the adaptive immune response and disrupts T cell receptors [4,6,7]. Arginine prevents the development and progression of certain renal diseases, increases hydroxyproline content and fuerzatensil wounds.

In recent years, standard nutritional formulas have been modified by the addition of specific components, such as arginine, ω-3 fatty acids, and glutamine, among others, demonstrating an elevated immune response, while modulating the inflammatory response, and enhancing protein synthesis after surgery.

However, few publications have investigated the use of immunonutrition in patients scheduled to undergo surgery for colorectal cancer.

Immunonutrition in Colorectal Surgery

Complications due to infections remain a major challenge in colorectal surgery despite the development of antibiotics. It is difficult to anticipate when this complication will arise because the causes are varied. However, immunosuppression due to surgical stress is one of the most important underlying causes [8]. This condition can be reduced with appropriate preoperative nutritional support (immunonutrition), even in patients with obesity [9]. In a prospective, randomized, double-blind study, Braga *et al.* [10] showed that perioperative administration of enteral supplements enriched with arginine, RNA and omega-3 fatty acids reduced the rate of postoperative infections.

This study included 171 patients (85 in the group who received immunonutrition and 86 in the control group, of which 27 and 21 patients in the supplemented and control groups, respectively, had colon cancer). They described an infection rate of 24% and 11% in the control and supplemented groups, respectively ($p = 0.02$). The same group at the University of San Rafael in Milan reported another interesting study comparing 4 experimental groups treated for 5 days: (1) preoperative arginine and omega-3 fatty acid, (2) pre- and postoperative supplements, (3) standard isoenergetic and isonitrogenous supplements and (4) no supplementation. They reported an overall infection rate of 12% in the preoperative group, 10% in the perioperative period, 32% in the control group and 30% in the conventional group ($p <0.04$ for a joint analysis of the groups receiving immunonutrition compared to those without immunonutrition). In addition, the groups that received immunonutrition had a better immune response and increased intestinal microperfusion and oxygenation. In addition, there were additional benefits to prolonging postoperative immunonutrition [11]. Alivizatos *et al.* [12] evaluated patients with gastrointestinal malignancies undergoing major surgery and demonstrated no differences between patients who received postoperative enteral immunonutrition and patients who received parenteral nutrition supplemented with glutamine. Based on the results described above, it appears that preoperative immunonutrition should be administered to provide the maximum benefit to the patient

Horie *et al.* [13] indicated that preoperative immunonutrition may reduce the rate of surgical site infections. In a study performed in 2006, among 67 normo-nourished patients, 33 patients received additional nutritional support with arginine, nucleotides, and omega-3 fatty acids for 5 days before surgery and 34 control patients did not receive any supplementation. Surgical site infection was described in 0% of the study group and 11.8% of the control group ($p <0.05$). However, these differences were not observed in the case of deep infection (0 vs. 0%) or intra-abdominal infection (0 and 2.9%) between the group that received nutritional supplementation and the control group, respectively. However, some published studies do not demonstrate a benefit of immunonutrition in terms of postoperative infection. Helminen *et al.* [14] studied 50 patients who underwent elective gastrointestinal surgery and received nutritional supplementation with arginine, omega-3 fatty acids and RNA, and 50 patients who served as the control group (26 and 25 patients had colon cancer, respectively). The authors concluded that there was no benefit to routinely prescribed immunonutrition based on results showing infectious complications in 28% of the immunonutrition group and 24% of the control group ($p> 0.05$). These results are identical to those presented by Sorensen *et al.* [15] for 148 elective surgical patients for colorectal cancer and by Finco *et al.* [16] for 28 patients undergoing laparoscopic colorectal surgery.

Recently, a shift toward Th2 dominance of the Th1 / Th2 balance in the early postoperative period has been directly associated with the appearance of infectious complications [17]. Matsuda *et al.* [18] described a correction of the Th1 / Th2 balance in 19 patients with colorectal cancer who were undergoing surgery and received an oral diet supplemented with arginine, omega-3 fatty acids and ribonucleic acid compared to 17 patients who formed the control group and did not receive supplementation. The results showed that this balance correction may be an important determinant in the clinical benefit of immunonutrition in decreasing postsurgical infections.

It is known that postoperative immunosuppression is associated with tumor growth, invasion and metastasis. The activity of NK cells, which are cytotoxic to many tumor cells, is suppressed during this period due to surgical stress [19]. Da Costa *et al.* [20] demonstrated that after open surgery in animal models, tumor growth resulted from suppression of the activity of these cells. Matsuda *et al.* [18] described an increase in NK cell activity in the supplemented group compared to the control group, but the results were not statistically significant. There seems to be an increase in the population of CD-4 (+) and CD-8 (+) cells expressing CD-56 antibody (+) in the tumor mucosa of patients with colon cancer after receiving immunonutrition, and this increase continues postoperatively in terms of CD-8 (+) cells [21]. Ateş *et al.* [22], in a study of 42 patients with gastric or colon cancer, observed increased levels of cortisol and CRP in response to surgical stress in patients who received either enteral immunonutrients or only parenteral nutrition; however, the levels were normalized to the previous immunonutrition group. They also described a decrease in NK and CD-8 (+) cells in both groups with prior standardization to the immunonutrition group, and there was an increase in CD-4 (+) cells in the same group. A preoperative increase was also described [10]. Therefore, the authors concluded that enteral nutrition provides a better postoperative immune response than parenteral immunonutrition. Interesting results have been reported regarding the important effects of alterations of the population of lymphocytes in tumor tissue on the prognosis of patients with colorectal cancer. However, further studies are needed to determine the actual role of these findings in the prognosis of colorectal cancer patients.

Questions remain concerning how an increase in intestinal microperfusion and oxygenation can decrease anastomotic leakage in colorectal surgery, as described by Marano *et al.* [23] in patients undergoing gastrectomy.

Table 1: *Clinical results*

	SUPPLEMENT	PATIENTS	RESULTS
Braga (1999)	Arginina, RNA and ω-3	85 IM pre (27 colon) / 86 control group (21 colon)	Decrease in infectious complications.
Braga (2002)	Arginina, ω-3	50 IM pre / 50 IM pre y post / 50 IM pre / 50 control group	Decrease in infectious complications. No prolonged post-surgical benefits
Horia (2006)	Arginina, nucleotides and ω-3	33 IM pre / 34 control group	Decrease in surface surgical site infections.
Helminen (2007)	Arginina, RNA and ω-3	50 IM (26 colon) / 50 control group (25 colon)	No benefits.
Sorensen (2014)	ω-3, EPA, DHA.	74 IM / 74 control group	No benefits.
Finco (2007)	Arginina, RNA and ω-3	14 IM / 14 control group	No differences in infectious complications

IM: Immunonutrition. Pre: Preoperative. Post: Postoperative

Table 2: *Analytical results.*

Matsuda (2006)	Increased NK activity. Increased preoperative levels of CD-4 and CD-8 cells expressing CD-56. Correction of the Th1 / Th2 balance.
Ateş *et al* (2004)	PCR and previous normalization to cortisol. Earlier augmented CD-8 levels. Augmented NK and CD-4 levels.
Caglagan (2012)	Increased postoperative CD-8 levels.
Finco (2007)	Increased preoperative CD-4 levels.

Conclusion

Enteral supplements enriched with immunonutrients decrease the overall rate of infections in patients with colon cancer who are scheduled to undergo colorectal surgery. They also reduce hospital stays while correcting the Th1 / Th2 balance, although subsequent studies are needed to understand the role of immunonutrition in the prognosis of patients with colorectal cancer. Concerning the route and optimal timing of administration, it appears that enteral administration is preferable when possible and administration during the days before the surgery provides the best results in terms of morbidity.

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