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# Perioperative Nutritional Intervention: Where Are We?

Teresa Hoos[a] · Malissa Warren[a] · Robert G. Martindale[b]

[a]VA Portland Health Care System and [b]Department of Surgery, Oregon Health and Science University, Portland, OR, USA

**Abstract**

As we look forward in 2015, attention to perioperative surgical nutrition continues to play a key role in optimizing outcomes and enhancing surgical recovery. Nutrition therapies for preoperative preparation include high protein intake combined with exercise, immune- and metabolic-modulating nutrients, carbohydrate loading, probiotic therapy and, occasionally, the need for specialized enteral or parenteral nutrition. Early enteral nutrition and probiotic therapy optimize gastrointestinal integrity and function in the postoperative setting. Some questions of who, when and how to optimally feed the surgical patient still exist. Despite these questions, the abundance of evidence supports a determined focus for nutrition optimization prior to major surgery.



## Introduction

The potential role of nutritional intervention to optimize surgical outcomes has yet to become fully realized and nutritional support is clearly underutilized [1]. Recent basic science literature and clinical trials continue to support the multiple benefits of preoperative nutrition therapy, and a recent push to recognize those patients who will benefit from pre- and perioperative nutrition has taken place [1]. In the preoperative period, the use of immune and metabolic modulation has increased exponentially, while in the postoperative period, early enteral feeding remained a primary recommendation and has moved from theory and animal models to daily practice [2]. To date, the science supporting who to feed, when to feed and how to feed the surgical population continues to be fine-tuned. The benefits of appropriate nutrition both to the patient and the institution are well established, and include decreases in surgical complications, length of hospital stay, use of posthospital skilled nursing care and costs of health care delivery as well as increases in patient satisfaction [3]. In-depth protocols or bundles of interventions to enhance recovery and minimize complications, such as ERAS (Enhanced Recovery after Surgery), are readily available. While the idea of optimization of perioperative nutrition is widely agreed upon, its practice and implementation are not broadly utilized [4]. This article will explore the data that support best practices surrounding perioperative nutrition as we go forward.

## Preoperative Nutrition Preparation

The preoperative period in the elective surgical candidate is an ideal time to assess and address modifiable risk factors to decrease the risk of surgical complications and poor outcomes. Preoperative preparations 1 month or more prior to surgery, including weight optimization, resistance exercise, improved glycemic control and smoking cessation, now have all been proven to improve postoperative outcomes. Though nutrition sometimes plays an integral role in preoperative preparation, it has yet to gain the attention it deserves. Evidence, however, is solid supporting nutritional preparation prior to surgery [1, 5–7]. A nutrition assessment can aid in identifying the degree of malnutrition and thus the level of preparation needed in the presurgical patient, including whether or not supplemental oral, enteral (EN) or parenteral nutrition (PN) is indicated.

## Preoperative Supplements Modulating Immune and Metabolic Responses

The most frequent complication in patients undergoing major surgery is infection, the majority being surgical site infection and pneumonia [8]. A substantial body of research has reported improved outcomes in patients undergoing major elective surgery when immunonutrition formulas (IMFs; formulations including arginine and ω-3 fatty acids) have been provided in the perioperative period [5–7, 9, 10]. Beneficial outcomes result in a lower risk of morbidity, including decreased infections and improved wound healing, as well as shorter lengths of stay and overall cost savings. Despite the significant benefits listed for the preoperative use of IMFs, mortality remains unchanged, as would be expected, due to low mortality rates at baseline in the elective surgery population. In order to show a statistical difference in mortality, a study in elective surgery would require several thousand patients [5]. Arginine is thought to be one of the primary nutrients driving the benefits reported for IMF [5]. In adults, arginine is considered a nonessential amino acid under normal physiologic conditions, but within hours of a major surgical intervention or trauma, plasma arginine levels fall significantly [11]. Providing supplemental arginine in the form of IMF increases arginine availability and promotes the arginine-dependent mechanisms of nitric oxide production, and T lymphocyte function and proliferation that improve the immune response. As a result of arginine metabolism via these processes, there is stimulation of anabolic hormones, such as growth hormone, prolactin and insulin, which enhance recovery, an increase in polyamine biosynthesis and proline synthesis for wound healing and tissue repair, and improved bactericidal action in the macrophage, contributing to decreased infection [12]. The importance of arginine metabolism and the effectiveness of its supplementation in the surgical and trauma population are demonstrated in clinical trials, and arginine supplementation is no longer controversial in these select groups [1, 12, 13].

The use of fish oil [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] is at the center of the concept of metabolic manipulation in the perioperative period. Appropriate use of DHA and EPA can partially attenuate the hyperdynamic metabolic response to surgical stress, reverse or stop the loss of lean body tissue, prevent oxidative injury and favorably modulate the inflammatory response [12, 14]. Traditionally, lipids were felt to be important in clinical nutrition but only as a caloric source providing essential fatty acids and supporting the absorption of fat-soluble vitamins via micelle formation in the proximal small bowel. Currently, specific lipids are being used to alter the metabolic response to stress by changes in cell membrane phospholipids, alterations in gene expression and by modulating endothelial expression of ICAM-1, E-selectin and other endothelial receptors regulating vascular integrity and function. Additionally, EPA and DHA derivatives, including resolvins, docosatrienes and neuroprotectins, are potent active effectors of resolution of inflammation [15]. These derivatives are now generally referred to as specialized proresolving molecules [15, 16]; they regulate class differentiation into M1 and M2 to control inflammation in the perioperative period. They also control polymorphonuclear neutrophil transmigration and timing of apoptosis. Docosanoids and neuroprotectins are both derived from DHA and have potent neuroprotective properties. Neuroprotectin decreases neutrophil infiltration, proinflammatory gene signaling and NF-κB binding. The neuroprotectin NPD1 has been found to reduce neural infarct volume by half in an animal ischemia-reperfusion model [15]. These protective mediators are found to be highly conserved among species, from fish to mammals [15]. With the discovery of these compounds, it is acknowledged that resolution of inflammation is an active process rather than a passive time-dependent process.

When the preoperative period is studied, supplementation with oral IMF for 5–7 days before surgery has been reported to be beneficial in most [17–21] but not all analyses [22–24]. Continuing IMF into the postoperative period strengthens the observed benefits in poorly nourished patients [4, 22]. The most commonly studied surgical populations are patients undergoing major surgery for upper and lower gastrointestinal (GI) malignancies. A few of the more recent studies include Okamoto et al. [22], who evaluated the outcomes of gastric cancer patients receiving IMF supplementation for 7 days compared to those who received isocaloric nutrition. The IMF group demonstrated significantly fewer infectious complications and shorter duration of the systemic inflammatory response syndrome following gastrectomy [21]. IMF has also been studied with positive results in cardiac [25] and hepatobiliary surgery patients [26]. The nutrition status of study groups was divided into well and poorly nourished, or not well defined. Several large meta-analyses that included patients who were well and not well nourished showed that IMF benefitted both groups [7, 9, 27].

In some cases, oral nutrition supplementation in the preoperative period is not feasible. For patients with a decreased ability to take oral nutrition, EN or even PN may be indicated while the patient is being prepared for surgery. Significant weight loss (>10%) in 6 months and a low serum albumin level are correlated with an increased risk of poor outcome [27]. Albumin and prealbumin are only surrogate nutrition markers. Prealbumin and C-reactive protein ratios can help predict the inflammatory state of the host, which can be useful in the postoperative setting if nutrition intervention is now showing benefit.

### Parenteral Nutrition in the Surgical Setting

The timing of when to use PN in the surgical patient remains controversial. In cases of intestinal obstruction, severe malabsorption, intestinal ischemia or multiple high-output fistulas that preclude the use of EN, evidence supports the use of PN for 7–10 days prior to surgery, delaying it, if possible, as needed to accomplish this. For optimal benefit, preoperative PN should be continued postoperatively until the patient can tolerate EN [28].

### Preoperative Carbohydrate Loading

It has been postulated that delivery of an isotonic carbohydrate solution the night before surgery and 3 h preoperatively serves to 'load' the muscles, myocardium and liver with glycogen and is of benefit to surgical patients [29, 30]. The theoretical basis for this intervention is that the patient will deplete glycogen stores by fasting for 12–18 h preoperatively. When carbohydrate stores are depleted, an alternate fuel source for metabolism would be required (either lipid or muscle protein) almost immediately following the start of the surgical procedure [31]. By carbohydrate 'loading', the body can utilize the stored carbohydrate for the first few hours of the catabolic stimulus instead of resorting to muscle protein stores [31]. Carbohydrate 'loading' has been a component of ERAS or fast-track surgical pathways designed to capitalize on the benefits of reduced preoperative fasting [29]. In addition to preserving skeletal muscle mass, carbohydrate loading decreases insulin resistance and improves perioperative glycemic response. In other studies, carbohydrate loading has been reported to promote rapid return of postoperative bowel function and shorten hospital stay [30, 32]. Carbohydrate loading beverages are typically fat free, isotonic and contain about 50 g of carbohydrates in a volume of 300–400 ml per serving. The majority of protocols recommend two servings of the carbohydrate loading beverage for a total of 100 g of carbohydrates the night before surgery (about 8 h prior to surgery), and one serving of 50 g of carbohydrates again the morning of surgery (about 3 h prior to surgery). This dosing practice improves patient comfort, is safe and effective, and has not been shown to increase the aspiration risk of general anesthesia [30].

### Postoperative Nutrition: Early Enteral Feeding

Appropriate and timely nutrition therapy in the postoperative setting can reduce infectious and surgical complications, including wound dehiscence and anastomotic leaks. EN or oral feeding within 24 h of surgery can speed recovery, reduce hospital stays and even lower patient mortality. Benefits have been reported over the past 15 years in many studies and a handful of meta-analyses of early EN delivery in the postoperative setting [33–35]. Due to the mounting supportive evidence, early EN has become a mainstay recommendation of fast-track protocols, as previously described [29]. Despite supporting evidence and globally adopted protocols, EN is too often delayed in the postoperative setting due to surgical dogma or common misperceptions regarding the contraindications to feeding [1]. Reasons for delayed EN in the postoperative setting include lack of bowel function or postoperative ileus, fear of aspiration, fear of bowel ischemia, concern for the integrity of a fresh anastomosis, need to return to the OR and general lack of knowledge concerning its benefits [1].

Evidence-based practices to overcome barriers and maximize the opportunity for early EN postoperatively include obtaining feeding access at the time of the operative procedure, avoiding nasogastric decompression and oral or enteral feeding restriction, considering pharmacotherapy to prevent nausea and vomiting, and early mobility to promote GI function [36].

In a recently published randomized controlled trial, Boelens et al. [37] found that early EN after rectal surgery for malignancy resulted in a lower occurrence of anastomotic leak and shorter hospital stays for patients compared to early PN. In another randomized controlled trial of upper GI surgery patients, Barlow et al. [38] also showed fewer infectious complications, decreased anastomotic leaks and shorter length of hospital stays by 3 days ($p = 0.023$) when EN was initiated within 12 h of surgery compared to the control (nil per os until oral intake could be initiated at approximately 7–10 days postoperatively). The benefits of EN thought to promote improved patient outcomes include preservation of gut integrity and enhancement of gut-mediated immunity [39]. New evidence has emerged describing the mechanisms of these benefits. It is not surprising that maintenance of the microbiome by enteral feeding seems to play an integral role. Luminal nutrient stimulation promotes microbial diversity, improves the integrity of tight junctions and supports epithelial proliferation, resulting in a 'bioecological control' of pathogenic bacterial overgrowth [39]. In addition, Lubbers et al. [40] described the activation of the vagal anti-inflammatory reflex stimulated by EN that increases microvascular blood flow to the gut, supporting epithelial barrier function. In another recent publication, Harmarneh et al. [41] described the maintenance of alkaline phosphatase levels in the intestinal brush border by enteral nutrient stimulation. Adequate alkaline phosphatase levels in the intestinal brush border detoxify bacterial toxins, preventing endotoxemia. Heneghan et al. [42] described the beneficial effects on the integrity of the GI tract when Paneth cells are activated by EN. Paneth cells release multiple antimicrobial substances such as defensins, lysosomes, cathelicidins, phospholipase $A_2$, and C-type proteins. Goblet cells, when stimulated by EN, also impact gut integrity by producing mucin that has pathogen-trapping capability [43].

An additional mechanism of benefit to maintain epithelial barrier function with enteral feeding is the reduction in proinflammatory cytokines in the gut wall that leads to epithelial cell apoptosis and contributes to increased intestinal permeability [44].

### Role of Parenteral Nutrition in the Postoperative Setting

The American Society of Parenteral and Enteral Nutrition and the Society of Critical Care Medicine provide evidence-based recommendations for the appropriate use of PN in the surgical patient. PN is appropriate in the postoperative setting for severely malnourished patients who require PN preoperatively until adequate EN is achieved after surgery [45]. In addition, PN is appropriate when EN is not feasible, such as in the case of bowel discontinuity and a high-output proximal fistula. If, however, the patient was well nourished prior to surgery, then PN should be delayed for up to 7 days postoperatively if EN is not feasible or attempts at enteral feeding have failed [45].

The use of PN has not been uniformly associated with the same positive outcomes as EN. This is likely related to the lack of luminal nutrient stimulation in the GI tract that results in improved mucosal immunity in addition to the multitude of previously described benefits of EN. Instead, PN is consistently associated with an increased risk of infections in the postoperative setting. In a recent large multicenter randomized trial evaluating early versus late initiation of PN, patients in the late PN group had fewer infections, fewer days on mechanical ventilation and were more likely to be discharged alive than those patients receiving PN early in their ICU stay [46]. Kutsogiannis et al. [47] investigated the use of supplemental PN in a multicenter observational study including nearly 3,000 medical and surgical ICU patients requiring mechanical ventilation. Early supplemental PN improved calorie and protein provision, but was not associated with any clinical benefits. Patients in the early and late PN subgroups experienced longer hospital stays and increased mortality. This study, looking at supplemental PN in addition to EN, confirms that there are other reasons that PN may be associated with an increased risk of infection than just the lack of nutrient stimulation of the GI tract.

### Probiotics in the Postoperative Setting

Disruption of the gut barrier function, increased intestinal permeability and immunologic compromise of the patient are unintended consequences of surgery. Probiotics may promote a positive balance and maintenance of the gut microbiota by strengthening intestinal barrier function, increasing numbers of beneficial bacteria and decreasing the number of pathogens. These are important roles for probiotics in the surgical patient, e.g. a beneficial effect on recovery. Recent evidence suggests that pre- and postoperative use of probiotics and synbiotics (prebiotics and probiotics) in the GI surgery patient reduces infectious complications, decreases the duration of antibiotic treatment and improves GI motility. The meta-analysis by Kinross et al. [48] reviewed 13 randomized studies for the use of probiotics and synbiotics in the elective surgery patient. No complications from the use of these therapies were reported. As in most probiotic research, doses and strains varied across studies. Nineteen different probiotic strains were used across 13 studies [48]. Data published on a more homogenous population showed greater benefit of probiotic therapy. The promising results for probiotic and synbiotic therapy in the elective GI surgery patient are not necessarily translatable to other heterogeneous populations, such as the critically ill. Future studies must define the population, strain and dose to be administered, determine the outcomes to be measured as well as assess issues of safety to appropriately evaluate the effectiveness of probiotics in the clinical setting.

## Conclusion

Currently, the concept of perioperative surgical nutrition is evolving to become routine practice in major surgery. The heterogeneity of the surgical population makes it very difficult to select a single specific formula, time or route for every patient. Each patient requires an individualized nutrition regimen that considers the severity of their surgical insult, their preexisting nutritional status and ongoing morbidities. By attenuating the metabolic response to stress, the appropriate nutrition regimen can facilitate improved outcomes and decrease health care costs by reducing postoperative morbidities, including deep vein thrombosis, pneumonia, infection, ventilator days, length of stay and mortality. The components of a successful nutrition regimen include IMF (orally and/or enterally) for the duration of 5–7 days preoperatively and in the early postoperative period, carbohydrate loading administered in the immediate preoperative setting and judicious occasional use of PN in the perioperative period. The evidence for probiotics and synbiotics is promising in the surgical setting, though further research is necessary to define the appropriate bacterial species or combinations of species and proper dose.

## Disclosure Statement

Robert G. Martindale is a member of the advisory board for Nestle Nutrition and Metagenics. There is nothing to disclose for Teresa Hoos and Malissa Warren.

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