Preoperative Standard Oral Nutrition Supplements vs Immunonutrition: Results of a Systematic Review and Meta-Analysis

Refaat A Hegazi, MD, PhD, MPH, MS, Deborah S Hustead, PhD, David C Evans, MD, FACS

SUMMARY

Multiple studies and meta-analyses have suggested some benefit to immunonutrition (IN) supplements. These studies have often included pre- and post-operative regimens and have utilized inconsistent controls ranging from standard non-supplemented oral diets to high-quality isonitrogenous controls. This study aims to compare outcomes after preoperative nutritional supplementation with IN vs. standard oral nutritional supplements (ONS) or a regular diet without supplements.

We performed a systematic literature review. 8 randomized controlled trials (RCTs) of preoperative IN vs. ONS were identified and 9 RCTs of IN vs. no supplements were also identified. Meta-analysis was performed for reported outcomes including wound infection, infectious and non-infectious complications, and length of stay (LOS). The meta-analysis was prepared in accordance with Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) recommendations.

We identified 561 patients in 8 RCTs of preoperative IN vs. ONS. 895 patients were identified in 9 RCTs of IN vs. no supplements. When compared to ONS, preoperative IN was not associated with reduced wound infection (OR 0.97, 95% Confidence Interval (CI) 0.45 to 2.11), all infectious complications (OR 0.71, 95% CI 0.30 to 1.68), non-infectious complications (OR 1.25, 95% CI 0.64 to 2.43), or LOS (mean difference 0.07 days, 95% CI −2.29 to 2.43). In RCTs controlled with non-supplemented standard diets, preoperative IN was associated with decreased infectious complications (OR 0.49, 95% CI 0.30 to 0.83, $p \leq 0.01$) and LOS (mean difference −2.22 days, 95% CI −2.99 to −1.45, $p \leq 0.01$).

In conclusion, there was no evidence for IN to be superior to ONS on several key clinical outcomes. Therefore standard ONS may offer an alternative to IN for preoperative nutritional supplementation.

INTRODUCTION

Surgery poses a catabolic stress characterized by the presence of an inflammatory response associated with depletion of conditionally essential nutrients, which leads to a dysregulated immune response that increases the risk for postoperative complications, especially infections. The role of immunonutrition (IN) in the nutritional management of surgical patients has been recommended by major society guidelines. One of only two grade-A recommendations by the 2009 American Society for Parenteral and Enteral Nutrition/Society of Critical Care Medicine guidelines was for the use of IN in surgical ICU patients.[1]

Within the last few years, several meta-analyses have examined this topic. The meta-analysis by Drover and colleagues[2] showed that IN improved clinical outcomes, especially postoperative infections, as compared with controls in the perioperative period. This meta-analysis combined studies with standard nutritional supplements and standard nonsupplemented diets as the control groups without clear differentiation between the two. More recent meta-analyses have suggested that both the dietary composition of the nutritional supplementation and timing of IN are equally important in determining the beneficial effect of IN. Osland and colleagues suggested that the evidence of IN is strong when it is used in the postoperative as compared with preoperative period.[3] In addition, Marik and Zaloga suggested that the effect of IN depends on the nutrient composition of the IN formula and that the most important outcomes benefits arise from IN formulations supplemented with fish oil and arginine in high-risk surgical patients.[4]

Fish oil—derived omega-3 fatty acids displacing the arachidonic acid of the cell membrane of immune cells attenuate the production of inflammatory prostaglandins and prostacyclins and reduce the cytotoxicity of

Disclosure Information: Dr Evans is the recipient of educational grants from Nestle Nutrition and Abbott Laboratories as well as speaking honoraria from Abbott Laboratories. Dr Hegazi and Hustead are full-time employees of Abbott Laboratories. The current review is based on the clinical evidence and not influenced by these financial relationships. The authors did not receive any funding to support this study.

Received April 26, 2014; Revised June 20, 2014; Accepted June 20, 2014.
From the Scientific and Medical Affairs Department, Abbott Nutrition (Hegazi, Hustead) and Department of Surgery, The Ohio State University (Evans), Columbus, OH.
Correspondence address: David C Evans, MD, FACS, Department of Surgery, The Ohio State University, 395 W 12th Ave, Rm 634D, Columbus OH 43214. email: david.evans@osumc.edu

http://dx.doi.org/10.1016/j.jamcollsurg.2014.06.016
ISSN 1072-7515/14

Abbreviations and Acronyms
IN = immunonutrition
LOS = length of stay
ONS = oral nutritional supplements
OR = odds ratio
RCT = randomized controlled trial

inflammatory cells. Fish oil–derived fatty acids eicosapentanoic and docohexanoic acids are the precursors of resolvins, shown to reduce cellular inflammation by inhibiting the transportation of inflammatory cells and mediators to the site of inflammation.[5] The conditionally essential amino acid arginine can function as a precursor of proline and polyamines, which are essential for tissue repair and wound healing. Arginine is also crucial for the integrity and function of immune cells. In addition, arginine is an important immune-modulating nutrient as a precursor of nitric oxide synthesis. Studies have shown that arginine deficiency occurs as a result of surgical injury.[6] Immunonutrition supplements have varying concentrations of these key ingredients and the ideal dosages are not well defined. In fact, the relative dosages of the immune-modulating ingredients even vary at times from country to country in products made by the same manufacturer. No consensus exists about standard dosages for these ingredients and immunonutrients are frequently included (albeit in lower quantities) in standard oral nutritional supplements (ONS).

The role of standard ONS for preoperative nutritional optimization is not well delineated. Standard ONS formulations are typically high in protein and supplemented with vitamins and minerals. They are inexpensive, widely distributed, and commonly used by patients who desire nutritional supplementation when recovering from an illness. Data describing the effects of standard ONS in the preoperative period are scarce. Whether the clinical benefits of preoperative IN are substantial when compared with isocaloric and isonitrogenous standard nutritional formulations is an unanswered question. It might be that the benefit of preoperative IN supplementation can be achieved by supplementation with high levels of protein and standard vitamins and minerals, not the additional arginine, fish oil, and other immunonutrients. In the current meta-analysis, we examine the effects of IN vs standard nutritional supplements and vs regular diet with no supplements.

METHODS

Inclusion and exclusion criteria

Studies of the preoperative provision of ONS identified as IN or immune-modulating as compared with standard oral nutrition formulas or no supplements were reviewed. Only randomized controlled trials (RCTs) with primary comparisons between the nutrition interventions were included. For inclusion, studies should have reported on clinically relevant outcomes pertaining to the postoperative period, namely wound infections, infectious and noninfectious complications, and length of hospital stay. Retrospective studies and those using perioperative IN or parenteral nutrition were excluded.

Study identification

We conducted a systematic review of the published literature to identify all relevant RCTs that used IN preoperatively. Using text word or MeSH headings containing "randomized," "blind," "clinical trial," "immunonutrition," "immune modulating," and "human," we performed searches for relevant articles on Analytical Abstracts, BIOSIS Previews, Embase, Foodline: SCIENCE, FSTA, MEDLINE, electronic databases Cochrane Controlled Trials Register from 1990 to January 2014.

The data were prepared in accordance with the Preferred Reporting of Systematic Reviews and Meta-Analyses statement[7] (Fig. 1). Data extraction and critical appraisal of identified studies were carried out by the authors for compliance with inclusion criteria. The authors were not blinded to the source of the document or authorship for the purpose of data extraction.

Statistical analysis

Among the primary outcomes of interest was infectious complications or the number of patients with infectious complications. We used infectious complications as defined by the original authors. Secondary outcomes included wound infections, noninfectious complications, and hospital length of stay.

For data expressed as an event, the numbers of patients with the event and sample size for each group in each study were entered into the analyses. All data reported from the individual studies are expressed as an odds ratio (OR) with the associated 95% CI. For length of stay (LOS), the mean, SD, and number of patients for each group were entered into the analyses. The difference in the means, SEs, and associated 95% CIs were calculated. A random effects model was used to calculate all summary parameters. The random effects model is used when studies are not functionally similar and/or cannot be assumed to all have a common effect size. Under the random effects model, the assumption is that each study is estimating a unique effect, and therefore, the null hypothesis is that the mean of the true effects is zero. The studies included in this analysis contained different populations (eg, cancer and noncancer),