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

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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

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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),

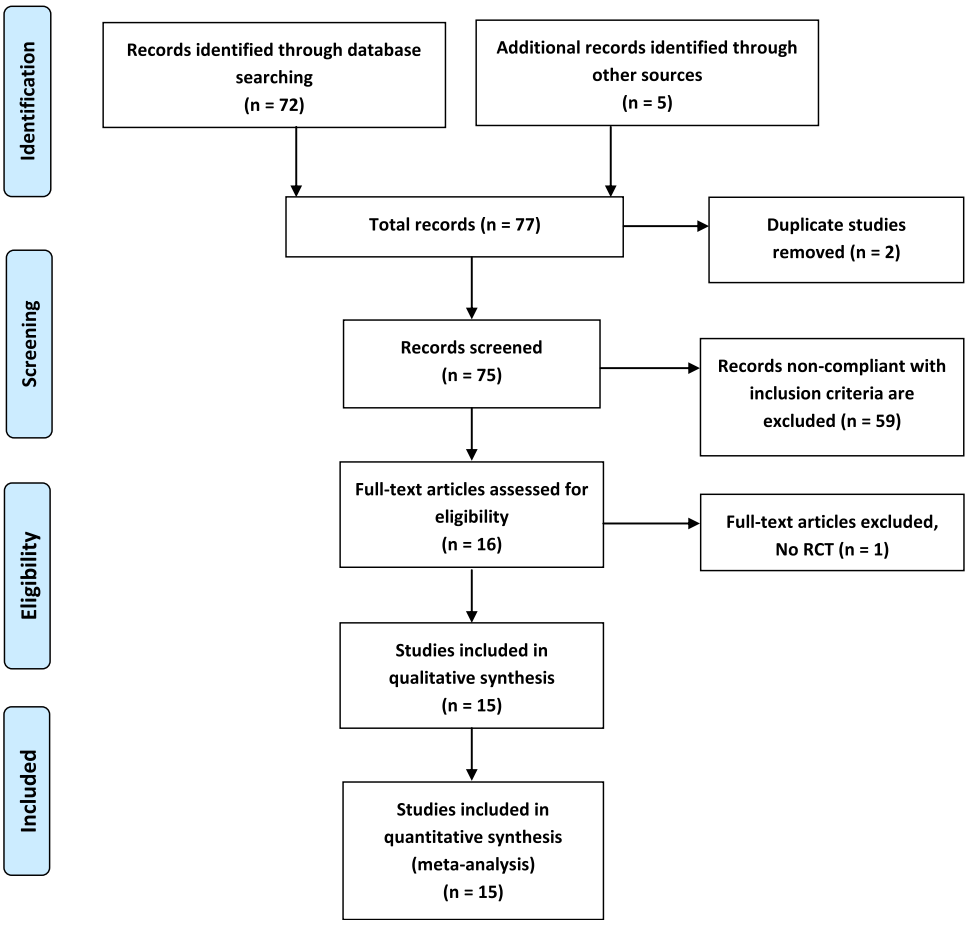


Figure 1. Preferred Reporting of Systematic Reviews and Meta-Analyses statement describing the identification, inclusion, and exclusion of randomized controlled trials evaluating the effect of preoperative immunonutrition on postoperative clinical outcomes compared with standard oral nutrition supplements and no supplements.

different supplement durations, and different control ONS products, therefore, a priori it was decided they were heterogeneous and the random effects model was appropriate. Forest plots were prepared to graphically represent the meta-analysis; the area of each square is proportional to the study's weight in the meta-analysis and the diamond depicts the overall summary and 95% CI of the analysis. Analyses were performed using the software package Comprehensive Meta-Analysis, version 2 (Biostat, Inc.).

RESULTS

Sixteen studies of the use of preoperative IN were identified. One study[8] was excluded from our analysis because it was a retrospective analysis of prospectively collected data. The Preferred Reporting of Systematic Reviews and Meta-Analyses flow diagram in Figure 1 summarizes the process. Of the 15 studies, 2 had multiple arms, which allowed them to be used in both subsets of analyses. Sufficient data were available for the analysis for 4 clinically relevant outcomes: wound infections, all infectious complications, noninfectious complications, and LOS. Five hundred and sixty-one patients in 8 RCTs[9-16] of preoperative IN vs ONS were identified (Table 1) and 895 patients in 9 RCTs of IN vs no supplements were also identified (Table 2).[11,14,17-23]

Preoperative immunonutrition vs standard oral nutritional supplements

When compared with ONS, preoperative IN was not associated with a reduced rate of wound infection (OR = 0.97; 95% CI, 0.45−2.11; p = 0.94), all infectious complications (OR = 0.71; 95% CI, 0.30−1.68; p = 0.44), noninfectious complications (OR = 1.25;

Table 1. Preoperative Use of Immunonutrition vs Standard Oral Nutrition Supplements Study Characteristics

First author, year, country	Study population	Study design	Immunonutrition, n	Oral nutrition supplements, n	Study end points
Wachtler, 1995, Germany[9]	Upper GI surgery for cancer	IN preoperatively for 5 d vs isocaloric ONS for 5 d preoperatively	20	20	Functional parameters of peripheral blood leukocytes
McCarter, 1998, United States[10]	GI CA	IN preoperatively for 7 d vs ONS preoperatively for 7 d vs ONS with arginine preoperatively for 7 d	13	11	Postoperative immunologic function and complications, and LOS
Braga, 2002, Italy[11]	Colorectal CA	IN preoperatively for 5 d vs isocaloric/ isonitrogenous ONS preoperatively for 5 d vs IN preoperatively for 5 d + IN postoperatively vs no supplementation	50	50	Immune response, gut oxygenation and postoperative infections
Xu, 2006, China[12]	Colorectal or GI CA	IN preoperatively for 7 d + ONS postoperatively vs ONS preoperatively for 7 d + ONS postoperatively	30	30	Nutritional status, immunity, and incidence of postoperative complications
Okamoto, 2009, Japan[13]	Gastric CA	IN preoperatively for 7 d vs isoenergetic ONS preoperatively for 7 d	30	30	Cellular immunity, duration of systemic inflammatory response syndrome, and postoperative complications
Gunerhan, 2009, Turkey[14]	GI tumors, mix of moderate and severe malnourished	IN preoperatively for 7 d vs ONS preoperatively for 7 d vs normal nutrition, isocaloric, isonitrogenous to ONS	13	11	Cellular immunity parameters, postoperative complications, LOS
Hübner, 2012, Switzerland[15]	GI surgery NRS score $\geq$3	IN preoperatively for 5 d vs isocaloric isonitrogenous ONS preoperatively for 5 d	73	72	30-day complication rate, infections, LOS
Giger-Pabst, 2013, Switzerland[16]	GI CA, well nourished (NRS score <3)	IN preoperatively for 3 d vs isocaloric isonitrogenous ONS preoperatively for 3 d	55	53	Postoperative infectious and noninfectious complications, length of ICU stay, LOS, antibiotic use

CA, cancer; GI, gastrointestinal; IN, immunonutrition; LOS, length of stay; NRS, Nutrition Risk Screening-2002; ONS, oral nutrition supplements.

Table 2. Preoperative Use of Immunonutrition vs No Supplements Study Characteristics

First author, year, country	Study population	Study design	Immunonutrition, n	No supplements, n	Study end points
Braga, 2002, Italy[11]	Colorectal CA	IN preoperatively for 5 d vs isocaloric/isonitrogenous ONS preoperatively for 5 d vs IN preoperatively for 5 d + IN postoperatively vs no supplementation	50	50	Immune response, gut oxygenation and postoperative infections
Braga, 2002, Italy[17]	Malnourished (weight loss ≥10%), GI CA	IN preoperatively for 7 d + ONS postoperatively vs IN preoperatively for 7 d + IN postoperatively vs postoperatively ONS	50	50	Postoperative complications and LOS
Gianotti, 2002, Italy[18]	GI CA	IN preoperatively for 5 d vs IN preoperatively + IN postoperatively vs no artificial nutrition	102	102	Postoperative infections and LOS, nutritional parameters, and gut function
Horie, 2006, Japan[19]	Colorectal CA, Without malnutrition	IN preoperatively for 5 d vs control group	33	34	Surgical site infection and postoperative inflammation
Gunerhan, 2009, Turkey[14]	GI tumors, mix of moderate and severe malnourished	IN preoperatively for 7 d vs ONS preoperatively for 7 d vs normal nutrition, isocaloric, isonitrogenous to ONS	13	9	Cellular immunity parameters, postoperative complications, LOS
Mikagi, 2011, Japan[20]	Liver CA	IN preoperatively for 5 d vs hospital meals preoperatively for 5 d	13	13	Clinical outcomes, extent of hepatectomy, operation time, volume blood loss, Pringle time, postoperative complications and LOS
Fujitani, 2012, Japan[21]	GI CA, well nourished	IN preoperatively for 5 days vs No nutritional supplements	120	111	Surgical site infection, infectious complications, postoperative morbidity and CRP levels
Barker, 2013, Australia[22]	Malnourished and well nourished, GI surgery	IN preoperatively for 5 d vs no supplements	46	49	LOS, infectious and noninfectious complications, ICU admission, mortality, 30-day follow-up of surgical wound required antibiotics for healing, and treatment costs
Aida, 2014, Japan[23]	Pancreaticoduodenectomy	IN preoperatively for 5 d vs no supplements	25	25	Operative complications and immune responses

CA, cancer; CRP, C-reactive protein; GI, gastrointestinal; IN, immunonutrition; LOS, length of stay; ONS, oral nutrition supplements.

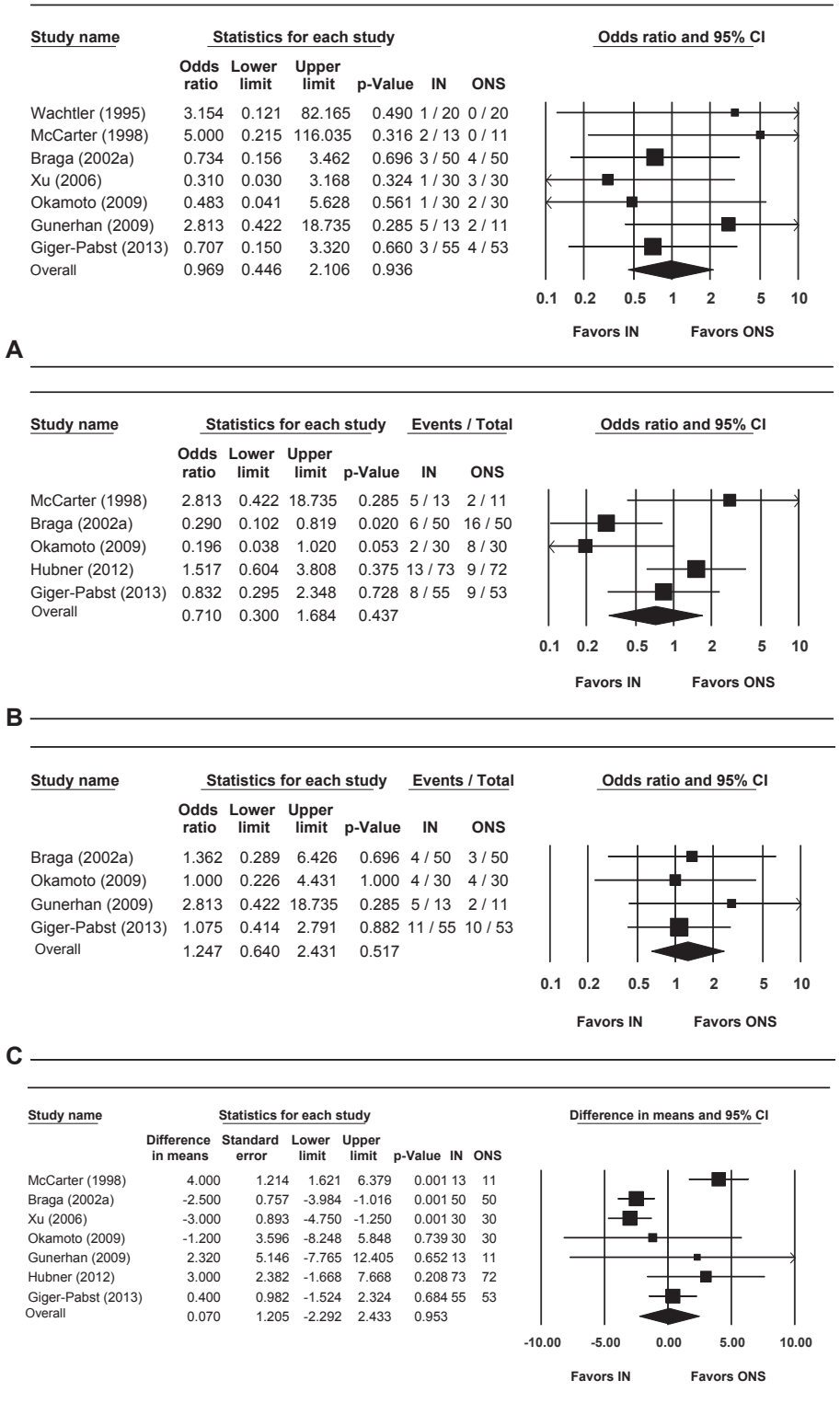
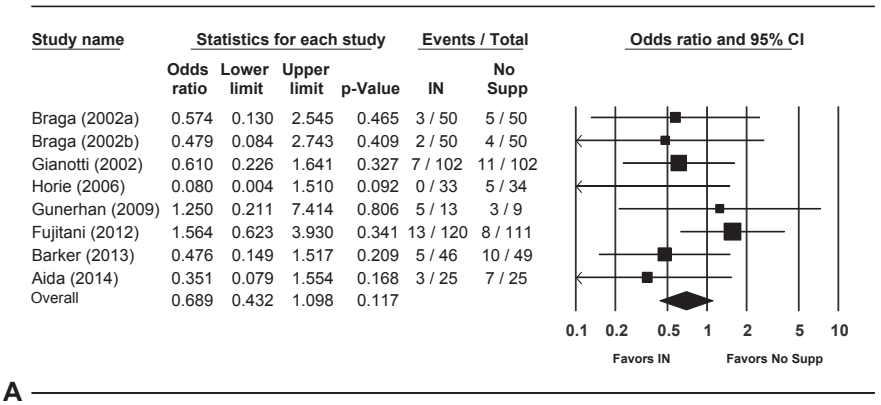


Figure 2. Forest plot results of meta-analysis of preoperative immunonutrition (IN) vs standard oral nutrition supplements (ONS). (A) Preoperative immunonutrition (IN) vs standard oral nutrition supplements (ONS) on wound infection using random effects model. (B) Preoperative IN vs standard ONS on infectious complications using random effects model. (C) Preoperative IN vs standard ONS on noninfectious complications using random effects model. (D) Preoperative IN vs standard ONS on length of stay using random effects model.



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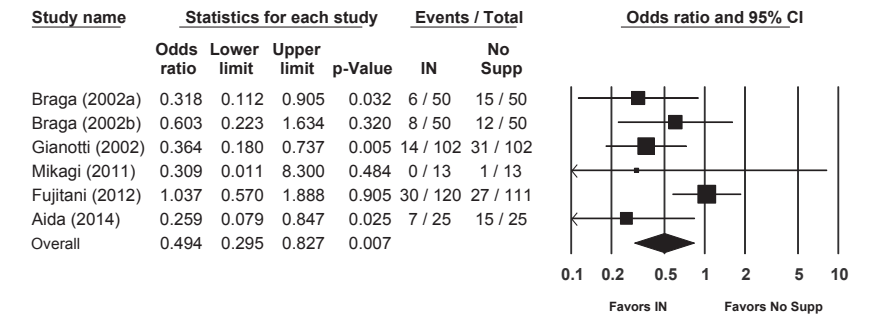

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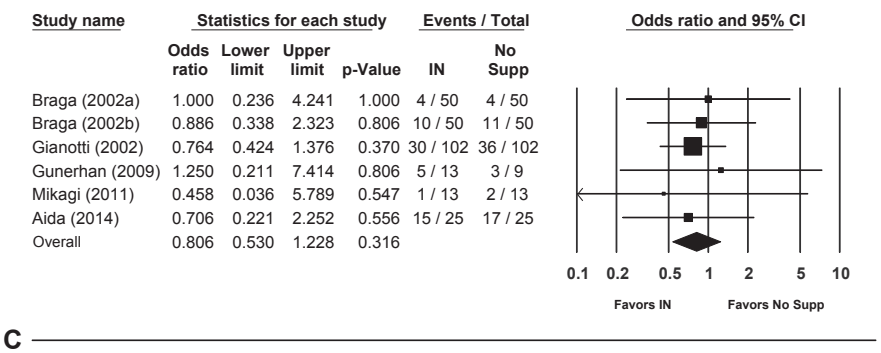

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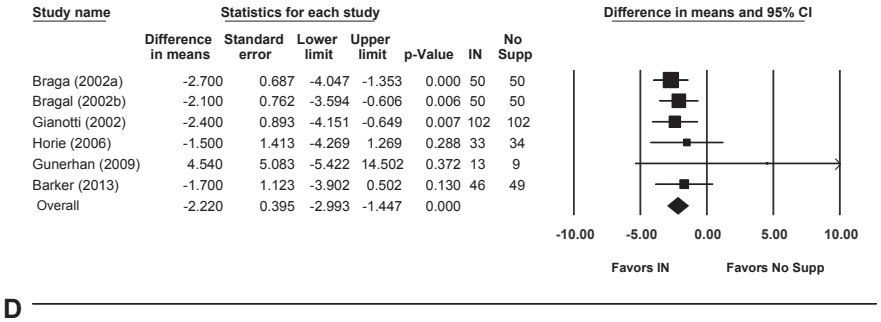

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Figure 3. Forest plot results of meta-analysis of preoperative immunonutrition (IN) vs regular diet without supplements. (A) Preoperative immunonutrition (IN) vs no supplements (No Supp) on wound infection using random effects model. (B) Preoperative IN vs No Supp on infectious complications using random effects model. (C) Preoperative IN vs No Supp on noninfectious complications using random effects model. (D) Preoperative IN vs No Supp on length of stay using random effects model.

95% CI, 0.64−2.43; p = 0.52), or LOS (mean difference 0.07; 95% CI, −2.29 to 2.43; p = 0.96) (Fig. 2).

Preoperative immunonutrition vs no oral nutritional supplements

In RCTs controlled with nonsupplemented standard diets, preoperative IN was associated with decreased infectious complications (OR = 0.49; 95% CI, 0.30−0.83; p < 0.01) and LOS (mean difference −2.22; 95% CI, −2.99 to −1.45; p < 0.01). There was no statistically significant reduction in noninfectious complications (OR = 0.81; 95% CI, 0.53−1.23; p = 0.32) or wound infections (OR = 0.69; 95% CI, 0.43−1.10; p = 0.12) (Fig. 3).

DISCUSSION

This meta-analysis demonstrates no significant difference in effect of preoperative IN as compared with standard ONS on postoperative clinical outcomes. Given the high costs, poor palatability, and limited retail availability of IN products, standard ONS can be a reasonable preoperative alternative. Standard ONS are inexpensive, widely available, and manufactured by multiple vendors in a variety of flavors to suite various tastes. Given the heterogeneity of the existing IN literature, the precise role of preoperative IN has not been clearly defined. Our results suggest that preoperative standard ONS is similar to IN.

The literature for postoperative IN is much stronger. Postoperative IN has been demonstrated in many trials and several meta-analyses to reduce infectious complications, ventilator days, and anastomotic leaks.[4,24-29] The theoretical grounding for IN is strong, particularly in concert with an early enteral feeding algorithm.[30] Arginine, one of the key components of an IN strategy, is rapidly depleted in surgery and after major metabolic stresses.[6] Supplementation can promote cell growth and differentiation and microvascular perfusion in these patients. Omega-3 fatty acids in several perioperative randomized trials have been demonstrated to modulate proinflammatory and anti-inflammatory mediators in the heart, gut, liver, and in tumor tissue.[31-34] Antioxidants are typically the other key ingredient in IN products. Preoperative antioxidants have been shown to increase serum and tissue antioxidant levels, but the clinical benefit is unclear.[35] Because these are combination products, it is challenging to sort out the effects of the various ingredients. The literature suggests the synergism of effects by combining distinct immune-modulating nutrients, especially arginine and fish oil.

Several other investigators have performed meta-analyses examining various aspects of perioperative IN. Existing literature has often blurred the lines between preoperative, postoperative, and perioperative (pre- and post-) regimens.[36] Many preoperative IN studies do not use isocaloric or isonitrogenous controls.[37] Only one preoperative trial has ever demonstrated a statistically significant reduction in infectious complications when IN is compared with an isocaloric, isonitrogenous control oral supplement.[11] This trial and two others without isonitrogenous controls also published by the same group in the same year are responsible for much of the signal of benefit detected in multiple previously published meta-analyses.[11,17,18] Other trials blend surgical, medical, and mixed critical care populations. Because many published studies do not clearly define or identify malnutrition and focus on cancer populations, they represent trials of nutrition vs malnutrition as much or more than they serve as trials of IN vs standard supplements.

Perhaps the most widely cited meta-analysis is that of Drover and colleagues in 2011.[2] This study demonstrated reduced infectious complications with preoperative IN, but included trials with both isonitrogenous and standard diet controls without a subanalysis of these groups. The same year, Cerantola and colleagues published their own meta-analysis with similar results, including a reduction in infectious and noninfectious complications and LOS, also without any subanalysis of studies with different types of controls.[38]

Recently, 4 small trials of preoperative IN have not shown any benefit.[15,16,21,22] Including some but not all of the new trials, Osland and colleagues recently published their own meta-analysis.[3] Like the others, their meta-analysis combined all trials examining preoperative supplementation regardless of the type of control used. This meta-analysis did, however, predate the larger Giger-Pabst and colleagues[16] and Hübner and colleagues[15] trials that were performed with isocaloric, isonitrogenous controls.

Our meta-analysis attempts to reduce the heterogeneity of the preoperative IN literature by clearly identifying which studies use ONS controls vs those that use regular nonsupplemented diets. As with other meta-analyses in the nutrition literature, there are some inherent limitations. Even when standard ONS controls were used, the exact ingredients of these control formulas do vary from study to study. Trials with nonsupplemented regular oral diets were subject to the same variability. Many studies failed to record patient compliance with supplements or total protein intake (both from supplements and regular diets). Most of the included studies used standard protocols with a typical length of supplementation of 5 days, but there was slight variation from study to study. Patients receiving preoperative supplementation in some trials might have received more monitoring in a nutrition support program resulting in improved outcomes.[39] Although IN is typically defined as nutrition with supplemental arginine, fish oil, and antioxidants, most standard ONS

contain these ingredients in some lower concentration. The ideal dose of these immunonutrients has not been defined and some standard ONS might contain therapeutic concentrations of these ingredients. Each study we included in our analysis was drawn from different patient populations undergoing various operations. Populations were randomized and controlled within each study, but were not consistent across all of the studies analyzed. We have used the random effects model approach to meta-analysis to address the presence of this heterogeneity. Despite these drawbacks, our meta-analysis of preoperative IN provides new insights because of its focus on preoperative IN only and the differentiation between trials controlled with ONS vs regular nonsupplemented diets. Commonly cited society guidelines supporting the use of preoperative IN were created using the results of other meta-analyses that did not account for this heterogeneity as in the current meta-analysis.[1,2]

Preoperative supplementation with standard ONS has not been studied extensively. Although our results suggest the similarity of standard and immune-modulating supplements, we cannot absolutely conclude that preoperative standard ONS will result in improved outcomes. One study evaluating preoperative supplementation with standard ONS vs nonsupplemented control diet demonstrated less postoperative weight loss and fewer minor complications with preoperative supplementation.[40] Several past studies have failed to identify a major benefit from the use of standard preoperative ONS.[41-43] This might be due to the lack of a clear definition of "malnutrition" and inclusion of well-nourished patients. Adherence to the new definitions of malnutrition, as is being popularized by several societies,[44] may serve to identify which patients will benefit the most from preoperative supplements. Future studies of preoperative nutrition should incorporate these new definitions. Additionally, the varied composition and individual nutrients of the standard ONS, particularly the amount and biologic value of protein contained, might explain these conflicting results. Dietary protein is critical to help promote muscle protein synthesis and decrease inflammation-associated loss of lean body mass and function. A meta-analysis by Cawood and colleagues of 36 RCTs (3,790 patients) showed that the use of high-protein supplements (>20% of calories from protein) was associated with reduced complications and readmission to hospital, improved grip strength, increased intake of protein and energy, and improvements in weight.[45]

CONCLUSIONS

Given the lack of a significant difference between IN and standard ONS in the preoperative setting, and the fact that standard ONS are less expensive and widely available, we recommend use of standard ONS for nutritional optimization of the surgical patient. Cost and accessibility are key factors to patient compliance. As with smoking cessation or exercise, achieving patient buy-in is crucial to any successful preoperative optimization regimen.

Author Contributions

Study conception and design: Hegazi, Evans
Acquisition of data: Hegazi, Hustead, Evans
Analysis and interpretation of data: Hegazi, Hustead, Evans
Drafting of manuscript: Hegazi, Hustead, Evans
Critical revision: Hegazi, Hustead, Evans

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