The Effect of Immunonutrition on Veterans Undergoing Major Surgery for Gastrointestinal Cancer

Sherri Lewis, MS, RDN, LD/N; Michelle Pugsley, RDN, LDN, CNSC; Christopher Schneider, PA-C, MPAS; Steven S. Rakita, MD; and Lisa J. Moudgill, MD

A randomized controlled trial found that providing immunonutrition supplementation before surgery reduced the rate of postoperative complications and the length of hospital stays.

Immunonutrition involves the use of omega-3 fatty acids, glutamine, arginine, and/or nucleotides individually or in combination at therapeutic levels to specifically modulate the immune system against altering inflammatory and metabolic pathways.[1] Current literature supports the routine use of immune-enhancing formulas (containing both arginine and fish oil) in surgical patients.[2-4] Although most of the literature favors the use of immunonutrition in surgical patients, some studies reported no benefit over standard oral nutrition supplementation.[5]

BACKGROUND

Most studies evaluating the effect of immunonutrition for those undergoing elective surgery have been conducted in surgical oncology patients.[6-12] Advanced cancers and older age can lead to cancer cachexia and sarcopenia, respectively. These conditions increase a patient's surgical morbidity and mortality risk likely because of the negative effects on lean body mass, nutrient intake, and inflammatory and metabolic profile.[13] However, early detection of some cancers through routine screening might lead to earlier surgical intervention that minimizes these negative tumor effects on the patient. Immunonutrition provided to well-nourished and malnourished patients has shown benefits, which supports the premise that a combination of immunonutrients included in immune-enhancing diets might have a beneficial pharmacotherapeutic effect beyond that of providing energy, protein, vitamins, and minerals for nutritional support.[7,14]

There are a lack of data regarding whether there is a window of opportunity for improved outcomes. Is the greatest need for immunonutrients during the peak of the injury, which might be immediately after surgery, or is it before the procedure? Arginine is a conditionally essential amino acid that has been shown to have a beneficial effect on the immune system by enhancing T-lymphocyte response when supplemented in surgical patients. When the arginase 1 (ARG 1) enzyme in myeloid cells is expressed during the inflammatory response to injury, accelerated use of arginine can deplete endogenous arginine, making it conditionally essential.

If adequate arginine cannot be synthesized or an exogenous source is not provided, T-cell dysfunction and decreased nitric oxide production leads to immune and vascular dysfunction, respectively.[15,16] Providing arginine and omega-3 fatty acids might have a synergistic effect by shifting to an anti-inflammatory prostaglandin profile that has been shown to decrease ARG 1 expression while providing an exogenous source of arginine.[17] Postsurgical inflammation might be caused in part by pro-inflammatory mediators and the anti-inflammatory properties of omega-3 fatty acids might offset this if cell membranes are loaded preoperatively.[18] Therefore, preoperative immunonutrition might allow tissues to recover from planned surgical trauma. Bouwens and colleagues demonstrated that intake of eicosapentaenoic acid/docosahexaenoic acid over 26 weeks can alter the gene expression profiles of immune cells to a more anti-inflammatory status.[19] However, Senkal and colleagues recommended that 3 to 7 days preoperatively is adequate to positively alter the lipid profile of tissues.[20]

Oncology patients preparing for surgery often are exposed to the physiologic stress of radiation and chemotherapy as neoadjuvant treatment to surgery. Oncology treatment and the

Ms. Lewis is a Dietetic Program Internship Director, **Ms. Pugsley** is a Clinical Dietitian, **Mr. Schneider** is the Lead Surgical Service Physician Assistant, **Dr. Rakita** is Chief of Surgical Service, **Dr. Moudgill** is Chief of Division of General Surgery, all at James A. Haley Veterans' Hospital in Tampa, Florida. Dr. Moudgill is an Assistant Professor, and Dr. Rakita is an Associate Professor in the Department of Surgery at University of South Florida. **Correspondence:** Mr. Schneider (christopher.schneider2@va.gov)

TABLE 1
Formula Nutrition per Serving

Characteristics	Immunonutrition Formula[a]	Standard Formula
Calories, kcal	340	375
Total protein, g	18.0	13.5
Total fat, g	9.2	13.5
Total carbohydrates, g	45.0	51
Dietary fiber, g	3.6	0.0
Sodium, mg	350	285
Potassium, mg	450	525

[a]Immunonutrition formula contains 1.7 g of omega-3 fatty acids, 12.5 g of arginine, and 1.2 g of nucleotides per 1,000 kcal.

adverse nutritional effects of treatment increase risk for arginine deficiency, such as poor nutrition intake, increased requirements, decreased production. Braga and colleagues demonstrated improved gut microprofusion and gut oxygenation intraoperatively, an effect that continued for up to 5 days after surgery.[21] Waitzberg conducted a systematic review of randomized clinical trials evaluating immunonutrition in preoperative, postoperative, and perioperative periods. The results showed that the greatest improvements in postoperative infections and length of stay occurred in patients receiving preoperative 0.5 to 1 L/d of an immune nutrition product containing supplemental omega-3 fatty acids, arginine, and nucleotides for 5 to 7 days.[22]

It is unclear which population of surgical patients benefit the most from immunonutrition. Some results in the literature favor use in malnourished patients.[18,23] However, other studies also have found benefit in well-nourished patients.[7,14,21]

Veterans who seek medical care at the Department of Veteran Affairs (VA) have higher rates of cancer, obesity, and diabetes mellitus, which complicate surgical outcomes.[24] In addition to comorbidities, veterans who seek medical care at the VA are more likely to have been deployed overseas and have more physical and mental health disorders compared with that of nonveteran patients or veterans who do not use the VA. Because of higher comorbidities, unique deployment history, and mental health disorders, all of which may impact quality of life concerns, veterans are clinically more complex, which makes comparisons with the private sector difficult. The VA has the advantage of providing comprehensive care to veterans in all settings, including preparation for surgery and postsurgical follow-up with an interdisciplinary team.

The objective of this study was to compare surgical outcomes in veterans who receive preoperative supplementation using an immune-modulating formula with veterans who received a standard oral supplement. Although practice guidelines have been developed from studies in US nonveteran populations, there are no high-quality randomized studies of veterans.

This study design also would allow the VA to gauge cost-effectiveness of immunonutrition before implementing new protocols. There is convincing data supporting significant economic benefit; however, more cost-benefit studies are needed to fully assess.[18,25-27] Immunonutrition products are more expensive than are standard nutrition supplements, but overall cost of care when immunonutrition products are used could be lower because of reduction of complications and hospital resources.

METHODS

From November 2011 to January 2016, the authors conducted a single-center, prospective, randomized parallel-group study in veterans undergoing elective gastrointestinal oncologic surgery. Inclusion criteria included planned esophageal, gastric, pancreatic, colorectal, or liver resections in veterans with histologically documented neoplasm of the gastrointestinal tract. Patients were excluded if they were admitted to the intensive care unit (ICU) before surgery, were receiving steroids or other immunosuppressive medications, had a recent hospital admission for pulmonary, cardiac, or renal disease, or were exhibiting signs or symptoms of infection or sepsis, including elevated white blood cells (WBC) > 10,000/mL or a temperature > 37.7° C.

The study was approved by the research and development committee and the institutional review board at James A. Haley Veterans' Hospital (JAHVH) in Tampa, Florida. The clinicaltrials.gov identifier for the study was NCT01471743.

Nutrition Formula

Subjects were randomized into 2 oral supplement groups: immunonutrition group (ING) patients received immunonutrition, and standard

nutrition group (SNG) received a standard formula (Table 1). Each participant received the supplement and were instructed to drink 3 servings per day (750 mL/d) for 5 days before their surgery.

Study Procedures

All veterans with planned gastrointestinal surgeries were evaluated in the JAHVH general surgery clinic. Veterans meeting the inclusion criteria were invited to participate in the study, and informed consent was obtained. A research randomizer program assigned subjects to the groups to reach equal 1:1 randomization. Enrolled participants were provided their randomized supplement (unblinded) in the general surgery clinic and instructed on the amount of supplement to consume and date to begin taking the supplement. Participants were instructed to continue with their normal diet in addition to the supplement. No additional nutrition education was provided. Participants were asked to keep track of their daily supplement intake. Patients in both groups also used preoperative bowel preparations when indicated.

At the time of enrollment, presurgical comorbidities, anthropometric data, and nutrition status parameters were obtained. Postoperatively, study personnel interviewed each patient about formula consumption and tolerance. Thirty days postoperatively, patient demographics, surgical characteristics (eg, surgery, operative time, blood loss), nutrition risk screening (NRS 2002) score, diet/enteral orders, days spent NPO, days in the hospital or in the ICU, and complications (eg, wound infection, abscess, sepsis, pneumonia, urinary tract infection, intestinal fistula, ileus, or anastomotic leakage) were collected from the electronic health record.

Statistical Analysis

The primary outcome measure was overall postoperative complication rate and postoperative infection rate. Based on reviews of similar studies available at the time of protocol development, it was assumed that a postoperative infection rate of 38% in the SNG and 15% in the ING would indicate treatment efficacy. A sample size of 54 patients in each group would provide a Type I error level $\alpha = .05$ and a power of 80%. A total of 108 patients enrolled in the study. Chi-square analysis was used to determine this primary outcome measure.

Secondary outcomes (mean number of complications, hospital days, NPO (nothing by mouth) days, and ICU days) were evaluated with Mann Whitney *U* test because of violation of assumptions for the *t* test. All *P* values were 2-tailed and statistical significance was accepted at $P < .05$ with clinical significance accepted at $P < .10$. Analysis for intention to treat (ITT) and per protocol are provided for outcome measures. For the ITT analysis, multiple imputation (last observation carried forward) was used. Sensitivity analysis found that the data were missing at random. SPSS software version 21.0 (Chicago, IL) was used for statistical analysis.

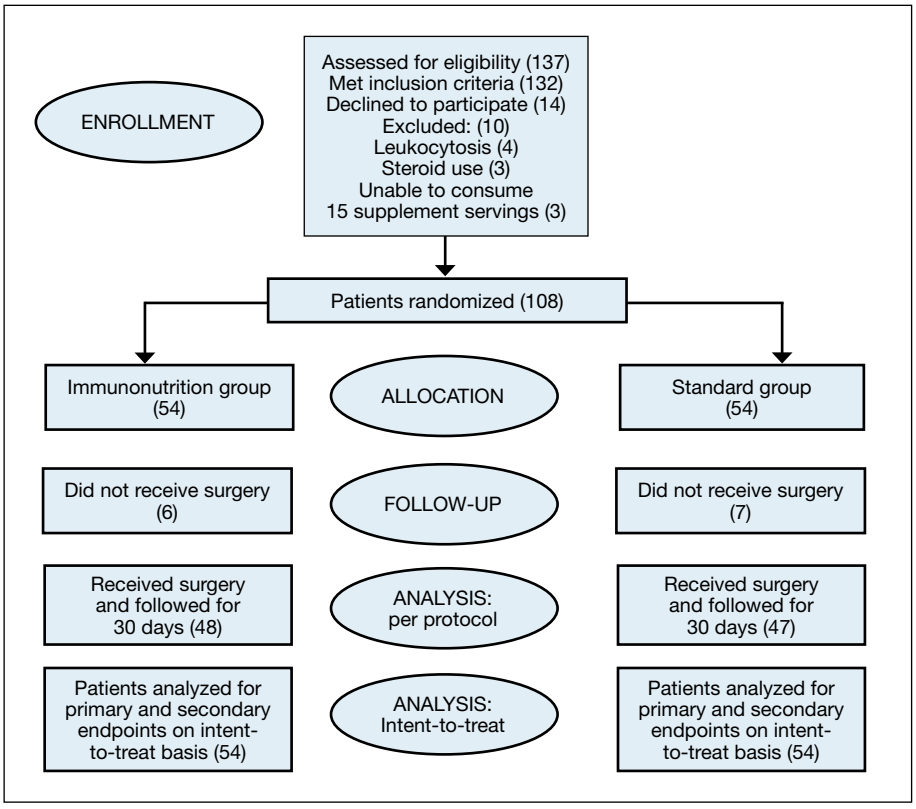
TABLE 2
Patient's Pre-Operative Demographics and Surgical Characteristics

Characteristics	Immuno-nutrition Group	Standard Nutrition Group	*P*
No.	54	54	
Sex, male/female	52/2	49/5	.24
Race, white/black/other	44/9/1	44/8/2	.82
Age, mean (SD), y	64.5 (8.7)	63.4 (10.1)	.56
Weight, mean (SD), kg	93.8 (18.2)	92.3 (22.0)	.70
Body mass index, mean (SD)	29.3 (.8)	29.3 (0.8)	.99
Comorbidities, mean (SD)	1.6 (1.2)	1.3 (1.1)	.17
Hypertension, no. (%)	33 (61)	34 (63)	
Cardiac, no. (%)	20 (37)	11 (20)	
Diabetes, no. (%)	13 (24)	13 (24)	
Liver disease, no. (%)	9 (17)	2 (4)	
Renal disease, no. (%)	6 (11)	3 (6)	
Nutrition risk screening score, no. (%)			.19
NRS 0 or 1	14 (26)	15 (28)	
NRS 2 or 3	40 (74)	39 (72)	
Primary resection, no. (%)			.09
Colon	30 (55)	26 (48)	
Rectal	7 (13)	10 (18)	
Stomach	5 (9)	2 (4)	
Pancreas	1 (2)	9 (16)	
Esophagus	5 (9)	3 (6)	
Liver	3 (6)	3 (6)	
Other	3 (6)	1 (2)	
Operative time, mean, min	249.5	294.4	.06
Blood loss, mean, mL	199.0	265.5	.11
Supplements consumed, mean	12.9	12.9	.75

RESULTS

During the study period, 137 patients were assessed for eligibility (Figure). An ITT as well as a per-protocol analysis was reviewed by the

FIGURE
Study Screening and Allocation



authors and presented to the hospital nutrition committee before making protocol decisions. A full review of all enrolled study subjects (including those who did not receive actual supplementation) was evaluated for factors that could influence bias from dropped treatment. However, the authors also wanted to evaluate treatment efficacy for only those who received supplementation; therefore, a per protocol analysis was reviewed. Both analyses are included. For the ITT analysis, 54 subjects in each group were analyzed. Six participants in the ING and 7 in the SNG did not receive surgical intervention, respectively. As a result, 47 SNG and 48 ING participants were included in the per-protocol analysis.

The sample was predominately white and male, which is consistent with the veteran population. There were no statistical differences for baseline patient or surgical characteristics between the groups (Table 2). The mean (SD) number of comorbidities was slightly higher in the ING compared with those of the SNG, 1.6 (1.2) vs 1.3 (1.1), respectively. In addition, there was a trend (P = .06) of longer operative time in the SNG (mean 294.4 minutes) compared with that of the ING (mean 249.5 minutes). There was no difference in supplemental intake between the groups and an overall adherence rate of 86% in both groups (Table 2). A total of 41 participants in the ING consumed ≥ 10 servings in 5 days vs 35 in the SNG.

There was a significant difference (P = .09) in the surgical procedures completed. There was only 1 pancreatic surgery completed in the ING and 9 pancreatic surgeries completed in the SNG.

Primary Outcomes

The overall rate of complications differed between the groups (Table 3). The percentage of subjects who experienced any type of complication was significantly higher (P = .03) in the SNG (52%) than it was in the ING (31%). The rate of infectious complications also was higher (P = .12) in the SNG (33%) compared with that in the ING (20%). The ITT and per-protocol analysis found higher numbers of complications for incidence of ileus, anastomotic leak, postoperative wound infection, pneumonia, urinary tract infections, sepsis, and death in the SNG vs the ING. There was no difference in incidence of intestinal fistula or abdominal abscess.

Given the large number of colorectal procedures, a separate per-protocol analysis included 37 patients from ING and 36 patients in the SNG (Table 4). The results are comparable with the original data analysis and indicated a higher total number of complications: 57.6% in the SNG compared with 36.4% in the ING (P = .08). Infectious complications were similar to the full analysis with 33.3% in the SNG and 21.2% in ING. Although the colorectal analysis was not planned and therefore underpowered, the authors felt it was appropriate to review because of the significant difference in surgical procedures completed.

Secondary Outcomes

The ITT analysis found that overall number of hospital days was slightly higher in the

ING compared with that of the SNG, 9.4 vs 9.3 days, respectively. In the per-protocol analysis there were 1.3 fewer hospital days for those who received immunonutrition (P = .059). No significant differences were found between the groups in the number of days spent in the ICU or number of days NPO (Table 3). Death within 30 days postoperative was twice as high for those in the SNG vs ING, with no deaths in the per-protocol analysis for those in the ING.

The colorectal analysis found 8.5 hospital days for ING patients vs 10.0 days for SNG patients, (P = .08). There were no deaths in the ING and 1 death in the SNG for colorectal procedure patients.

DISCUSSION

Surgery is traumatic to healthy patients with or without cancer. Patients with cancer who receive surgical intervention might be at an even higher risk for complications because of altered metabolic pathways, nutritional deficiencies, and depressed immune function.[13] Meta-analyses of immunonutrition studies conducted over the past 2 decades have come to different conclusions regarding the benefit of immunonutrition in the elective gastrointestinal cancer surgery population.[3,5,18] Although practice guidelines from the American Society of Parenteral and Enteral Nutrition and the European Society of Parenteral and Enteral Nutrition recommend routine use of immune-modulating formulas in surgical oncology patients, there is still some debate about the optimal timing, dose, individual formula constituents, and populations that will benefit.[2,25] Earlier studies evaluating the economics of immunonutrition have shown significant cost savings related to reduction in length of stay and decrease in infectious complications even after accounting for the extra cost of the formula.[26,27] More recent economic analyses confirmed these cost savings showing a savings of about $1,000 to $2,500 per patient with higher savings when immunonutrition was given preoperatively.[28,29]

For practitioners treating veterans with cancer, good stewardship of federal dollars and optimal outcomes are important considerations before implementing new therapies. Therefore, JAHVH set out to evaluate whether standard oral nutrition supplementation would be as effective as the higher cost immunonutrition supplementation in cancer patients receiving elective surgical procedures.

TABLE 3
Outcomes for Total Sample

Variables	Intent-to-Treat		Per-Protocol	
	ING (n = 54)	SNG (n = 54)	ING (n = 48)	SNG (n = 47)
Subjects with infections, No. (%)	11 (20)	18 (33)[a]	9 (19)	14 (30)[a]
Subjects with complications, No. (%)	17 (31)	28 (52)[b]	14 (29)	24 (51)[b]
Total complications, mean	1.0	1.4[c]	0.5	0.9[c]
Ileus, No.	11	17	8	14
Intestinal fistula, No.	5	5	2	1
Anastomotic leak, No.	5	8	3	4
Postoperative wound infection, No.	5	8	2	4
Abdominal abscess, No.	10	10	7	7
Pneumonia, No.	5	7	0	3
UTI, No.	3	5	0	2
Sepsis, No.	4	7	1	4
Death within 30 d, No.	3	6	0	2
Days admitted, mean	9.4	9.3	8.2	9.51[d]
Days NPO, mean	4.9	5.3	4.0	5.0
Days in ICU, mean	2.5	3.0	1.8	2.8

Abbreviations: ICU, intensive care unit; IMG, immunonutrition group; NPO, nothing by mouth; SNG, standard nutrition group; UTI, urinary tract infection.

[a]P = .12.
[b]P = .029.
[c]P = .032.
[d]P = .059.

Rates of Complications

In this study, favorable effects of immunonutrition were found on total postoperative complications and number of hospital days. The total number of patients who experienced complications was 39% lower in the ING than it was in SNG in the ITT analysis and 37% lower in the colorectal per-protocol analysis. These rates are similar to the 48% lower rate Braga and colleagues found in their study in patients with colorectal cancer who received 5 days of preoperative immunonutrition.[21] Because more than half of the patients in this study had colorectal cancer, the group is comparable to the Braga and colleagues study population. The overall supplement adherence rate was 86%, which was slightly lower than the 90% adherence rate that Braga and colleagues found. Lower consumption rates might have been a factor in not achieving a greater therapeutic benefit for infectious complications. Some studies suggest a therapeutic goal intake of greater than two-thirds of the prescribed

TABLE 4
Per-Protocol Results for Colorectal Sample Only

	Per-Protocol Results	
	Immunonutrition Group (n = 37)	Standard Nutitrition Group (n = 36)
Demographics		
Sex, male/female	36/1	31/5
Age, mean, y	65.3	62.9
Weight, mean, kg	95.7	93.3
Body mass index, mean	29.6	30.0
Comorbidities, mean, No.	1.7	1.2
Nutrition risk screening score.		
NRS 1-2 No. (%)	10 (27.4)	13 (35.8)
NRS 3-4 No. (%)	27 (73)	23 (63.9)
Supplements consumed, mean	12.5	12.7
Outcomes		
Subjects with infections, No. (%)	7 (21.2)	11(33.3)
Subjects with complications, No. (%)	12 (36.4)	19 (57.6)[a]
Total complications, mean	0.54	1.03[b]
Death within 30 d, No.	0	1
Days admitted, mean	8.5	10.0[a]
Days NPO, mean	3.8	4.9
Days in intensive care unit, mean	1.5	2.3

Abbreviations: NPO, nothing by mouth; NRS, nutrition risk screening.
[a]*P* = .08.
[b]*P* = .054.

amount.[10,30] In the present study, 70.4% of the ING and 83% of the SNG met that recommended therapeutic goal, which is more than Hübner colleagues reported in their study (53% of the ING and 60% in the SNG meeting therapeutic intake goal).

Okamoto and colleagues also reported a much lower complication rate in gastric cancer patients who received immunonutrition (13.3%) compared with that of those receiving an isoenergetic formula (40%).[11] The group receiving immunonutrition in the Okamoto and colleagues study had 4 times fewer infectious complications than did the standard group (*P* = .039), and a contributing reason might be that they supplemented for 7 days preoperatively. Similar to the current study's results, Giger-Pabst and colleagues and Hübner and colleagues did not find any significant difference in infectious complications.[10,30] Important notes of comparison include a low adherence rate in the study conducted by Hübner and colleagues and the lower dose of immunonutrition used by Giger-Pabst and colleagues who used 3 days of preoperative supplementation, which may not be long enough to promote the tissue benefits of immunonutrition.

Although, the current study did not find any statistically significant difference in infectious complications, the SNG experienced 1.8 times more infections than did the ING, which indicates that immunonutrition support may be clinically beneficial. Based on previous literature and the results of this study, the authors speculate that at least 5 days of intake of the study immunonutrition formula could positively affect outcomes.

The authors suspect that the added arginine and fish oil in the immunonutrition product act synergistically as therapeutic ingredients to shift toward a preoperative anti-inflammatory prostaglandin environment while providing exogenous arginine to possibly prevent or correct a conditionally essential need for arginine that would promote adequate nitric oxide production. Another crucial factor is that the a priori power analysis was looking at a 38% complication rate in the SNG and only 15% complication rate in the ING, which generated a sample size of 108 participants. The post hoc power analysis indicates that this study is underpowered based on the complication rates, which could be a reason for insignificant infectious complications.

The benefits of immunonutrients are still being studied. Future studies in a controlled surgical setting could determine whether immunonutrition has a clinical outcome effect on operative time and surgical blood loss. A challenge for the investigators was to decide whether the difference in operative time and blood loss was a surgical characteristic or a clinical outcome. The positive impact of immunonutrients on tissue perfusion and cell integrity have been shown in other studies to reduce tissue inflammation and alter gene expression, which could affect how tissues respond to surgical insults.[10,11] Because JAHVH is a teaching institution and multiple surgeons are involved with the patients, this question will continue to be unresolved. Future research may want to consider controlling for variability in surgical technique and perioperative protocols to evaluate this as a clinical outcome.

Limitations

Several limitations of this trial need to be addressed. Although the design of the study was a randomized controlled trial, it was an unblinded, single-center study with a small sample size. Surgeons were not aware of which supplement each subject had received; however, researchers took no measures to ensure the surgeons were blinded. To minimize bias, 2 investigators evaluated the records for complication rates to confirm consistency, and any

discrepancies were resolved by a third investigator. Although adherence was evaluated, it was patient-reported, and lab testing was not conducted to ensure that tissues were loaded with therapeutic amounts of immunonutrients or to determine baseline levels of nutrient intake, which could show a nutrient response curve.

The use of other nutritional supplements, such as vitamins, probiotics, or additional fatty acids were not monitored, and the study formulas differed in protein and fiber content, which could have impacted the overall nutrient intake and affected the primary outcomes. Another limitation includes the variety of surgeons used over the period of the study. At a teaching institution, it is not feasible to limit the number of surgeons performing surgery.

Additionally, the study period was 5 years, and there have been changes in fasting times, medications, and bowel preparation over the course of that period, which could not be accounted for. Postoperative immunonutrition was not provided in this study based on the limited evidence available when the protocol was initiated. However, since that time, evidence supports and encourages postoperative therapy and might have proven beneficial to the patients. Data were not collected on the need for additional surgery within the study period, which could significantly impact outcomes.

Future studies would benefit from a longer postoperative monitoring period because this study looked only at the 30-day postoperative period. Last, randomization did not account for equal allocation of surgical procedures, and a higher number of pancreatic surgeries in the SNG could account for the higher complication rate found in that group. Although the colorectal analysis is underpowered, the results continue to show beneficial results with the use of immunonutrition.

CONCLUSION

The primary purpose of this research was to determine whether the veteran population would benefit from an immunonutrition preoperative protocol as recommended by several practice guidelines. The results of the initial analysis and the colorectal analysis were presented to the hospital interdisciplinary nutrition committee who voted that a preoperative immunonutrition protocol will be implemented at JAHVH because of the high comorbidity rate experienced by veterans.

AUTHOR DISCLOSURES

The authors report no actual or potential conflicts of interest with regard to this article.

DISCLAIMER

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