ISSN: 1607-8322, e-ISSN: 2220-5799 **Anaesthesia, Pain & Intensive Care**
Vol 28(6); December 2024 DOI:10.35975/apic.v28i6.2602

ORIGINAL RESEARCH **ANESTHESIA FOR ENT SURGERY**

Perioperative supplementation with immunonutrition and its impact on surgical outcome and pain in oral cavity or mandibular tumor resection; A randomized controlled study

Tamer A Kotb [1], Samia Y El Baradie [2], Maha Abdelwahab [3], Sayed M Abed [4*], Samar Saeed [5], Mohamed H Zedan [6], Taher Thabet [7]

Author affiliations:

1. Tamer A. Kotb, Anesthesiology, Surgical Intensive Care & Pain Relief Department, National Cancer Institute, Cairo University, Cairo, Egypt; E-mail: Tamerkotb5@gmail.com

2. Samia Y. El Baradie, Anesthesiology, Surgical Intensive Care & Pain Relief Department, National Cancer Institute, Cairo University, Cairo, Egypt; E-mail: elbaradie58@hotmail.com

3. Maha Abdelwahab, Anesthesiology, Surgical Intensive Care & Pain Relief Department, National Cancer Institute, Cairo University, Cairo, Egypt; E-mail: maha.mohamed.nci@gmail.com

4. Sayed M. Abed, Anesthesiology, Surgical Intensive Care & Pain Relief Department, National Cancer Institute, Cairo University, Cairo, Egypt; E-mail: Sydabed2020@outlook.com

5. Samar Saeed, Anesthesiology, Surgical Intensive Care & Pain Relief Department, National Cancer Institute, Cairo University, Cairo, Egypt; E-mail: samar.saed.ramadan1988@gmail.com

6. Mohamed H. Zedan, Surgical Oncology Department, National Cancer Institute, Cairo University, Cairo,Egypt; E-mail: mhzedan@gmail.com

7. Taher Thabet, Anesthesiology, Surgical Intensive Care & Pain Relief Department, National Cancer Institute, Cairo University, Cairo, Egypt; E-mail: dr.taherthabet@gmail.com

Correspondence: Sayed M. Abed, **E-mail:** Sydabed2020@outlook.com; **Telephone:** +01226806532

ABSTRACT

Objectives: The current research investigated the impact of adding immunonutrition mixture before surgery to the standard feeding regimen for patients undergoing oral cavity or mandibular tumor resections.

Methodology: This randomized double-blind controlled trial comprised 176 cancer patients undergoing resection of oral cavity or mandibular tumors. Participants were evenly divided into two groups: Group I (Immunonutrition group) got perioperative supplementation with omega-3 taken orally and L-Alanyl-L-Glutamine (Dipeptiven) administered via intravenous infusion, in addition to the standard feeding. Group C (Control group) received only standard feeding, which included a caloric distribution of protein 10-35%, fats 20-35%, and carbohydrates 45-65%. Both groups were followed for the primary outcome, set as wound infection and duration of hospital stays. The secondary outcome, included total dose of intraoperative opioids, postoperative VAS at 0 h ,4 h, 8 h and 12 h, intraoperative hemodynamics and any postoperative complications e.g., fever, neutropenia and pneumonia.

Results: A significant difference in postoperative complications in both groups was observed; wound infection was (1.14% vs. 7.95%) for Groups I and C respectively (P = 0.03). Group I was significantly lower in fever and neutropenia vs Group C (P < 0.01). No significant difference in hospital stay, intraoperative opioid consumption, Postoperative VAS score at 0 h ,4 h, 8 h and 12 h and intraoperative HR, MAP, SBP, DBP in both groups.

Conclusion: Immunonutrition has a substantial effect in lowering the rate of postoperativecomplications. However, it does not affect decreasing postoperative pain or length of hospital stay.

Keywords: Perioperative Supplementation; Immunonutrition, Outcome; Pain; Oral CavityTumors; Mandibular Tumors

Citation: Kotb TA, El Baradie SY, Abdelwahab M, Abed SM, Saeed S, Zedan MH, Thabet T. Perioperative supplementation with immunonutrition and its impact on surgical outcome and pain in oral cavity or mandibular tumor resection; a randomized controlled study. Anaesth. pain intensive care 2024;28(6):982-989; DOI: 10.35975/apic.v28i6.2602

Received: May 23, 2024; **Revised:** October 14, 2024; **Accepted:** October 26, 2024

1. INTRODUCTION

Malnutrition is a critical issue that detrimentally affects patients' quality of life and recovery process, leading to higher morbidity rates, extended hospital stays, increased mortality, and elevated healthcare costs.[1] The causes of malnutrition are complex and varied. In developed countries, disease is frequently identified as the primary cause, with both acute and chronic illnesses potentially leading to or exacerbating malnutrition. Older adults are particularly susceptible to nutritional deficiencies and malnutrition.[2]

Malnutrition is common in individuals diagnosed with cancer, with rates varying from 20% to more than 70%. Surprisingly, a significant proportion ranging from 10 to 20 percent of mortality among cancer patients can be attributed to malnutrition rather than the illness. Early diagnosis of malnutrition is essential to counteract weight loss, improve patients' quality of life, minimize treatment toxicity and psychological distress, and reduce the risk of morbidity and mortality.[3]

Malnutrition has been linked to unfavorable postoperative outcomes, such as increased mortality, higher rates of infection, wound complications, prolonged length of stay (LOS), and elevated hospitalization costs.[4]

The term "immunonutrition" refers to the ability to influence immune system activity through nutrients interferences. This concept can be applied to various scenarios where the provision of specific nutrients is utilized to alter inflammatory or immune responses.[5]

Postoperative pain arises from a blend of inflammatory and neuropathic mechanisms, both contributing to hyperalgesia. Fast-track protocols prioritize effective analgesia with minimal side effects, empowering patients to function autonomously and facilitating earlier discharge.[6] An essential component of Enhanced Recovery After Surgery (ERAS) protocols is effective pain control[7] Omega 3 (O3FA) supplement correlated with weight loss before surgery, reduced pain post operation, lower C-reactive protein levels after surgery as well.[8]

Perioperative amino acid solutions containing glutamine exhibit anti-inflammatory properties in surgical patients, consequently reducing the incidence of pain.[9,10]

This research investigated the impact of incorporating preoperative immunonutrition, consisting of oral omega-3 supplementation and L-Alanyl-L-Glutamine (Dipeptiven) administered via intravenous infusion, to the standard nutritional support for individuals head and neck undergoing resection surgery for mandibular or oral cavity tumor.

2. METHODOLOGY

This prospective comparative controlled randomized study involved 176 cancer patients aged (18-60) years, both sexes, with American Society of Anesthesiologists (ASA) physical status I or II, underwent tumor resection of oral cavity or mandible, and with (18.5 - 24.9) BMI and serum albumin levels above 3 g/dL. The study was conducted from December 2019 to August 2023 after receiving approval from the Ethical Committee of Cairo University Hospitals (AP 1912-30102) and registration on clinicaltrials.gov (NCT06339372). Informed written consent was obtained from all participating patients.

Exclusion criteria encompassed patients classified as ASA physical status III or IV, those aged over 60 or under 18, individuals with serum albumin levels below 3 g/dL, pre-existing severe malnutrition, known medication allergies, patients currently using hypnotics, sedatives, tranquilizers, steroids, NSAIDs, or chronic pain therapy, and individuals scheduled for surgeries exceeding 4 hours, such as free flap procedures.

The patients were divided into two equal groups and assigned at random: Group I (immunonutrition group) got perioperative supplementation with omega-3 orally and L-Alanyl-L-Glutamine (Dipeptiven) administered via intravenous infusion (immunonutrition mixture) in addition to standard feeding. Group C (control group) got only basic feeding with caloric distribution consisting of protein 10-35%, fats 20-35%, carbohydrates 45-65%.[11, 12]

All patients underwent comprehensive assessments, including medical history evaluations and laboratory investigations such as alanine transaminase (ALT), aspartate, aminotransferase (AST), complete blood

Table 1: Demographic data, duration of surgery, cancer type, preoperative serum albumin and albumin difference of the studied groups

Variable		Group I (n = 88)	Group C (n = 88)	P
Age (years)		40.59 ± 11.36	39.05 ± 9.79	0.335
Sex	**Male**	44 (52.38)	42 (47.73)	0.763
	Female	44 (50)	46 (52.27)	
BMI (kg/m^2)		22.01 ± 0.86	21.63 ± 1.76	0.067
Duration of surgery (min)		118.81 ± 11.01	118.35 ± 10.61	0.781
Cancer type	**Tongue mass WLE**	14(15.91)	18(20.45)	0.493
	Hard palate mass resection	21(23.86)	13(14.77)	
	Alveolar margin massresection	21(23.86)	20(22.73)	
	Hemiglossectomy+_ submental flap	23(26.14)	22 (25)	
	Retromolar mass resection	4 (4.55)	10 (25)	
	Buccal mucosa massresection	2 (2.27)	3 (11.36)	
	Mouth floor mass resection	3 (3.41)	2 (3.41)	
Preoperative serum albumin (g/dl)		4.01 ± 0.25	4 ± 0.27	0.863
Albumin difference		2 (2.27)	1 (1.14)	0.560

Data presented as mean ± SD or frequency (%). Group I (Immunonutrition group), Group C (control group), BMI: Bodymass index, WLE: wide local excision.

count (CBC), international normalized ratio (INR), partial thromboplastin time (PTT), prothrombin time (PT), albumin, bilirubin, creatinine, urea, and fasting blood sugar (FBS). Additionally, electrocardiograms (ECGs) were performed.

Both groups spent five days in the hospital prior to surgery. The Group I received standard feed plus the immunonutrition mixture L-Alanyl-L-Glutamine

(Dipeptiven) at a dose of 1 gm/kg/day through intravenous infusion and Omega-3 at a dosage of 3 gm

daily orally. The control group only received standard feed without supplements. The nutrition support team determined that the usual feeding diet's calorie distribution should be 45–50% carbohydrates, 20–35% fats, and 10–35% protein.[12, 13]

Upon arrival at the holding area, the patient received midazolam 0.02 mg/kg IV before being transferred to the operating room. Postoperative assessors were blinded to the type of nutrition regimen.

Upon arrival in the operating room, pulse oximetry, electrocardiography, and non-invasive blood pressure monitoring was done. Induction of general anesthesia followed a standardized regimen comprising 2 mg/kg propofol and 1 µg/kg fentanyl. Atracurium at 0.5 mg/kg, preceded by 1.5 mg/kg of lidocaine 2%, facilitated endotracheal intubation. The end-tidal carbon dioxide levels were meticulously maintained within 35-40 mmHg range. Anesthesia maintenance included isoflurane at a minimum alveolar concentration (MAC) of 1.2, with additional atracurium at 0.1 mg/kg administered as necessary. Morphine 0.1 mg/kg was given if tachycardia (exceeding 20% of the initial preinduction value) and an increase in mean arterial blood pressure (more than 20% of baseline value) suggested insufficient analgesia. After completion of the procedure, extubation was performed and the patient was moved to the PACU. The total intraoperative opioid dosage was documented for both groups. Visual analogue scale (VAS) was utilized for assessing pain following surgery.

In our investigation, we employed rescue analgesics to address varying levels of pain. Ketorolac at a dose of 30 mg intravenously was administered as a single dosage if VAS score was less than 4. In cases of severe pain, morphine 3 mg/kg IV was used if the VAS score exceeded 4.

2.1. Postoperative:

Both study groups were monitored for several outcomes, including the incidence and severity of pain by VAS, as well as the occurrence of wound infections, neutropenia, or fever. Additionally, we assessed differences in serum albumin levels, length of hospital stays and opioid consumption.

The primary outcome was set as wound infection and duration of hospital stays. The secondary outcome, which is total dose of intraoperative opioids, postoperative VAS at 0, 4, 8 and 12 hr, intraoperative hemodynamics and other postoperative complications as fever, neutropenia and pneumonia.

2.2. Sample size:

The sample size was determined based on the findings of Oguz M et al. in 2007, which investigated the impact of L-alanine-L-glutamine (Gln) on the rate of complications

following surgery and duration of hospitalization in patients undergoing colorectal cancer surgery. Their study revealed a significantly lower incidence of wound infection in the intervention group compared to the control group.[12]

The proportion of individuals with wound infection in the intervention group was 0.0175, while it was 0.1154 in the control group. To detect a similar effect size with an acceptable alpha error of 0.05 and a test power of 80%, using one-tailed testing and an allocation ratio of 1 (N1 = N2), the minimum required sample size was calculated to be 88 patients per group, totaling 176 patients. G*Power version 3.0.10 software was utilized for sample size calculation.

2.3. Statistical analysis

Statistical analysis was conducted using SPSS v26 (IBM Inc., Chicago, IL, USA). The normality of data distribution was assessed using the Shapiro-Wilks test and histograms. Quantitative parametric variables were expressed as mean and standard deviation (SD) and compared between groups using unpaired Student's t-test. Quantitative non-parametric data were presented as median and interquartile range (IQR) and analyzed using the Mann-Whitney U test. Qualitative variables were presented as frequency and percentage (%) and analyzed using the Chi-square test or Fisher's exact test when appropriate. A two-tailed p-value < 0.05 was considered statistically significant.

3. RESULTS

From an initial of 187 eligible patients assessed, 176 patients completed the study after 11 were excluded (4 didn't meet criteria, 7 declined participation). The remaining 176 participants were then randomly allocated into two comparative groups of 88 patients each for further analysis (Figure 1).

Table 2: Inra-operative opioids requirements of the studied groups

Parameter	Group I (n = 88)	Group C (n = 88)	P
Patients required Ketorolac 30 mg	5 (5.68)	9 (10.23)	0.265
Patients required fentanyl	*85 (96.59)*	*84 (95.45)*	*1*
Patients required fentanyl and morphine	3 (3.41)	4 (4.55)	
Fentanyl consumption (µg)	74.92 ± 6.46	76.02 ± 5.32	0.218
Morphine consumption (mg)	7.67 ± 0.29	7.5 ± 0.35	0.519

Data are presented as mean ± SD or frequency (%). Group I (Immunonutrition group), Group C.

Table 3: VAS was insignificantly different at 0h ,4h, 8h and 12h between both groups: Post operative VAS of the studied patients

Time	Group I (n = 88)	Group C (n = 88)	P
0 h	0 (0 - 0)	0 (0 - 0)	0.082
4 h	0 (0 - 1)	0 (0 - 1)	0.849
8 h	2 (1.75 - 2)	2 (1 - 2)	0.576
12 h	2 (2 - 3)	3 (2 - 3)	0.772

Data are presented as median (IQR). Group I (Immunonutrition group), Group C (control group), VAS: Visual analogue scale.

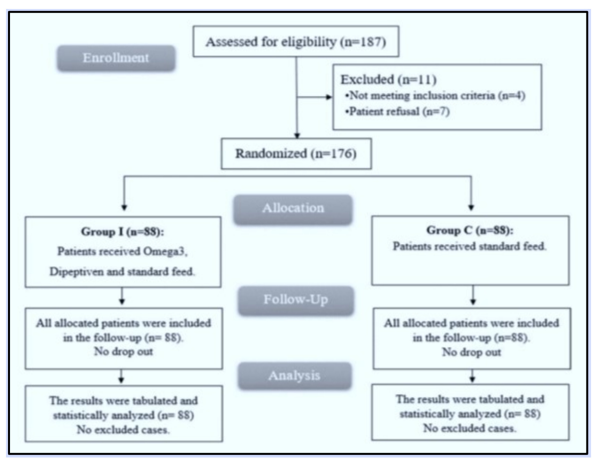

Figure 1: CONSORT flowchart of the enrolled patients.

Age, sex, BMI, cancer type, preoperative serum albumin and albumin differences from preoperative level were insignificantly different between both groups (Table).

Wound infection showed a significant difference (P = 0.03) between groups, with 1.14% in group I and 7.95% in group C (Table 4). Length of hospital stay was insignificantly different (P = 0.071). Total intraoperative opioid dose (Table 2), intraoperative HR, SBP, DBP, and MAP (starting measurement to the end of the surgery time) (Figure 2), postoperative VAS at 0 h, 4 h, 8 h, and 12 h (Table 4), and use of ketorolac as rescue analgesic (P = 0.265) were insignificantly different between groups. Preoperative serum albumin and albumin difference were also insignificantly different (Table 1). Pulmonary tract infection was insignificant (P = 1), while fever were

significantly lower in group I than C (P < 0.01) and neutropenia were significantly lower in group I than C (P < 0.01) (Table 4)

4. DISCUSSION

Malnutrition exhibits a greater incidence among the elderly compared to the younger population, and notably, among individuals grappling with advanced stages of cancer rather than its initial phases. Cancer patients who are malnourished may be treated in

hospital settings, nursing homes, or their homes; each situation may require a different approach to care. Malnutrition is documented for individuals under 60 years of age in

hospitals (30%), nursing homes (11%), and home care (23%), per a study. On the other hand, for people 60 years of age and older, the percentages are 39%, 20%, and 23%, respectively.[14, 15]

There were notable contrasts in postoperative complications between the two cohorts. Wound infections were recorded at 1.14% in Group I and 7.95% in Group C, yielding a statistically significant difference (P = 0.03). Additionally, Group I exhibited lower incidences of fever and neutropenia compared to Group C, with p-values below 0.01. However, no significant variations were observed in hospital stays for either group, nor in intraoperative opioid usage. Furthermore, postoperative pain levels, as measured by the VAS at 0 hr, 4 hr, 8 hr, and 12 hr, showed insignificant disparities between the two groups. Similarly, there were no significant discrepancies in Arterial pressure (MAP), Diastolic blood pressure (DBP), Heart rate (HR), Systolic blood pressure (SBP) concerning the groups.

On the same side Mohsen et al. [16] found no significant differences in inflammatory markers (IL-6, CRP) or hospital stay between patients receiving preoperative omega-3 supplementation versus control/placebo groups undergoing abdominal surgery, based on data from randomized controlled trials. Also, Ruiz-Tovar et al, [8] conducted a randomized prospective trial involving laparoscopic surgery patients, one group received a preoperative balanced energy high-protein formula (Control), while the other group received the same formula enriched with omega-3 fatty acids (Experimental). The Experimental group experienced reduced postoperative pain and lower C-reactive protein levels than the control group. Notably, the nutritional intervention began 10 days before surgery and continued until 8 hours before the procedure.

Another study suggested that dietary supplementation with omega-3 polyunsaturated fatty acids (PUFAs) could potentially alleviate neuropathic pain symptoms in individuals with type 2 diabetes [17]. However, this finding may differ from the current study due to the population being non-cancer patients.

For this reseach, Group (I) had significantly fewer postoperative complications than Group (C) (P < 0.01). This research indicates that immunonutritional intervention, as opposed to standard nutritional treatment, may decrease postoperative complications, notably infections. Likewise, a separate study found that pre-surgical immunonutrition reduced inflammatory markers and post-surgery infectious complications. Nevertheless, uncertainties persist regarding hospital stay duration and factors [18]. Similarly, Howes et al.[19] noticed there was mortality due to associated

Table *4*: Postoperative complications and length of hospital stay of the studied groups

Variable		Group I (n = 88)	Group C (n = 88)	P
Postoperative Complications	Wound infection	1 (1.14)	7 (7.95)	**0.03***
	Fever	0 (0)	11 (12.5)	**0.001***
	Pulmonary tract infection	4 (4.55)	5 (5.68)	1
	Neutropenia	0 (0)	11 (12.5)	**<0.001***
Length of hospital stay (days)		7.5 ± 0.61	7.76 ± 1.2	0.071

*Data are presented as frequency (%). *Significantly different as P value ≤0.05. Group I: (Immunonutrition group), Group C (control group).*

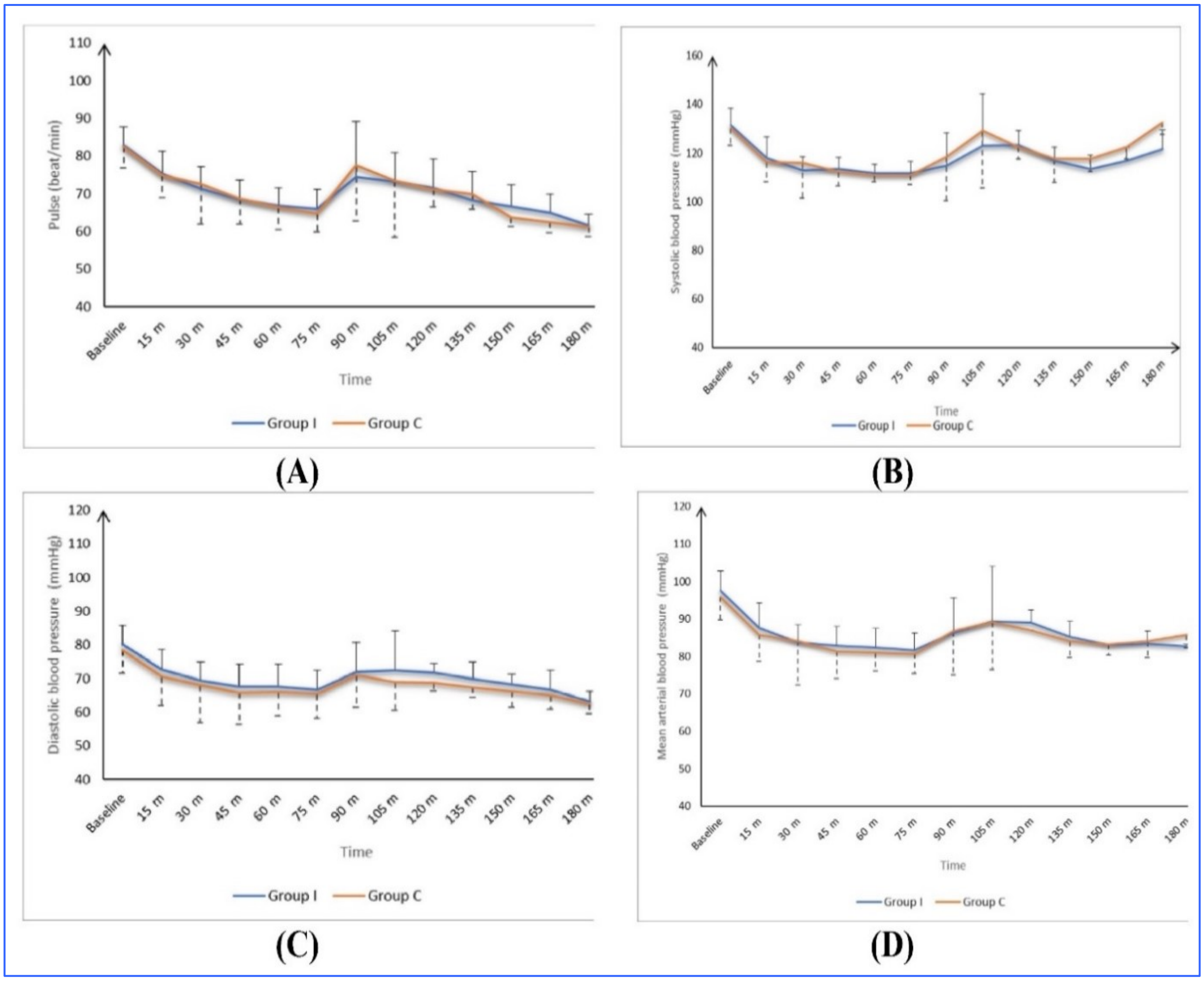

Figure 2: (A) Pulse, (B) systolic blood pressure, (C) diastolic blood pressure and (D) mean arterial blood pressure of the studied groups

risk no indication of immunonutrition's influence on other measured results. The length of hospital stay remained unaffected, and wound infection rates showed no change. However, the studies examined were often limited or had substantial biases, underscoring the necessity for more robust investigations.

Similarly, Matsui et al.[20] illustrated that Immunonutrition likely reduces postoperative complications in elective head and neck cancer surgery, notably infectious complications and hospital stays. However, it's unlikely to affect noninfectious complications, mortality, severe complications, or pneumonia rates. Compared to standard nutrition, it's improbable to increase adverse events. Subgroup analysis showed shorter hospital stays but no difference in complications or mortality.

The findings of this study align with those of Casas-Rodera et al.[21] which also illustrated no significant difference in hospital stay (LOS). Similarly, other studies utilizing the same immunonutrition (Oral Impact) in patients with head and neck squamous cell carcinoma (HNSCC) did not exhibit a notable reduction in hospital LOS.

However, Mueller et al.[13] presented contrasting results, implying preoperative immunonutrition may lessen complications in high-risk groups, showing notably shorter hospital stays, with no differences in mortality.

Furthermore, Aeberhard et al.[22] proposed that immunonutrition might improve surgical recovery in this patient group. They observed a notable decrease in wound infections post-immunonutrition implementation, with significantly shorter hospital stays (25.65 days) in immunonutrition recipients, particularly evident after its introduction, reducing confounding factors' influence on hospital duration.

Limitations of this study included that the number of participants (sample size) in the research was somewhat restricted. The investigation took place at a single location (single center). The monitoring and tracking of the patients after the initial study period lasted for a relatively brief duration of time.

5. CONCLUSION

Immunonutrition has a substantial effect on lowering of postoperative complications (e.g., wound infection, fever, pulmonary tract infection, neutropenia); however, it does not affect decreasing postoperative pain and length of hospital stay. Based on this evidence, we suggest a comprehensive nutrition management pathway to be implemented into existing clinical frameworks to improve perioperative nutrition in head and neck cancer (HNC)patients.

6. Financial support and sponsorship

The study was completed through institutional resources

7. Conflict of Interest

The authors declare no conflict of interest.

8. Author contribution

SS, MHZ, TAK, and SYE developed the original idea and the protocol, abstracted and analyzed data, wrote the manuscript. TT, MA, and SMA contributed to the development of the protocol, abstracted data, and prepared the manuscript.

9. REFERENCES

1. Benfaremo D, Pacenti N, Paterno I, Dichiara C, Galli FL, Moroncini G. Role of cognitive impairment and malnutrition as determinants of quality of life in patients with systemic sclerosis. Journal of Scleroderma and Related Disorders. 2024:23971983231224522.
2. Dent E, Wright ORL, Woo J, Hoogendijk EO. Malnutrition in older adults. Lancet. 2023;401:951-66.
3. Beirer A. Malnutrition and cancer, diagnosis and treatment. Memo-Magazine of European Medical Oncology. 2021;14:168-73.
4. Lee DU, Fan GH, Hastie DJ, Addonizio EA, Han J, Prakasam VN, et al. The clinical impact of malnutrition on the postoperative outcomes of patients undergoing gastrectomy for gastric cancer: Propensity score matched analysis of 2011–2017 hospital database. Clinical Nutrition ESPEN. 2021;46:484-90.
5. Calder PC. Immunonutrition. Bmj. 2003;327:117-8.
6. White PF, Kehlet H, Neal JM, Schricker T, Carr DB, Carli F. The role of the anesthesiologist in fast-track surgery: from multimodal analgesia to perioperative medical care. Anesth Analg. 2007;104:1380-96, table of contents.
7. Pirie K, Traer E, Finniss D, Myles PS, Riedel B. Current approaches to acute postoperative pain management after major abdominal surgery: a narrative review and future directions. Br J Anaesth. 2022;129:378-93.
8. Ruiz-Tovar J, Blanca M, Garcia A, Gonzalez J, Gutierrez S, Paniagua A, et al. Preoperative administration of Omega-3 fatty acids on postoperative pain and acute-phase reactants in patients undergoing Roux-en-Y gastric bypass: A randomized clinical trial. Clin Nutr. 2019;38:1588-93.
9. Jabłońska B, Mrowiec S. The Role of Immunonutrition in Patients Undergoing Pancreaticoduodenectomy. Nutrients. 2020;12.
10. Shu XL, Yu TT, Kang K, Zhao J. Effects of glutamine on markers of intestinal inflammatory response and mucosal permeability in abdominal surgery patients: A meta-analysis. Exp Ther Med. 2016;12:3499-506.
11. Trumbo P, Schlicker S, Yates AA, Poos M. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. J Am Diet Assoc. 2002;102:1621-30.
12. Oguz M, Kerem M, Bedirli A, Mentes BB, Sakrak O, Salman B, et al. L-alanin-L-glutamine supplementation improves the outcome after colorectal surgery for cancer. Colorectal Dis. 2007;9:515-20.
13. Mueller SA, Mayer C, Bojaxhiu B, Aeberhard C, Schuetz P, Stanga Z, et al. Effect of preoperative immunonutrition on complications after salvage surgery in head and neck cancer. J Otolaryngol Head Neck Surg. 2019;48:25.
14. Freijer K, Tan SS, Koopmanschap MA, Meijers JM, Halfens RJ, Nuijten MJ. The economic costs of disease related malnutrition. Clin Nutr. 2013;32:136-41.
15. Aaldriks AA, van der Geest LG, Giltay EJ, le Cessie S, Portielje JE, Tanis BC, et al. Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy. J Geriatr Oncol. 2013;4:218-26.
16. Mohsen G, Stroemer A, Mayr A, Kunsorg A, Stoppe C, Wittmann M, et al. Effects of Omega-3 Fatty Acids on Postoperative Inflammatory Response: A Systematic Review and Meta-Analysis. Nutrients. 2023;15.
17. Durán AM, Salto LM, Câmara J, Basu A, Paquien I, Beeson WL, et al. Effects of omega-3 polyunsaturated fatty-acid supplementation on neuropathic pain symptoms and sphingosine levels in Mexican-Americans with type 2 diabetes. Diabetes Metab Syndr Obes. 2019;12:109-20.
18. García-Malpartida K, Aragón-Valera C, Botella-Romero F, Ocón-Bretón MJ, López-Gómez JJ. Effects of Immunonutrition on Cancer Patients Undergoing Surgery: A Scoping Review. Nutrients. 2023;15.
19. Howes N, Atkinson C, Thomas S, Lewis SJ. Immunonutrition for patients undergoing surgery for head and neck cancer. Cochrane Database Syst Rev. 2018;8:Cd010954.

20. Matsui R, Sagawa M, Sano A, Sakai M, Hiraoka SI, Tabei I, et al. Impact of Perioperative Immunonutrition on Postoperative Outcomes for Patients Undergoing Head and Neck or Gastrointestinal Cancer Surgeries: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Ann Surg. 2024;279:419-28.

21. Casas-Rodera P, Gómez-Candela C, Benítez S, Mateo R, Armero M, Castillo R, et al. Immunoenhanced enteral nutrition formulas in head and neck cancer surgery: a prospective, randomized clinical trial. Nutr Hosp. 2008;23:105-10.

22. Aeberhard C, Mayer C, Meyer S, Mueller SA, Schuetz P, Stanga Z, et al. Effect of preoperative immunonutrition on postoperative short-term outcomes of patients with head and neck squamous cell carcinoma. Head Neck. 2018;40:1057-67.

