IJHRMLP
ISSN 2394–806X (Print), ISSN 2454-5139 (Online)

International Journal of Health Research and Medico-Legal Practice

RESEARCH PAPER

Role of immune nutrients in postoperative outcome in patients undergoing gastrointestinal anastomosis

Manuscript ID: 568

Das PP[1], Barman K[2], Malakar B[3]

Address for correspondence:

[1]Professor
Mobile: +919864063284
[2]Post Graduate Trainee (Corresponding Author)
Mobile: +916901572352
Email: kangkanabarman2012@gmail.com
[3]Registrar
Department of Surgery
Gauhati Medical College and Hospital, Guwahati-785001, Assam, India

Article received: 20-11-2022
Received (revised): 12-12-2022
Editorial approval: 15-12-2022
Checked for plagiarism: Yes
Peer-reviewed: Yes
Peer review comments: Six
Editor who approved:
Prof. (Dr.) Narendra N Ganguly

Background and aims: The science of immunonutrition involves enhancing immunity through macro or micronutrients. The present study aims to determine whether postoperative immunonutrition could improve the clinical outcomes in a patient undergoing gastrointestinal anastomosis. Materials and methods: The hospital-based prospective interventional study involved patients undergoing emergency hand-sewn gastrointestinal anastomosis from July 2021 to Augustc 2022, in the department of General Surgery. The sample was selected using systematic random sampling. Every 4th patient was included in the control group and treated with a conventional approach, while every 5th patient was given immunonutrition in the postoperative period and included in the intervention group. Written informed consent was taken from all the participants. Various postoperative parameters were studied and compared between the two groups using appropriate tests of significance. A p-value<0.05 is significant. Results: The rates of reduction in the anastomotic leak, wound infection and mean hospital stay in the intervention vs control group were 10% vs 32% (p-value<0.05), 12.5% vs 35% (p-value<0.05) and 8 days vs 10 days (p-value<0.05) respectively. The mean postoperative day-2 and day-6 serum albumin levels in control vs intervention groups were 3.04mg/dl vs 3.47 mg/dl (p-value<0.05) and 3.02mg/dl vs 3.64mg/dl (p-value<0.05), respectively. Conclusion: The study showed a substantial reduction in rates of anastomotic leak, postoperative infections and length of hospital stay following administration of immunonutrition formula with glutamine, arginine, omega-3 fatty acids and nucleotides in postoperative patients undergoing gastrointestinal anastomosis.

Keywords: Immunonutrition; glutamine; arginine; omega-3 fatty acids; postoperative complications.

***Cite this article**: Das PP, Barman K, Malakar B. Role of immune nutrients in postoperative outcome in patients undergoing gastrointestinal anastomosis. Int J Health Res Medico Leg Prae 2022 July-Dec;8(2):28-35. Doi: 10.31741/ijhrmlp.v8.i2.2022.5*

INTRODUCTION

The science of using macro or micronutrients to manipulate immunity positively is known as immunonutrition (IMN) or nutritional immunology.[1] It is generally known that immunity is impaired by malnutrition, but this effect can be reversed by achieving nutritional balance. The two main objectives of immunonutrition are improving the host immune response or reducing the increased inflammatory response.[2] Immunonutrition goes a step further and uses specific nutrients at levels higher than those typically found in food to augment immunity. It has been demonstrated that the immunonutrients arginine, glutamine, omega-3 fatty acids, and nucleotides have immunomodulatory effects.[3-7] Enteral delivery is the preferred method in most clinical investigations; however, parenteral delivery is also possible.[1]

In our study, gastrointestinal anastomosis is crucial for various conditions, including bowel obstruction, incarcerated hernias, benign and malignant tumours of the small and large bowel, etc. Anastomotic leak, which causes peritonitis, abscesses, fistulas, necrosis, stricture development, etc., after bowel anastomosis and affects about 1.3 to 15% of patients, is a severe complication that is frequently linked to higher morbidity and mortality rates and more extended hospital stays.[8-11] Other often observed consequences include

chest infection, an intra-abdominal abscess, and wound infections. The patient's overall health, the suturing method, the suture material used, the existence of concurrent infection, vascular compromise, and many other factors are all linked to these complications.

Major abdominal surgeries lead to post-traumatic dysregulation of the immune system, characterized by the suppression of immune functions.[12,13] Various immunonutrients can modulate the immune system and improve host defence mechanisms after significant surgery. In our setup, this study was undertaken to determine whether postoperative immune nutrition could improve the clinical outcomes in gastrointestinal anastomosis patients.

The present study aimed to compare the effect of immunonutrients supplementation (both oral and parenteral) in the postoperative period after gastrointestinal anastomosis in preventing postoperative complications compared to the conventional approach. The study's primary objective was to investigate whether supplementation with immunonutrients in the postoperative period is beneficial for patients after gastrointestinal anastomosis in reducing various complications, including anastomotic leak, wound infection, intra-abdominal abscess formation, chest infection, noninfectious complications, mortality and length of hospital stay.

MATERIALS AND METHODS

It was a hospital-based prospective interventional study involving emergency patients undergoing hand-sewn gastrointestinal anastomosis done by a group of surgeons with experience of more than 20 cases of bowel anastomosis during the study period from July 2021 to August 2022, under the Department of Surgery, Gauhati Medical College and Hospital (GMCH), Guwahati. Written informed consent was taken from all the participants. The study approval was obtained from the Institutional Ethics Committee of GMCH.

Sample selection: A total number of 243 patients had undergone gastrointestinal anastomosis during the study period, out of which exclusion criteria excluded 41 patients due to refusal to consent to participate in the study. The remaining 202 patients were randomized by systematic random sampling. Every 4th and 5th patient was selected irrespective of age and sex. Every 4th patient was selected as a control and treated with a conventional approach, while every 5th patient was given immunonutrition in the postoperative period and considered as an intervention. After randomization total of 80 patients were selected into two groups, i.e., intervention and control, each having 40 patients.

Inclusion criteria: Patients older than 12 years who have undergone emergency hand-sewn gastrointestinal anastomosis during the study period in the department of Surgery, GMCH, were included.

Type of patients: All emergency cases undergoing hand-sewn gastrointestinal anastomosis.

Surgeon criteria: Surgeon with an experience of more than 20 bowel anastomoses.

Type of anastomosis: Hand-sewed 4-layered bowel anastomosis.

Type of suture: Polyglactin 3-0 (Johnson and Johnson made) for the mucosal anastomosis and silk 3-0 (Johnson and Johnson made) for the seromuscular anastomosis.

Exclusion criteria: Patients with ASA (American Society of Anaesthesiologists) Grade III (patients with severe systemic disease), IV (a severe systemic disease with a constant threat to life) and V (moribund patients unlikely to survive 24 hours or more without operation). Re-laparotomies were excluded from the study. Also, the efficacy and safety of immunonutrients supplementation are yet to be adequately studied in the pediatric age group, in patients with renal failure and pregnant females; immunosuppressed patients and patients with acute or chronic renal failure were also not included in the study.

The 40 patients comprising the intervention group were given parenteral formulations of immunonutrients until orally allowed. Then immunonutrients enriched powder containing glutamine, arginine and omega three fatty acids dissolved in water was started twice a day, and immunonutrient supplementation was continued up to the 7th postoperative day.

The control group comprising 40 patients was kept on intravenous maintenance fluids containing normal saline and Hartmann's solution until orally allowed. The nasogastric tube was removed, and feed was started orally depending on the patient's clinical condition and the appearance of bowel sounds as done conventionally.

The parameters studied in the postoperative period were an anastomotic leak, intra-abdominal abscess, wound infection, chest infection, noninfectious complications, pre and postoperative immune-metabolic parameters, length of hospital stay and mortality. The anastomotic leak is usually present between 5-7 days postoperatively. An urgent CT scan diagnoses an anastomotic leak with a contrast of the abdomen and pelvis, which shows the presence of extraluminal contents. Patients with intra-abdominal abscesses generally present with pain abdomen with fever and raised WBC counts. USG of the whole abdomen can

detect the collection, but the CT scan with contrast can give a definitive diagnosis. It can also be confirmed by percutaneous drainage or after re-laparotomy. Wound infections were diagnosed by the presence of purulent exudate in the surgical wound with positive bacterial culture. Abnormal chest radiographs revealing lung infection in the larger airways (bronchitis) or, the smaller air sacs (pneumonia) were used to diagnose chest infections. Noninfectious complications included haemorrhage, deep vein thrombosis, pulmonary embolism, heart failure, atelectasis, paralytic ileus, wound dehiscence etc.

Data were collected from patient record files, haematological and biochemical examination reports for complete haemogram, sugar, urea, creatinine, LFT, mainly albumin level, CRP, and electrolytes levels. Radiological reports of straight x-ray chest and x-ray abdomen were also evaluated, and USG and CECT of the abdomen was done as and when required. The data collected were recorded on a pre-structured proforma for data tabulation and analysis.

Statistical analysis: Data were entered into a Microsoft excel spread sheet and then analyzed using software SPSS 20.0.1 and Graph Pad Prism version 5. Data were expressed in terms of mean and standard deviation for numerical variables and the count for categorical variables. Student's independent sample's t-test was applied to compare normally distributed numerical variables between groups; unpaired proportions were compared by Chi-square test or Fisher's exact test, as appropriate. For statistical significance, a p-value<0.05 is considered to be significant.

RESULTS

The demographic profile of the intervention and control group shows that there was no significant difference in age (p-value>0.05), weight (p-value>0.05), gender (p-value>0.05) and comorbidities between the two groups. Thus, both groups were comparable in terms of demographic distribution (Table 1).

Table 1 Demographic profile of intervention and control group

Variables	Intervention group (N=40)	Control group (N=40)	P-value
Age#	46.30(15.64)	45.22 (14.83)	0.75
Weight (Kg)#	66.37 (10.00)	67.12 (10.90)	0.74
Gender			
Male	21	17	0.50
Female	19	23	
Comorbidities			
Absent	29	27	0.80
Present	11	13	

#expressed as mean (standard deviation)

Anastomotic leak was found in 32% of patients in the control group compared to 10% in the intervention group. This showed a significant positive effect of immunonutrition in reducing anastomotic leaks (p-value<0.05). Surgical wound infection was also substantially reduced (p-value<0.05) after giving immunonutrition postoperatively. The study showed wound infection in 35% of patients in the control group compared to 12.5% in the intervention group. The intra-abdominal abscess was observed only in 5 patients. The Chi-square test revealed no significant effect of immunonutrition in reducing intra-abdominal abscess formation. Respiratory tract infections were found in 22.5% of patients in the control group compared to 7.5% in the intervention group. However, the two groups observed no significant difference in respiratory tract infection. Also, no significant decrease in noninfectious complications was found between the two groups (Table 2).

Table 2 Comparison of postoperative parameters between interventions and control group

Parameters	Control group (N=40)	Intervention group (N=40)	P-value
Anastomotic leak			
Absent (n=63)	27	36	0.029
Present (n=17)	13	4	
Surgical wound infection			
Absent (n=61)	26	35	0.036
Present (n=19)	14	5	
Abdominal abscess			
Absent (n=75)	36	39	0.36
Present (n=5)	4	1	
Respiratory tract infections			
Absent (n=68)	31	37	0.11
Present (n=12)	9	3	
Noninfectious complication			
Absent (n=68)	30	33	0.58
Present (n=12)	10	7	

Table 3 shows no significant difference in the two groups preoperative serum albumin levels, as the mean albumin level in the intervention group was 3.47±0.53 while in the controls, it was 3.45±0.85. However, a significant decline (p-value<0.05) in serum albumin levels was noted postoperatively in controls compared to the intervention group. The control group observed a significant reduction in preoperative mean serum albumin levels from 3.45g/dl to 3.03g/dl six days post-operation. While in the intervention group, the serum albumin levels were noted to obtain a steady rise in the post the operative period. Immunonutrition supplementation seemed to have a positive effect on increasing the postoperative albumin level.

Table 3 Mean pre and postoperative albumin levels in intervention and control group

Mean serum albumin level	Intervention group (N=40)	Control group (N=40)	P-value
Preoperative	3.47 (0.53)	3.45 (0.65)	0.85
postoperative day- 2	3.47 (0.62)	3.05 (0.65)	0.004
postoperative day- 6	3.64 (0.48)	3.03 (0.47)	0.0001

Out of 80 total participants, three deaths were recorded during treatment, among whom 2 (5%) were from the intervention group, and one (2.5%) was from the control group. There was no significant effect of immunonutrition noted over the mortality rate.

The median length of hospital stay in the intervention group was eight days, while it was ten days in the control group. The mean length of stay in the hospital was significantly lower in the intervention group signifying a positive effect of immunonutrition on the recovery rate of the patients (Table 4).

Table 4 Comparison of hospital stay duration between the two groups

Hospital stay duration	Mean	Standard deviation	Min-max	Median	P-value
Intervention group (N=40)	8.92	2.56	6.0-16.0	8.0	0.011
Control group (N=40)	10.45	2.72	7.0-19.0	10.0	

DISCUSSION

The essential purpose of immunonutrition is the ability to modify immune system activity through the use of specific nutrients. The nutrients that are currently most frequently used in clinical investigations are arginine, glutamine, omega-3 fatty acids, and nucleotides. The present hospital-based interventional study aimed to evaluate the effect of immunonutrients supplementation after gastrointestinal anastomosis in preventing postoperative complications and to compare the results with that of the conventional approach. All the patients undergoing gastrointestinal anastomosis in the study period of 1 year, i.e., from July 2021 to August 2022, were observed and randomized by systematic random sampling. After randomization, 40 patients were included in the study group and given immunonutrition postoperatively, and 40 were treated conventionally.

Anastomotic leak was found in 32% of patients in the control group against 10% of patients in the intervention group. The difference was statistically significant (p-value <0.05), indicating immunonutrients supplementation in the postoperative period is beneficial in preventing anastomotic leak after gastrointestinal anastomosis. The findings are in support of other similar studies.[14,15]

In this study, it is found that patients treated with immunonutrients in the postoperative period have significantly fewer (p-value<0.05) wound infections (12%) as compared to those treated conventionally (35%). Various other studies reported similar observations.[14,16-19]

The mean length of hospital stay in the control group was 10.45 days compared to 8.9 days in the intervention group. Postoperative immunonutrients supplementation showed a significant decrease (p-value<0.05) in the duration of hospital stay, signifying a quicker recovery. This finding was at par with various systematic reviews.[20-21]

The mean serum albumin levels after six days postoperative period was 3.02mg/dl in the control group compared to 3.64mg/dl in the intervention group. The difference was found to be highly significant (p-value<0.0001). The finding is in agreement with another similar study.[22]

Compared to 17.5% in the intervention group, 25% of patients in the control group had noninfectious complications. Not much significant improvement is noticed in preventing noninfectious complications after administering immunonutrients. A similar study done outside India is in concordance with this present study.[23]

One patient in the control group lost their life during treatment in the postoperative period compared to 2 patients in the intervention group. There was no significant effect of immunonutrition on the mortality rate. Various other studies also failed to establish any significant association between immunonutrition andmortality.[14,16] A more extensive sample size study may give a better picture of mortality rates.

Mucosal lesions and increased intestinal permeability after major abdominal surgeries can cause the transfer of bacteria and endotoxins and start an inflammatory immune response, which significantly impacts the progression of infections-related problems.[12,13,24,25] Enteral nutrition supports the gut-associated lymphoid tissue (GALT) and supplies nutrients to the intestinal mucosa, which may lessen bacterial translocation.[26,27] Postoperative administration of immune-enhancing formulae has been proven in several early trials to promote gut health and favourably modify the post-surgical immune-suppressive and inflammatory response.[17,28-31] In agreement with the earlier studies, the present study also showed that administration of immunonutrition formula supplemented with glutamine, arginine, omega-3 fatty acids, and nucleotides in the postoperative period to pa-

tients undergoing gastrointestinal anastomosis significantly improves clinical outcomes, as evidenced by a substantial reduction in the anastomotic leak and postoperative infections by improving immunity and hence decreasing the length of hospital stay.

CONCLUSION

The study showed that administering immunonutrition formula supplemented with glutamine, arginine, omega-3 fatty acids, and nucleotides in the postoperative period to patients undergoing gastrointestinal anastomosis significantly improves clinical outcomes. Postoperative immune-nutrient supplementation may considerably reduce the rates of various complications, especially anastomotic leaks, wound infection and the length of stay in the hospital.

Acknowledgements: We acknowledge all the participants who participated in the study for their help and support in carrying out the research work.

Ethical Clearance: Taken.

Financial Support: None declared.

Conflict of interest: No conflict of interest associated with this work.

Contribution of Authors: We declare that this work was done by the authors named in this article, and the authors will bear all liabilities about claims relating to the content of this article.

REFERENCES

1. Beisel WR. History of nutritional immunology: introduction and overview. J Nutr 1992 Mar;122(3 Suppl):591-6. doi: 10.1093/jn/122.suppl_3.591.
2. Calder PC. Immunonutrition. BMJ 2003 Jul 19;327(7407):117-8. Doi: 10.1136/bmj.327.7407.117.
3. Suchner U, Heyland DK, Peter K. Immune-modulatory actions of arginine in the critically ill. Br J Nutr 2002 Jan;87 Suppl 1:S121-32. doi: 10.1079/bjn2001465.
4. Andrews FJ, Griffiths RD. Glutamine: essential for immune nutrition in the critically ill. Br J Nutr 2002 Jan;87 Suppl 1:S3-8. doi: 10.1079/bjn2001451.
5. Calder PC. Dietary modification of inflammation with lipids. Proc Nutr Soc 2002 Aug;61(3):345-58. Doi: 10.1079/pns2002166.
6. Grimble GK, Westwood OM. Nucleotides as immunomodulators in clinical nutrition. CurrOpin Clin NutrMetab Care 2001 Jan;4(1):57-64. doi: 10.1097/00075197-200101000-00011.
7. Suchner U, Kuhn KS, Fürst P. The scientific basis of immunonutrition. Proc Nutr Soc 2000 Nov;59(4):553-63. Doi: 10.1017/s0029665100000793.
8. Matthiessen P, Hallböök O, Andersson M, Rutegård J, Sjödahl R. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis 2004 Nov;6(6):462-9. doi: 10.1111/j.1463-1318.2004.00657.x.
9. Parc Y, Frileux P, Schmitt G, Dehni N, Ollivier JM, Parc R. Management of postoperative peritonitis after anterior resection: experience from a referral intensive care unit. Dis Colon Rectum 2000 May;43(5):579-87; discussion 587-9. doi: 10.1007/BF02235565.
10. Hedrick TL, Sawyer RG, Foley EF, Friel CM. Anastomotic leak and the loop ileostomy: friend or foe? Dis Colon Rectum 2006 Aug;49(8):1167-76. Doi: 10.1007/s10350-006-0602-6.
11. Brunicardi FC, Anderson D, Billiar TR, Dunn DL, Hunter JG, Pollock RE. Schwartz's manual of surgery. McGraw Hill Professional; 2006 Apr 7.
12. Chieveley-Williams S, Hamilton-Davies C. The role of the gut in major surgical postoperative morbidity. Int Anesthesiol Clin 1999 Spring;37(2):81-110. doi: 10.1097/00004311-199903720-00006.
13. Kanwar S, Windsor AC, Welsh F, Barclay GR, Guillou PJ, Reynolds JV. Lack of correlation between failure of gut barrier function and septic complications after major upper gastrointestinal surgery. Ann Surg 2000 Jan;231(1):88-95. Doi: 10.1097/00000658-200001000-00013.
14. Marano L, Porfidia R, Pezzella M, Grassia M, Petrillo M, Esposito G, et al. Clinical and immu-

nological impact of early postoperative enteral immunonutrition after total gastrectomy in gastric cancer patients: a prospective randomized study. Ann Surg Oncol 2013 Nov;20(12):3912-8. Doi: 10.1245/s10434-013-3088-1.

15. Yildiz SY, Yazicioglu MB, Tiryaki Ç, Çiftçi A, Boyacioglu Z. The effect of enteral immunonutrition in upper gastrointestinal surgery for cancer: a prospective study. Turk J Med Sci 2016 Feb 17;46(2):393-400. doi: 10.3906/sag-1411-102.
16. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. JAMA 2001 Aug 22-29;286(8):944-53. doi: 10.1001/jama.286.8.944.
17. Gianotti L, Braga M, Fortis C, Soldini L, Vignali A, Colombo S, et al. A prospective, randomized clinical trial on perioperative feeding with an arginine-, omega-3 fatty acid-, and RNA-enriched enteral diet: effect on host response and nutritional status. JPEN J Parenter Enteral Nutr 1999 Nov-Dec;23(6):314-20. Doi: 10.1177/0148607199023006314.
18. Zheng Y, Li F, Qi B, Luo B, Sun H, Liu S, et al. Application of perioperative immunonutrition for gastrointestinal surgery: a meta-analysis of randomized controlled trials. Asia Pac J Clin Nutr 2007;16 Suppl 1:253-7.
19. Klek S, Szybinski P, Szczepanek K. Perioperative immunonutrition in surgical cancer patients: a summary of a decade of research. World J Surg 2014 Apr;38(4):803-12. doi: 10.1007/s00268-013-2323-z.
20. Zhang Y, Gu Y, Guo T, Li Y, Cai H. Perioperative immunonutrition for gastrointestinal cancer: a systematic review of randomized controlled trials. Surg Oncol 2012 Jun;21(2):e87-95. doi: 10.1016/j.suronc.2012.01.002.
21. Wong CS, Aly EH. The effects of enteral immunonutrition in upper gastrointestinal surgery: A systematic review and meta-analysis. Int J Surg 2016 May;29:137-50. doi: 10.1016/j.ijsu.2016.03.043.
22. Yildiz SY, Yazicioglu MB, Tiryaki Ç, Çiftçi A, Boyacioglu Z. The effect of enteral immunonutrition in upper gastrointestinal surgery for cancer: a prospective study. Turk J Med Sci 2016 Feb 17;46(2):393-400. doi: 10.3906/sag-1411-102.
23. Braga M, Gianotti L, Radaelli G, Vignali A, Mari G, Gentilini O, et al. Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial Arch Surg. 1999 Apr;134(4):428-33. doi: 10.1001/archsurg.134.4.428.
24. Poulin E. Prophylactic nutrition. Can J Surg 1991 Dec;34(6):555-9.
25. Ward N. Nutrition support to patients undergoing gastrointestinal surgery. Nutr J 2003 Dec 1;2:18. Doi: 10.1186/1475-2891-2-18.
26. Wilmore DW, Smith RJ, O'Dwyer ST, Jacobs DO, Ziegler TR, Wang XD. The gut: a central organ after surgical stress. Surgery 1988 Nov;104(5):917-23.
27. Martindale RG, Cresci G. Preventing infectious complications with nutrition intervention. JPEN J Parenter Enteral Nutr 2005 Jan-Feb;29(1 Suppl):S53-6. Doi: 10.1177/01486071050290S1S53.
28. Kemen M, Senkal M, Homann HH, Mumme A, Dauphin AK, Baier J, et al. Early postoperative enteral nutrition with arginine-omega-3 fatty acids and ribonucleic acid-supplemented diet versus placebo in cancer patients: an immunologic evaluation of Impact. Crit Care Med 1995 Apr;23(4):652-9. Doi: 10.1097/00003246-199504000-00012.
29. Braga M, Gianotti L, Vignali A, Carlo VD. Preoperative oral arginine and n-3 fatty acid supple-

mentation improves the immunometabolic host response and outcome after colorectal resection for cancer. Surgery 2002 Nov;132(5):805-14. doi: 10.1067/msy.2002.128350.

30. Senkal M, Kemen M, Homann HH, Eickhoff U, Baier J, Zumtobel V. Modulation of postoperative immune response by enteral nutrition with a diet enriched with arginine, RNA, and omega-3 fatty acids in patients with upper gastrointestinal cancer. Eur J Surg 1995 Feb;161(2):115-22.
31. Braga M, Gianotti L, Cestari A, Vignali A, Pellegatta F, Dolci A, et al. Gut function and immune and inflammatory responses in patients perioperatively fed with supplemented enteral formulas. Arch Surg 1996 Dec;131(12):1257-64; discussion 1264-5. doi: 10.1001/archsurg.1996.01430240011001.

***