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ORIGINAL ARTICLE

Preoperative immunonutrition in patients at nutritional risk: results of a double-blinded randomized clinical trial

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BACKGROUND/OBJECTIVES: To evaluate the impact of preoperative immunonutrition (IN) on postoperative morbidity in patients at risk of malnutrition undergoing major gastrointestinal (GI) surgery.

SUBJECTS/METHODS: The combination of malnutrition and major GI surgery entails high morbidity. The Nutritional Risk Score (NRS) reliably identifies patients who need preoperative nutrition; the optimal nutritional formula for these patients still needs to be defined. In all, 152 patients with a NRS $\geqslant 3$ and undergoing elective major GI surgery were randomized between IN or isocaloric-isonitrogenous nutrition (ICN) given for 5 days preoperatively. Patients and caregivers were blinded for the allocated intervention. Thirty days complication rate was the primary endpoint. Infections, length of hospital stay and compliance were considered as secondary outcomes.

RESULTS: Overall, 145 patients were available for analysis; the 73 patients in the IN group matched well with the 72 ICN patients with regards to patient's and surgical characteristics. In all, 39 IN and 33 ICN patients experienced a total of 48 and 50 postoperative complications, respectively ($P = 0.723$). Both groups did not differ significantly concerning infectious (13 vs 9) complications. Independent risk factors for overall complications were malignant disease (odds ratio (OR) = 4.304; confidence interval (CI) 1.317–14.002) and operative time (OR = 1.004; CI 1.000–1.008).

CONCLUSION: In patients at nutritional risk, complications, infections and hospital stay after major GI surgery were comparable regardless of preoperative supplementation with IN or ICN.

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Keywords: abdominal surgery; immunonutrition; complications; compliance

INTRODUCTION

Careful perioperative risk reduction in patients undergoing major gastrointestinal (GI) surgery is an evolving key concept to decrease postoperative morbidity rates, which range from 35 to 50%.[1–3] Many risk factors, such as repeated radio-chemotherapy regimens, pre-existing co-morbidities and increased age can hardly be influenced, and rigorous selection is the only possibility to identify patient at risk. In contrast, malnutrition, which affects up to 40% of surgical patients,[4–6] represents an ideal target for perioperative risk reduction, as its screening and treatment are easily performed. The nutritional risk score 2002 (NRS) represents a reliable tool for identification of malnourished patients and control of perioperative nutritional support.[7,8]

There is increasing evidence that perioperative nutrition improves outcome after major surgery; therefore, it is recommended as indispensable adjunct of care for patients undergoing major GI interventions.[9–12] Nutritional formulas containing immune-modulating agents, for example, glutamine, arginine, n-3 fatty acids and RNA have proven particularly effective in reducing postoperative complications, infections and length of hospital stay.[12–14] Nevertheless, the vast majority of studies have been performed in high-volume centers with a particular interest in perioperative nutrition. It remains unclear whether the pivotal role of perioperative immunonutrition (IN) can be confirmed in a heterogenous patient group at nutritional risk undergoing hepatobiliary, upper GI and colorectal surgery.

The aim of this prospective randomized trial was to assess the clinical benefit of preoperative IN compared with standard enteral nutrition on postoperative complication rates in patients at nutritional risk scheduled for major GI surgery.

SUBJECTS AND METHODS

Study design

The current study was designed as a single-center, prospective, double-blinded, not placebo-controlled, parallel-group superiority study with balanced randomization (1:1). We tested the effects of two different preoperative enteral nutritional formulas on overall complication rates in surgical patients undergoing elective major GI surgery.

The study protocol was approved by the institutional ethics committee (#20 407), and all patients gave written informed consent before enrollment. This trial was conducted in accordance with the Good Clinical Practice Guidelines and registered as NCT00512213 (clinicaltrial.gov trial #).

Patients and setting

All patients undergoing elective GI surgery at the University Hospital of Lausanne (CHUV), a tertiary referral center in Switzerland, underwent routine preoperative nutritional screening by use of the NRS. Only patients undergoing major GI surgery who had a NRS $\geqslant 3$ were considered eligible for the present trial.

The NRS is a multimodal screening tool that integrates patient's nutritional status, the severity of the disease or intervention and age[7,8] (Supplementary appendix S1). Validation studies have proven the reliability

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of the NRS to identify patients at risk who benefit from perioperative nutritional interventions.[5,6] Patients with a NRS $\geqslant 3$ are considered to be 'at nutritional risk' to develop postoperative complications.[6–8]

Major GI surgery was defined as any esophageal, gastric, hepatic, pancreatic, intestinal and colorectal resection for benign or malignant disease and including other intraabdominal open or laparoscopic procedures lasting more than 2 h.

Exclusion criteria were age below 18 years, emergency procedure, incapability to consume clear fluids and inability to obtain informed consent.

Implementation

Patients were enrolled at preadmission consultation by the operating surgeons, and written informed consent was obtained. Allocation consignment was performed by an independent study nurse. She dispersed either immuno-enhanced oral nutrition (IN) or isocaloric iso-nitrogeneous standard oral feed (INC) according to the online randomization procedure. (Randomizer, Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Austria; Url: http://www.randomizer.at/).

Intervention/enteral regimens

Patients were randomly assigned to receive 5 days of preoperative oral supplementation three times a day of (I) an immune-enhanced oral nutrition (IN) (Oral Impact, Novartis/ Nestlé Nutrition, Vevey, Switzerland) or (II) an isocaloric iso-nitrogeneous standard oral feed (ICN) (Meritene, Novartis/ Nestlé Nutrition). The composition of the two diets is displayed in Table 1. Preoperative nutritional supplementation was scheduled to end the day prior to the surgical intervention.

In both groups, oral nutrition was mostly started on the first postoperative day according to institutional guidelines that adheres largely to recently published guidelines on enhanced recovery after surgery.[1,15]

Allocation concealment and blinding

IN and ICN consisted of powder form of identical appearance. They were delivered by the manufacturer in identical opaque bags labeled as 'A' or 'B'. Each patient was given a pre-packed sack containing a shaker and 15 'A' or 'B' bags by the independent study nurse. Patients, care providers, outcome assessors and data analysts were kept blinded to the allocation.

Outcomes/study endpoints

Outcomes were measured based on an intention-to-treat analysis. The primary endpoint was overall complication rate. Postoperative complications (30-day morbidity) were graded according to its severity. A validated therapy-orientated complication score was used.[16] Complications were reported as number of complications. Hence, more than one complication per patient was possible. Major complications were defined as complication grade 3–5 according to the Zürich classification.[16] Secondary endpoints were infectious complications, intensive care unit and hospital stay, compliance and postoperative stress response.

Infectious complications included wound infections, intraabdominal abscess, pneumonia, urinary tract infection and sepsis.

Postoperative stress response was evaluated by measurements of interleukin (IL)-6 and IL-10 (measured 2 h after surgery and at day 1 and 2 postoperatively) and by the presence of postoperative systemic immune response syndrome (SIRS), measured 2 h after surgery and three times a day at day 1, 2 and 3 postoperatively. SIRS was diagnosed clinically by at least two of the following: (I) body core temperature $>38^{\circ}$ or $<36\,^{\circ}C$; (II) heart rate >90 beats/min; (III) respiratory rate >20 breaths/min or $P_aCO_2<32$ mm Hg; and (IV) white blood cell count $>12\,000$ or <4000 /mm^3.[17]

Table 1. Composition of the two diets (per dose)

Component	*IN*	*ICN*
Weight (g)	74	79.7
Energy (kcal)	303	303
Proteins (g)	16.8	15.5
Arginine (g)	3.8	0.51
Lipids (g)	8.3	2
Omega-3-FA (g)	1	0.02
RNA (g)	0.45	0
Carbohydrates (g)	40.2	57.7

Abbreviations: ICN, isocaloric-isonitrogenous nutrition; IN, immunonutrition; FA, fatty acids.

Patient's compliance was recorded by asking the patient how many nutritional supplements he had drunk preoperatively (ranging from 1 to 15 bags). To objectively assess patient's compliance with the allocated nutritional supplementation, serum arginine and glutamine levels were measured in 30 patients, both before and after nutritional intervention.

Demographic information included gender, age, body mass index, Charlson co-morbidity index[18] and the American Society of Anesthetists class. In addition, diverse nutritional parameters and pertinent serum biochemistry values were carefully recorded.

Two pre-specified subgroups of patients were determined: (I) non-colorectal surgical patients and (II) compliant patients drinking at least 10 of the 15 allocated nutritional supplements. Subgroup analyses were performed for descriptive purposes only, as the study was not designed to have sufficient power for subgroup analyses.

Statistics

For sample size calculation, we assumed overall complication rates of 25% for IN and 50% for ICN.[13,19] Adopting a power of 0.9, a two-sided type I error of 0.05, the required sample size was 75 procedures per group, given an anticipated dropout rate of 20%.

Descriptive statistics are reported as median (range) or mean ($\pm$ s.d.) for continuous variables and absolute or relative frequencies for categorical variables. Fisher's exact test was used for the comparison of categorical variables. Student's *t*-test and Mann–Whitney U-test were employed to compare normal and non-normal continuous variables, respectively. An odds ratio including the 95% asymptotic confidence interval (CI) was calculated for the binary endpoint of overall complications. Adjustment for confounding factors was performed using multiple logistic regression models. Univariate risk factors with a $P\leqslant 0.1$ entered the model and $P<0.05$ was the criterion for remaining in it. All tests were two-tailed. A *P*-value of less than 0.05 was considered significant.

Data analysis was performed with Prism 5.2 (GraphPad Software, Inc., La Jolla, CA, USA) and the Statistical Package for the Social Sciences (SPSS 14.0, Inc., Chicago, IL, USA).

The trial was performed and data are presented in accordance to the recently updated CONSORT statement.[20]

RESULTS

Between October 2007 and September 2010, 310 patients were assessed for eligibility and 152 of them were enrolled in the trial. There were 83 men and 62 women, with a mean age of 67 ($\pm$ 14) years. In all, 73 patients receiving IN and 72 patients receiving ICN entered final analysis (Figure 1). Both groups matched well with regards to demographic parameters and operation characteristic (Table 2, Supplementary appendix S2). Of note, although all patients included in the present study were attributed at least 2 points because of the type of surgery, 24 patients receiving IN and 21 ICN patients had a NRS $\geqslant 3$ only because of increased age of >70 years. The remaining patients (49 and 51 patients, respectively, $P=0.720$) fulfilled the inclusion criteria because of an impaired nutritional status. There were 60/73 patients in the IN and 63/72 patients in the ICN group with malignant disease, respectively. Overall, 22 upper GI, 62 hepatobiliary, 46 colorectal and 15 miscellaneous procedures were performed (Supplementary appendix S2). In the IN group, 18 procedures were performed laparoscopically, compared with 12 in the ICN group ($P=0.306$).

Main outcome

Overall, 39 IN and 33 ICN patients (53% vs 46%; $P=0.408$) experienced a total of 48 and 50 postoperative complications (Supplementary appendix S3), respectively ($P=0.723$) (Table 3). There were no significant differences between the two groups with regards to major complications (16 in the IN vs 18 in the ICN group, $P=0.699$)

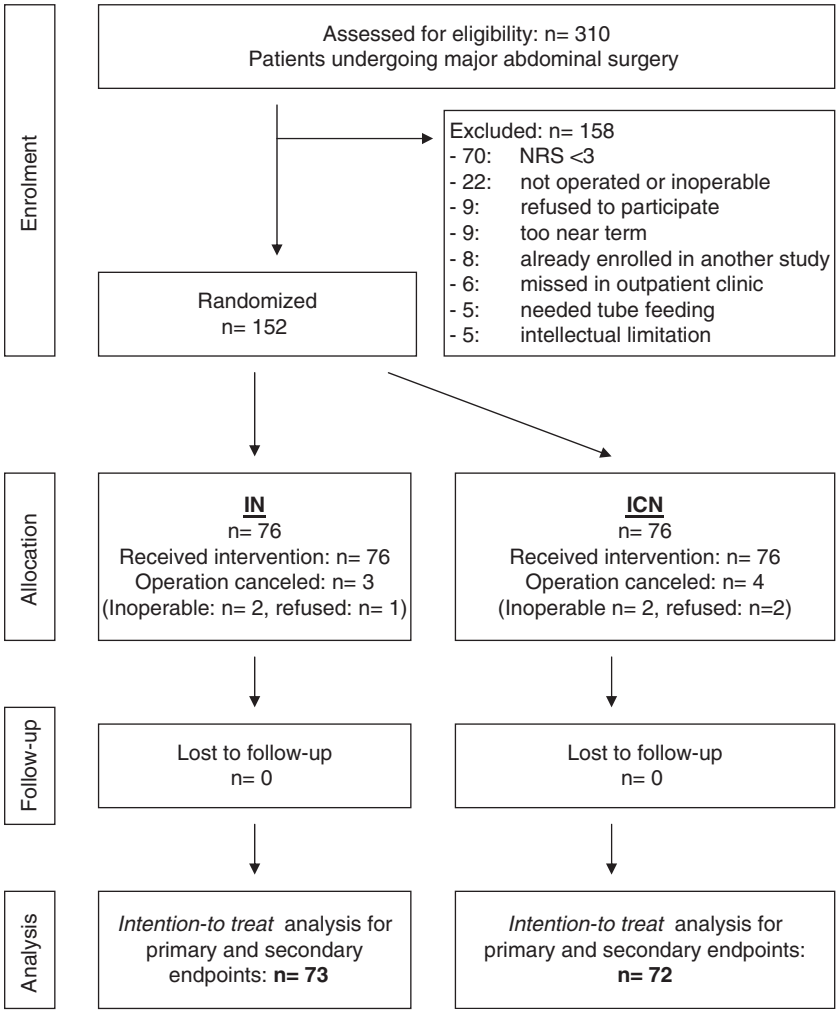

Figure 1. Study flow chart. CONSORT diagram. Double-blind randomized trial comparing IN and ICN before major gastrointestinal surgery.

Table 2. Comparison of demographics and operation characteristics between IN and ICN groups

	IN N = *73*	*ICN* N = *72*	P
Sex ratio (M/F)	45/28	38/34	0.316
Age (years)[a]	67 (± 15)	68 (± 13)	0.532
BMI (kg/m^2)[a]	24 (± 4.2)	23 (± 4.0)	0.090
Albumin pre-OP (g/l)[a]	42 (± 4.3)	41 (± 5.3)	0.350
Pre-albumin pre-OP (g/l)[a]	0.23 (± 0.07)	0.24 (± 0.08)	0.388
ASA ⩾3	22	22	0.859
Charlson (0/1–2/>2)	7/42/24	10/33/29	0.355
Malignant/benign	60/13	63/9	0.488
Colorectal/other[b]	28/45	20/52	0.217
OR time (min)[a]	264 (± 101)	288 (± 102)	0.169
Transfusions[c]	24	31	0.233
Epidural analgesia[c]	56	63	0.129
Post-OP antibiotics[c]	15	17	0.693

Abbreviations: ASA, American Society of Anesthetists; BMI, body mass index; ICN, isocaloric-isonitrogenous nutrition; IN, immunonutrition; OP, operative; OR, operation room. [a]Means are given with s.d. [b]Supplementary appendix S1. [c]Number of patients having transfusions, epidural analgesia or postoperative antibiotics, respectively.

Table 3. Preoperative IN and ICN before major gastrointestinal surgery: outcomes and secondary descriptive analyses

	IN N = *73*	*ICN* N = *72*	P
Patients with complications	39	33	0.408
Total number of complications	48	50	0.723
Class I	6	3	0.494
Class II	22	27	0.383
Class III a/b	6/6	2/8	0.275/0.587
Class IV a/b	4/0	8/0	0.245
Class V (mortality)	4	2	0.681
Infectious complications	13	9	0.488
ICU stay (days)	1.3	1.8	0.365
Hospital stay (days)	19	16	0.345
Re-admissions (number of)	4	6	0.533

Abbreviations: ICU, intensive care unit; ICN, isocaloric-isonitrogenous nutrition; IN, immunonutrition.

Secondary outcomes

While there were 13 infectious complications in the IN group, another 9 infectious complications occurred in the ICN group ($P = 0.488$).

Mean intensive care and hospital stay for the IN group and ICN group were 1.3 (± 3.1) vs 1.8 days (± 3.7) ($P = 0.365$) and 16 (± 11) vs 19 (± 17) days ($P = 0.345$), respectively.

Compliance with the nutritional intervention was comparable between the two groups. In all, 39 (53%) IN patients and 43 (60%) ICN patients were able to drink at least 2/3 of the allocated nutritional supplements ($P = 0.617$). Of note, the actual intake of

the allocated nutritional supplements remained below manufacturer's current recommendations in 43% of the included patients.

Serum arginine levels were measured before and after nutritional intervention in 33 consecutive patients (16 IN and 17 ICN patients). Compliance in both subgroups was comparable (10 and 13 patients taking at least 10 supplements, respectively; $P=0.456$). Mean preoperative arginine levels did not differ significantly between IN and ICN patients (51 vs 62 μmol/l, respectively; $P=0.122$). A significant increase in serum arginine was measured in IN patients after nutritional intervention (51 vs 83 μmol/l; $P=0.009$), whereas no changes were observed in the ICN group (62 vs 71 μmol/l; $P=0.340$). To prove that the increased arginine level was due to the intake of the product, glutamine, which is not contained in IN supplements, was also measured. Preoperative mean levels of glutamine did not differ between the two subgroups (529 vs 511 μmol/l; $P=0.585$). Compliance with both regimens did not significantly modify mean postoperative glutamine levels (529 vs 482 μmol/l for IN patients; $P=0.318$; 511 vs 525 μmol/l for ICN patients; $P=0.679$).

Prevalence of SIRS was low and only slightly different for both groups (Figure 2a). Postoperative IL-6 and IL-10 levels increase was prominent in the ICN group within the first 24 h, as displayed in Figures 2b and c. At postoperative day 2, interleukin levels were similar between the two groups, and almost at preoperative levels. There was no difference with regards to white blood cell counts and C-reactive protein levels.

Pre-specified subgroup analysis

When non-colorectal surgery was considered, patients allocated to IN ($n=45$) and ICN ($n=52$) developed 27 and 35 postoperative complications ($P=0.527$), including 7 vs 4 major complications ($P=0.741$), and 8 vs 9 infectious complications ($P=0.799$).

An additional *per-protocol* analysis was performed in 39 IN- and 43 ICN-compliant patients, who were able to drink at least 10 of the 15 allocated nutritional supplements. There were no statistically significant differences in overall (23 vs 31; $P=0.249$) or infectious (4 vs 7; $P=0.525$) complications.

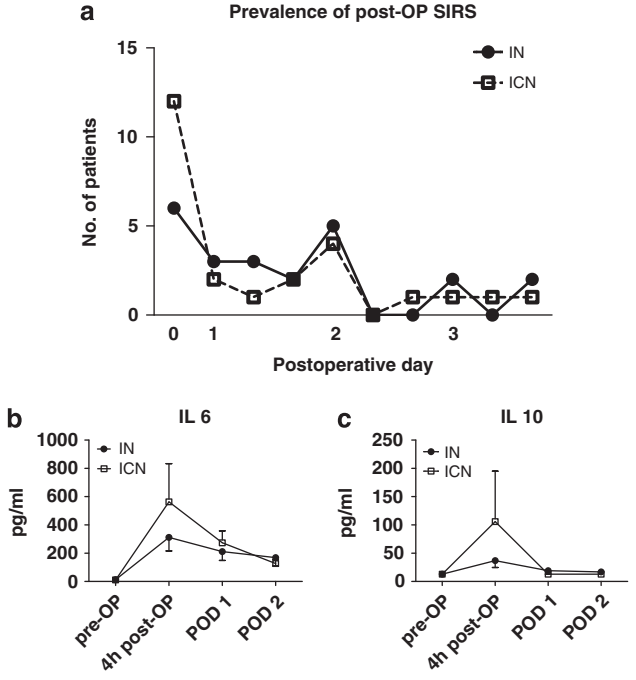

Figure 2. Comparison of (**a**) the prevalence of SIRS, (**b**) the levels of IL-6 and (**c**) IL-10 between IN and ICN patients. POD, postoperative day.

Uni- and multivariate analysis of possible risk factors for complications

Patient-related univariate risk factors for postoperative complications were higher NRS ($P=0.100$), male gender ($P=0.092$), malignant disease ($P=0.001$) and decreased preoperative levels of albumin ($P=0.026$) and pre-albumin ($P=0.079$). Prolonged operation time ($P=0.008$), blood transfusion ($P=0.024$) and no epidural analgesia ($P=0.083$) were also identified as surgical procedure-related risk factors on univariate analysis.

After multivariate analysis, only malignant disease and operation time were identified as independent risk factors for postoperative morbidity with odds ratios of 4.304 (confidence interval 1.317–14.002) and 1.004 (1.000–1.008), respectively.

DISCUSSION

This study was performed to assess clinical effects of preoperative oral IN in patients at nutritional risk undergoing elective major GI surgery. To this end, 152 patients with a NRS $\geqslant 3$ were included into a prospective randomized trial comparing IN vs standard oral isocaloric-isonitrogenous nutrition (ICN). We did not find any superiority of IN in terms of overall and infectious complications as well as length of hospital stay. Nevertheless, there was a trend towards a decrease of severe complications (grade IV) and a shortened ICU stay in the IN group. Furthermore, the early postoperative stress response was downregulated by the use of IN. Careful interpretation of the results is yet needed, as 46% of all patients had a limited intake of oral nutritional support.

At a first glance, the non-superiority of IN in the current study seems to be contradictory to our recently published meta-analysis, where we could demonstrate a significant benefit of IN on postoperative morbidity.[14] The meta-analysis provides robust data, but the 21 included studies showed a significant 'heterogeneity' in terms of demographics, definition of nutritional risk, operation characteristics and nutritional regimens.[14] There were several trials that either showed no or just a minor benefit of IN on the incidence of postoperative complications, and only by pooling the trials, an overall benefit became really overt.[13,21–29] In the present study, we enrolled all patients at nutritional risk who were identified by using the NRS, and no restriction on the type of operation was made, as this patient group is likely to benefit most from nutritional interventions.[6–8] So far, no randomized trial on IN has used the NRS before.[14] Of note, many patients were identified to be at risk owing to their age rather than by a real pre-existing malnutrition.

Although a dose–effect relationship for the use of IN is assumed, current recommendations for daily dose, duration and timing of nutritional interventions still show a large variability.[7,12,14,30] Mitochondria have probably a pivotal role in the early postoperative phase, and its dysfunction caused by oxidative stress is supposed to become irreversible after 6–24 h. Hence, using a preoperative IN regimen is generally emphasized.[31] The preoperative treatment should last 5–7 days with a daily intake of 500–1000 ml of an enteral immuno-nutritional formula, and this common regimen was adopted for our study.[13,14,19] Yet, there is some evidence that only a combined pre- and postoperative administration of IN is able to reduce postoperative morbidity rates.[13,21] Furthermore, early postoperative nutrition and oral nutritional supplements in the postoperative recovery period have gained wide acceptance and are an established part of postoperative care within enhanced recovery pathways.[1,12]

Like any other treatment, preoperative nutritional support needs to be performed appropriately to act effectively. One of the major finding of this study was the limited compliance despite patient's high motivation and exhaustive education by the surgical team and the nutritionists. Only 82 out of 145 analyzed patients reported an intake of at least ten supplements.

The observed impaired compliance also inherits an aspect of 'non-tolerance'. As described by Stratton *et al.*,[32] psychosocial factors such as anxiety and depression rather impair compliance; other disease-related factors, for example, anorexia, nausea or changes in taste and smell related to chemotherapy mainly contribute to non-tolerance. Of note, powder supplements that need to be reconstituted before consumption may have a negative impact and its use is not generally recommended.[10,32] An impaired compliance was also found in the study of Hiesmayr *et al.*[33] who showed that $\geqslant$50% of their patients had an insufficient nutritional intake. In fact, despite a 100% compliance is always implied, no randomized trial on IN reported the real nutritional intake.[14] As a consequence, careful interpretation of the effects of IN is required. Stratton *et al.*[32] stated that supplements with higher energy density might improve nutritional intake and thus compliance by reducing the volume needed to ingest. Therefore, further assessments are not only needed to investigate the problems of non-compliance and non-tolerance to nutritional supplementation, but also to improve oral nutritional formulas.

Nutritional support is still considered as adjunctive care to provide sufficient caloric intake to malnourished patients with rather an unclear benefit.[30,33,34] Modern nutritional formulas entail however 'pharmacological' effects beyond the mere improvement of patients' nutritional status.[35,36] A distinct attribute of immune-enhancing agents is a modulation of the humoral and cellular immune function, that is, a reduction of SIRS and postoperative infection rates.[14,26,37] Prevalence of SIRS was very low in both arms of our study and no significant difference could be detected. IN trended to diminish early postoperative IL-6 and IL-10 response, whereas white blood cell counts and CRP levels remained unchanged, as shown by others.[37,38]

Several limitations of this trial need to be mentioned. Type II error is an inherent possible explanation for all 'negative' clinical studies. Sample size calculations are recommended to overcome this problem and to avoid overpowered studies including more patients than necessary to demonstrate a clinically relevant effect. Our computed sample size was based on several similar studies; and lies in the upper range of studies published in this field.[13,14,19] We cannot exclude that a better compliance or the inclusion of much more patients would have allowed demonstrating some statistically significant differences between the two nutritional interventions. But would these small benefits and the inevitably associated high numbers needed-to-treat really correspond to a clinical significance? Furthermore, a power of 90%, a lower than expected dropout rate and a higher complication rate than assumed render the results of this intention-to-treat analysis even more reliable.

In conclusion, this randomized study could not detect a significant benefit of IN vs ICN in an unselected group of patients at nutritional risk undergoing major GI surgery. Compliance and tolerance are key issues that need to be further investigated.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Sven Müller and Michel Roulet participated in the study design. Giustina Mariotti was the departmental study nurse responsible for data collection and management. Finally, we acknowledge all surgical residents, staff surgeons and nutritionists who were implicated in patients' recruitment and follow-up. This study was supported by a research grant from Novartis Consumer Health Schweiz AG (Protocol SC-IMP.O-07-06–CH).

DISCLAIMER

During the study period, the nutrition branch of Novartis was incorporated into Nestlé Nutrition. The investigators had full control of the data and performed statistical analysis.

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