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The Effects of Low Dietary Inflammatory Index Formula on the Inflammatory and Metabolic Biomarkers of Patients with Multiple Traumas in Intensive Care Units: A Study Protocol for a Single-blind, Randomized, Controlled Trial

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ABSTRACT

Introduction: Acute inflammation in critically ill patients could affect the metabolism, including nutritional needs and nutrient uptake. Diet also affects the body through various mechanisms, such as the reduction of inflammatory processes, antioxidant capacity, and alteration of lipid profiles and the microbial balance of the intestine. The dietary inflammatory index is a predictive index of inflammatory dietary potential. The present study aimed to hypothesize whether designing a new low dietary inflammatory index formula with high antioxidants could reduce the inflammatory factors in critically ill patients.

Methods: This single-center, prospective, randomized, single-blind, controlled study was conducted on patients with severe trauma, who were randomly assigned to the standard formula (n=10) and intervention formula (n=10) upon admission to the intensive care unit.

Result: The primary outcomes of the study were the clinical status, metabolic factors, and inflammatory biomarkers.

Conclusion: Since no studies have been focused on the formulation of antioxidant micronutrients in terms of dietary inflammation indices, this research aimed to investigate the effects of this formulation with a low inflammatory profile on the metabolic and inflammatory markers of patients with multiple traumas.

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Introduction

Trauma was reported to be the second leading cause of death in Iran in 2017 (1). Severe trauma threatens the life of the victims even in intensive care units (ICUs) due to the metabolic changes and inflammatory responses that lead to the progression of the systemic inflammatory response syndrome and the subsequent severe infections, sepsis, and multiple organ dysfunction syndrome (2).

Evidence suggests that nutritional support in critically ill patients is the primary therapeutic strategy (3). In this regard, some studies have demonstrated that early enteral nutrition (EN) has beneficial effects on the reduction of inflammation, infections, and metabolic complications (4, 5). Furthermore, dietary agents such as macronutrients, antioxidant vitamins, and minerals could modulate the inflammatory status in the body, thereby altering the response to injuries and infections (6, 7). The dietary inflammatory index (DII) is recognized as a highly prestigious indication of dietary inflammatory potential based on the levels of inflammatory biomarkers, such as high-sensitivity C-reactive protein (hsCRP) (8).

The present study aimed to design a formula based on the DII to reduce the inflammatory factors in patients admitted to the ICU.

Materials and Methods

Research Hypothesis and Objectives

Objective One

The first objective of the research was to determine the effects of a low-DII formula on

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the APACHE II, NUTRIC, and SOFA scores in patients with multiple traumas.

Objective Two

The second objective of the study was to evaluate the effects of the low-DII formula on the fasting blood sugar (FBS), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglyceride in patients with multiple traumas.

Objective Three

The third objective of the research was to assess the effects of the low-DII formula on the liver function tests of patients with multiple traumas, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), *and alkaline phosphatase* (ALP), and direct and total bilirubin.

Objective Four

The fourth objective of the study was to determine the effects of the low-DII formula on the serum electrolytes (sodium, potassium, magnesium, Na, K, total calcium, and ph) of patients with multiple traumas.

Objective Five

The fifth objective of the research was to evaluate the effects of the low-DII formula on the serum albumin and total protein of patients with multiple traumas.

- ***Objective Six***

The final objective of the study was to investigate the effects of the low-DII formula on the serum hsCRP and tumor necrosis factor-alpha (TNF-α) of patients with multiple traumas.

Study Design

This single-center, prospective, randomized, single-blind, controlled clinical trial was conducted in 2018. The study was retrospectively registered in the Iranian Registry of Clinical Trials (IRCT; registry number: IRCT20180515039674N1). The study protocol was approved on August 25, 2018, and the central ethical approval was also obtained from the Institutional Review Board of Mashhad University of Medical Sciences in Mashhad, Iran (reference approval number: IR.MUMS.REC.1397.149). Prior to randomization, informed consent was obtained from the patients or their legal representatives if possible or an independent physician if they were not available.

Study Setting

The present study was conducted at the neurosurgical ICU of Shahid Kamyab Hospital in Mashhad (Iran), which is the leading trauma center affiliated to the medical university of this city.

Sample Size

To estimate the sample size based on a previous study in this regard (9), TNF-α was considered as the main variable based on type I and type II errors of 0.05 and 0.2, respectively (test power: 84%). In total, eight patients were allocated to each group. Assuming 10% sample loss per each group, the final sample size was determined to be 10 patients per group based on the following formula:

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \left(\sigma_1^2 + \sigma_2^2\right)}{\left(\mu_1 - \mu_2\right)^2}$$

Participants

Inclusion Criteria

In total, 20 adult patients aged 18-65 years were enrolled in the study, who had been diagnosed with moderate-to-severe trauma based on the Glasgow coma scale (GCS) scores of 4-14. In addition, the selected patients had proper gastrointestinal tract function and indications of EN and were enrolled within 24-48 hours after ICU admission at Shahid Kamyab Hospital.

Exclusion Criteria

The exclusion criteria of the study were as follows: 1) failure to start EN within the first 48 hours of admission; 2) history of cardiovascular diseases; 3) ICU admission length of less than 96 hours; 4) patients expected to die within 12 hours of admission; 5) contraindications for receiving EN and 6) unwillingness of the patients or their legal guardians for participation in the study.

Ethical Considerations

The study protocol was approved by the local Institutional Review Board. Prior to randomization, informed consent was obtained from the patients or their legal guardians if possible or from an independent physician if they were unavailable.

Data Collection at the Outset

At baseline, data were collected on the demographic and clinical characteristics of the patients.

Randomization and Blinding

The present study had a prospective, randomized, controlled, single-blind design. The patients were randomly assigned to two groups of low DII formula and standard DII formula using serially numbered sealed bottles. The randomization of the study groups was carried out by the first author based on the inclusion and exclusion criteria. The patients were stratified upon randomization based on their age (18-65 years), gender, and disease severity (APACHE II score) in order to ensure the equal distribution of these variables in both groups. Due to the different colors of the formulas in the present study, the physician and nurses could not be blinded to the study procedure, while the patients and outcome evaluators were blinded, and the investigator was not directly involved in the intervention process and patients care. In addition, the laboratory personnel, pathologists, and statisticians were blinded to the treatment allocation.

Statistical Analysis

Data analysis was performed using the Kolmogorov-Smirnov test to assess the normal distribution of the variables, and the intention-to-treat approach was also applied. In addition, one-way analysis of variance (ANOVA) or multivariate analysis of covariance (ANCOVA) was used to determine the differences in the general characteristics, APACHE II, SOFA, and NUTRIC scores, dietary intakes, and inflammatory and metabolic biomarkers at baseline between the study groups. In the case of the data with non-normal distribution, the study groups were compared using the Kruskal-Wallis test, and the intergroup comparisons were performed using the Wilcoxon test. In all the statistical analyses, the P-value of less than 0.05 was considered significant.

The discrete variables were summarized in frequencies and percentages, and the continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range as appropriate. Moreover, the variables were compared at baseline and on days seven and 14 using student's t-test, Fisher's exact test, Chi-square, and Mann-Whitney U test. All the outcomes were analyzed in an uncorrected manner, as well as an equally corrected manner in the case of risk factors (e.g., disease type and severity, age, actual body weight, and APACHE II score). Notably, disease type was determined in accordance with diagnostic categories, and the APACHE II, SOFA, and SAPS questionnaires were employed to determine the disease severity score.

Procedures

Phase I: Low DII Formula from Design to Production

The standard PNC Entera Meal formula was prepared based on the DII. Considering the upper intake level and recommended daily allowance standard formulation and in order to synthesize an anti-inflammatory formulation, specific amounts of vitamins, minerals, and two nutrients with a negative inflammatory index and anti-inflammatory properties were applied. After consulting with the pharmaceutics advisory professors, a new formulation was designed and sent to James Hebert and Nitin Shivappa (advisory professors in the field of DII).

After the final confirmation of the significant difference between the DII of the standard and designed formulations, the powder preparation and enrichment method was designed. Initially, the stock sample (400X magnification) was prepared from extremely low-weight compounds (micrograms), which could not be weighed with the available scales in the laboratories of the School of Pharmacy. The compounds included vitamin A, vitamin D3, vitamin B9, and selenium. The exact amount of each vitamin was obtained by mixing each gram of the stock sample in two kilograms or five cans of the standard Entera Meal. Furthermore, the following steps were taken to prepare each five cans or two kilograms of the low-DII formula powder:

1. The vitamins and minerals were precisely weighed using a three-point scale.
2. One gram of the stock powder was added and mixed using a mortar.
3. The geometrical dilution method was used to add the standard formula powder with the exact same size as the powder containing the vitamins, minerals, and nutrients prepared in the previous step and mixed geometrically for 15-20 minutes. The process continued until obtaining a homogeneous mixture of five cans or two kilograms of the standard formula powder.
4. The five prepared cans were mixed for 15-20 minutes using a mixer in two steps.
5. At the final stage, the geometric dilution procedure was repeated as described earlier in

order to ensure the complete uniformity of the powder.

Phase 2: Intervention Process

The patients were selected via non-probability purposive sampling based on the inclusion and exclusion criteria within 24-48 hours after ICU admission and matched in terms of age, gender, type of lesions, GCS score, and type of lesions, and randomly divided into two groups. Data collection was performed using observational laboratory methods, and two treatment modalities were implemented after obtaining the demographic data (age, gender, diagnosis upon admission, and classification of hospitalization). Among the other collected data were the personal information of the patients, which were obtained using the comprehensive hospital management software, medicinal and medical history, and informed consent of the patients; in case they were unconscious, the legal guardians would provide the consent. Following that, the patients were randomly divided into two groups of low inflammatory formula (control) and standard formula (case).

In the case and control groups, hemodynamic resuscitation and stabilization were carried out within the first 24-48 hours of admission. Afterwards, EN was initiated to provide 80-100% of the energy requirement of the patients, which was calculated to be 25 kilocalories of energy per kilogram of the body weight. The amount of the required formula for each patient was determined individually. The treatment commenced within the first 24-48 hours of hospitalization and administered in the bolus form at three-hour intervals (seven times per every 24 hours). The intervention continued for 14 days, after which the case and control groups returned to the standard formula feeding. In addition, blood sampling was performed after the last gavage meal at night similarly in both groups on days zero and 14, and the following assessments were also carried out:

1. The APACHE II scoring system was applied to assess the disease severity based on 12 routine physiological measurements, including the body temperature, heart rate, hematocrit level, white blood cell count, respiratory rate, PaO_2/FiO_2, pH, sodium, potassium, creatinine level, blood pressure, and GCS score.
2. The levels of inflammatory factors were evaluated by measuring hsCRP and TNF-α.
3. Nutritional assessment was performed based on the NUTRIC score and measurement of the body mass index and mid-arm circumference.
4. Lipid profiles were also measured, including the LDL, HDL, triglyceride, and total cholesterol.
5. The levels of blood glucose, liver enzymes, and electrolytes (sodium, magnesium, potassium, and phosphorus) were measured on days zero, seven, and 14 of the intervention for the early detection of the possible effects of the nutritional intervention and monitoring of refeeding syndrome.

Blood Sampling

Fasting blood tests were performed on days zero, seven, and 14, and 10 milliliters of blood was obtained from the patients and collected in plastic tubes. To extract the serum, the samples were centrifuged at 3,600 rpm for 3-4 minutes and placed in microtubes (1.5 ml). Following that, the samples were stored in the freezer at the temperature of -70°C. To reduce measurement errors, sampling was entirely performed at 10 AM in the fasting state.

Study Outcomes

Primary Outcomes

The primary outcomes of the study included the clinical status, inflammatory biomarkers, and APACII II, SOFA, SAPS, and NUTRIC scores.

Secondary Outcomes

The secondary outcomes of the study included the plasma protein levels (total proteins, albumin, direct and total bilirubin), liver function tests (AST, ALT, and ALP), FBS, lipid profiles (HDL-C, LDL-C, triglyceride, total cholesterol), total energy expenditure (measured by the Harris-Benedict equation), gastrointestinal complications (e.g., abdominal distension, vomiting, diarrhea, excessive gastric residue), and metabolic acidosis.

Discussion and Conclusion

The current RCT aimed to assess the effects of a low-DII formula on the inflammation response of the patients admitted to the ICU. Our findings provide evidence regarding the value of low DII as an intervention for inflammatory responses in patients with multiple traumas admitted to the ICU.

Nutritional support is defined as the prescription of formulated enteral or parenteral nutrients to the patients who cannot meet their nutritional requirements through normal diets

in order to maintain and enhance their nutritional status. EN refers to the nutrient delivery via a tube or catheter, which is inserted into the gastrointestinal tract in the patients for whom oral nutrition is impossible or inadequate. In some cases, EN formulas are prescribed as oral supplements or meal replacements. Nutritional support is also provided via parenteral routes in patients with functional gastrointestinal disorders or EN intolerance, which is also referred to as parenteral nutrition (PN) (10).

Great emphasis has been placed on the early initiation of nutritional support via PN or EN to significantly reduce the associated complications and accelerate recovery. EN could have a major impact on the function and structural health of the gastrointestinal tract, thereby preventing the transmission of gastrointestinal bacteria, various hospital-acquired complications and infections, increasing the resistance of patients to metabolic stress, and improving clinical performance (11).

In the late 1970s, EN support was in its infancy, and only 16 enteral formulas were available. Within the past few decades, these formulas have increased dramatically. Today, more than 100 enteral formulas are available on the market, many of which are prescribed for critically ill patients (12, 13). As such, selecting the most appropriate formula is rather challenging considering the wide array of the available formulas. Enteral formulas have been regarded as dietary supplements by the United States Food and Drug Administration (FDA) and are not under the same regulatory control as medicines. As a result, the enteral formulas that are labeled 'Compounds and Functions' could be claimed alone without an FDA approval. However, only a few prospective, randomized, controlled interventions support the claimed indications for the specific formulas that are currently available on the market. Therefore, conducting further investigations in this regard and using the positive results obtained by modified formulas play a key role in the selection of the most proper formula (12).

In the past two decades, numerous clinical studies have investigated the role of antioxidant micronutrients in the form of monotherapy or polytherapy in the mortality and clinical outcomes of critically ill patients. Accordingly, pharmaconutrition and immunomodulatory formulas have beneficial effects, which are associated with the negative regulation of pro-inflammatory responses in patients with trauma, sepsis, and other inflammatory injuries (14). Nevertheless, evidence regarding the benefits of these formulas remains controversial. Since no studies have been focused on the formulation of these antioxidant micronutrients in terms of their dietary inflammation indices, the current research aimed to investigate the effects of this formulation with a low inflammatory profile on the metabolic and inflammatory markers of patients with multiple traumas.

Availability of Data and Materials

The applied datasets and documented/analyzed results in the present study will be available to researchers after obtaining the required permit from the Deputy of Research of Mashhad University of Medical Sciences and the main executor of the research project.

Conflicts of interest

None declared.

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