Therapeutic effects of supplementation with Curcuminoids in critically ill patients receiving enteral nutrition: a randomized controlled trial protocol

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Abstract

Background Curcuminoids are dietary polyphenols that can improve health indices through different mechanisms such as anti-inflammatory, antioxidant and immunoregulatory properties. Due to the lack of evidences on the efficacy of curcuminoids in critically ill patients, this study was designed to investigate the effects of short-term curcuminoids supplementation on inflammatory, oxidative stress and adipokine indices as well as nutritional and clinical status in Traumatic Brain Injury (TBI) patients admitted in the Intensive Care Unit (ICU).

Methods The present trial will be performed in the ICU of Sina and Shohadaye Tajrish hospitals of Tehran, Iran. Sixty-two critically ill patients with TBI will be enrolled based on the eligibility criteria. The patients will be randomly assigned into two groups. For 7 days, they will received either 500 mg curcuminoids in combination with 5 mg piperine or matched placebo. A general questionnaire, consent form as well as NUTRIC, SOFA and APACHEII scoring system and anthropometrics will be assessed at baseline. The inflammatory markers including TNF- α , IL-6, MCP-1 and CRP, oxidative stress indices (GPx and SOD) and adipokines (leptin and adiponectin) will be measured at baseline and at the end of the study. In addition, dietary intake, concomitant drugs and laboratory tests will be recorded daily.

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Discussion To the best of our knowledge, this is the first clinical trial investigating the effect of curcuminoids supplementation in critically ill patient with TBI. The findings of the present study will provide evidence on the efficacy and safety of curcuminoids in these patients.

Trial registration number (<http://www.irct.ir>, identifier: IRCT20180619040151N1), Registration date: 18.09.2018.

Keywords Clinical trial protocol · Intensive care unit · Curcumin

Introduction

Traumatic brain injury (TBI) is an important public health problem accounting for one of the leading causes of death and long-term disability throughout the world [1]. It is a kind of an intracranial damage resulted from an external force to the head, for example direct impact or rapid acceleration/deceleration, which surpasses the protective capacity of the brain [2, 3]. According to the WHO reports, road accidents will be the third major causes of disease and injury burden worldwide by 2020. TBI is more common in children and young adults, particularly among men and low and middle-income countries due to increasing use of motorcycle [4, 5]. Since mostly affected young people, it leads to high medical and social costs especially to countries with high traffic accidents such as Iran [6]. It has been estimated that the incidence of TBI in Iran is approximately 56.3/100,000, about one third of these cases will result in disabilities [7].

TBI is a heterogeneous disorder due to presence of several mechanisms of injury as consequence of various forms of TBI presentation and different severity levels. TBI severity has been categorized as mild, moderate and severe according to several approaches such as mechanism of injury and level of consciousness; however, because of its heterogenic nature, precise classification is difficult [3, 8]. There are different severity of illness scoring systems in ICU of which Acute Physiology And Chronic Health Evaluation II (APACHEII) and Sequential Organ Failure Assessment (SOFA) are the most commonly used for prediction of outcomes in patients with TBI [9]. Another validated tool in critically ill patients is Nutrition Risk in the Critically Ill (NUTRIC) score developed to identify patients with high nutritional risk and associated outcomes [10].

Over the past decades, consumption of polyphenols has attracted a great attention, probably due to their pivotal role against a wide range of diseases including cancers [11], cardiovascular and metabolic diseases [12], osteoarthritis [13, 14], dyslipidemia [15] and non-alcoholic fatty liver disease [16]. Curcuminoids are unique bioactive lipophilic compounds found in popular dietary spice, turmeric [12]. Owing polyphenolic structure and multiple molecular targets, they possess various biological activities against oxidative damage and inflammation, which

are key factors in the pathogenesis of several neurological disorders particularly TBI [17, 18]. Having hydroxyl and methoxy groups, curcuminoids have extensively known as antioxidant and anti-inflammatory agents [19]. The underlying mechanisms of such effects include suppressing the activation of various transcription factors, specifically Nuclear factor-kappa B (NF- κ B), inhibiting enzymes involved in inflammation (e.g. Cyclooxygenase-2 and lipoxygenase), down regulating of pro-inflammatory interleukins (e.g. IL-1 β , IL-6), cytokines (e.g. Tumor Necrosis Factor- α) and monocyte chemoattractant protein-1 (MCP-1) as well as stimulating of Nuclear Factor erythroid 2-related Factor 2 (Nrf2) expression, which leads to protection against free radicals by up-regulating of antioxidant enzymes such as Glutathione Peroxidase (GPx) and Superoxide Dismutase (SOD) [20, 21]. On the other hand, some experimental studies have reported the anti-obesity property of this orange-yellow natural phytochemical via targeting adipokines including leptin and adiponectin [22]. However, evidences regarding the efficacy of curcuminoids supplementation on these adipokines are scarce and more studies are needed. In spite of these beneficial effects of this natural product, no study has yet investigate the effects of curcuminoids in patients with TBI. Thus, the present parallel study will assess efficacy of supplementation with curcuminoids on inflammation, oxidative stress and adipokines as well as nutritional and clinical status of critically ill patients with TBI.

Methods

Study design

A double-blind, placebo-controlled randomized clinical trial will be conducted in this study as presented in Fig. 1.

Objectives

1. Comparing the means of serum levels of inflammatory biomarkers including TNF- α , IL-6, MCP-1 and C-reactive Protein (CRP) within each group and between the two groups before and after the intervention

Fig. 1 Flow diagram of trial

2. Comparing the means of serum levels of antioxidant markers including GPx and SOD within each group and between the two groups before and after the intervention
3. Comparing the means of serum levels of adipokines including leptin and adiponectin within each group and between the two groups before and after the intervention
4. Comparing the means of APACHEII score within each group and between the two groups before and after the intervention
5. Comparing the means of NUTRIC score within each group and between the two groups before and after the intervention
6. Comparing the means of SOFA score within each group and between the two groups before and after the intervention

Inclusion criteria

1. Adults (male/female) aged 18–65 years
2. Admission to the ICU due to TBI
3. Glasgow Coma Score (GCS) ≥ 7
4. Submission of written informed consent from patients or their legal guardians

Exclusion criteria

1. Pregnancy or breast feeding
2. Patients with sepsis
3. Patients not eligible for initiating nutritional support during 24–48 h after ICU admission

4. History of any autoimmune disease
5. History of any type of cancer
6. History of chemotherapy or radiotherapy during the last month
7. Intake of positive inotropic agents
8. History of liver failure
9. Severe and active bleeding
10. History of HIV
11. History of food allergies
12. Morbid obesity ($BMI \geq 40$)
13. Death or discharge from ICU before day 7
14. Significant changes in treatment protocol of patients

Subjects and sample size

This double-blind, placebo-controlled, randomised clinical trial will be conducted in ICU of Sina and Shohada Tajrish hospitals, which are referral tertiary teaching hospitals. The patients who will meet the inclusion criteria can participate in the study. At the beginning, all details of the study will be explained to patients or their legal guardians and a written informed consent will be obtained.

The sample size was calculated using following equation:

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

The calculation of the sample size showed 26 subjects in each group is required, according to a previous study and using two means comparison formula [23]. In this formula, the type 1 and 2 errors were considered as 0.05 and 0.2 (80% power), respectively. The mean difference of IL-6 between two groups was 0.5 and SD of intervention group and placebo group was 0.67 and 0.73 respectively. With consideration of 20% drop out rate, a total of 62 patients will be included and divided into two groups as follows:

1. Thirty-one patients with TBI will receive curcumin supplement for 7 days
2. Thirty-one patients with TBI will receive placebo supplement for 7 days

Intervention and randomization

The patients will be randomly allocated into two groups to receive either curcuminoids (C3 complex, Sami Labs Ltd.,) plus piperine (black pepper extract containing 95% piperine, Sami Labs Ltd.) or matched placebo for 7 days. The premixed block randomization method will be used to divide the patients into two equal groups. Age (18–40 or 41–65) and

gender (male/female) will be controlled by stratified randomization. The randomization will be conducted by research assistant; however, investigator, patients, staffs and outcome assessors will be blinded to the type of intervention during the study.

In view of the existing evidence, curcuminoids have been characterized as excellently safe and tolerable supplements even at high doses between 4000 and 8000 mg/day. Furthermore, they have been approved as “Generally Recognized As Safe (GRAS) by the Food and Drug Administration (FDA) in the USA [24, 25]. Despite these advantages of curcumin, it has weak absorption and rapid metabolism in the liver. Thus in several approaches have been recommended to augment its bioavailability such as adding piperine. Accordingly, in the present study, patients will receive curcuminoids at a daily dose of 500 mg in combination with 5 mg piperine or matched placebo adding to their enteral nutrition, respectively. It is of note that C3 Complex® preparation used in this study contains three major curcuminoids including curcumin, demethoxycurcumin and bisdemethoxycurcumin in patented ratio.

Anthropometric measurements

At the beginning and at the end of the study, APACHEII, SOFA and NUTRIC score will be recorded using relevant questionnaires. Anthropometrics data including weight and height will be measured using bed scale (Balas company, Iran) and estimating by ulna length (using flexible tape) with accuracy of 100 g and 0.5 cm respectively at baseline. Then, Body Mass Index (BMI) will be calculated as weight (kg) divided by height square (m^2). In addition, dietary intake, laboratory tests and medications will be recorded for each patient daily.

Blood sampling

In order to measure the blood factors, venous blood sample (10 ml) will be collected before and after the intervention. Then blood samples will be centrifuged at 3000 rpm for 10 min at 4 °C to obtain the serum and will be stored at –80 °C until the biochemical analysis.

Biochemical measurements

The serum levels of inflammatory biomarkers (TNF- α , IL-6, MCP-1) and adipokines (leptin and adiponectin) will be measured using Enzyme-linked immunosorbent Assay (ELISA) kits. Serum levels of CRP will be determined by immunoturbidimetric method. Also, Serum activities of antioxidant enzymes including GPx and SOD will be determined on the basis of colorimetric method. The details of the study procedure are presented in Table 1.

Table 1 Details of the study procedure

Trial contents	Duration of study		
	Before intervention	Intervention period	After intervention
Timepoint	Day 1	Day 1–7	Day 8
Eligibility screen	×		
Informed consent	×		
Anthropometrics	×		
APACHEII	×		×
SOFA	×		×
NUTRIC	×		×
Blood sampling	×		×
Dietary intake	×	×	
Laboratory tests	×	×	
Concomitant drugs	×	×	
Inflammatory markers	×		×
Antioxidant enzymes	×		×
Adipokines	×		×

Data analysis

Statistical analysis will be performed using SPSS 21 software (SPSS Inc., Chicago, USA). Normal distribution of continuous variables will be checked using Kolmogorov-Smirnov test. Continuous and categorical variables will be presented as mean (SD) and frequency (percentage) respectively. Distribution of categorical variables between two groups (intervention and control) at baseline will be assessed using Chi-square test. Mean of continuous variables with and without normal distribution between groups at baseline will be compared using T-test and Mann-Whitney test. A multivariate two way repeated measures ANOVA will be used to compare the effect of curcuminoids supplementation on outcomes. All analysis will be assessed based on intention-to-treat (ITT) and per protocol analysis. Missing data will be imputed using “regression imputation” method. $P < 0.05$ will be considered as statistically significant.

Ethics and dissemination

Ethical approval has been obtained from ethics committee of Tehran University of Medical Sciences (IR.TUMS.VC.R.REC.1397.141) and Semnan University of Medical sciences and Health Services (IR.SEMUMS.REC.1397.001). Accessibility to the final data will be limited to the principle investigators and the findings will be disseminated only via publication in peer-reviewed journals and scientific conference presentations.

The results of the study will be presented via publication in peer-reviewed journals as well as scientific conference

presentations. However, accessibility to the final data will be limited to the major investigator.

Discussion

To the best of our knowledge, this is the first study investigating the effects of curcuminoids on various parameters including inflammatory and oxidative stress markers, adipokines and nutritional and clinical status among critically ill patients with TBI. The topic is of high relevance due to the lack of evidence regarding advantages and disadvantages of clinical uses of curcuminoids in ICU.

The strengths of this study are included its randomized double-blind placebo-controlled design and dissemination of study protocol, providing insights on the feasibility of curcumin administration in ICU admitted patients as the first human study as well as reporting any adverse events. The potential limitations are possible unwillingness of some patients or their legal guardians to participate in the trial and presence of multiple inclusion and exclusion criteria leading to slow recruitments of the patients.

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Author's contributions Ablodreza Norouzy cooperated on the initial study concept and design of this research, which was further developed by Mahdi Shadnough and Mohammad-Javad Hosseinzadeh-Attar. Saeed Hoseeini revised the study. Mostafa Qorbani advised on statistical analysis and interpretation of data. Atabak Najafi, Arezoo Ahmadi and Seyed-Hoseein Ardehali coordinated participant management and data collection and relevant

questionnaires. Hoda Zahedi and Amirhossein Sahebkar took part in drafting the manuscript and technical or material support. Hamideh Moravvej and Gholamreza Pourmand will corporate in laboratory activities. The manuscript has been read and approved by all authors.

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Compliance with ethical standards

Ethics approval and consent to participate The Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1397.141) and Semnan University of Medical Sciences and Health Services (IR.SEMUMS.REC.1397.001) has approved the protocol of this study. A written informed consent form will be signed and dated by subjects or their legal guardians and investigators at the beginning of the study.

Conflict of interests The authors declared that they have no competing interests.

Abbreviations *TBI*, Traumatic brain injury; *ICU*, Intensive care unit; *TNF- α* , Necrosis factor- α ; *IL-6*, Interleukine-6; *MCP-1*, Monocyte chemoattractant protein-1; *CRP*, C-reactive protein; *APACHEII*, Acute physiology and chronic health evaluation II; *SOFA*, Sequential organ failure assessment; *NUTRIC*, Nutrition risk in the critically ill; *SDH*, Acute subdural hematoma; *ICH*, Intracranial hemorrhage; *DAI*, Diffuse axonal injury; *NF- κ B*, Nuclear factor-kappa B; *Nrf2*, Nuclear factor erythroid 2-related factor 2; *GPx*, Glutathione peroxidase; *SOD*, Superoxide dismutase; *GCS*, Glasgow coma score; *BMI*, Body mass index; *GRAS*, Generally recognized as safe; *FDA*, Food and Drug Administration; *ELISA*, Enzyme-linked immunosorbent Assay; *ANOVA*, Analysis of variance (ANOVA).

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