AJKD
Original Investigation

Intradialytic Oral Protein Supplementation and Nutritional and Inflammation Outcomes in Hemodialysis: A Randomized Controlled Trial

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Background: Malnutrition is a common finding in hemodialysis patients and can increase oxidative stress and inflammation levels.

Study Design: A randomized, controlled, nonblinded, parallel trial.

Setting & Participants: 92 hemodialysis patients from a single center with malnutrition according to subjective global assessment (SGA) score (SGA score > 7).

Intervention: 3 treatment groups (23 patients each) received 220 mL of fermented vitamin E−fortified whey beverage (15 g of whey protein concentrate + 600 IU of vitamin E) or 220 mL of fermented whey beverage (15 g of whey protein concentrate) or vitamin E (600 IU) 3 times a week for 8 weeks. The control group (23 patients) received no intervention.

Outcome & Measurements: Primary outcomes were change in SGA score and malnutrition-inflammation score (MIS) from baseline to the end of the trial.

Results: At the end of the study, 83 patients were analyzed (2, 3, 1, and 3 patients left the study in the vitamin E–fortified whey beverage, whey beverage, vitamin E, and control groups, respectively). Changes in SGA scores were −3.48 (95% CI, −4.90 to −2.00), −3.22 (95% CI, −4.13 to −2.30), −1.70 (95% CI, −3.20 to −0.24), and 1.56 (95% CI, 0.60 to 2.50) for the vitamin E–fortified whey beverage, whey beverage, vitamin E, and control groups, respectively (overall $P < 0.001$; $P \leq 0.001$ for each treatment group vs control). Changes in MISs were −3.17 (95% CI, −4.40 to −1.90), −1.83 (95% CI, −2.50 to −1.10), −2.30 (95% CI, −3.50 to −1.10), and 1.48 (95% CI, 0.65 to 2.30) for the vitamin E–fortified whey beverage, whey beverage, vitamin E, and control groups, respectively (overall $P < 0.001$; $P < 0.001$ for each treatment group vs control). Few adverse effects were reported in any group.

Limitations: Lack of blinding, small sample size, and short duration.

Conclusions: Whey protein in the form of a new fermented whey beverage and vitamin E supplementation may improve SGA score and MIS in the short term.

Am J Kidney Dis. 68(1):122-130.

INDEX WORDS: Protein supplementation; malnutrition-inflammation complex syndrome (MICS); malnourishment; subjective global assessment (SGA); malnutrition-inflammation score (MIS); hemodialysis; end-stage renal disease (ESRD); whey protein; vitamin E; antioxidant; randomized controlled trial.

Protein-energy wasting[1] and insufficient protein-calorie intake are common among hemodialysis (HD) patients.[2] Increased risk for atherosclerotic cardiovascular diseases (CVDs), hospitalization, and mortality in HD patients is associated with malnutrition-inflammation complex syndrome.[2]

Whey protein can stimulate protein synthesis due to its branched-chain amino acid content and its activation of the mTOR pathway.[3] Whey protein can cause a positive nitrogen balance with its high and fast absorption[4] and is regarded as an anabolic agent by its stimulation of the insulin-like growth factor 1 pathway through insulin.[5,6] In addition, among the leading causes of malnutrition-inflammation complex syndrome in HD patients, high oxidative stress is of great importance.[7] High oxidative stress emanates from an imbalance between pro- and antioxidant systems.[5,8-10] Whey protein is an anabolic,[5] antioxidant,[11,12] and anti-inflammatory[12] protein. As an antioxidant enhancer, it increases glutathione concentration with its cysteine content[13] and decreases DNA damage.[11] Similarly, vitamin E, as a potent antioxidant,

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Received May 6, 2015. Accepted in revised form February 21, 2016. Originally published online April 15, 2016.

Trial registration: www.ClinicalTrials.gov; study number: NCT02163070.

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0272-6386
http://dx.doi.org/10.1053/j.ajkd.2016.02.050

increases levels of the endogenous antioxidant enzymes glutathione peroxidase, catalase, and superoxide dismutase and decreases levels of oxidative markers, including malondialdehyde. Several studies have demonstrated vitamin E deficiency in HD patients and its correlation with nutritional status.[14-16]

To our knowledge, no controlled trial has evaluated the efficacy of whey protein supplementation on improving clinical outcomes such as malnutrition in HD patients. Hence, this trial was carried out to evaluate the efficacy of a new fermented whey beverage on nutritional, oxidative, and inflammatory markers such as subjective global assessment (SGA) score, malnutrition-inflammation score (MIS), serum albumin level, and transferrin level.

METHODS

Study Design and Patient Characteristics

This was a randomized controlled parallel trial that conformed to the Declaration of Helsinki and the Good Clinical Practice Guidelines of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. The study protocol was reviewed and approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran.

Patients who were aged 17 to 65 years and receiving regular HD at the Shahid Faghihi HD center were eligible for participation. Shahid Faghihi HD center is affiliated with Shiraz University of Medical Sciences, with health care providers including nurses, nutritionists, and physicians. We excluded patients who were taking antioxidant supplements, including vitamins E and C, lipoic acid, coenzyme Q10, soy extracts, green tea preparations, amino acids, protein or keto-acid supplements, or immunosuppressive medications, within the 2 months prior to recruitment to the study or having active infection or hospitalization in the previous month before the beginning of the trial. Those who had malnutrition (mild, moderate, or severe) according to SGA scoring were eligible for participation.

Sample size was determined according to SGA score (as one of the primary outcomes) in a previous study of malnourished HD patients receiving a nutritional oral supplement.[17] A sample size of 20 patients per group was determined with a mean difference of 0.7, standard deviation of 0.8 for SGA score, and probability of 80% at the predetermined level of $\alpha = 0.05$. To allow for up to 3 dropouts in each group, 23 patients per group were determined as the final sample size.

We screened 280 HD patients and found 92 stable patients eligible for participation who signed the informed consent to participate in this trial. Patients were recruited by referral to the specified HD center. Eligible patients were dialyzed with polysulfone/polyamide membranes, reverse-osmosis purified water, and bicarbonate-containing dialysate.

Randomization and Adherence

We randomly assigned patients in a 1:1:1:1 ratio into 4 groups. Patients in group 1 received 3 bottles of vitamin E−fortified fermented whey beverage per week for 8 weeks (each 220-mL bottle had 15 g of whey protein concentrate + 600 IU of vitamin E (all-racemic-α-tocopherol). Those in group 2 received 3 bottles of fermented whey beverage per week for 8 weeks (each 220-mL bottle had 15 g of whey protein concentrate). Those in group 3 received 3 capsules of vitamin E per week for 8 weeks (each capsule had 600 IU of vitamin E in the form of all-racemic-α-tocopherol). Patients in group 4 as the control group received no intervention (receiving usual care, including drug assessment, routine biochemical and laboratory assessments, nutrition consultation, and standard measures to prevent complications such as anemia).

Investigators who had no clinical involvement in the trial used random allocation software to randomly assign patients using blocked randomization with a fixed block size of 4.[18] Enrollment, sequence generation, allocation concealment, and randomization process implementation in the trial were all done by the principal investigators.

The fermented whey beverages (with and without vitamin E fortification) were 220-mL bottles providing 15 g of whey protein concentrate (18.5 g of 80% whey protein concentrate), 1.4% of permeate (as a source of lactose for fermentation), 0.4% fat, and 0.01% sterile mint flavor. Carbohydrate, fat, and calorie contents of the beverages were 0.4%, 2.43%, and 45.3 kcal/100 g, respectively. The beverages were fermented using a yogurt starter (TY17A) for better acceptability and taste. After mixing the ingredients based on the predetermined amounts or percentages that were defined by various experimental productions, the mixture was heated and pasteurized and fermentation was triggered by adding the starter and regulating the optimum temperature. For the vitamin E–fortified beverage, vitamin E (600 IU as all-racemic-α-tocopherol) was added and homogenized throughout the mixture. That was followed by the addition of sterile mint flavor and final pasteurization. Microbial and sensory analyses of the beverages (microbial count, appearance, flavor, and color) were performed to ensure the safety and acceptability of the product before starting the trial.

The beverages were processed by Ramak Dairy Company in prepackaged bottles numbered for each patient based on the randomization sequence. According to the randomization order, a number was given to each person to receive 1 of the 2 whey beverages or the vitamin E capsules. A safe dose for vitamin E supplementation for HD patients has been reported as being 600 IU/d.[19] Fifteen grams of whey protein concentrate in the beverage was found to be acceptable by the sensory analyses conducted prior to the trial. This low-phosphorus (9.35 mg/100 g), low-sodium (62.5 mg/100 g), and low-potassium (0.0295%) protein source was used to replace animal protein in diets, and participants were instructed about the amount of animal protein they were permitted to consume per day according to their needs (1.2 g/kg).

Participants were visited at each dialysis session to assess their adherence. They were asked to return the empty bottles to receive the next set of bottles. Participants were to consume the beverages or capsules with their meals after the dialysis sessions or at home (for those who were dialyzed twice per week).

Outcomes

We assessed the nutritional status of patients by SGA score and MIS as primary outcomes, with body mass index (BMI), serum albumin, and transferrin values as secondary outcomes. The SGA is a comprehensive tool that serves as an inexpensive and rapid way of assessing patients' nutritional status. It needs no laboratory evaluation and is considered a valid reliable tool in HD patients.[20,21] To compensate for the lack of visceral protein assessment by SGA, the MIS was determined; this score incorporates serum laboratory markers of malnutrition, including serum albumin and transferrin levels.[22,23] At baseline and at the end of the treatment phase, the main investigator of this study (Z. Sohrabi), an experienced nutritionist working regularly with HD patients, completed the SGA questionnaires and performed physical examinations. Any changes in weight (during the preceding 6 months and 2 weeks), dietary intake, gastrointestinal problems, functional capacity, and any metabolic demand of the underlying disease were assessed. The physical examination assessed loss of subcutaneous fat, muscle wasting, and the presence of ankle/sacral edema. Each feature was separately rated as A, B, or C to show the degree of malnutrition. We then converted the