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Randomized control trials

Readmission and mortality in malnourished, older, hospitalized adults treated with a specialized oral nutritional supplement: A randomized clinical trial

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SUMMARY

Background: Hospitalized, malnourished older adults have a high risk of readmission and mortality.
Objective: Evaluation of a high-protein oral nutritional supplement (HP-HMB) containing beta-hydroxy-beta-methylbutyrate on postdischarge outcomes of nonelective readmission and mortality in malnourished, hospitalized older adults.
Design: Multicenter, randomized, placebo-controlled, double-blind trial.
Setting: Inpatient and posthospital discharge.
Patients: Older (≥65 years), malnourished (Subjective Global Assessment [SGA] class B or C) adults hospitalized for congestive heart failure, acute myocardial infarction, pneumonia, or chronic obstructive pulmonary disease.
Interventions: Standard-of-care plus HP-HMB ($n = 328$) or a placebo supplement ($n = 324$), 2 servings/day.
Measurements: Primary composite endpoint was 90-day postdischarge incidence of death or nonelective readmission. Other endpoints included 30- and 60-day postdischarge incidence of death or readmission, length of stay (LOS), SGA class, body weight, and activities of daily living (ADL).
Results: The primary composite endpoint was similar between HP-HMB (26.8%) and placebo (31.1%). No between-group differences were observed for 90-day readmission rate, but 90-day mortality was significantly lower with HP-HMB relative to placebo (4.8% vs. 9.7%; relative risk 0.49, 95% confidence interval [CI], 0.27 to 0.90; $p = 0.018$). The number-needed-to-treat to prevent 1 death was 20.3 (95% CI: 10.9, 121.4). Compared with placebo, HP-HMB resulted in improved odds of better nutritional status (SGA class, OR, 2.04, 95% CI: 1.28, 3.25, $p = 0.009$) at day 90, and an increase in body weight at day 30 ($p = 0.035$). LOS and ADL were similar between treatments.
Limitations: Limited generalizability; patients represent a selected hospitalized population.
Conclusions: Although no effects were observed for the primary composite endpoint, compared with placebo HP-HMB decreased mortality and improved indices of nutritional status during the 90-day observation period.
Clinical trial registration: www.ClinicalTrials.gov NCT01626742.

Abbreviations: ADL, activities of daily living; AMI, acute myocardial infarction; CHF, congestive heart failure; CI, confidence interval; COPD, chronic pulmonary obstructive disease; HMB, beta-hydroxy-beta-methylbutyrate; HP-HMB, high-protein beta-hydroxy-beta-methylbutyrate; ITT, intention-to-treat; LBM, lean body mass; LOS, length of stay; LS, least squares; MMSE, Mini Mental State Examination; NNT, number needed to treat; NOURISH, Nutrition effect On Unplanned ReadmIssions and Survival in Hospitalized patients; ONS, oral nutritional supplements; PNA, pneumonia; QoL, quality of life; SD, standard deviation; SE, standard error; SGA, Subjective Global Assessment.

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1. Introduction

Hospitalized older adults (≥65 years) are at high risk of malnutrition [1], which has a negative impact on subsequent clinical and economic outcomes, including a greater risk of mortality and a high rate of nonelective hospital readmission [2]. In particular, malnutrition at hospital admission is an independent predictor of subsequent hospital readmission [3] and is associated with higher mortality after hospital discharge [4].

Even short hospitalizations in older adults may have clinical consequences, such as loss of lean body mass (LBM) with accelerated functional decline [5]. This loss of LBM involves dysfunction of several cellular and physiologic processes [6] and may be exacerbated by malnutrition [7]. Patients often continue to lose body weight and LBM after hospital discharge, further adversely affecting outcomes [8].

Studies have shown that the use of oral nutritional supplements (ONS) in malnourished patients in community and hospital settings may reduce complications, mortality, and hospital readmissions [9–11]. While the prevalence of malnutrition is high [1], in a retrospective analysis of data over 11 years, only 1.6% of inpatient episodes out of 44.0 million involved ONS use [10]. In older patients, the effects of ONS have been extensively studied and have been consistently shown to increase body weight and improve nutritional status [11]. However, effects of ONS on readmission rates and mortality specifically in older adults have only been evaluated in small- to medium-sized trials, often involving heterogeneous populations [11–13]. While systematic reviews suggested that high-protein ONS (providing ≥20% total calories from protein) significantly reduced readmissions [14] and mortality [11] compared with controls, other systematic reviews and meta-analyses failed to show consistent results [12,13]. Thus, the efficacy of ONS on readmission and mortality in hospitalized, older adults remains uncertain.

Targeted ONS strategies for maintaining or protecting nutritional status in older adults have used a variety of supplements with different components including vitamin D, higher caloric content, amino acids, protein, and beta-hydroxy-beta-methylbutyrate (HMB) [14–16]. In particular, a role for supplemental protein has been suggested, since increased protein intake has been associated with improvement in LBM [17]. HMB, which is found naturally in the diet at very low levels and is an active metabolite of leucine, has been shown to regulate muscle protein metabolism with evidence supporting its safety and ability to prevent LBM loss during bed rest [18] and in patients with chronic diseases [15]. The current study evaluated a specialized, nutrient-dense ONS, containing both a high-protein content and HMB (HP-HMB), on postdischarge outcomes including nonelective readmission and mortality in initially hospitalized, malnourished, older adults. Eligible patients were those admitted for congestive heart failure (CHF), acute myocardial infarction (AMI), pneumonia (PNA), or chronic obstructive pulmonary disease (COPD), conditions previously shown to result in a high risk of 30-day readmission [19,20].

2. Methods

2.1. Study design

The NOURISH (Nutrition effect On Unplanned ReadmIssions and Survival in Hospitalized patients) study was a multicenter, prospective, randomized, double-blind, placebo-controlled, parallel-group study conducted in the United States between May 2012 and October 2014 (Fig. 1A). The study evaluated the effects of HP-HMB on the postdischarge incidence of hospital readmission, nutritional status indices and morbid events in older hospitalized adults. As per the initial protocol, the incidence of nonelective readmission within 90 days postdischarge was the primary outcome. Since death, which was a safety endpoint, and readmission are competing events, the composite event of death or nonelective readmission within 90 days postdischarge was defined as the primary efficacy endpoint. This definition was incorporated into the finalized statistical analysis plan subsequent to the interim analysis and prior to unblinding of the data; the sequence of finalization was consistent with Food and Drug Administration guidance and International Conference on Harmonisation guidelines.

During hospitalization, patients received the individual hospitals' standard nutritional care at the discretion of the attending physicians. Patients were instructed to consume 2 servings of their allocated study intervention (ie, HP-HMB or placebo) each day. During the 90-day postdischarge period, patients were instructed to continue to supplement their regular dietary intake with 2 servings daily of their allocated intervention, which was provided to the patients without charge. In order to maintain the blind, HP-HMB and placebo were packaged in identical Tetra Paks® identified only by product codes that were blinded to study investigators and sites; opaque straws were provided and used for consumption. Two flavors were available for each arm; patients were exposed only to the flavors of the assigned study arm product.

Patient assessments were performed at days 30, 60, and 90 or at study discontinuation and included intake of allocated intervention, morbidity, readmissions, functional and nutritional status, use of medications/dietary supplements, quality-of-life indices, medical care utilization, and adverse events (Fig. 1A). Blood was drawn at baseline and days 30 and 60. Additional contact via home visit or telephone was performed weekly to encourage compliance and collect information on morbid events, medical-care utilization and intake of allocated intervention, which were recorded by the patient in a provided record handbook. At the time of each clinical visit, the record was returned to the site coordinator to assess product intake compliance.

The protocol received approval from the appropriate site Institutional Review Board. All patients provided written informed consent.

2.2. Patients

Eligible patients were aged ≥65 years with a recent hospital admission (within 72 h) with a primary diagnosis of CHF, AMI, PNA, or COPD. Patients were required to have a Subjective Global Assessment (SGA) class of B (moderate or suspected malnutrition) or C (severe malnutrition); SGA is a validated tool that is considered the gold standard for assessment of malnutrition in hospitalized patients. All site personnel were trained on SGA and an instruction video was provided. Exclusion criteria were diabetes mellitus (type 1 or 2) due to product composition not intended for patients with diabetes mellitus; current active or treated cancer, and impaired renal or liver function. For details, see the Study Inclusion and Exclusion Criteria section (Supplementary Table 1).

Sites prescreened patients per hospital protocol, which ranged from screening all hospital admissions daily to reviewing computer-generated lists. If at least 1 eligibility criterion was not met, the reason was recorded and the patient was excluded.