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Oral Nutrition Supplement Improved Nutritional Status in Malnourished Hip Fracture Patients: A Randomized Controlled Study

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Authors' contributions

This work was carried out in collaboration between all authors. Authors ML, JSO and ACV designed the study, wrote the protocol, and interpreted the data. Author JSO performed statistical analysis. Authors ML and ACV participated in study conduction and data interpretation. Author ML drafted the manuscript. Authors GG, IK, LR and GK carried out the subject's enrollment, assignment, and clinical evaluation, and collected clinical data. All authors read and approved the final manuscript.

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ABSTRACT

Background: Nutritional status has been shown to predict post-surgical recovery and clinical outcomes in orthopedic patients. This study evaluated the effects of an oral nutrition supplement (ONS) in patients undergoing hip fracture surgery.
Materials and Methods: In a multicenter, prospective, randomized study (ClincialTrials.gov, registration number NCT01011608), malnourished patients (n=127) who had surgery within 14

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days of hip fracture and had screening serum albumin levels ⩽ 38 g/L were enrolled. Patients in the ONS group were fed a calorically dense, high protein ONS, providing 798 kcal, 34 g protein/day for 28 days following surgery. Control patients received standard hospital diet only. Weight, nutritional and clinical markers were measured at Baseline, days 14 and 28. Suture status and functional recovery were evaluated on days 14 and 28.Means ± SEM are reported.

Results: Baseline characteristics were similar between groups. On day 28, albumin level was improved in the ONS group (4.9±1.4 g/L) compared to the control group (1.2±1.0 g/L, p=0.054). A significant increase in prealbumin was observed in the ONS group (5.0±1.0 mg/dL) vs. control (1.0±1.2 mg/dL, p=0.007). Body weight increased in the ONS group (2.1±0.6 kg) but decreased in the control group (-0.8±0.8 kg; p=0.01).

Conclusion: Supplementation of a nutritionally complete, calorically dense, high protein ONS for 28 days significantly improved nutritional status in mild to moderately malnourished patients undergoing hip fracture surgery.

Keywords: Oral nutrition supplement; ONS; nutritional status; malnutrition; hip fracture surgery.

1. INTRODUCTION

Nutritional status significantly impacts the recovery process in patients after surgery. While nutritional demand significantly increases, postoperative loss of appetite decreases the exogenous caloric and nutrient supply necessary for energy and wound healing [1]. A number of studies have reported that elderly patients undergoing hip fracture or hip replacement surgeries are at increased risk of malnutrition [2-4], which is associated with an increased incidence of adverse clinical outcomes, such as impaired wound healing, infections, longer hospital length of stay, and the development of pressure ulcers [5]. The *ESPEN Guidelines on Enteral Nutrition: Geriatrics* (2006) recommends the use of oral nutrition supplements (ONS) to reduce unfavorable outcomes in geriatric patients after hip fracture and orthopedic surgery [6].

Use of ONS has been shown to increase nutrient intake and improve nutritional status in a variety of patient groups in the hospital setting, including patients after hip fracture surgery [7,8]. However, the effect on functional outcomes has not been well defined [7]. Systematic reviews and a meta-analysis reported protein and energy supplementation may be beneficial for hip fracture patients, but the evidence is weak [9,10]. A previous study by Neumann et al showed that a high protein containing ONS, providing 30 g of protein/d, significantly improved serum albumin levels after 28 days of supplementation in elderly patients undergoing surgical repair of a hip fracture compared to control patients who received an ONS providing 17.8 g/d protein [11]. However, it showed no effect on rehabilitation length of stay or functional independence [11]. The effect of supplementation with ONS before and during hospitalization for hip fracture surgery is still not clear, particularly in malnourished elderly patients. Thus, the purpose of this study was to examine the effect of a nutritionally complete, energy and protein-dense ONS on nutritional status and clinical course in malnourished patients admitted to the hospital for hip fracture surgery.

2. MATERIALS AND METHODS

2.1 Participants and Study Design

This multi-center, prospective, randomized, unblinded, two-arm study was conducted in Russia from 2009 to 2010 and approved by an Independent Ethics Committee (IEC) at each of the local hospitals in which the study was conducted (ClinicalTrials.gov identifier: NCT01011608). Male or female patients who provided written informed consent (age ⩾ 45 years) and were expected to undergo surgical hip fracture repair within 14 days from fracture, had admission total protein level ⩽ 70 g/L and screening serum albumin ⩽ 38 g/L, Subjective Global Assessment (SGA) score B or C, and able to consume foods and beverages orally were eligible for this study. The age cut-off of 45 years old was chosen because women who were over 45 years of age appeared to have longer length of hospital stay due to risks of osteoporosis [12]. Patients were excluded from the study if they had: type 1 diabetes, uncontrolled type 2 diabetes (defined HbA1c > 8%), active malignancy, chronic, contagious, infectious disease (such as active tuberculosis, Hepatitis B or C, or HIV), alcohol or substance abuse, severe dementia, gastrointestinal conditions that may interfere with nutrient intake or digestion, or known allergy or intolerance to

any ingredient found in the ONS. All patients stayed in hospitals for 28 days after surgery for the study.

Procedures were in accordance with the International Committee for Harmonization, Good Clinical Practice, and the Helsinki Declaration. After the informed consent and any applicable privacy authorization were obtained, eligible patients were randomized to either the ONS group or the control group using a computer-generated randomization plan on a 1:1 ratio. Each study center had its own randomization schedule. As eligible subjects were enrolled, they were assigned a subject number sequentially starting with the first envelope indicating the group assignment. Randomization envelopes were opened and used in ascending numerical order.

Subjects in the ONS group received standard hospital food plus ONS supplementation (Ensure TwoCal; Abbott Nutrition, Columbus, Ohio, USA). The ONS was a nutritionally complete, energy and protein-dense drink including 30 vitamins and minerals. A total of two containers (200 mL per container) were given 3 times a day - 100 mL between breakfast and noon meal, 100 mL serving between noon and evening meal, and 200 mL as a snack before going to bed. This regimen provided an additional 798 kcal and 34 g protein per day. Those in the control group received usual care and standard hospital food. All patients were recruited before the hip repair surgery and were followed for 28 days after the resumption of oral diet following surgery. The ONS was given when informed consent was obtained and baseline procedures were completed. Study procedures are shown in (Fig. 1) Clinical data and blood chemistries were evaluated at baseline (before surgery), on day 14 from the resumption of oral diet after surgery, and on day 28. Functionality and surgical site assessment were evaluated on day 14 and day 28. Adverse events (AE) and ONS intake were also recorded.

2.2 Nutritional, Clinical and Functional Status

Patient's weight was measured using a calibrated bed scale at the screening. If patients were able to stand without support, a calibrated standing scale was used on days 14 and 28. Height reported by patients or their family members was collected at the screening and used to estimate patient's energy needs. Standing height was measured at the study exit to calculate BMI.

The total calculated daily energy needs were estimated based on the Harris-Benedict equation adjusted by activity, injury and infection factors (Table 1). Adjusted body weight was used if a patient had a BMI $\geqslant$ 30. All patients consumed standard hospital food post-surgery. Actual dietary intake was not measured because it was not standard practice in Russia and infrastructure to support such data collection was unavailable. Instead, the calculated percent of energy met by ONS intake was used to estimate the amount of calories provided by the ONS based on the patient's energy requirement.

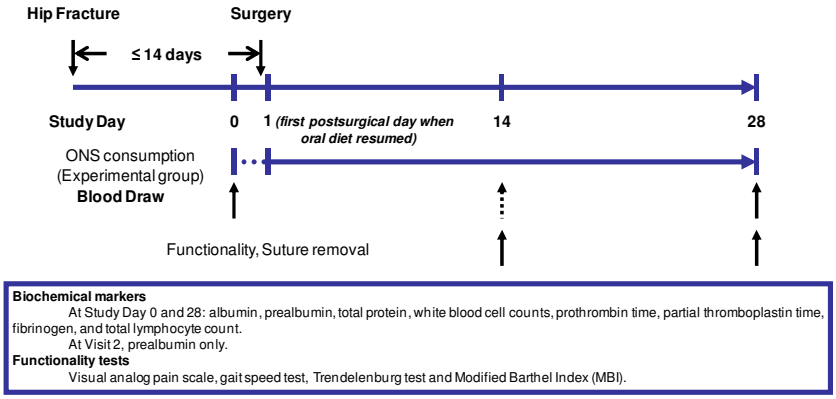

Fig. 1. Study design scheme

At baseline and on day 28, fasting blood samples were obtained and sent to a central laboratory to measure serum albumin, prealbumin, total protein, prothrombin time, partial thromboplastin time, fibrinogen, and total lymphocyte count levels. Samples for albumin measurement were redrawn within 7 days of original blood draw if blood was hemolyzed during the process. On day 14, only serum prealbumin level was measured. On study day 14 and 28, surgical site status was assessed and functional outcomes including pain (measured by Visual Analog Pain Scale (VAS)), gait speed (time in seconds to walk 10 meters), Trendelenburg test, and Modified Barthel Index (MBI) score were evaluated.

No further data other than adverse events were collected on patients in the ONS group if they never consumed the ONS or did not consume the ONS for more than 3 continuous days. Data are shown for patients who received the ONS according to the randomization scheme, consumed $\geqslant$ 75% ONS over the post-surgery study period, and had serum albumin level measured at baseline and on day 28.

2.3 Statistical Analysis

Analysis of variance (ANOVA), analysis of covariance (ANCOVA), and repeated measures analyses were used to analyze continuous data. When a parametric model failed to fit the data, a nonparametric test (Wilcoxon rank-sum test) was used. Cochran-Mantel-Haenszel (CMH) general association and row mean scores differ test statistics were used to analyze categorical data. Mean ± SEM are reported for continuous data. Frequencies and percentages are reported for categorical data. P values $\leqslant$ 0.05 were considered to be statistically significant.

A power analysis was conducted using nQuery Advisor® Version 5.0 software and determined that 86 patients (43 per study group) were needed to provide 80% power (for a two-sided, 0.05 level t-test) to detect at least a 3.0 g/L difference in change in albumin from baseline to day 28 assuming a standard deviation of 4.9 g/L. Due to higher drop-out rate, the study enrollment was increased to 127 patients total.

3. RESULTS

A total of 127 patients from 6 study sites were enrolled. Data were evaluated only in subjects for whom medical records were available for source verification of study data. The CONSORT diagram (Fig. 2), shows the disposition of patients. Blood and other data were analyzed in 46 evaluable patients (n=22 in the ONS group; n=24 in the control group) and weight data were analyzed in 21 patients.

There were no statistical differences between the ONS and control groups in patient characteristics at baseline (Table 2). Although the cut-off age for the study was 45 years old, the mean age of the ONS group was 72.4±1.9 years and that of the controls was 67.3±2.4 years. All patients had SGA score of B. Patients in both groups had similar use of types of anticoagulant medications and duration of use (data not shown).

3.1 Oral Nutrition Supplement

Patients in the ONS group had good compliance and consumed91 to 100% of recommended intake. Prior to surgery, 11 patients consumed the ONS for an average of 3.5±0.7 days. The mean daily ONS consumption was 348±30 mL/day, providing 694±60 kcal and 30±2.6 g protein each day. After surgery, all patients resumed oral intake either on the same day (10 in the ONS group and 13 in control group) or on the following day (12 in the ONS group and 11 in the control group). The patients in the ONS group consumed the supplemented ONS for at least 27 days from initiation of oral intake following surgery. The mean daily ONS intake after surgery was 395±1 mL, which provided 768±3 kcal per day. The mean daily caloric need in the ONS group was 1727±40 kcal, 45±1% of which was provided by the ONS.

A total of 44 AEs were reported in the study; 20 from the ONS group and 24 from the control group. Two AEs (one for nausea and one for pruritus) were assessed as possibly related to the consumption of ONS. The remaining 18 AEs from the ONS group were assessed as not associated with the ONS. No serious AEs were reported in either study group. Therefore, the ONS was well tolerated in the study.

3.2 Nutritional and Blood Chemistry Data

The baseline blood chemistries were similar between the ONS and control groups except that control patients had higher monocyte counts than patients in the ONS group (0.70±0.06 vs. 0.54±0.04 x 10^3 / μL, p = 0.039; Table 3).

Table 1. Calculation of energy needs

Harris-Benedict equation of basal energy expenditure (BEE)					
Male	BEE = 66.5 + (13.75 x Weight in kg) + (5.003 x Height in cm) – (6.775 x Age in years)				
Female	BEE = 665.1 + (9.563 x Weight in kg) + (1.850 x Height in cm) – (4.676 x Age in years)				
Activity factor		**Injury factor**		**Infection factor**	
1.2	confined to bed	1.0	no surgery	1.0	no infection
1.3	out of bed	1.3	surgery	1.1	mild
				1.5	moderate
				1.8	severe

Table 2. Baseline demographic characteristics

	ONS(n=22)	Control(n=24)
Gender, n (%)		
Male	4 (18)	7 (29)
Female	18 (82)	17 (71)
Age (yrs)	72.4±1.9	67.3±2.4
Height (cm)[a]	167.8±2.3	165.5±2.7
Weight (kg)[a]	70.5±3.6	72.9±4.6
BMI (kg/m^2)[a]	25.1±1.4	26.7±1.7
BEE (Kcal/day)[a, b]	1311±34	1304±68

[a]Data based on 12 control and 9 ONS group patients; [b]BEE: basal energy expenditure

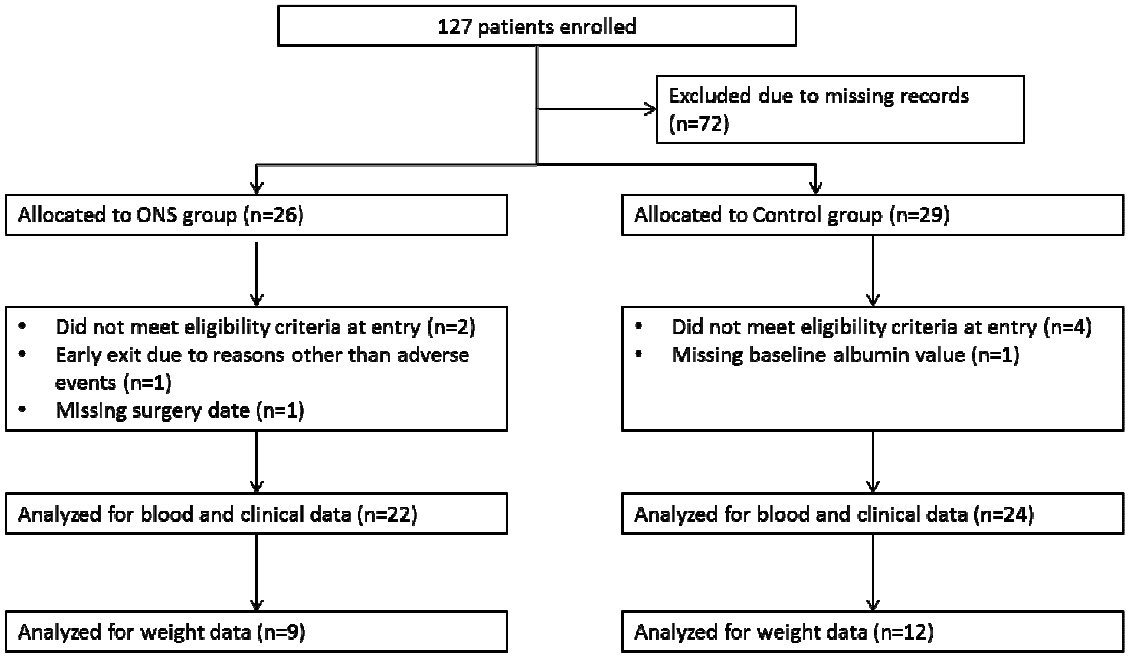

Fig. 2. CONSORT diagram representing study enrollment and evaluable sample size

Table 3. Nutritional and clinical markers over time

	ONS group				Control group				*p-value*[b]
	Baseline	**Day 14[a]**	**Day 28[a]**	**Change from baseline to day 28**	**Baseline**	**Day 14[a]**	**Day 28[a]**	**Change from baseline to day 28**	
Total protein (g/L)	62.4±1.3	--	69.3±1.4	6.9±1.4	63.2±1.2	--	66.1±1.7	2.9±1.7	NS[d]
Albumin (g/L)	40.4±1.2	--	45.2±1.2	4.9±1.4	41.0±0.9	--	42.2±1.2	1.2±1.0	0.054
Prealbumin (mg/dL)	18.8±1.0	19.6±1.1	23.8±1.1	5.0±1.0	18.3±1.2	17.8±1.2	19.3±1.2	1.0±1.2	0.007
Weight (kg)	70.5±3.6	71.4±3.4	72.6±3.5	2.1±0.6	72.9±4.6	72.1±4.2	72.1±4.1	-0.8±0.8	0.010
Monocytes ($10^3/\mu L$)	0.54±0.04	--	0.62±0.03	0.08±0.05	0.70±0.06[c]	--	0.55±0.04	-0.11±0.06	0.025
Lymphocytes ($10^3/\mu L$)	1.49±0.11	--	2.06±0.13	0.63±0.14	1.86±0.18	--	1.87±0.12	0.06±0.18	0.020
Fibrinogen (g/L)	4.74±0.37	--	3.10±0.28	-1.73±0.35	4.61±0.25	--	3.95±0.35	-0.98±0.38	NS
prothrombin time (%)	96.0±4.4	--	93.8±5.6	1.3±6.9	102.3±2.9	--	99.3±5.0	1.0±3.3	NS
partial thromboplastin time (seconds)	36.7±4.8	--	41.5±5.0	1.7±7.7	30.9±2.0	--	37.6±3.8	6.9±3.8	NS

[a]: Day 1: the first postsurgical day that control group resumes oral diet or ONS group resumes Ensure 2 consumption; [b]: comparison in changes from baseline to day 28 between the ONS and control groups; [c]: comparison between two groups at baseline ($p < 0.05$). [d]: NS=not significant

From baseline to day 28, the changes in total lymphocyte count were higher in the ONS group than the control group (0.63±0.14 vs. 0.06±0.18 x 103 / µL, p = 0.020). The monocyte count was increased in the ONS group (0.08±0.05 x 103 / µL) but decreased in the control group (-0.11±0.06 x 103 / µL; p = 0.025). There was no difference between the two groups in prothrombin time, partial thromboplastin time, fibrinogen, or any other hematology laboratory values (Table 3).

3.3 Functional Status

There were no differences between the study groups in pain VAS score, gait speed, Trendelenburg test and total MBI scores at days 14 and 28 (). Notably, one of the MBI domains, moving from wheelchair to bed and return, tended to be better in the ONS group than the control group on day 14; however, it did not reach statistical significance (p = 0.10). However, on day 28, there were no differences in any MBI domains between the two groups.

3.4 Surgical Site Status

The sutures were removed 12.9±0.2 days after surgery in the ONS group and 13.5±0.4 days after surgery in the control group. The proportion of patients whose sutures were removed within 12 days was similar between the ONS and control groups (32% vs. 21%, respectively, NS). According to Russian standard practice, surgical sutures are commonly removed approximately 12 days after surgery.

4. DISCUSSION

Deteriorated nutritional status is common (28 – 59%) in adults undergoing orthopedic surgeries, particularly in elderly population [2,3]. Worsened clinical outcomes and longer hospital length of stays have been repeatedly reported in patients with low albumin levels [4]. Better nutritional status has been shown to be associated with lower incidence and severity of post-surgical complications such as impaired wound healing, infection, pressure ulcer, and shorter hospital stay [3,5,13]. ONS is given to patients to meet their caloric and protein goals and improve clinical outcomes. An 11 year retrospective study showed that provision of ONS to hospitalized adult patients led to shortened hospital length of stay, reduced hospital cost and decreased 30-day hospital readmission rates [14]. In a recent randomized controlled study conducted in 50 patients after hip fracture surgery, ONS use to provide additional calories to meet energy needs calculated by indirect calorimetry improved energy balance, resulting in fewer complications and shorter hospital length of stay [15]. In hip fracture patients receiving rehabilitation therapy, ONS reduced the length of stay in rehabilitation by about 10% and the overall number of infection episodes by about 50% [16]. Although actual food intake was not measured in the present study and the total amount of protein and calories consumed was unknown, energy requirement was estimated based on the widely used equation with adjustment of activity, injury and infection factors. It is possible that the use of Harris-Benedict equation may over-estimated the caloric needs, the ONS supplementation at 2 servings per day indeed provided a significant amount of daily caloric requirement (~45%), which resulted in improved nutritional status and blood parameters in malnourished hip fracture patients despite the metabolic challenge from fracture and subsequent surgery.

One limitation of this study is that data from many patients were excluded from analysis. This study underwent a rigorous data monitoring process conducted by a Contract Research Organization. If a patient's data could not be source-verified from the patient's hospital or related records, data from the patient were not included in the analysis. As a result, the data for 72 out of 127 enrolled patients were not included due to missing medical records; 46 patients remained in the study for analysis of blood and clinical variables and 21 remained for analysis of weight due to eligibility criteria not met, early exit and missing data. The planned sample size (43 per group) was not reached. This may potentially bias the study results and imbalance the study groups. However, the baseline demographic and clinical characteristics were similar between the two groups except the control group had slightly higher monocytes count (Table 3). In addition, the magnitudes of changes in the outcomes, such as albumin, prealbumin are similar to the literature.

Lately, it has been recognized that albumin and prealbumin may function as inflammatory markers and reflect changes in inflammation and stress during acute and chronic diseases [17]. Therefore, their levels are good indicators of nutritional status. Similar to earlier studies, [11,18,19] this study observed significant increase in serum albumin (4.9±1.4 g/L) and

prealbumin levels (5.0±1.0 mg/dL) after the 28-day consumption of study ONS. These changes were significantly different compared to changes in the control groups. The small increase in the albumin and prealbumin level in the control group is possibly due to attenuated metabolic stress during the recovery process. In addition, weight was increased in the patients receiving ONS (2.1±0.6 kg) but decreased in the control group (-0.8±0.8 kg, p = 0.01). Therefore, it is reasonable to link increased albumin and prealbumin levels, at least partly, to a better nutritional status in this study population.

Different types of supplements are available for patients who are malnourished or at risk of malnutrition. This study provided ~800 kcal and 34 g protein every day and resulted better albumin and prealbumin levels and weight. The intervention started 3.5 (±0.7) days before the surgery or right after surgery (if not started before the surgery) and lasted for 28 days post-operatively. The study conducted by Neumann et al. [11] tested the effects of 3-week ONS supplementation at two protein levels but similar amount of calories in an elderly hip fracture population ($\geqslant$60 years) with BMI $\leqslant$30 kg/m^2. The experimental group received 30 grams of protein versus 17.8 grams per day in the control group [11]. The high protein consumption group had a 7 g/L increase in albumin level versus a 2 g/L increase in the low protein consumption group after a 28 day supplementation [11]. These data suggest that provision of ~ 30 grams protein per day may be necessary to improve nutritional status in patients undergoing orthopedic surgery. This is particularly important for patients who are malnourished before surgery.

ONS supplementation decreases risks of postoperative complications in elderly patients after hip fracture surgery or orthopedic surgery [18,20,21]. This study was not designed to show the effect of ONS on hospital-acquired infection and no infection data was collected. There were no differences between groups in the time for suture removal and pain status. However, improved lymphocyte and monocyte counts were noted in the ONS group.

Functionality in elderly patients is commonly assessed by gait speed, total MBI score, and Trendelenburg test. [22-25] Multiple factors determine recovery process and functional improvement in patients undergoing orthopedic surgery. Nutritional status is one of them. For example, a 6-month follow up study in elderly patients after hip fracture did not show benefit of ONS consumption for 60 days on functional recovery and fracture-related mortality during the 6 months follow-up [21]. However, less in-hospital and total complications were reported [21]. The present study was powered to detect differences in albumin changes over time rather than changes in functionality. Moreover, the rehabilitation programs were not standardized at the 5 sites in this study. Therefore, that no difference in these functionality measures was observed is not surprising. Future studies should include muscle power and strength measures.

The study ONS was well tolerated; only two adverse events reported were possibly related to the consumption of the ONS (one each nausea and pruritus). Comparing subjects who received ONS to controls, there were no differences in blood coagulation parameters including prothrombin time, partial thromboplastin time, and fibrinogen. This indicates that study ONS has no effect on alteration of blood coagulation status. This information strongly suggests there should be no medical concerns with the intake of this nutritional supplement.

Table 4. Functional status on day 14 and day 28

	ONS group		Control group		*P value*
	Day 14[a]	Day 28	Day 14	Day 28	
Pain VAS score	3.1±0.3	1.0±0.2	2.5±0.3	1.0±0.2	NS[b]
Gait speed (seconds)[c]	61±7	56±7	71±6	66±6	NS
Total MBI score	56±5	74±5	51±4	68±4	NS
Trendelenburg test (positive / negative, n)	11 / 1	15 / 3	14 / 2	20 /3	NS

[a]: Day 1: the first postsurgical day that control group resumes oral diet or ONS group resumes Ensure 2 consumption; [b]: NS = not significant; [c]: gait speed is reported as time in seconds to walk 10 meters

5. CONCLUSION

ONS supplementation for 28 days post-surgery is a safe, effective and non-invasive way to improve nutritional status and immunity in patients after hip fracture surgery. This regimen may be considered for mildly to moderately malnourished patients undergoing orthopedic surgery.

COMPETING INTERESTS

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