Effects of Oral Nutritional Supplements on Mortality, Missed Dialysis Treatments, and Nutritional Markers in Hemodialysis Patients

Debbie Benner, MA, RD, CSR, Steven M. Brunelli, MD, MSCE,† Becky Brosch, RD, CSR,* Jane Wheeler, MS, RD,* and Allen R. Nissenson, MD*'‡*

Objective: Protein-energy wasting is common in end-stage renal disease patients undergoing dialysis and is strongly associated with mortality and adverse outcomes. Intradialytic oral nutritional supplements (ONS) reduce risk of mortality in these patients. Large studies characterizing the impact of ONS on other outcomes are lacking. We assessed the associations between administration of ONS and clinical and nutritional outcomes.

Design: Retrospective evaluation of a pilot program providing ONS to patients at a large dialysis organization in the United States. The pilot program provided ONS to in-center hemodialysis patients with serum albumin ≤3.5 g/dL at 408 facilities.

Subjects: ONS patients were compared to matched controls with serum albumin ≤3.5 g/dL, identified from facilities not participating in the ONS program (n = 3,374 per group).

Intervention: Receipt of ONS.

Main Outcome Measures: Death, missed dialysis treatments, hospitalizations, serum albumin, normalized protein catabolic rate, and postdialysis body weight were abstracted from large dialysis organization electronic medical records.

Results: There was a 69% reduction in deaths (hazard ratio = 0.31; 95% confidence interval = 0.25-0.39), and 33% fewer missed dialysis treatments (incidence rate ratio = 0.77; 95% confidence interval = 0.73-0.82) among ONS patients compared to controls ($P < .001$ for both). The effects of ONS on nutritional indices were mixed: serum albumin was lower, whereas normalized protein catabolic rate values, a surrogate for dietary protein intake, and postdialysis body weights were higher for ONS patients compared to controls during follow-up.

Conclusions: Our evaluation confirmed the beneficial effects of ONS in reducing mortality and improving some indices of nutritional status for hypoalbuminemic hemodialysis patients. We also report the novel finding that ONS can reduce the number of missed dialysis treatments. These results support the use of intradialytic ONS as an effective intervention to improve the outcomes in hemodialysis patients with low serum albumin.

Introduction

PROTEIN-ENERGY WASTING (PEW) is a complex clinical condition characterized by multiple metabolic and nutritional derangements and is highly prevalent among end-stage renal disease (ESRD) patients receiving dialysis.[1-3] Several factors contribute to the development of PEW in ESRD, including lack of uremic toxin clearance, inflammation, inadequate protein intake, and catabolic consequences of hemodialysis.[1,4] Low serum albumin concentration, which though nonspecific is by far the most commonly used marker for PEW in clinical practice, is a strong predictor of mortality and poor clinical outcomes in dialysis patients.[5-7] Targeting PEW through dietary interventions has been proposed as a strategy to improve clinical outcomes in dialysis patients.[8,9] Observational studies have shown that intradialytic administration of oral nutritional supplements (ONS) can reduce risk of mortality for patients with low serum albumin.[10,11] However, there is a lack of data from large, well-powered studies on the effects of ONS on other outcomes. Here, we report the findings from a retrospective evaluation of a pilot program to provide ONS to hypoalbuminemic hemodialysis patients at a large dialysis organization (LDO) where we assessed the effects of ONS on mortality, missed dialysis treatments, hospitalizations, and nutritional markers.

Materials and Methods

Study Design

This was a retrospective evaluation of a pilot program at 408 facilities within an LDO that provided ONS to patients with serum albumin concentrations ≤3.5 g/dL as measured

*DaVita Inc, Denver, Colorado.
†DaVita Clinical Research, Minneapolis, Minnesota.
‡David Geffen School of Medicine, University of California, Los Angeles, California.

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Address correspondence to Debbie Benner, MA, RD, CSR, 2000 16th St., Denver, CO 80202. E-mail: debbie.benner@davita.com

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by bromocresol green. We conducted our retrospective evaluation using deidentified patient data collected during the course of routine patient care; therefore, according to 45 Code of Federal Regulations (CFR) part 46 from the US Department of Health and Human Services, this study was exempt from institutional review board or ethics committee approval. We adhered to the Declaration of Helsinki, and informed consent was not required.

Data Source and Study Patients

Data were derived from the electronic health records (EHRs) of the LDO. This evaluation included patients from all payors except for those who were US Veterans Affairs beneficiaries (contractual stipulation). Eligible patients were those who between September 01, 2012, and January 31, 2013: were ≥18 years; received in-center hemodialysis (ICHD) at LDO facilities; had a recorded body mass index; if treated at participating facilities, had albumin ≤3.5 and received at least 1 dose of ONS; and if treated at nonparticipating facilities, had albumin ≤3.5 g/dL. ONS was prescribed as one serving per treatment that was to be consumed in the dialysis center unless extenuating circumstances, such as nausea, prevented in-center consumption. There were 2 different ONS product formulary options Novasource Renal (21.6 g protein, 475 calories/237 mL serving) or Liquacel (16 g protein, 70 calories/30 mL serving) from which the patients could choose. ONS treatment continued until serum albumin concentrations were >3.9 g/dL for 1 month, or >3.7 g/dL for 2 consecutive months or the patient refused the supplement for 6 consecutive sessions, or ONS was discontinued by a physician. Participation in the ONS program was re-evaluated for hyporesponse by a physician and registered dietitian after 6 consecutive albumin concentrations <3.6 g/dL. Patients exhibiting contraindications, such as dysphagia or intolerance to food or supplements during dialysis, were not included in the ONS program.

Exposure

Exposure status was adjudicated as above. Date of entry was defined as the first date of the first month following initial ONS treatment (for ONS patients) or qualifying albumin measurement (for control patients). ONS patients were propensity matched to eligible controls. Propensity scores were estimated using a logistic model in which the receipt of ONS was the dependent variable and was predicted as of entry date on the basis of: qualifying albumin level, month of entry, age, sex, race, etiology of ESRD, access type, diabetes, Charlson comorbidity score, dialysis vintage, body mass index, hospitalization in the prior month, hemoglobin level, and serum phosphorus. ONS patients were matched 1:1 to controls using a nearest neighbor matching algorithm.

Outcomes

Patients were followed for 8 months starting on the date of entry. Outcomes were considered beginning on entry date and continuing until end of study or censoring due to death, transfer of care, transplant, recovery of renal function, withdrawal from dialysis or modality change. Clinical outcomes considered in this study were patient deaths and missed dialysis treatments. We also analyzed serum albumin, normalized protein catabolic rate (nPCR), and postdialysis body weight as nutritional markers.

Statistical Analysis

Baseline demographics and characteristics were considered as of date of entry and were summarized for each group as means, standard deviations, medians, interquartile ranges, counts, and proportions, as dictated by data type. Comparisons between groups were made with t-tests and chi-square tests as appropriate.

Risk of death during follow-up was compared between ONS patients and matched controls using Cox proportional hazard models. Crude incidence rates for missed dialysis treatments were calculated by dividing the sum of events by the sum of cumulative at-risk time in ONS patients and matched controls. Incidence rate ratios were estimated by negative binomial regression. Serum albumin, nPCR, and postdialysis weight were examined using mixed linear models with patient-level random intercepts. For clinical laboratory tests measured more than once in a month, the first recorded value in the month was used.

Results

Baseline Characteristics

There were 3,374 qualifying ICHD patients treated with ONS and 48,298 eligible controls. Prior to matching, there was significant imbalance between cohorts on the majority of variables (Supplementary Data, Table S1). Notably, ONS patients were older, were more likely to use arteriovenous fistulas for vascular access, and had higher Charlson comorbidity index scores. All ONS patients were successfully matched to one control patient. In the matched analytical cohort, patient characteristics were well balanced (Table 1). Subsequent results pertain to the matched analytical cohort.

Clinical Outcomes

Overall, there were 555 deaths during 2,850 patient-years of at-risk time. Survival was significantly greater among ONS patients compared to controls (Fig. 1). The mortality rate among ONS patients was 10.9 deaths per patient-year, which was significantly lower when compared to 29.1 deaths per patient-year in matched controls (hazard ratio [95% confidence interval {CI}] = 0.31 [0.25, 0.39]; $P < .001$).

The association of ONS with missed dialysis treatments is presented in Figure 2. Patients treated with ONS missed 1.35 dialysis treatments per patient-month, which was significantly lower when compared to 1.69 missed dialysis

treatments per patient-month in matched controls (incidence rate ratio [95% CI] = 0.77 [0.73, 0.82]; $P < .001$). In this era, hospitalization data were incompletely captured in the EHR. Despite the implied bias, we examined the apparent association between ONS use and risk of hospitalization (incidence rate ratio [95% CI] = 0.92 [0.86, 0.97]; $P = .006$).

Table 1. Demographics and Baseline Characteristics for Matched Control and ONS Patients

Variable	Control, N = 3,374	ONS, N = 3,374	*P*-value
Age, y; mean ± SD	67.2 ± 13.9	66.8 ± 13.7	.25
Female, n (%)	1,623 (48.1)	1,590 (47.1)	.42
Race, n (%)			.69
White	1,469 (43.5)	1,501 (44.5)	
Black	1,055 (31.3)	1,055 (31.3)	
Hispanic	506 (15.0)	501 (14.9)	
Other	344 (10.2)	317 (9.4)	
ESRD etiology, n (%)			.95
Hypertension	846 (25.1)	849 (25.2)	
Diabetes mellitus	1,716 (50.9)	1,704 (50.5)	
Other/unknown	812 (24.1)	821 (24.3)	
Vascular access, n (%)			.92
Arteriovenous fistula	1,715 (50.8)	1,718 (50.9)	
Arteriovenous graft	549 (16.3)	559 (16.6)	
Center venous catheter	1,110 (32.9)	1,097 (32.5)	
Diabetes, n (%)	2,427 (71.9)	2,419 (71.7)	.83
Charlson score, n (%)			.87
2	108 (3.2)	107 (3.2)	
3	133 (3.9)	152 (4.5)	
4	340 (10.1)	361 (10.7)	
5	538 (16.0)	527 (15.6)	
6	725 (21.5)	705 (20.9)	
7	670 (19.9)	679 (20.1)	
8+	860 (25.5)	843 (25.0)	
Vintage, mo, n (%)			.79
≤3	603 (17.9)	575 (17.0)	
3–12	605 (17.9)	586 (17.4)	
12–24	489 (14.5)	475 (14.1)	
24–48	620 (18.4)	654 (19.4)	
>48	932 (27.6)	955 (28.3)	
Missing	125 (3.7)	129 (3.8)	
Postdialysis weight, kg mean ± SD	76.8 ± 21.9	77.8 ± 22.3	.08
BMI, kg/m^2 mean ± SD	27.2 ± 7.3	27.3 ± 7.4	.61
Qualifying albumin, g/dL mean ± SD	3.3 ± 0.3	3.3 ± 0.3	.97
Hospitalization in prior month, n (%)	762 (22.6)	768 (22.8)	.86
Hemoglobin, g/dL, n (%)			.94
≤9	420 (12.5)	399 (11.8)	
9–10	740 (21.9)	754 (22.4)	
10–11	1,235 (36.6)	1,245 (36.9)	
11–12	721 (21.4)	706 (20.9)	
>12	241 (7.1)	254 (7.5)	
Missing	17 (0.5)	16 (0.5)	
Phosphorus, mg/dL, n (%)			.81
≤3.5	762 (22.6)	762 (22.6)	
3.5–5.5	2,212 (65.6)	2,202 (65.3)	
>5.5	366 (10.9)	382 (11.3)	
Missing	34 (1.0)	28 (0.8)	

BMI, body mass index; ESRD, end-stage renal disease; ONS, oral nutritional supplements; SD, standard deviation.

Nutritional Markers

We considered serum albumin, nPCR, and postdialysis body weight as markers of nutritional status in ONS and matched control patients (Fig. 3). Relative to matched controls, mean monthly serum albumin concentrations were significantly lower in ONS patients ($P < .001$). By contrast, mean nPCR values were higher in all months for ONS patients relative to matched controls. Mean differences in nPCR were statistically significant in all months except month 8. Relative to matched controls, mean postdialysis body weights were higher for ONS patients in all months during follow-up; differences were statistically significant in months 7 and 8.

Discussion

In this study, we retrospectively evaluated the association between intradialytic ONS and outcomes for an ONS pilot program at an LDO. We found that patients who received ONS had a 69% lower risk of death relative to matched controls. This reduction is consistent with but markedly larger than previous observational studies of ONS at LDOs, despite having the same ONS qualification criteria of serum albumin ≤3.5 g/dL. For comparison, one study reported 5–9% and 29–34% reductions in intention-to-treat and as-treated analyses, respectively,[10] while another reported a 29% reduction in death for patients receiving ONS.[11]

We also found a 33% reduction in the missed dialysis treatments among ONS recipients. Prior work by our group has shown that about 50% of missed treatments are due to hospitalizations, while the remainder are due to absenteeism,[12] suggesting that reductions in missed treatments may be a good marker for effects on hospitalization in studies such as this where reliable hospitalization data are not available. We did examine the hospitalization data that were available

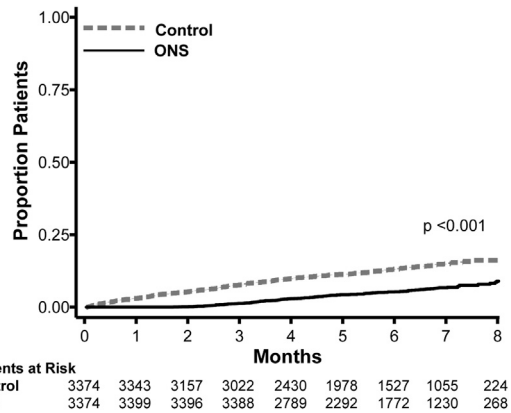

Figure 1. Cumulative incidence curve for death for ONS patients and matched controls. ONS, oral nutritional supplements.

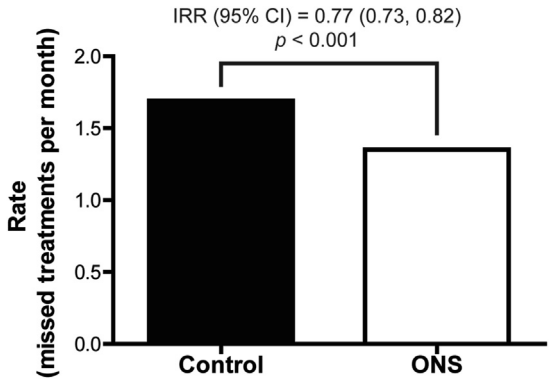

Figure 2. Association of ONS with missed dialysis treatments. CI, confidence interval; IRR, incidence rate ratio; ONS, oral nutritional supplements.

(notwithstanding its poor sensitivity): although ONS was associated with a reduction, the magnitude of this reduction (8%) was less than that would have been anticipated based on the missed treatment data. Given the speculative nature of the extrapolation of missed treatment effects to hospitalization effects on the one hand and the poor sensitivity of the available hospitalization data on the other, the magnitude of the effect of ONS on hospitalization is unknown; best estimates from this study would suggest it is between 8% and 33%. In addition, missing dialysis sessions puts patients at significantly increased risk for death[12-14] and can thus be viewed as a general indicator of health status. Therefore, our observation that ONS is associated with lower missed treatment rates, to our knowledge the being the first reporting of said, is noteworthy irrespective of implied effects on hospitalization.

The effects of ONS on markers of nutritional status were mixed. Despite being equivalent at baseline in the matched sample, mean serum albumin was lower for ONS patients in all months during follow-up. This may be explained by a survivor bias effect whereby more nutritionally marginal patients survived in the ONS group. Smaller studies have shown some benefits of ONS on serum albumin,[15-18] but results of larger studies showed only marginal differences.[11] Moreover, serum albumin is not purely a marker of nutritional status but is also associated with inflammation (reviewed in Ref.[19]).

We observed significantly higher nPCR values for ONS patients compared with matched controls during follow-up. nPCR is a surrogate measure of dietary protein intake and is calculated based on the change in serum urea nitrogen levels using urea-kinetic modeling. Low nPCR is associated with mortality and morbidity.[20,21] A longitudinal analysis demonstrated that decreases in nPCR values over a 6-month period were associated with increased mortality risk over the following 18 months and, conversely, that increases were generally protective.[22] Some smaller studies have demonstrated increases in nPCR with ONS,[23,24] but to our knowledge, this is the first large observational study to report the effects of ONS on nPCR. Because nPCR is routinely measured in dialysis patients, it may offer an easily accessible biomarker for ONS efficacy. Importantly, a recent study demonstrated that nPCR calculations should be corrected for renal urea clearance among patients with residual renal function in order to most accurately estimate dietary protein intake.[20]

The hemodialysis procedure results in a catabolic state with decreases in whole-body protein synthesis and concomitant increases in whole-body and skeletal muscle breakdown. Furthermore, these catabolic processes persist for hours after the dialysis session is complete.[25] Administration of intradialytic ONS has been shown to shift this balance to a positive protein anabolic state.[26,27] Consistent with many previous studies (reviewed in Ref.[3]), ONS patients in the pilot program evaluated here had greater postdialysis body weights during follow-up. This may be due to ONS patients having had slightly greater body weights at baseline compared to matched control patients. Alternatively, greater postdialysis body weights could be the result of increases in lean body mass for patients receiving ONS.

This study adds to the growing body of literature investigating the efficacy of dietary interventions in the treatment of PEW in hemodialysis patients. It has been proposed that differences in nutrition practices may in part account for the observed greater mortality rate among US hemodialysis patients compared to other countries.[9,28] In many countries, it is common for dialysis centers to provide meals during treatments. US practitioners have

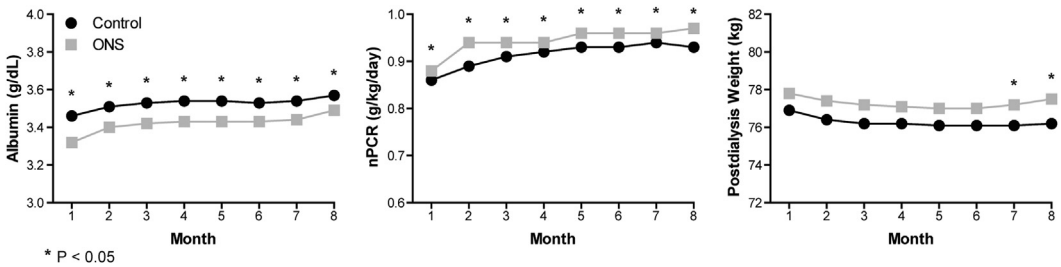

Figure 3. Nutritional markers. ONS, oral nutritional supplement.

historically expressed reluctance to allow this practice citing concerns such as increased risk of hypotension, respiratory complications, infection controls, and staff burden[8] although a recent US randomized controlled trial has demonstrated providing lunch boxes during dialysis is safe and effective.[29] In contrast, adoption of ONS programs has been strong throughout the Untied States.

There are several limitations to this study. Due to the observational design, associations between exposures and outcomes can be measured, but cause and effect are not determined. Despite matching, it is possible that unknown confounding may influence results. Finally, complete records of hospitalizations among LDO patients during this study period were not available in the EHR, and therefore, the present results may not represent the true magnitude of association between ONS utilization and this outcome.

ONS provided at dialysis treatments is associated with markedly and significantly better survival and reduced missed dialysis treatment rates as well as improvements in some nutritional indices. The novel finding that provision of intradialytic ONS to hypoaluminemic ICHD patients is associated with fewer missed dialysis treatments is of particular interest given that failure to attend dialysis sessions is associated with poor outcomes for patients. ONS may represent a simple and inexpensive strategy for dialysis centers to improve patient attendance. Along with the other large studies, these results provide a persuasive argument for the administration of ONS to hypoalbuminemic dialysis patients. Future research should investigate whether ONS is beneficial to patients with albumin levels above 3.5 g/dL.

Practical Application

Administration of ONS to patients with serum albumin ≤3.5 g/dL is associated with improved survival, dialysis session attendance, and nutritional status as measured by nPCR and postdialysis body weight.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1053/j.jrn.2017.10.002.

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