An Open Label Randomized Clinical Study Evaluating Impact of Nutritional Supplement in Malnourished Dialysis Patients (IMPROVES Trial) Protocol No PBL/PROS/07-11

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Abstract

Background: Protein energy wasting (PEW) affects survival in patients on maintenance dialysis. Objective to evaluate effect of oral nutritional supplement on hypoalbuminemic dialysis patients.

Methods: Multicenter randomized intervention on maintenance dialysis (MD) patients with serum albumin <3.8g/dL. 180 patients were randomly assigned to 1:1 standard treatment (1.2 g/kg/d and 35 kcal/kg/d control) or standard treatment plus an oral nutritional supplement (ONS) for 6 months. The supplemented group received in addition 30 g/d of a renal-specific ONS (Proseventy©) containing 70% soy protein. At month 0, 3 and 6 routine biochemistry, subjective global assessment (SGA), dietary recalls, and skinfold thickness (SFT) were done.

Results: At inclusion, no difference was found in age, sex,dietary intake, SGA, CRP and biochemistry. Control group had significantly higher serum albumin (3.2±0.41 and 3.37±0.36 p 0.013) and subscapular SFT (14±6.0, 12.1±5.0 p 0.032) than supplemented group. At month 3, the supplemented group significantly increased their albumin (3.3 ±0.48 vs 3.4 ±0.43) and illiac SFT (15.5 ±8.5 and 18.1 ± 8.6 p 0.043). Protein intake was significantly higher in supplemented group compared to controls at 3 and 6 months (64±21.5 54±16.3 p 0.004 and 69±28.4 and 53.5 ±15.1 p 0.000) respectively. In supplemented group subscapular SFT (16 ±5 12±5.1 p 0.000) was significantly high and albumin increased to 3.4±0.049 versus 3.3 ±0.51 in controls at 6 months but difference in albumin was not significant. Serum phosphorus and lipid were not altered.

Conclusions: Addition of protein-rich renal specific ONS to standard nutritional counseling raised serum albumin and increased SFT in PEW patients undergoing dialysis. However, despite supplementation the serum albumin did not rise to ≥3.8 g/dL (ISRNM criteria). To correct PEW, ONS has to be given for longer period.

Keywords: Protein Energy Wasting (PEW), Oral Nutritional Supplement, Hypoalbuninemia, Dialysis

Introduction

Nutritional status in patients on hemodialysis is always a concern because of rampant morbidity and mortality due to malnutrition. Large scale dietary surveys of patients undergoing maintenance dialysis indicate that protein energy wasting (PEW) occurs in 17-85 percent of patients with chronic kidney disease (CKD) [1-3]. This in turn increases oxidative stress, inflammation, aggravates pre-existing heart failure and increases susceptibility to infections and mortality [4,5]. Hospitalization [6] and overall decreased quality of life (QOL) [7]. It is estimated that 50%-70% of PEW is related to inadequate dietary intake which is a consequence of uremia induced anorexia [8].

Given the poor dietary intake of energy and protein intake, renal specific dietary supplement is often the most effective measure to improve nutritional status of patients with CKD. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) [9] best clinical practice guidelines for nutrition in chronic renal failure recommends a dietary protein intake of 1.2 g protein/kg body weight/day for patients on maintenance hemodialysis (MHD) and peritoneal dialysis and for clinically unstable chronic peritoneal dialysis (CPD) patients protein intake of 1.3 g/kg/day in clinically unstable PD patients. Fifty percent of protein should be of high biological value from poultry, dairy and soy products. Hypoalbuninemia is most likely the strongest predictor of mortality among maintenance dialysis patients. KDOQI guidelines recommend that individuals undergoing maintenance dialysis who are unable to meet their nutritional requirements should receive a protein-enriched nutritional supplement. The supplement should contain 70% soy protein and 92% of the daily recommended dietary allowance of protein [10]. Therefore, the present study was undertaken to determine whether the addition of kidney specific oral nutritional supplement (ONS) containing higher percentage of soy protein and calorie content than usual renal specific ONS [11] improve nutritional status in dialysis patients with low albumin, without increasing serum phosphorus and lipid.

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protein and energy requirements with food intake for an extended period of time should receive nutritional support. Clinical trials on oral nutrition supplements (ONS) for dialysis patients have shown that enteral therapy improves nutritional status which manifests as increase in serum albumin, prealbumin, and improvement in improvement in quality of life (QOL).

Thus, early identification of patients with eating behaviour disturbances can potentially reduce the burden of malnutrition through appropriate intervention.

With this background, a multicentre study, sponsored by Panacea Biotech Ltd. was designed to see the effectiveness of high protein supplementation in improving nutritional status of patients and the overall QOL in dialysis patient. The primary end points for efficacy and safety were to evaluate the efficacy of ONS on the nutritional status of hypo-albuminemic malnourished patients on maintenance dialysis as increase in serum albumin from baseline to the end of the study. Other additional clinical parameters for efficacy were increase in body mass index (BMI), anthropometric measurement like skin folds thickness of biceps, triceps, suprailiac, and subscapular, mid upper arm circumference, subjective global assessment (SGA) and quality of life (QOL).

Material and Methods

Patients and Methods

Study Design: It was an open label, comparative, multicentric study of 6 months duration. The study product and the study (Protocol No PBL/PROS/07-11) was approved by the Drugs Controller General Of India (DCGI) and was later approved by the ethics committees of all the three participating centers.

In addition to screening visit, there were three visits, visit 1 was baseline, visit 2 was at 3 months and visit 3 was at 6 months and end of the study. Safety endpoint were assessed by biochemical parameters, adverse events and tolerability.

For diagnosis of PEW recommendation of the expert panel international society of renal nutrition and metabolism (ISRNM) was used [7].

Study product: ProSeventy is an artificial food supplement containing 70% soy protein, hence the name. The quality of this protein is high and contains all the essential amino acids.

Selection of Patients:

Inclusion criteria: Those patients who were willing to sign informed consent form, were above the age of 18 years, had clinical PEW as per ISRNM criteria [7], serum albumin < 3.8g/100 ml, were on maintenance dialysis for at least 3 months and adequately dialyzed as per investigator, with no uremic symptoms, and were from middle to high socioeconomic group were included in the study. Exclusion criteria included patients with no clinical PEW as per ISRNM criteria [7], patients with systemic infection like tuberculosis or malaria, patients who were on oral nutritional supplement (ONS) or had discontinued use of ONS, or patients planned for kidney transplantation within study period, pregnant or breast-feeding females, patient whose life expectancy was less than 6 month and patients who had switched over from hemodialysis to peritoneal dialysis.

A total of 180 patients on maintenance dialysis (haemodialysis and peritoneal dialysis), matched for age, sex and income were recruited for the study from 3 centers (Figure 1). Out of 180 patients, 90 patients were in group 1 and 90 were in group 2 but later there were 2 drop outs from group 1. On visit 2 there were 141 patients, 70 in group 1 and 71 in group 2; 128 patients completed visit 3, 39 were in group 1 and 89 were in controls.

The groups were randomized equally and divided into two groups: group 1: treatment group and group 2: control group. The treatment group was given 30 g of Proseventy in two divide doses along with standard 1.2g/kg/d protein and 35 kcal/kg/d energy diet for a period of 6 months while the control group received standard 1.2g/kg/d protein and 35 kcal/kg/d energy diet with no ONS. To assess compliance with the nutritional supplements, patients were asked to return empty cans of the ONS and a ONS dispensing log was maintained.

Dietary Record and Food Intake: Dietary intake was taken by a renal dietician on dialysis day, non-dialysis day and weekend day. Three days food diaries were maintained for all the patients. The amounts were recorded in household measures using standardized bowls, cups, spoons and glasses. Patients were taught to complete diaries using household measures and food models. Complete dietary record included the day and time when meals, snacks and beverages were taken, a description of the food or drink, methods of food preparations, missed meals, amount consumed in restaurants and the amount of consumed convenient and processed foods. For identifying sizes of bread (chapatti/paratha/bhakri etc.), etc., food models of dough were used as also cardboard cut-outs. The cooked amount was converted to raw weight in grams [21-23]. Nutrients were calculated based on nutritive values published by ICMR [24]. Figure 2

Observation of Efficacy and Safety With Physical And

Figure 1: Schematic presentation of patient groups.

Figure 2: Visit wise schematic presentation of groups and parameters assessed.
Biochemical Investigation

Patients were screened for inclusion in the study. At the onset, baseline data pertaining to personal information, medical history and treatment, biochemical parameters such as hemoglobin, serum albumin, serum cholesterol-LDL, VLDL or HDL, HbA1c (at baseline for all patients and at all the visits for diabetics), serum sodium, potassium, phosphorus, C reactive protein, PTH (at baseline and 6 months) serum calcium, blood urea nitrogen, coagulation profile: partial thromboplastin (PT) activated APTT were taken. Anthropometric measurements were taken using standard equipment and techniques [24-26]. BMI, skin folds thickness of biceps, triceps, suprailliac, and subscapular, mid upper arm and waist circumference and waist hip ratio were taken [24-26]. Subjective global assessment (SGA) was done at baseline and after 6 months. SF36 (baseline and after 6 month) and dietary intakes was recorded using a validated questionnaire and assessment. Following initiation of the study protocol, anthropometric, biochemical and dietary intake data as

Figure 5a: 24 Hour Dietary Recall - Energy Intake Repeated Measures ANOVA Sign. Difference Between Groups p 0.000.

Figure 5b: 24 Hour Dietary Recall - Protein Intake Repeated Measures ANOVA Sign. Difference Between Groups p 0.000.

Figure 6a: Effect of ONS on Serum Albumin: Serum albumin significantly increased (3.3 ±0.48 vs 3.4 ±0.43) and at 6 months serum albumin was higher than the controls p= 0.000.

Figure 6b: Paired Comparison using Anova Analysis Significant Difference in Albumin level at 3 and 6 months p=0.000 Higher in supplemented group.

Figure 7a: Effect of ONS on Biceps Skinfold Significant Difference in visit 2 and 3 p 0.000 Higher in Supplemented Group.

Figure 7b: Effect of ONS on Triceps Skinfold Significant Difference in visit 2 and 3 p 0.000 Higher in Supplemented Group.

Figure 7c: Effect of ONS On Subscapular Skinfold Significant difference at visit 2 and 3 p=0.000 Higher in supplemented group.

Figure 7d: Effect of ONS On suprailliac Skinfold Significant difference at visit 2 and 3 p=0.000 Higher in supplemented group.
Assessment of Quality of Life (QOL): The SF-36 (Medical Outcomes Trust, Boston, MA), a multipurpose, short-form health survey with only 36 questions was used for assessing QOL. The SF-36 consists of eight scaled scores. Each scale is directly transformed into a lower boundary of 0 and an upper boundary of 100. The eight scales are vitality, physical functioning, bodily pain, general health perceptions, social role functioning, emotional role functioning, mental health, and general health. A higher score indicates better health-related quality of life. The lower the score, the more the disability. The eight sections are vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health [30].

Statistical Methodology: Data were normalized and analyzed for mean standard deviation, correlation and repeated measure anova for paired comparison using SPSS for windows version 17.0 version.

Results:
At visit 1, there was no statistically significant difference in the two groups in age, sex, dietary intake, SGA, and lipid profile, serum sodium, potassium, phosphorus, calcium, PTH, coagulation profile except serum albumin level which was 3.2 ±0.41g /dL in group 1 and 3.37±0.35 g /dL in group 2 (Table 1). In the control group the serum albumin level declined. At baseline the dietary energy and protein intake were higher in the control group but with intervention, the energy and protein intake increased significantly in the intervention group compared to control group (Figures 3-5(a,b)). By the end of the study the serum albumin increased above 3.8 g /dL in the intervention group (Figure 6(a,b)). CRP levels though were high in both the groups, but they were significantly higher in the control group compared to the intervention group (Figure 7(a,b,c,d), Figure 8). The quality of life in terms of regular daily activities, social role, mental health significantly improved intervention group compared to control group (Table 2,3).

Discussion:
Malnutrition is common in patients on maintenance hemodialysis, affecting 40-70% patients [1]. Uremic toxins lower appetite and contribute to decline in nutrition once the patient is on maintenance hemodialysis (HD) [3]. Malnutrition leads to increased morbidity and mortality with increased hospitalization rates, increased susceptibility to infections, wound healing impairment, fatigue and poor rehabilitation [12]. It is known that enteral multinutrient support

### Table 1: Characteristics of Patient Groups

<table>
<thead>
<tr>
<th></th>
<th>Supplement</th>
<th>Control</th>
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<tbody>
<tr>
<td>Age</td>
<td>56.7±9.9</td>
<td>57.8±10.3</td>
</tr>
<tr>
<td>Sex</td>
<td>59% (N=77)</td>
<td>55% (N=77)</td>
</tr>
<tr>
<td>Smoking Status</td>
<td>29% (N=27)</td>
<td>31% (N=30)</td>
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</table>

### Table 2: Three Days and 24 Hour Dietary Energy and Protein Intake of Patient Groups.

<table>
<thead>
<tr>
<th></th>
<th>Supplement</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>Energy (kcal)</td>
<td>3072±904</td>
<td>2594±720</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>81.3±14.2</td>
<td>68.5±12.6</td>
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</table>

### Table 3: SF36 Questionnaire: Comparison of Visit 1 and 3.

<table>
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<tr>
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<th>Questions</th>
<th>P values</th>
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<tbody>
<tr>
<td>1</td>
<td>In general, would you say your health</td>
<td>0.026</td>
</tr>
<tr>
<td>2</td>
<td>Compared to one year ago, your health now</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>Vitality: limitation in movements</td>
<td>0.44</td>
</tr>
<tr>
<td>4</td>
<td>Problems with work or regular daily activities as a result of physical health</td>
<td>0.001</td>
</tr>
<tr>
<td>5</td>
<td>Problems with work or regular daily activities as a result of any emotional problems</td>
<td>0.004</td>
</tr>
<tr>
<td>6</td>
<td>Physical health or emotional problems interfered with normal social activities</td>
<td>0.005</td>
</tr>
<tr>
<td>7</td>
<td>Bodily pain</td>
<td>0.19</td>
</tr>
<tr>
<td>8</td>
<td>Social Role Functioning: Pain interference with work both outside the home and housework</td>
<td>0.102</td>
</tr>
<tr>
<td>9</td>
<td>Mental Health</td>
<td>0.001</td>
</tr>
<tr>
<td>10</td>
<td>General health perceptions</td>
<td>0.554</td>
</tr>
<tr>
<td>11</td>
<td>Final Score</td>
<td>0.001 Improved</td>
</tr>
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significantly increases serum albumin and improves total dietary intake which may improve clinical outcome [12]. Oral nutritional supplementation given during hemodialysis improves nutritional markers in malnourished chronic hemodialysis patients [29].

A randomized crossover design evaluated impact of oral protein supplementation given during hemodialysis and peritoneal dialysis (n=49) showed increase in serum albumin, normalized protein catabolic rate (nPCR), and reduction total hospitalizations, and length of stay were compared in patients who received protein supplements with those who did not30-35. A randomized, controlled, nonblinded, parallel trial on 92 hemodialysis patients evaluated change in SGA score and malnutrition-inflammation score (MIS) with 3 treatment groups (23 patients each) received 220mL of fermented vitamin E-fortified whey beverage (15g of whey protein concentrate + 600IU of vitamin E) or 220mL of fermented whey beverage (15g of whey protein concentrate) or vitamin E (600IU) 3 times a week for 8 weeks. The control group (23 patients) received no intervention and concluded that 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. The overall caloric intake and protein intake of patients on hemodialysis was found to be deficient. This has been found in Indian study previously also where malnutrition was found in 58% of patients on HD [30-37].

The present study explored effect of renal specific nutritional supplement on hypoalbuminemic patients on maintenance dialysis [19,20] and found that intervention with renal specific oral nutritional supplements improves nutritional status as seen in improvement of serum albumin, and skinfold thickness. A similar study as ours was conducted on patients with CKD in which 3 daily servings of ONS given for 6 months improved serum albumin and anthropometric measures, as well as reduced EPO dose [12]. A recently published prospective controlled trial [34] showed that nutritional supplementation with renal specific nutrients during hemodialysis have significant positive impact on nutritional parameters, glycemic variability, hospitalization rate in malnourished hemodialysis patients. Among several factors that contribute to protein energy malnutrition, decrease protein and energy intake is one important factor that is treatable. Several reports indicated that protein and energy intake is usually low than recommended value in maintenance hemodialysis patients [18,19]. Decreased nutritional intake may be a function of uremia itself, leading to anorexia that may also be associated with disorders in taste, fatigue, and nausea and/or vomiting [20,21]. Dietary advice carried forth from predialysis days that may have advocated for a low-protein diet coupled with intake restrictions for potassium, sodium, and phosphorus also may have residual effects on the patient’s will to eat even after initiation of dialysis therapy [22,23]. It is estimated that approximately 6-8 grams of amino acids (approximately 40 grams of protein) are lost into the dialysate and 200 Kcal of extra energy is utilized during hemodialysis [24-26]. In addition to that hemodialysis has been shown to result in a net catabolic state that predisposes to protein breakdown due to activation of inflammatory mediators [27-28]. Supplementing renal specific oral nutrition during hemodialysis session when amino acid loss is maximum and catabolism is at its peak, will compensate the dialysis associated catabolism. Another important aspect of oral nutritional supplementation is its financial advantages over intradialytic parental nutrition (IDPN). Moreover studies showed that IDPN when compared with oral nutritional supplement does not improve 2 year mortality event, hospitalization rate, BMI or laboratory markers of nutritional status in malnourished hemodialysis patients [29]. Hemodialysis patients are particularly at risk of developing protein energy malnutrition and use of oral nutritional supplements may have been responsible at least in part (in addition to focus on vascular access and other issues) for improved survival as reported in the Right Start Program Right Start program showed that consuming a meal enriched in protein and energy during hemodialysis treatments led to a positive protein balance to the same extent as on a nondialysis day. In a multicenter Right Start Program [30], a total of 918 CHD incident patients were prospectively enrolled and compared with a time-concurrent group of 1020 control patient from non-RightStart clinics. RightStart patients received 3 months of intervention in management of anemia, dosage of dialysis, nutrition, and dialysis access and a comprehensive educational program. At 3 months, RightStart patients had higher albumin and hematocrit values and after 12 months follow up mean hospitalization days per patient year were reduced with RightStart versus control subjects. Compared with baseline, Mental Composite Score for RightStart patients improved significantly as was observed in improvement of mental health and quality of life in our study using SF-36 questionnaire. This study shows that supplementation with ONS significantly improved health, able to deal better with problems related to work or regular daily activities as a result of physical health, there was improvement in physical health or emotional problems which interfered with normal social activities and mental health.

Pupim et al [38] extended these observations by showing not only protein accumulation and skeletal muscle protein homeostasis during dialysis with intradialytic oral nutritional supplements, but also continued anabolic benefit for muscle protein metabolism in the postdialysis period. Although the inflammatory state adds complexity to the management and prognosis of malnourished maintenance hemodialysis patients, nutritional interventions in this patient population may still contribute to a net anabolic effect in the presence of inflammation.

Hypoalbuminemia is most likely the strongest predictor of mortality among MHD patients [19,30-39]. Seven randomized and nonrandomized trials with ONS reported significant improvements in serum albumin levels [6-10,12,14]. In our study population, a significant increase in serum albumin was observed only in the renal specific ONS group with serum albumin increasing to >3.8 g/dL at the end of the follow-up period. Therefore, it seems reasonable to consider the significant improvement in serum albumin as well as nutrition status in patients receiving ONS to result in lower inflammatory status [40,41]. It is worth noting that a significant increase in skinfold thickness was evident in the RS-ONS group, while the control group showed a significant decline as also observed in other studies.

Conclusion

This study shows that supplementation with ONS significantly improved health, and patients were able to deal better with problems related to work or regular daily activities as a result of physical health, there was improvement in physical health or emotional problems which interfered with normal social activities and mental health. Protein-rich renal specific nutritional supplement given daily along with standard nutritional diet of 1.2 g/kg/d raised serum albumin and increased skinfold thickness in patients with PEW undergoing dialysis. At the end of the study, patients in supplemented group showed improvement in nutritional status compared to controls. The functional capability as per SGA score improved significantly in supplemented group compared to control (p=0.001). There was significant improvement in Quality of life of supplemented group after 6 months in terms of vitality, emotional, mental and social health. Given the poor dietary intake of adequate energy and protein in dialysis patients, renal specific dietary supplements form the most effective measure to improve nutritional status and quality of life of patients on dialysis to correct PEW.

Future directions

Whether protein-energy-wasting(PEW) is causally related to adverse outcomes in CKD needs to be verified in randomized
controlled trials of nutritional interventions. The initiation of major clinical trials targeting nutritional interventions with the goal of improving survival in CKD offer the promise of extending the survival of this vulnerable patient population.

This work was presented at ASN Renal week 2016.

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40. HALT PKD, Quality of Life Questionnaire (SF-36v2 TM Health Survey), Form 38 Version 1, 05/06/2009

