

Effects of Replacing Intradialytic Parenteral Nutrition by Oral Nutritional Supplements and Polyester-Polyarylate Membrane on Nutritional Status in Maintenance Hemodialysis Patients with End-Stage Kidney Disease

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Keywords

Nephrology · Hemodialysis · Chronic kidney disease · Nutrition

placing IDPN to maintain nutritional markers in high-risk patients receiving hemodialysis might warrant further research with robust methodology.

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Abstract

Introduction: In patients receiving hemodialysis, protein-energy wasting may be frequent and is associated with nutritional and metabolic alterations. This study aimed to describe the effects of a new therapeutic strategy, i.e., oral nutritional supplements (ONS) associated with a polyester-polyarylate (PEPA) membrane, on nutritional markers in high-risk patients with intradialytic parenteral nutrition (IDPN) history. **Methods:** Patients, who received individually IDPN (M-6 to M0) then ONS (M0 to M6), were followed over a 12-month period. **Results:** There was no change in serum albumin over time. The BMI increased between M-6 and M6. Food intake showed increase between M0 and M3. Quality-of-life score was stable between M0 and M6. None of the adverse events was judged related to ONS, PEPA, or research procedure. **Conclusion:** This study focusing on a new therapeutic strategy composed of ONS and PEPA membrane re-

Introduction

Among patients undergoing hemodialysis, 43% (median), 28%–56% (25th–75th percentiles) present with protein-energy wasting (PEW) which encompasses nutritional and metabolic alterations [1]. Indeed, the dialysis procedure involves loss of amino acids in the dialyzate during blood purification and may facilitate development and worsening of PEW through infectious, inflammatory, and volume-related complications [2]. In chronic dialysis patients, the prevalence of PEW in chronic kidney disease is highest due to multiple mechanisms inherent to the disease, which may negatively affect nutritional status, including loss of appetite, systemic inflammation, comorbidities, and hormonal derangements [1, 2].

PEW diagnosis refers to the presence of three relevant nutritional markers i.e., biological markers, body mass or weight loss with reduced calorie and protein intake, and muscle mass [1, 2]. Low serum albumin [3, 4], low body mass index (BMI) [5–8], low food intake, and low muscle mass have all shown correlations with high rates of mortality on dialysis.

In this context, any nutritional therapy should be considered [9–11]. Intradialytic parenteral nutrition (IDPN) limits PEW and improves nutritional markers compared to intensive dietary counseling [12]. However, it is a costly procedure known to affect patients' quality of life and requiring careful monitoring of perfusion, planning and equipment [13]. Conversely, several studies pointed out its limits in improving clinically relevant outcomes compared to dietary counseling or oral nutritional supplements (ONS) [14, 15]. The advantages of ONS include efficacy and safety due to its non-invasive nature.

The polyester-polyarylate (PEPA) dialyzers are made of a synthetic polymer membrane composed of polyethersulfone and polyarylate. By adjusting the ratio of the two polymers, the size of the membrane pores can be controlled, and the permeability of water and other substances can be regulated. As a result, the PEPA membrane can be considered a high-performance dialyzer [16]. High-performance membrane dialyzers are quickly becoming conventional in Japan with over 90% of patients on hemodialysis being managed with these dialyzers [17] and 7.5% using PEPA membrane dialyzers [18]. These membranes might be beneficial in hemodialysis patients [17] and should be used only in the hemodialysis modality to avoid high albumin losses observed in post-dilution hemodiafiltration [19].

This study aimed to describe the preliminary effects of a novel therapeutic approach combining ONS and a high permeability and adsorbent membrane dialysis (i.e., PEPA dialyzer) on relevant nutritional markers in a small cohort of end-stage kidney disease (ESKD) patients on hemodialysis with IDPN history.

Methods

Patients

This was an ambispective, longitudinal, and multicenter study (NCT 04445558). The inclusion criteria were (i) adults with kidney failure receiving hemodialysis in medical dialysis units for at least 12 months, (ii) poor nutritional status demonstrated by receiving IDPN for ≥ 6 months, and (iii) patients who can benefit from a

change of dialysis strategy according to the investigator. The non-inclusion criteria were (i) known allergy to PEPA components, (ii) ongoing chronic infection, (iii) life expectancy < 6 months, and (iv) inability to understand information related to the study. The patients' routine dialysis care was 3 sessions per week, each session lasted 240 min (online suppl. Table S2; for all online suppl. material, see <https://doi.org/10.1159/000545460>). Patients who participated to this study had 7 study visits that coincided with their medical routine. All patient specific information data were coded to ensure confidentiality. Eleven patients were enrolled in the study from July 2020 to April 2021, from which 5 were not evaluable: 3 did not receive the strategy switch (due to patient move, deterioration in general condition or death), 1 died before M3, and 1 had a deterioration of the nutritional status before M1. None of these events was related to ONS, PEPA, or study protocol. There are 6 patients studied in the results.

Procedure

Patients were enrolled at M0, date of the switch from the conventional strategy (IDPN + standard permeability membrane) to the experimental one (concentrated milk or fruit beverages, puddings, and biscuits (i.e., ONS) + a membrane with high permeability and adsorption properties [PEPA® FDX GW, Nikkiso]). Data were collected over a 12-month period: retrospective data during IDPN (M-6, M-3, and M0) and prospective data during ONS + PEPA (M0, M3, and M6). For ONS set up, patients were prescribed total calorie and protein intake of 30 kCal/kg/day (≥ 60 years of age) and 1.2 g/kg/day, respectively. The ONS were prescribed twice during daytime, preferably 1 h after meals. Compliance was observed by the dietitians regularly visiting patients at home and encouraging them to properly take ONS.

Visits and Exams

Baseline patients' demographics data, chronic kidney disease history, IDPN duration, and clinical characteristics including age adjusted Charlson index of comorbidities and weight change during IDPN were collected at M0. Serum albumin and BMI, other biological parameters (serum prealbumin, Buzby index or Geriatric Nutritional Risk Index [GNRI]), C-reactive protein [CRP]), and dialysis parameters (Kt/V, urea concentration before and after dialysis, purified blood volume, and nPCR) were collected at M-6, M-3, M0, M3, and M6. The simple evaluation of food intake (SEFI) score, total daily spontaneous oral intakes (calorie and protein) measured on a day without dialysis, brachial circumference, grip

Table 1. Patients' demographic data and clinical characteristics at baseline (M0)

Variables	Total (N = 6)
Age (years)	
Median	81.55
Q1; Q3	79.70; 85.40
Min; Max	72.8; 89.8
Sex	
Men	2 (33.3%)
Women	4 (66.7%)
Height, m	
Median	1.610
Q1; Q3	1.520; 1.650
Min; Max	1.5; 1.72
Dry weight, kg	
Median	50.75
Q1; Q3	46.30; 77.50
Min; Max	37.2; 102.5
Etiology of ESKD	
Diabetic nephropathy	1 (16.7%)
Chronic glomerulopathy	1 (16.7%)
Chronic tubulointerstitial nephropathy	1 (16.7%)
Vascular nephropathy	3 (50%)
Charlson Index (adjusted to age)	
Median	8.0
Q1; Q3	7.0; 13.0
Min; Max	7; 14
Weight change % in 1 month	
+1%	3 (50%)
+5%	1 (16.7%)
−0%	2 (33.3%)
−1%	0 (0.0%)
Weight change % in 6 months	
+1%	1 (16.7%)
−0%	1 (16.7%)
−1%	2 (33.3%)
−2%	2 (33.3%)

ESKD, end-stage kidney disease; Q1, first quartile; Q3, third quartile; Min, minimum; Max, maximum. No missing value.

strength (hand grip) and EORTC QLQ-C30 quality-of-life questionnaire were collected at M0, M3, and M6. Adverse events were also reported.

Results

All the patients had IDPN for ≥ 6 months before M0 and all of them continued the ONS + PEPA strategy after M6. The median duration of dialysis at M0 was 2.75 years.

The median age was 81.55 [79.7; 85.4] with 33.3% men. The median age adjusted Charlson index was 8 [7, 13], and 66.7% experienced weight loss within the last 6 months of IDPN (M-6 to M0) (Table 1).

There was no change in serum albumin between M0 and M6 (estimated difference [ED]: 1.33 ± 2.90 g/L and 95% confidence interval (CI) = [−4.37; 1.71]) or between M-6 and M6 (ED: 1.27 ± 5.02 g/L and 95% CI = [−4.01; 6.54]). The BMI increased between M-6 and M6 (ED: 0.55 ± 0.33 kg/m² and 95% CI = [0.20; 0.90]). The prealbumin change was very small between M-6 and M6 (ED: -0.01 ± 0.00 g/L and 95% CI not estimated). There was no change in Buzby index between M-6 and M6 (ED: 1.61 ± 26.86 and 95% CI = [−26.58; 29.80]). The CRP level was particularly high at M-3 with a mean of 11.79 ± 20.93 g/L and stabilized between M0 and M6. The overall health status and quality-of-life score remained stable between M0 and M6 (Table 2). Dialysis parameters are described in online supplementary Tables S1 and S2. None of the adverse events that occurred was judged related to ONS, PEPA, or research procedure.

Discussion

According to the literature, albumin [4] and BMI [5] remain the most reliable early predictors of mortality in patients on hemodialysis. The stability of albumin, strengthened by the stabilization of the CRP between M0 and M6, which is inversely proportional to that of albumin concentration [3], indicates that ONS + PEPA allowed to maintain albumin level. The BMI increased during the successive dialysis strategies. In contrast to what is reported in the general population, increased BMI is associated with improved survival in patients on hemodialysis including above the upper “normal” limit [6, 7]. In patients with ESKD, BMI is associated with better survival, named “obesity paradox” [8]. The BMI is a surrogate for malnutrition that is “modifiable” and, therefore, a variable of interest for better managing consequences of ESKD and hemodialysis on nutritional status.

Regarding the nutritional strategies in hemodialysis patients, an increase in survival has been reported when nutritional status was improved by ONS [10]. Besides, the only prospective and the largest randomized study that focused on 2-year mortality rates with ONS or with IDPN, showed that the addition of IDPN to ONS over 1 year did not improve survival, hospitalization rates or general well-being compared to ONS alone [14]. In addition, the use of a membrane with high purification

Table 2. Biological, clinical, nutritional, and quality-of-life parameters during IDPN (M-6, M-3, and M0) and/or ONS (M0, M3, and M6)

Variables	M-6	M-3	M0	M3	M6
Albumin, g/L					
N	6	5	6	6	6
Median	29.80	32.60	33.45	30.60	32.00
Q1; Q3	26.00; 34.10	29.80; 34.60	31.90; 33.90	30.10; 36.00	31.70; 35.00
Min; Max	25.8; 37	24.7; 36	29.4; 36	28.2; 36.3	23; 36.4
Missing	0	1	0	0	0
Prealbumin, g/L					
N	4	2	5	4	4
Median	0.18	0.21	0.22	0.255	0.240
Q1; Q3	0.15; 0.21	0.15; 0.27	0.22; 0.35	0.185; 0.365	0.155; 0.365
Min; Max	0.14; 0.22	0.15; 0.27	0.14; 0.4	0.18; 0.41	0.13; 0.43
Missing	2	4	1	2	2
Buzby index (GNRI)					
N	6	5	6	6	6
Median	83.35	85.00	85.85	83.440	88.050
Q1; Q3	79.00; 86.00	79.23; 86.90	80.80; 91.00	78.970; 95.300	78.900; 97.000
Min; Max	75.5; 92	73.2; 90	79.6; 93.9	78.39; 96.14	35.86; 121
Missing	0	1	0	0	0
CRP, g/L					
N	5	5	6	6	6
Median	1.60	1.03	2.40	1.60	2.20
Q1; Q3	0.50; 3.00	1.00; 7.30	1.50; 8.70	1.00; 9.90	0.90; 7.80
Min; Max	0.05; 11.4	0.70; 48.9	1; 22.7	0; 15.6	0.3; 22
Missing	1	1	0	0	0
BMI, kg/m ²					
N			6	6	6
Median			20.25	20.60	20.70
Q1; Q3			17.60; 26.20	17.90; 26.40	18.30; 26.40
Min; Max			16.5; 40	17.3; 39.8	16.9; 40.8
Missing			0	0	0
Brachial circumference, cm					
N			6	5	6
Median			22.80	23.0	22.50
Q1; Q3			22.00; 28.50	22.0; 30.0	20.00; 28.00
Min; Max			21; 31	21; 31	15.9; 30.5
Missing			0	1	0
Grip strength (grip test), kg					
N			6	5	6
Median			17.40	12.20	15.25
Q1; Q3			8.00; 26.00	7.00; 18.00	5.60; 20.00
Min; Max			6.1; 35	6.3; 35	4; 30
Missing			0	1	0
Simple evaluation of food intake (SEFI) score					
N			6	6	6
Median			7.00	7.75	5.25
Q1; Q3			5.00; 8.00	5.00; 9.00	5.00; 7.50
Min; Max			2.5; 10	3; 10	3; 10
Missing			0	0	0

Table 2 (continued)

Variables	M-6	M-3	M0	M3	M6
Spontaneous calorie oral intake, kCal/day					
N			6	6	6
Median			1,510.5	1,590.5	1,194.5
Q1; Q3			940.0; 1,905.0	1,235.0; 1,880.0	900.0; 1,561.0
Min; Max			894; 1,930	1,021; 1,925	884; 1,770
Missing			0	0	0
Spontaneous protein oral intake, kCal/day					
N			6	6	6
Median			219.0	228.0	232.0
Q1; Q3			156.0; 260.0	192.0; 256.0	160.0; 296.0
Min; Max			92; 332	108; 352	140; 328
Missing			0	0	0
Overall health status and quality-of-life score					
N			6	6	6
Median			58.35	50.00	54.15
Q1; Q3			50.00; 75.00	33.30; 83.30	50.00; 75.00
Min; Max			33.3; 100	16.7; 83.3	33.3; 83.3
Missing			0	0	0

N, number of observations; Q1, first quartile; Q3, third quartile; Min, minimum; Max, maximum; Missing, missing value; GNRI, Geriatric Nutritional Risk Index; BMI, body mass index.

properties avoiding retro-filtration of endotoxins toward the blood compartment appears to be clinically relevant for hemodialysis patients with poor nutritional status. The internal architecture of these types of membranes, also classified as medium cut off membranes [16], comprises a higher pore size and smaller fiber inner diameter to favor internal filtration rate that allow an increased removal of larger middle molecules in conventional hemodialysis [20]. Therefore, the heightening of the elimination of uremic toxins, particularly those of medium molecular size, i.e., between 500 and 45,000 daltons, might be beneficial and should ensure a safe within-person IDPN replacement by ONS.

The optimal duration of IDPN should be at least 3 months [12–14], up to 6 months, to allow for meaningful evaluation, and reassessment might guide the continuation [1]. The same recommendations exist for ONS [15]. In the study, patients had poor nutritional status necessitating IDPN (often associated with inflammation). Another characterization of the sample is, indeed, older age (the median age [25th–75th percentiles] of patients was 81.55 [79.7; 85.4]). Older age may affect muscle mass loss and accelerate muscle protein breakdown in patients receiving hemodialysis. Besides, 66.7% experienced weight loss within the last 6 months of IDPN (M-6 to M0), suggesting the need to reassess the nutritional strategy probably combined with a normal effect of age and disease severity. Finally, patients

had a high rate of comorbidities, with the age adjusted Charlson index of 8 (median), 7–13 (25th–75th percentiles), indicating a high risk of morbidity. In summary, this work tried to assess another clinical strategy on a specific sample of patients receiving hemodialysis and aimed to go toward a simple nutritional strategy that is clinically consistent on a population having increased frailty.

This study has some limitations. First, out of 11 patients included across 4 centers and over a period of 10 months, only 6 completed the study. Second, further research looking at other markers of nutritional status (e.g., bio-electrical impedance analysis) could provide valuable insights, especially in this population. Third, it is hard to know what the benefits of the IDPN versus ONS since there is no washout period. Finally, a better compliance assessment should be relevant to assess the efficacy of ONS since compliance to the prescribed ONS might be reduced with time. This study has also strengths. First, the longitudinal methodology made it possible to follow up and evaluate patients on a regular basis over a span of time (7 study visits in 6 months). Second, each participant was both patient and control over time. Third, such study remains scarce since the population studied here is mostly excluded from clinical trials because of their high rates of comorbidity.

To conclude, this study focusing on a new therapeutic strategy composed of ONS associated with PEPA membrane replacing IDPN to maintain nutritional status

in high-risk patients on hemodialysis might warrant further research with robust methodology. Such minimally or non-invasive low-cost nutritional strategies for managing PEW in patients on hemodialysis are immediately applicable to patient care. PEPA membrane dialyzer seems safe in hemodialysis patients with increased frailty.

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Statement of Ethics

This study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments, the International Conference on Harmonization of Good Clinical Practice guidelines. The protocol (#ID-RCB 2020-A01267-32), patient information and consent sheet, and case report form were reviewed and approved by an appropriate independent Ethics Committee (*Comité de protection des personnes Sud-Est I*) on May 12, 2020, before the study started, in compliance with French legislation and ethical regulations. Written informed consent was obtained from all patients after the nature of the procedure had been explained and before the research had started.

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Conflict of Interest Statement

The authors have no personal or financial interests that are directly or indirectly related to the work submitted for publication.

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Author Contributions

M.H. contributed substantially to the conception or design of the work. M.H., R.A., A.B.H., and O.M. contributed to data acquisition and analysis. M.H. contributed to interpretation of data for the work and drafted the work. All the authors revised the work critically for important intellectual content, approved the final version of the manuscript to be published, and ensured that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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