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Trabajo Original

Nutrición artificial

Does intradialytic oral nutrition impact hemodialysis patients' quality of life, appetite, and safety? A pilot study of a crossover clinical trial

¿La nutrición oral intradialítica impacta en la calidad de vida, el apetito y la seguridad de los pacientes en hemodiálisis? Estudio piloto de un ensayo clínico cruzado

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Abstract

Introduction: due to the catabolic characteristics of hemodialysis (HD), patients should consume foods or supplements during this treatment to meet their energy requirements and maintain a neutral nitrogen balance; however, there are some outcomes in which the effect of intradialytic oral nutrition (ION) is scarcely known.

Objectives: this study aims to evaluate the effect of two types of ION (liquid and solid) on Quality of Life (QoL), appetite, and safety in HD patients.

Methods: a pilot randomized, crossover clinical trial was performed in 18 patients on chronic HD. One group received ION for 18 HD sessions, after the crossover continued for 18 more sessions in the control group, and vice versa. We recorded QoL, appetite, systolic blood pressure (SBP), and intradialytic hypotension (IH) events.

Results: clinical improvement was observed for most QoL components. Regardless of the consistency of supplementation, SBP increased to 4.10 mmHg. Both study groups reported a "very good-to-good" appetite.

Conclusion: favorable clinical changes were observed in QoL scores during the study. Five of six IH events were reported for patients in the ION group, and SBP increased within the safe range (≤ 10 mmHg); appetite remained stable in both groups. Therefore, we concluded that this strategy, regardless of implementation consistency, is safe to be used in stable patients.

Keywords:

Intradialytic oral nutrition. Intradialytic hypotension. Quality of life. Appetite. Blood pressure.

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Ethics approval: this protocol was approved by the Research Ethics Committee of the Institution, with the reference number 3082.

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Resumen

Introducción: debido a las características catabólicas de la hemodiálisis (HD), los pacientes deben consumir alimentos o suplementos durante este tratamiento para cubrir sus requerimientos energéticos y mantener un balance nitrogenado neutro; sin embargo, existen algunos desenlaces en los que el efecto de la nutrición oral intradialítica (NOID) es poco conocido.

Objetivo: este estudio tiene como objetivo evaluar el efecto de dos tipos de NOID (líquido y sólido) sobre la calidad de vida, el apetito y la seguridad en pacientes en HD.

Métodos: se realizó un estudio piloto en forma de ensayo clínico aleatorizado y cruzado con 18 pacientes en HD crónica. Un grupo recibió NOID durante 18 sesiones de HD, después del cruzamiento continuaron durante 18 sesiones más en el grupo de control, y viceversa. Se registraron la calidad de vida, el apetito, la presión arterial sistólica (PAS) y la hipotensión intradialítica (HI).

Resultados: se observó mejoría clínica en la mayoría de los componentes de la calidad de vida. Independientemente de la consistencia de la suplementación, la PAS aumentó hasta 4,10 mmHg. Ambos grupos de estudio informaron de un apetito "muy bueno-bueno".

Conclusiones: se observaron cambios clínicos favorables en las puntuaciones de calidad de vida durante el estudio. Cinco de seis eventos de HI se reportaron en pacientes del grupo de NOID y la PAS aumentó dentro del rango seguro (≤ 10 mmHg); el apetito se mantuvo estable en ambos grupos. Por lo tanto, se puede concluir que esta estrategia, independientemente de la consistencia implementada, es segura para ser utilizada en pacientes estables.

Palabras clave:

Nutrición oral intradialítica. Hipotensión intradialítica. Calidad de vida. Apetito. Presión arterial.

INTRODUCTION

Protein-energy wasting (PEW) is a highly prevalent complication in patients with chronic kidney disease (CKD) (1). It compromises patient nutritional status due to decreased nutrient intake, changes in taste (2), loss of appetite, systemic inflammation, worsening of quality of life (QoL), and others (3).

About 38 % of patients on hemodialysis (HD) experience a decrease in appetite and other unfavourable outcomes such as risk of first-time hospitalization, increased risk of mortality, and deterioration of QoL as assessed by the Kidney Disease Quality of Life Short Form tool 36 (KDQOL-SF36) (4).

Usually, as the condition of CKD progresses, QoL worsens. The authors reported that the physical function and mental function scores of the KDQOL-SF36 diminished in those with end-stage renal disease and on dialysis therapies (5). Malnutrition has also been associated with poor QoL. Furthermore, patients with severe malnutrition reported lower health and functionality scores (6). In contrast, an increase in the Malnutrition Inflammation Score (MIS) and the presence of PEW have been predictors of a lower physical component ($p \leq 0.01$) (7).

Intradialytic oral nutrition (ION) (8) is an inexpensive strategy for improving or preventing PEW by improving nitrogen balance and serum albumin levels (9), leading to a significant increase in the physical score, as compared with the control group, of the KDQOL-SF36 tool (10). The use of oral supplementation is considered a therapeutic alternative that can provide 7-10 kcal/kg/day and 0.3-0.4 g/kg/day of protein intake, which helps to meet recommended goals, as well as to cover the skipped meal during the day the patient attends an HD session (11,12).

Although the potential beneficial effects of ION have been demonstrated in the literature (13,14), in some countries its usage is not yet common (15). Its impact on QoL, appetite, and potential adverse events has been scantily explored. Therefore, this study aims to evaluate the effect of ION (liquid or solid) on QoL, appetite, and safety in HD patients.

METHODS

We performed a pilot randomized crossover trial. This study was conducted in compliance with the ethical principles of good clinical practice guidelines, and approved by the research ethics committee of our institution.

The eligible patients were adults (≥ 18 years) of both sexes on chronic HD (≥ 3 months, three times a week), Kt/V > 1.2, or who had urea reduction rate > 65 % and for whom oral intake was possible. Those patients on HD as an induction treatment to remission of renal function, with ultrafiltration (UF) > 3000 ml for more than two consecutive sessions, and who presented allergies to the components of the experimental maneuver were excluded. Patients were informed about the nature of the study and signed an informed consent form.

Patients were assigned to study groups using simple block randomization (randomizer.org) by an external investigator. During the first phase of the study, the ION group received an alternative oral nutritional supplement (liquid or solid) for 18 HD sessions. In contrast, the control group received standard care (without supplementation) simultaneously. After a one-week washout period, the groups were crossed over and continued for another 18 sessions, forming the study's second phase (Fig. 1).

INTRADIALYTIC ORAL NUTRITION (ION)

After the randomization process and before starting the study, the patients in the ION group received nine liquid supplements and 18 cookies during six weeks: a) the liquid supplement (234 ml) was designed for patients with renal replacement therapy (with 432 kcal and 19.2 g of protein) and was divided into two shots of 117 ml each; the first dose was administered one hour after starting the dialysis treatment, and the second dose 45 min before the end of the HD session, considering the first and final volume changes within the treatment, or b) two hyperproteic cookies (490 kcal and 16 g of protein) (Fig. 1). We considered the treatment adherence according to the total missed dialysis sessions.

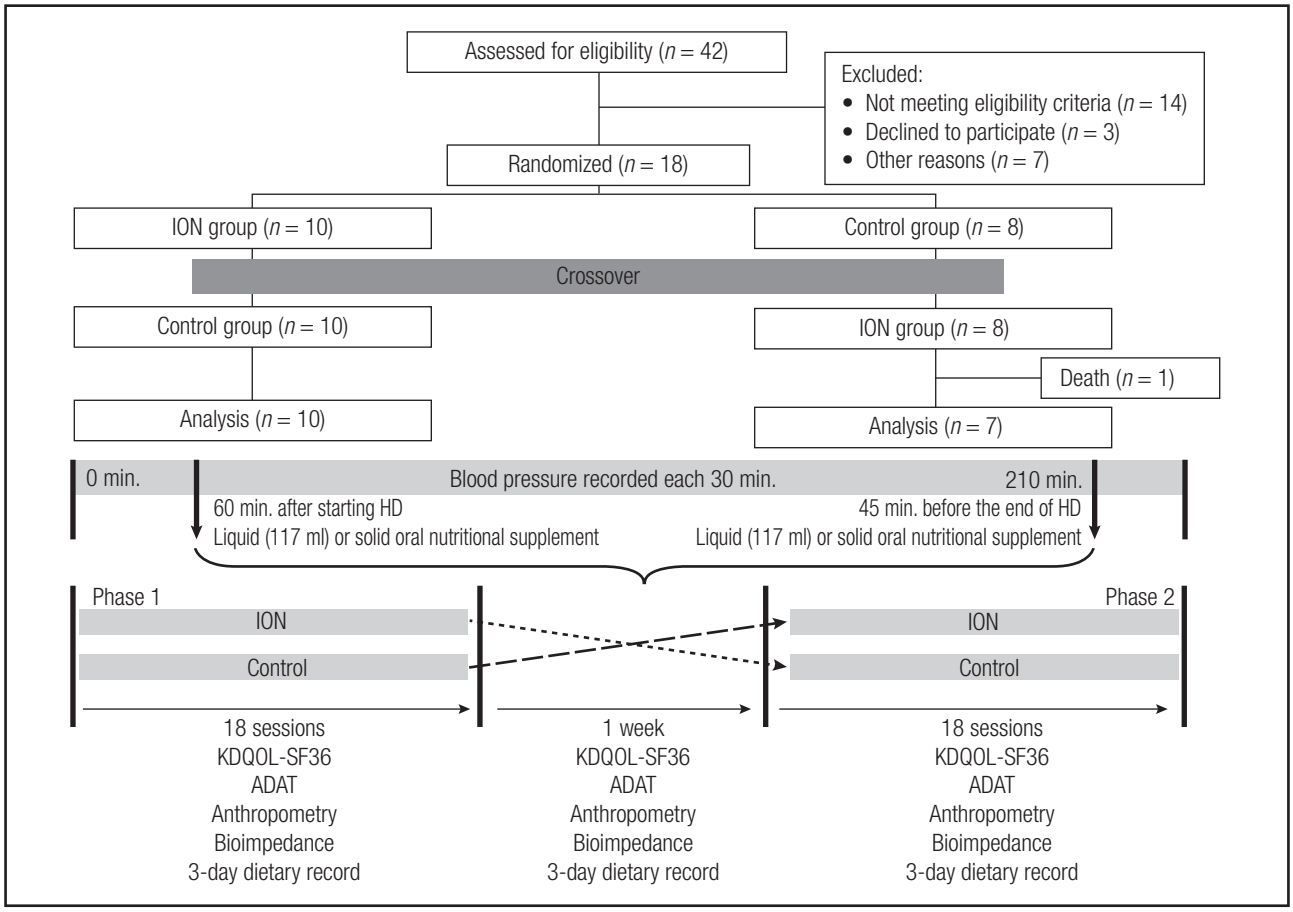

Figure 1.
Flowchart of the pilot trial.

MEASUREMENTS

Assessments of QoL, appetite, nutritional status, bioelectrical impedance analysis (BIA), and dietary intake were performed at the beginning, during the crossover period, and at the end of the study (Fig. 1). We recorded daily the blood pressure (BP) and intradialytic hypotension (IH) events during the 36 HD sessions.

QUALITY OF LIFE (QoL)

QoL was assessed using KDQOL-SF36 v.1.3 (16). This self-administered tool is composed of eight dimensions of physical and mental health scores: physical function component (ten items), limitations due to physical health problems or role physical (four items), emotional role (three items), social function (two items), mental health (five items), body pain (two items), vitality/fatigue (four items), and global perception of health (five items). We extracted the data collected from an Excel database [KDQOL™–36 Scoring Program (v 2.0)] obtained from the tool's main page, we transformed the scores and presented them in this document. A family member supported patients with visual problems or low literacy in answering the questionnaire.

APPETITE

Appetite was assessed using the first question of the Appetite and Diet Assessment Tool (ADAT) self-administered questionnaire (17,18). Patients with visual problems or low literacy were supported in answering the questionnaire with the help of a family member.

DIETARY INTAKE

The patients registered three-day food records, reporting the portion and type of food consumed on an HD session day, a session-free day, and a weekend day. A researcher corroborated each patient's dietary record using food replicas and kitchen utensils to facilitate the registries. The three-day records were averaged to determine the total energy and protein intake. To obtain the macro and micronutrient data, we used Food Processor Nutrition Analysis Software (esha RESEARCH v-11.9). Furthermore, the protein nitrogen clearance rate or normalized protein nitrogen appereance (nPNA) was recorded from the registry of each patient.

NUTRITIONAL STATUS AND BODY COMPOSITION

The Malnutrition Inflammation Score (MIS) tool, anthropometric measurements (weight, height, BMI, skinfold thickness, and mid-arm circumference), and bioimpedance analysis (BIA) after the HD session (Bodystat® Quadscan 4000) (19).

GENERAL CHARACTERISTICS AND LABORATORY DATA

Information regarding the dialysis vintage and comorbidities were registered from the clinical records, as well as albumin, transferrin, hemoglobin, total lymphocyte count, urea, nitrogen, creatinine, uric acid, sodium, potassium, phosphorus, calcium, and serum glucose.

BLOOD PRESSURE (BP)

BP was recorded every 30 min directly from the HD machine. BP measurements were analyzed for 60 min (20) after starting the HD session and up to 210-240 min, considering that at 60 min patients started receiving the ION. We recorded the intradialytic hypotension (IH) events. The presence of IH was defined as a decrease by 20 mmHg or more in systolic blood pressure (SBP), the presence of any symptoms related to hypotension (dizziness, nausea, or cramps), as well as the maneuver of the health staff to control BP (decrease in the rate of UF, the need to stop UF, interruption of treatment, administration of the saline solution, etc.) (14,20).

STATISTICAL ANALYSIS

Skewness and kurtosis were performed to determine the distribution of the data. Descriptive analysis of the quantitative variables was expressed as means and standard deviation or medians and interquartile ranges according to their dispersion. The qualitative variables were expressed as frequencies and proportions.

Quantitative differences between the ION and control groups were analyzed with the Student's t-test or the Mann-Whitney U-test based on their distribution. In contrast, qualitative variables were analyzed using the chi-square or Fisher's exact test. We assessed the group changes as basal-end study (B-ES) before and after analysis.

An ANOVA with repeated measures was performed to evaluate the means differences for the KDQOL-SF36 and dietary intake outcomes. The Friedman statistic was calculated if the variables did not have a parametric distribution. Moreover, we estimated the effect size with Cohen's D and its confidence intervals. The results of the SBP were analyzed with linear regression models in repeated measures with random effects due to the presence of heteroskedasticity (Wald test $p < 0.05$). A $p \leq 0.05$ was considered statistically significant, and the data were analyzed using STATA v. 14.1.

RESULTS

Eighteen patients met the selection criteria. However, in phase two, a patient in the ION group passed away due to gastrointestinal bleeding. The cause of death was not related to the intervention. Data recorded up to the moment of the patient's death were analyzed (Fig. 1).

At baseline, the duration of the dialysis session was 240 min (210-240), without significant differences between groups. In the sample, 61 % were men, with a median age of 46 years, and well dialyzed. Patients in both groups had a stable nutritional status, as reflected by anthropometric and biochemical measurements and by BIA (Phase Angle 6.0 ± 1.0). Both groups met the energy and protein requirements established in the current nutritional guidelines (Table I). There were no differences in the anthropometric and biochemical data during the study (data not shown).

APPETITE

In figure 2 most patients in both groups (around 60 %) reported a "very good" appetite at the end of the study. The results of the dietary analysis did not show significant differences concerning any specific nutrient (Table II).

QUALITY OF LIFE

Most patients in the intervention group presented clinically better scores in the QoL components, although they were not statistically significant. The scores for body pain and vitality experienced the greatest change, while emotional role decreased for both groups (Table III, Supplementary Table I).

EFFECT OF ION ON SYSTOLIC BLOOD PRESSURE

During the 36 HD sessions, there were only six cases of IH, of which five were in the ION group. After 30 minutes post-ION (90 min) the SBP increased up to 4.10 mmHg ($p = 0.002$) for the ION group, in contrast to the control group, which decreased by -3.38 mmHg ($p = 0.007$). The results remained constant in the models adjusted with the variables that could influence the BP due to biological plausibility. Figure 3 shows that the liquid consistency increased SBP at 150 and 180 minutes whereas solid supplementation increased it at 90 min. The complete analysis is presented in table IV.

Table I. Baseline characteristics of patients in the ION and control groups

Variable	General (*n* = 18)	ION (*n* = 10)	Control (*n* = 8)	*p*-value
Demographic characteristics				
Sex, M (*n,* %)	11 (61.1)	5 (50)	6 (75)	0.367
Age (years)	46 (33-62)	46.5 (33-65)	46 (36.5-60)	0.893
Comorbidities				
Diabetes *mellitus (n, %)*	11 (61.1 %)	6 (54.55)	5 (45.45)	
Hypertension *(n, %)*	12 (66.66 %)	8 (66.67)	4 (33.33)	0.627
Others *(n, %)*	11 (61.1 %)	5 (54.55)	6 (54.44)	
Clinical characteristics				
Dialysis vintage (months)	35 (60-62)	48 (30-64)	35 (30-40)	0.449
Kt/V	1.6 ± 0.3	1.7 ± 0.2	1.5 ± 0.3	0.051
Ultrafiltration (ml)	2917.4 ± 941.6	3000.0 ± 1010.0	2825.0 ± 917.7	0.715
SBP (mmHg, 30 min)	132.2 ± 24.5	133.4 ± 30.3	130.8 ± 17.9	0.824
DBP (mmHg, 30 min)	70.1 ± 24.9	69.7 ± 31.7	70.6 ± 16.4	0.939
Anthropometry and body composition				
Weight post HD (kg)	70.8 ± 23.3	66.9 ± 19.9	75.9 ± 27.5	0.428
BMI (kg/m^2)	25.9 ± 6.8	25.5 ± 7.4	26.4 ± 6.3	0.786
R/H (Ω)	362.7 ± 82.8	357.8 ± 64.2	368.3 ± 104.3	0.804
Xc/H (Ω)	37.8 ± 11.4	37.7 ± 9.8	37.8 ± 13.6	0.985
Phase Angle (°)	6.0 ± 1.0	5.9 ± 1.0	6.0 ± 1.0	0.827
Dominant grip strength (kg)	25.5 ± 7.4	23.9 ± 7.9	27.6 ± 6.7	0.305
Biochemical				
Hemoglobin (mg/dL)	11.2 ± 2.0	10.5 ± 1.9	12.2 ± 1.9	0.080
Glucose (mg/dL)	122.5 (87-180)	122.5 (107-199)	107.5 (87-154.5)	0.304
BUN (mg/dL)	71.3 (58.8-94.9)	75.3 (60.7-94.9)	63.7 (58.3-83.9)	0.534
Creatinine (mg/dL)	12.7 (10.7-13.5)	12.9 (0.7-13.9)	12.5 (10.6-13.3)	0.789
Uric acid (mg/dL)	7.9 ± 1.6	8.5 ± 1.7	7.1 ± 1.2	0.076
Potassium (mEq/L)	5.5 (4.7-5.8)	5.3 (4.6-5.7)	5.6 (5.4-6)	0.265
Phosphorous (mg/dL)	4.3 ± 1.9	3.8 ± 1.5	5.0 ± 2.1	0.171
Albumin (g/dl)	3.8 (3.7-3.9)	3.8 (3.8-3.9)	3.8 (3.6-4.0)	0.928
Dietary intake				
Energy (kcal)	1967.5 (1528.4-2568.9)	1779.3 (1528.4-2390.2)	2121.9 (1686.1-2839.0)	0.248
Energy (kcal/kg)	34.2 ± 19.7	32.3 ± 19.5	36.5 ± 21.2	0.664
Protein (g)	79.3 ± 23.5	68.3 ± 24.6	93.0 ± 13.5	0.021
Protein (g/kg)	1.2 ± 0.6	1.1 ± 0.6	1.4 ± 0.5	0.344
nPNA (g/kg)	1.3 (1.1-1.5)	1.4 (1.1-1.7)	1.2 (1.1-1.3)	0.328

BMI: body mass index; R/H: resistance adjusted by height; Xc/H: reactance adjusted by height; BUN: blood urea nitrogen; nPNA: normalized protein nitrogen appereance. Quantitative data analyzed with Student's t-test and Mann-Whitney U test. Qualitative data analyzed with the Chi^2 test and Fisher's exact test.

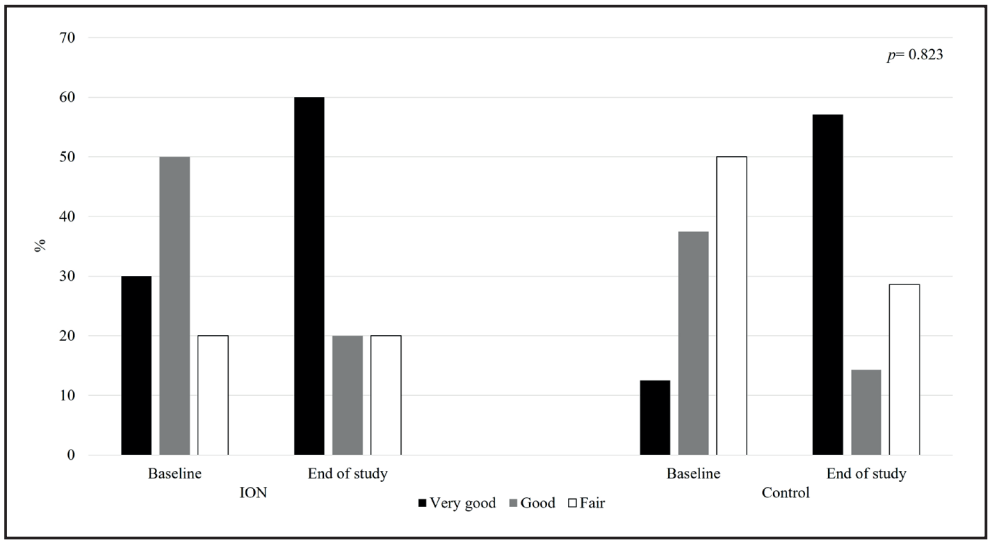

Figure 2.
Appetite assessment with ADAT question 1.

Table II. Changes in dietary intake during the study

	Baseline	Intermediate	End of study	*p*-value*	*p*-value† B-ES
Energy (kg/d)					
ION	32.3 ± 19.5	26.2 ± 14.2	37.4 ± 16.6	0.189	0.600
Control	36.5 ± 21.2	27.2 ± 13.3	26.1 ± 11.6		0.202
Protein (g/kg)					
ION	1.1 ± 0.6	1.3 ± 0.8	1.5 ± 0.7	0.681	0.271
Control	1.4 ± 0.5	1.2 ± 0.6	1.2 ± 0.4		0.454
nPNA (g/kg)					
ION	1.4 (1.1-1.7)	1.6 (1.3-1.8)	1.2 (1.1-1.4)	0.893	0.379
Control	1.2 (1.1-1.3)	1.4 (1.2-1.5)	1.3 (1.2-1.7)		0.211
Phosphorous (mg)					
ION	705.1 (534.4-944.3)	705.3 (564.8-864.9)	1005.7 (747.9-1176.7)	0.234	0.193
Control	896.9 (714.7-1055.4)	734.5 (690.6-900.4)	631.6 (499.2-914.7)		0.076
Potassium (mg)					
ION	1533.7 (1286.3-1817.0)	1623.4 (1259.7-1940.9)	1721.6 (1576.7-2003.2)	0.839	0.233
Control	1755.9 (1478.0-1954.9)	1752.2 (1559.5-2083.2)	1656.9 (1068.9-1768.8)		0.477

*ION: intradialytic oral nutrition; nPNA: normalized protein nitrogen appereance. *Repeated measures ANOVA, Box's conservative epsilon sphericity test; Friedman's repeated measures test for nonparametric data. Pre-post analysis; †Student's-t test and Mann-Whitney U-test; B-ES: Baseline-End of Study.*

DISCUSSION

It has been demonstrated that the dietary intake of energy and protein is lower on dialysis days than on non-dialysis days (21). Therefore, ION has been proposed as a way to counteract the catabolic effects of the disease and dialytic therapy (12).

In the existing literature, several studies have described the benefits of ION, such as the increase in serum albumin, maintenance of body composition and trace elements, better sleep quality, and others. (9,13,22). Moreover, some reviews have suggested that eating during HD would enhance QoL (8,23,24). It is important to note that, despite the benefits described in our

Table III. Repeated measures ANOVA of the components of KDQOL-SF36

	Baseline	Intermediate	End of the study	*p*-value† B-ES	*p*-value*	Δ‡ B-ES	*p*-value†
Physical function							
ION	43.7 ± 21.5	40 ± 20.0	49.6 ± 18.4	0.567	0.536	0.29 (-0.68, 1.25)	0.206
Control	48.1 ± 17.7	46 ± 17.8	38.4 ± 17.3	0.259		-0.55 (-1.52, 0.44)	
Role physical							
ION	26.3 ± 25.3	22.5 ± 24.9	35.7 ± 18.3	0.392	0.496	0.41 (-0.57, 1.38)	0.197
Control	37.5 ± 20.0	31.3 ± 22.2	27.5 ± 24.2	0.362		-0.45 (-1.43, 0.52)	
Role emotional							
ION	35 ± 18.3	23.4 ± 21.0	23.9 ± 8.6	0.135	0.279	-0.73 (-1.71, 0.28)	0.528
Control	37.5 ± 19.4	31 ± 5.7	31.5 ± 18.3	0.510		-0.31 (-1.28, 0.66)	
Body pain							
ION	64.3 ± 25.4	60.3 ± 23.6	66.6 ± 24.8	0.850	0.612	0.91 (-0.87, 1.05)	0.145
Control	62.6 ± 20.3	58.1 ± 25.7	61.5 ± 21.2	0.913		-0.05 (-1.01, 0.91)	
General health							
ION	39.8 ± 21.6	34.8 ± 22.3	51.0 ± 25.0	0.323	0.073	0.48 (-0.50, 1.45)	0.470
Control	35.6 ± 17.0	46.5 ± 20.7	35.7 ± 18.7	0.991		0.005 (-0.96, 0.97)	
Vitality							
ION	52.5 ± 22.5	46.9 ± 20.3	64.9 ± 23.0	0.267	0.364	0.54 (-0.44, 1.52)	0.670
Control	54.1 ± 26.6	60.4 ± 18.2	60.0 ± 11.7	0.536		0.26 (-0.70, 1.23)	
Social function							
ION	58 ± 18.1	62 ± 18.1	58.6 ± 28.5	0.957	0.799	0.26 (-0.94, 0.99)	0.634
Control	60 ± 19.2	60 ± 21.4	59 ± 18.0	0.911		-0.05 (-1.01, 0.91)	
Mental health							
ION	62.3 ± 15.6	62.3 ± 14.8	70.9 ± 17.9	0.292	0.989	0.51 (-0.47, 1.49)	0.796
Control	59.8 ± 19.0	70.8 ± 12.8	65.3 ± 10.6	0.447		0.34 (-0.63, 1.30)	

*ION: intradialytic oral nutrition. *Repeated measures ANOVA, Box's conservative epsilon sphericity test. Pre-post analysis; ‡Effect size: Δ Cohen's D; †Paired-t test; B-ES: Baseline-End of study.*

environment, using ION is not yet a common practice (15). However, the benefits of this anabolic strategy must be continuously demonstrated, not only from the nutritional point of view but also from the perspective of other scarcely explored aspects such as QoL, appetite, and IH events.

The presence of physical, functional, metabolic, social, and mental conditions negatively impacts the social, financial, and psychological well-being of HD patients as compared to healthy subjects (25). Patients with HD presented lower scores on the KDQOL-SF36, especially in the components of physical function, mental function, and physical pain compared to those with glomerular filtration rates ≤ 50 ml/min/m^2 and healthy subjects (26). Furthermore, PEW and inflammation led to unfavorable outcomes such as poor appetite and decreased QoL components. In a cohort of 331 HD patients, "regular-poor" appetite was associated with anorexia after the decrease of QoL by KDQOL-SF36 (4). Something similar was reported in the HEMO cohort study with self-reports of appetite and unfavorable outcomes where physical function and mental health roles of the KDQOL-SF36 presented lower scores in the group with a regular, poor, and very poor appetite compared to those with a good and very good appetite (21).

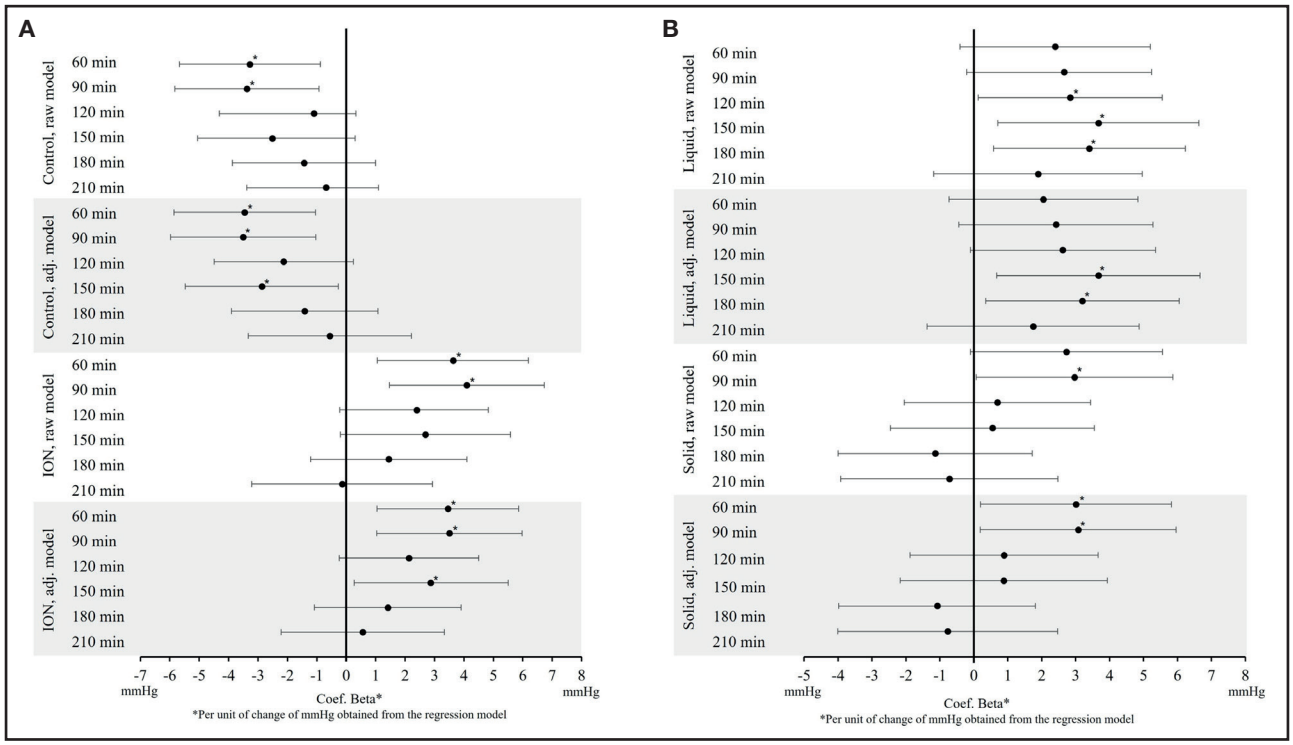

Figure 3.

Changes in SBP during the HD session for 18 sessions: A. Combined models between ION vs. control groups. B. Combined models between both consistencies, solid vs. liquid; *$p = 0.05$.

Table IV. Random-effect repeated measures analysis of systolic blood pressure

According to the groups				
	Control	***p* value**	**ION**	***p* value**
60 min	-3.46 (-1.05, -5.86)	*0.005*	3.46 (1.05, 5.86)	*0.005*
90 min	-3.51 (-1.04, -5.98)	*0.005*	3.51 (1.04, 5.98)	*0.005*
120 min	-2.13 (-4.49, 0.24)	0.078	2.13 (-0.24, 4.50)	0.078
150 min	-2.87 (-0.27, -5.47)	*0.030*	2.87 (0.27, 5.50)	*0.030*
180 min	-1.41 (-3.90, 1.08)	0.268	1.41 ((-1.08, 3.90)	0.268
210 min	-0.56 (-3.33, 2.21)	0.691	0.56 (-2.21, 3.33)	0.691
According to the consistencies				
	Liquid	***p* value**	**Solid**	***p* value**
60 min	2.05 (-0.73, 4.83)	0.148	3.01 (0.20, 5.82)	*0.036*
90 min	2.42 (-0.44, 5.28)	0.097	3.08 (0.19, 5.96)	*0.037*
120 min	2.62 (-0.10, 5.35)	0.059	0.89 (-1.88, 3.66)	0.528
150 min	3.67 (0.67, 6.66)	*0.016*	0.88 (-2.17, 3.93)	0.573
180 min	3.20 (0.35, 6.05)	*0.028*	-1.08 (-3.98, 1.81)	0.463
210 min	1.75 (-1.38, 4.87)	0.273	-0.77 (-4.01, 2.47)	0.640

The model adjusted by sex, age, diabetes mellitus, hypertension, Kt/v and UF, and is reported as coefficients (interval confidence at 95 %).

The effect of ION and QoL has been scarcely explored in the literature. Using a similar methodology, other authors reported clinical improvements in the role of physical function and body pain when comparing a homemade liquid supplementation with standard care for three months (27).

Our results did not show statistical differences in the components of the KDQOL-SF36. When we assessed the differences before-after the intervention, we observed favourable changes when patients were in the ION group, with an increase in the scores of most items, except those on the emotional role. This finding contradicted other results; for example, a three-month clinical trial administered an hyperproteic oral nutritional supplement and reported that the emotional role presented statistically significant differences, while the rest of the components showed favourable clinical changes in the ION group (10).

In our study, when we performed the before-after analysis, we found that the emotional role decreased by the end of the study. The possible causes of these could be due to the short duration of the trial and season of the year, as we performed this study during the end-of-year holidays, which could have interfered with these results.

Loss of appetite may be a consequence of the progression of CKD, the presence of uremia, and the pro-inflammatory environment; nearly 30-40 % of patients on HD experience a decreased appetite, which leads to the development of unfavorable events such as decreased QoL, recurrent hospitalizations, and an increased risk of mortality (4).

Previous works have evaluated the effect of ION on appetite perception using semi-quantitative tools. When assessing the postprandial response of various oral nutritional supplements in patients with HD and analyzing seven appetite parameters with a visual analog scale showed no effects in any nutritional supplement (28).

It is crucial to consider patients' perceptions after receiving food during HD, for example, a study that evaluated patients' experiences after receiving food during HD sessions found that 71 % were interested in receiving food (29); this might be because patients felt personalized attention and special care. In our study, we observed that 80% of the ION group reported a "very good-good" appetite at the end of the intervention.

In some countries, the use of ION is still limited due to the perception of various related complications (15), such as IH events (30). This idea is based on previously published articles with deficient methodology due to poor sample size, shorter durations of nutritional intervention (29,31-33), and clinical characteristics that may counteract the intervention (34). Intradialytic hypotension is believed to be caused by reduced total peripheral resistance and is associated with increased splenic and hepatic blood flow (35). Hence internal regulations, the risk of infections, IH events, and the risk of aspiration are the main reasons why the staff (doctors, nurses, and nutritionists) do not allow patients to eat during HD (15,30).

An observational study recorded food and liquids intake during HD for 23 patients (166 sessions); around thirty-two sessions reported hypotension and found that IH events were twice as common when > 200 kcal were consumed (36). On the other hand, other authors described the presence of IH events and their symptoms in 48 patients who received an ION of 350 kcal during two HD sessions; they reported that patient´s SBP decreased during the first hour and a half of in only two sessions. Comparing the changes in BP between the time of these sessions, they found that the effect was not statistically significant, nor was the presence of gastrointestinal symptoms (37).

In recent years, some studies reported the effect of ION with a better methodological rigor, including BP and IH parameters. These studies found that after using ION, BP does not exhibit any statistical differences (38) or IH events between the control and ION groups, as well as for SBP and the mean BP (29).

In a clinical trial, the effect of ION and home supplementation was demonstrated during 36 HD sessions; nine IH events in the group with home supplementation (control) and seven events in those in the ION group were observed, concluding that this anabolic strategy is safe (14). One of the strengths of our trial is the statistical analysis in repeated measures, which allowed for the analysis of patient´s BP throughout the study.

In the present study, the SBP in the supplementation group (of any consistency) can increase up to 3.51 mmHg (at 90 min in HD), regardless of the confounding variables (age, sex, comorbidities, and dialysis characteristics). In comparison, the liquid (at 150 min) and solid (at 90 min) consistencies can increase to 3.67 mmHg and 3.08 mmHg, respectively. This increment is safe during HD since the values do not exceed the 10 mmHg recommended in international guidelines for the management of BP (39). Finally, IH events were relatively few (ION: 5 vs. control: 1), contrary to what was reported in the literature, concluding that this nutritional intervention is safe regarding IH events.

The nutritional benefits of nutritional supplementation in patients with dialysis have been described in a systematic review with meta-analysis, where the oral nutritional supplementation with proteins increases serum albumin and prealbumin in the group of patients with HD (without this intervention being necessarily intradialysis) and in both replacement therapies. Concerning body composition, no significant effects were observed in weight and BMI, but there was an increase in the mean arm circumference [1.33 cm, (95 % CI, 0.24, 2.43)], regardless of the dialysis therapy (13).

Some authors administered a solid ION during 25 HD sessions, reporting that the intervention group's protein catabolic rate significantly increased. In contrast, a decrease was observed in the control group (29). These results are consistent with other studies that have recommended different types of foods, such as milk and egg whites, in a three-month intervention period (27) and nutritional supplementation with two hyperproteic supplements in patients with albumin < 3.8 g/dl (40).

In our study, no significant differences were reported for biochemical markers, body composition, and dietary parameters, which could be due to the trial's short duration, as serum and body changes are observed over longer periods of time. The ION

group had a clinically significant increase in energy and protein intake at the end of the study, whereas the control group had a decrease.

The main strengths of this trial are that it evaluates different types of ION consistencies (liquid and solid), as well as quantitatively explored outcomes such as QoL, appetite, and the number of BP observations recorded throughout the study (36 HD sessions in 18 patients, with an HD duration of 210 min leading to a total of 3888 observations). On the other hand, our limitations were the study's short duration, small sample size, and short wash-out period.

Trials with larger sample sizes and longer periods are required to analyze the effect of ION on scarcely studied clinical outcomes described in the narrative literature.

CONCLUSIONS

There were clinical improvements in QoL scores and perceived appetite after using ION. Despite the supplementation consistency (liquid or solid), this strategy is not associated with blood pressure changes.

Supplementary Table I. Comparison of quality of life items, analysis between baseline and end of the study

	Group	Baseline	End of study	*p*-value*
Body pain	Control	58.4 (55-60)	60 (52.5-70)	0.162
	ION	53.8 (50-57.5)	55 (52.5-57.5)	0.105
Vitality	Control	33.3 (29.2-33.3)	33.3 (25-37.5)	0.779
	ION	32.3 (25-43.8)	33.3 (25-41.7)	1.000
Role physical	Control	2.8 (2.3-2.9)	2.6 (2.5-2.9)	0.894
	ION	2.8 (2.5-3)	2.6 (2.5-3)	0.695
Physical function	Control	45.6 (41.1-50.9)	45.8 (33.6-51.0)	0.183
	ION	47.8 (33.5-50.2)	38.4 (35.8-42.4)	0.845
Mental health	Control	35.6 (28.3-45.9)	42.2 (29.8-47.5)	0.328
	ION	39.7 (34.8-43.0)	42.8 (34.5-46.0)	1.000

*Pre-post analysis. ION n = 18; Control n = 18. *Mann-Whitney U-test; B-ES: Baseline-End of study.*

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