Renal Replacement Therapy

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Intradialytic parenteral nutrition using a standard amino acid solution not for renal failure in maintenance hemodialysis patients with malnutrition: a multicenter pilot study

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Abstract

Background: Standard amino acid solutions have recently been removed from the contraindications for use in dialysis patients in Japan. However, the details of their safety and efficacy in these patients are still not known. In this study, we investigated the safety and efficacy of intradialytic parenteral nutrition (IDPN) using ENEFLUID® injection containing standard amino acids, glucose, electrolytes, fats, and water-soluble vitamins in maintenance hemodialysis patients with malnutrition.

Methods: This clinical trial was designed as a multicenter, prospective, non-randomized, open-label, single-arm, observational pilot study. The participants were patients on maintenance hemodialysis who were in the nutritional high-risk group according to the Nutritional Risk Index for Japanese Hemodialysis Patients. One bag of ENEFLUID® injection was administered during every hemodialysis session for 12 weeks. The primary endpoint was change in serum transthyretin levels between before and after the 12-week period. As safety endpoints, we evaluated changes in body fluid volume and blood biochemical tests, including blood urea nitrogen and electrolytes, as well as blood glucose variability using flash glucose monitoring (FGM).

Results: The mean age and body mass index of the 13 participants were 79.0 ± 10.7 years and 18.0 ± 1.7 kg/m^2, respectively. No significant changes were observed in nutritional parameters, including serum transthyretin, between before and after the start of the study. After IDPN initiation, there was no obvious fluid overload or significant changes in blood biochemical tests, including electrolytes, and the treatment could be safely continued for 12 weeks. In the FGM analysis, asymptomatic hypoglycemia during hemodialysis was observed at the beginning of the study, but there was a trend toward improvement after 12 weeks (area over the curve < 70 mg/dl per dialysis session: 747.5 ± 1333.9 to 21.6 ± 54.3, $P = 0.09$).

Conclusions: IDPN using ENEFLUID® injection can be safely continued, although it does not significantly improve markers of nutritional status. It also showed the potential to ameliorate asymptomatic hypoglycemia during hemodialysis sessions. More detailed studies of the improvement in nutritional indicators are needed.

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Trial registration: This study was registered with the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) on May 9, 2021 (registration ID, UMIN000044051).

Keywords: Hypoglycemia, Intradialytic parenteral nutrition, Nutritional Risk Index for Japanese Hemodialysis Patients, Malnutrition, Transthyretin

Background

Advances in hemodialysis and hemodiafiltration treatment have enabled patients to survive longer, and an increasing number of elderly patients are starting dialysis, resulting in aging of the overall dialysis patient population [1, 2]. Under these circumstances, low nutrition and wasting among chronic maintenance dialysis patients have become key issues. Indeed, the numbers of patients developing sarcopenia and frailty are increasing [3]. Chronic dialysis patients are thought to require the same protein intake as healthy people, but protein intake from the diet is insufficient in many patients due to, for example, uremic anorexia, constipation, and polypharmacy [4–6]. In chronic dialysis patients, protein catabolism is accelerated by the decrease in plasma amino acid levels associated with dialysis. In addition, concomitant infections and inflammation associated with heart failure accelerate protein catabolism [7].

In Japan, standard amino acid solutions (highly concentrated amino acid infusions and kit infusions containing larger amounts of amino acids) were contraindicated in patients with severe renal failure because they may easily lead to fluid overload and electrolyte imbalance and because residual urea, a metabolite of amino acids, may worsen patients' symptoms. However, urea and other uremic toxins are removed from patients during dialysis, so these patients are not expected to have aggravation of symptom due to urea retention. Accordingly, standard amino acid solutions have recently been removed from the contraindications for use in dialysis patients in Japan, as in European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines [8]. Nonetheless, excessive administration of intravenous nutritional products to dialysis patients may aggravate fluid overload, azotemia, hyperkalemia, and hyperphosphatemia.

Recent guidelines recommend oral nutritional supplements (ONS) and intradialytic parenteral nutrition (IDPN) for chronic hemodialysis patients with protein–energy wasting as described above [9]. On the other hand, although IDPN is expected to improve nutritional parameters such as serum albumin and prealbumin [10], there is currently insufficient evidence on whether standard amino acid solutions can be safely used in actual clinical practice and for the extent to which they are clinically effective. Therefore, in this study, we investigated the safety and efficacy of intravenous nutrition during hemodialysis using ENEFLUID® injection, a newly launched standard amino acid solution, in maintenance hemodialysis patients with malnutrition.

Methods

Study participants

The study participants were enrolled from April to June 2021 at Niigata University Medical and Dental Hospital or affiliated hospitals (Nagaoka Central General Hospital, Nagaoka City, Japan; Saiseikai Sanjo Hospital, Sanjo City, Japan; Sado General Hospital, Sado City, Japan). The participants were patients aged 20 years or older, on maintenance hemodialysis for chronic kidney disease, and in the nutritional high-risk group according to the Nutritional Risk Index for Japanese Hemodialysis Patients (NRI-JH), which was developed as a tool for assessing the nutritional risk of mortality at 1 year based on statistical survey data collected by the physicians belonging to the Japanese Society of Dialysis Therapy [11]. Four clinical factors are included in the NRI-JH: low body mass index (BMI < 20), yes = 3, no = 0; low serum albumin level (young < 3.7 g/dl; old < 3.5 g/dl), yes = 4, no = 0; abnormal serum total cholesterol level, low (< 130 mg/dl) = 1, no = 0; low serum creatinine level (young female, < 9.7 mg/dl; old female, < 8.0 mg/dl; young male, < 11.6 mg/dl; old male, < 9.7 mg/dl), yes = 4, no = 0. In an analysis of data from a nationwide prospective cohort study of the Japanese Society for Dialysis Therapy Renal Data Registry, 10.5% of patients were classified as medium risk (total score 8 to 10) and 8.2% as high risk (total score 11 or higher), and the adjusted hazard ratios compared with the low-risk group were 1.96 and 3.91, respectively [11]. Patients who met any of the following criteria were excluded from the study: pregnant or wanting to become pregnant, started hemodialysis less than 180 days earlier, expected survival of less than 12 weeks due to severe infection or malignancy, and deemed ineligible for this trial by their attending physician for any medical reason.

Study design

This clinical trial was designed as a multicenter, prospective, non-randomized, open-label, single-arm, observational pilot study. This uncontrolled exploratory study was approved by the Ethics Committee of Niigata University School of Medicine (approval number,

2020-0442) and was performed in accordance with the principles embodied in the Declaration of Helsinki. Furthermore, the study was registered with the University Hospital Medical Information Network–Clinical Trials Registry (UMIN000044051). Written informed consent was obtained from all patients prior to any study-related measures.

One bag of ENEFLUID® injection (550 ml), a solution of standard amino acids, glucose, electrolytes, fats, and water-soluble vitamins, was administered at a rate of 150 ml/h to be completed within the dialysis session (Table 1). The infusion was administered during every hemodialysis session for 12 weeks. No intravenous nutrition containing glucose, amino acids, or fats other than ENEFLUID® injection was added during hemodialysis, and no new ONS was started during the study period. The composition of the dialysate and the dialyzer was not changed during the study period whenever possible.

Venous blood samples were taken at the start, 2 weeks, 4 weeks, 8 weeks, and 12 weeks (2 weeks, 4 weeks, and 8 weeks are for safety assessment). The flash glucose monitoring (FGM) system (Libre Pro®) was applied for 2 weeks prior to the start of administration of ENEFLUID® injection, for 2 weeks from the start, and for 2 weeks from 10 weeks. Administration of ENEFLUID® injection was discontinued if the FGM system showed persistent glucose levels > 500 mg/dl during a hemodialysis session or if glucose levels < 50 mg/dl appeared after a hemodialysis session in response to the infusion.

The primary endpoint was change in the serum transthyretin level between before and after 12 weeks of IDPN using ENEFLUID® injection. Secondary endpoints for assessing clinical utility were changes in serum albumin, the normalized protein catabolic rate (nPCR) [12], and nutritional indicators such as BMI, the Geriatric Nutritional Risk Index (GNRI) [13], the Survival Index (SI) [14], and the NRI-JH before and 12 weeks after IDPN. In addition, for safety endpoints, we evaluated body fluid volume and blood biochemical tests including blood urea nitrogen and electrolytes before and after the start of IDPN as well as blood glucose variability including assessment of reactive hypoglycemia at 2 weeks before, 2 weeks after, and 12 weeks after the start of IDPN using FGM.

Table 1 Composition of ENEFLUID® injection

Ingredients (500 ml)		
Carbohydrate		
Dextrose	(g)	37.5
Amino acids		
Total free amino acids	(g)	15
Total nitrogen	(g)	2.37
Essential/nonessential amino acids		1.8
Fat		
Purified soybean oil	(g)	10
Electrolytes		
$Sodium^{+}$	(mEq)	17.5
$Potassium^{+}$	(mEq)	10
$Magnesium^{2+}$	(mEq)	2.5
$Calcium^{2+}$	(mEq)	2.5
$Crawl^{-}$	(mEq)	17.5
$Sulfate^{2-}$	(mEq)	2.5
$Acetate^{-}$	(mEq)	8.2
$Gluconate^{-}$	(mEq)	2.5
$L\text{-}Lactate^{-}$	(mEq)	10.5
$Citrate^{3-}$	(mEq)	3.2
Phosphorus	(mmol)	5
Zinc	(μmol)	2.5
Vitamins		
Thiamine chloride hydrochloride	(mg)	1.91
Riboflavin sodium phosphate	(mg)	1.15
Pyridoxine hydrochloride	(mg)	1.83
Cyanocobalamin	(μg)	1.25
Nicotinamide	(mg)	10
Panthenol	(mg)	3.52
Folic acid	(μg)	150
Biotin	(μg)	15
Ascorbic acid	(mg)	50
pH		Approx. 6.4
Osmotic pressure ratio (relative to saline solution)		Approx. 3
Total calories	(kcal)	310
Non-protein calories	(kcal)	250

Laboratory investigations

General blood biochemical tests were analyzed in each facility's laboratory. Glycated hemoglobin (HbA1c), glycoalbumin, transthyretin, serum copper, and serum zinc were measured at SRL Co., Ltd. (Tokyo, Japan). Clinical and nutritional status parameters monitored in this study included age, sex, height, weight, BMI, GNRI, SI, NRI-JH, primary disease, concomitant medications (including erythropoietin-stimulating agent dose), dialysate composition, dialysis membrane, and blood access. Dry weight was defined as the weight at the end of the weekend dialysis session. BMI was calculated by dividing the average weight (kg) after hemodialysis by the square of height (m).

Statistical methods

Data are presented as the mean ± standard deviation unless otherwise specified. The paired t test was used to compare the values before and after the start of IDPN. P values less than 0.05 were considered significant. All

statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University; http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html), which is a graphical user interface for R (The R Foundation for Statistical Computing). EZR is a modified version of R Commander designed to add statistical functions frequently used in biostatistics [15].

Results

In this study, only hemodialysis patients classified as high risk according to the NRI-JH were included. Therefore, of 347 patients screened, 309 low- and intermediate-risk patients were excluded, leaving 38 high-risk patients with a score of 11 or higher. Of these 38 patients, 14 consented to participate. One of the 14 patients died of old age before the study began. Thirteen patients completed the trial, but FGM analysis was not possible in 2 patients due to an inability to wear the device because of pacemaker insertion and due to loss of the device.

The mean age of the 13 participants (7 male) was 78.8 ± 10.3 years, and the mean BMI was 18.1 ± 1.6 kg/m^2. Mean C-reactive protein levels in the 13 participants were 0.8 ± 0.8 mg/dl before the start of IDPN, and 9 of the patients had persistent chronic inflammation, which was a possible reason for malnutrition. Other possible reasons were comorbid conditions such as dementia, systemic lupus erythematosus, rheumatoid arthritis, and papillary thyroid cancer. Nutritional indices before and after the start of IDPN are shown in Table 2.

Table 2 Baseline characteristics and nutritional indices before and after the start of the study

N = 13 patients		Before	After	*p*
Age	Years	78.8 ± 10.3		
Male/female	*n/N*	7/6		
Dry weight	kg	43.0 ± 7.4	42.7 ± 7.8	0.42
BMI	kg/m^2	18.1 ± 1.6	17.9 ± 1.8	0.42
Diabetes	*n* (%)	6 (46)		
Dialysis fluid glucose concentration				
100 mg/dl	*n* (%)	10 (77)		
150 mg/dl	*n* (%)	3 (23)		
Transthyretin	mg/dl	19.0 ± 7.0	19.0 ± 7.8	0.97
Albumin	g/dl	3.1 ± 0.5	3.0 ± 0.6	0.34
Copper	μg/dl	93 ± 25	101 ± 36	0.15
Zinc	μg/dl	53 ± 16	54 ± 11	0.71
GNRI		80.0 ± 8.0	78.6 ± 10.5	0.29
Survival index		7.1 ± 5.2	5.8 ± 6.1	0.10
nPCR	g/kg/day	0.82 ± 0.23	0.88 ± 0.19	0.29
NRI-JH		10.8 ± 1.6	10.5 ± 2.0	0.51

GNRI Geriatric Nutritional Risk Index, *nPCR* normalized protein catabolic rate, *NRI-JH* Nutritional Risk Index for Japanese Hemodialysis Patients

No significant changes were observed in nutritional parameters, including serum transthyretin (19.0 ± 7.0 to 19.0 ± 7.8 mg/dl, $P = 0.97$). In addition, there was no obvious fluid overload and no significant changes in blood biochemical tests, including electrolytes, and the treatment could be safely continued for 12 weeks (Table 3; data for 2 weeks, 4 weeks, and 8 weeks are not shown). Dry weight was defined as the weight at the end of the weekend dialysis session. As shown in Table 2, there was no significant difference in weekend dry weight between the start and end of IDPN (43.0 kg vs. 42.7 kg, respectively; $P = 0.42$). There was also no significant difference in serum brain natriuretic peptide (BNP) levels. Furthermore, an additional analysis of volume overload showed no significant difference in the rate of weight gain at the beginning of the week before and after the start of IDPN (4.4% vs. 4.1%, $P = 0.38$). Serum total cholesterol (TC) decreased, but serum triglyceride exhibited no significant change between before and after the start of this study. No adverse events were observed during dialysis sessions with ENEFLUID® injection.

Table 4 shows the changes in blood glucose levels during dialysis using FGM at the beginning and end of the

Table 3 Laboratory parameters before and after the start of the study

N = 13 patients		Before	After	*p*
Hemoglobin	g/dl	10.0 ± 1.7	10.5 ± 1.7	0.35
Blood urea nitrogen	mg/dl	57.6 ± 20.1	62.6 ± 17.1	0.30
Creatinine	mg/dl	7.5 ± 1.7	7.6 ± 1.8	0.64
Sodium	mEq/l	137 ± 3	136 ± 3	0.15
Potassium	mEq/l	4.6 ± 1.1	4.6 ± 0.9	0.76
Calcium	mg/dl	8.7 ± 0.9	8.4 ± 0.8	0.15
Inorganic phosphorus	mg/dl	5.2 ± 1.9	5.6 ± 1.6	0.64
Cholinesterase	U/l	174 ± 48	171 ± 54	0.69
Total cholesterol	mg/dl	156 ± 45	142 ± 39	0.01
Triglyceride	mg/dl	89 ± 53	87 ± 40	0.84
Brain natriuretic peptide	pg/ml	903 ± 1379	1033 ± 1749	0.41
Hemoglobin A1c	%	5.3 ± 0.8	5.4 ± 0.7	0.47
Glycoalbumin	%	19.3 ± 4.3	20.3 ± 5.5	0.21

Table 4 Changes in blood glucose levels during dialysis using flash glucose monitoring between the beginning and end of the study

N = 11 patients		Beginning	End	*p*
Mean glucose	mg/dl	85.4 ± 20.9	125.5 ± 36.5	< 0.001
Glucose SD	mg/dl	13.5 ± 6.9	15.0 ± 7.0	0.36
AOC < 70 per dialysis session	mg/dl	747.5 ± 1333.9	21.6 ± 54.3	0.09

AOC area over the curve, *SD* standard deviation

study, each for 2 weeks. None of the participants had hyperglycemia over 400 mg/dl. The mean blood glucose during dialysis significantly increased between before and after the start of this study, and asymptomatic hypoglycemia, indicated by an area over the curve (AOC) < 70 mg/dl per session, showed a decreasing trend (AOC < 70 mg/dl per dialysis session: 747.5 ± 1333.9 to 21.6 ± 54.3, $P = 0.09$) (Fig. 1).

Discussion

The aim of this study was to investigate the safety and usefulness of IDPN using ENEFLUID® injection, a standard amino acid solution, in hemodialysis patients who were in the nutritional high-risk group according to the NRI-JH. ENEFLUID® injection could be safely continued during the study period. In addition, there were no significant changes in serum transthyretin levels between before and after 12 weeks. Moreover, there was no improvement in the nutritional indices nPCR, BMI, GNRI, and SI. Although serum TC decreased significantly, there was no significant change in NRI-JH or Controlling Nutritional Status (CONUT) score (data not shown), both of which are nutritional indices based on serum TC levels. Therefore, it is unlikely that the change in TC alone was large enough to suggest that nutritional status had worsened. By contrast, FGM before the start of IDPN showed a tendency for a steep decrease in blood glucose during dialysis, but it disappeared after the start of IDPN.

ESPEN [16] and KDOQI [9] guidelines recommend the use of IDPN only after dietary counseling, ONS, and enteral tube feeding are attempted. However, whereas there are barriers to the use of ONS due to their taste, nausea, and lack of support, IDPN is currently given at an early stage due to its ease of administration. In this study, patients were selected from a nutritional high-risk group according to the NRI-JH at facilities where dialysis specialists provide nutritional guidance and explain the risks of undernutrition to patients and they agreed to participate in the study.

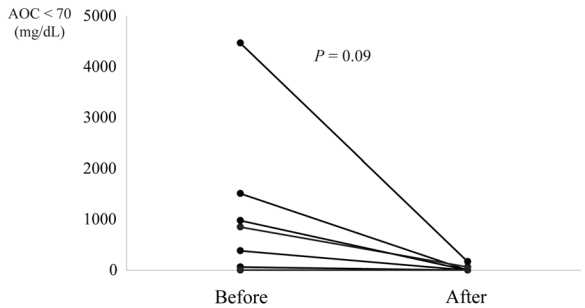

Fig. 1 Changes in blood glucose for an area over the curve < 70 mg/dl per dialysis session before and after the start of this study. Changes in blood glucose levels during dialysis using flash glucose monitoring at the beginning and end of the study, each for 2 weeks, were compared. Asymptomatic hypoglycemia, indicated by the area over the curve (AOC) < 70 mg/dl per dialysis session, showed a decreasing trend

A previous report showed that weight and serum albumin improved in malnourished dialysis patients treated with IDPN [17]. However, one change in the consensus statement [18] is that serum albumin is no longer included as a desirable marker of nutritional status because serum albumin levels are commonly lowered by inflammation. Therefore, low albumin levels do not necessarily indicate malnutrition. On the other hand, serum transthyretin levels are believed to be an indicator of morbidity and mortality in malnourished hemodialysis patients on nutritional therapy and have been shown to best reflect nutritional status [19]. Moreover, increased serum transthyretin levels are accepted as a positive marker of prognosis, predicting improved survival [10]. In addition, in a randomized controlled trial reported by a German group that administered 16 weeks of IDPN to maintenance hemodialysis patients with protein–energy wasting, serum transthyretin levels were higher in the group with IDPN compared with the group without IDPN in hemodialysis patients with inadequate oral intake, suggesting that IDPN may be effective during dialysis. As for the lack of change in serum transthyretin levels in our study, it is possible that the administration duration was too short, that the amount of nutrients in the ENEFLUID® injection was insufficient, and that our participants were so malnourished that the ENEFLUID® injection was not sufficiently effective. Regarding the possible short duration of administration in this study, a systematic review of 12 clinical trials [20] in which IDPN was administered to hemodialysis patients reported that IDPN did not show any advantage over ONS but did improve some nutrition-related indices such as serum transthyretin and body weight. However, because most of the studies included in the systematic review had a study duration exceeding 6 months, we expect that the serum transthyretin levels would improve with continued administration of ENEFLUID® injection. The composition of the IDPN formula reported to improve serum transthyretin levels was 800 kcal and 14.1 g of amino acids [21] or 14 kcal and 0.68 g of amino acids per kg of body weight [22] during one dialysis session. The ENEFLUID® injection used in this study contained 15 g of amino acids but just 310 kcal, so the nutrient content may be too low. In Japan, the 200-ml and 500-ml 50% dextrose injection products have been approved for continuous intravenous infusion into a central vein under national health insurance coverage, but these are

not covered for administration through a dialysis circuit. In patients with renal failure, a non-protein calorie/nitrogen ratio of ≥ 200 is generally considered to be adequate intake, but ENEFLUID® injection contains 2.37 g total nitrogen and 250 kcal non-protein calories, resulting in a lower non-protein calorie/nitrogen ratio of 105.5. Therefore, this study was conducted to examine whether the effect of this smaller amount of nutritional supplement can be observed in actual clinical practice. In the present study, 550 ml of the ENEFLUID® injection could be used safely, but the amount of calories and protein administered was less than in previous reports [21, 22]. There is room to examine whether it would be safe to use more of the ENEFLUID® injection than in this study to achieve greater nutritional improvement. On the other hand, since the participants in this study were in the high-risk group, another possibility is that the use of ENEFLUID® injection maintained serum transthyretin levels. Since there was no control group in this study, we cannot prove this and further study is needed.

In Japan, IDPN using standard amino acid solutions was contraindicated due to the possibility of exacerbating fluid overload, azotemia, hyperkalemia, and hyperphosphatemia, and its use had been limited to KIDMIN® injection and Neoamiyu®, which are infusions for renal failure. In this study, conducted using standard amino acids, there was no obvious fluid overload or significant changes in blood biochemical tests, including electrolytes, and the ENEFLUID® injection could be safely continued for 12 weeks.

No cases of acute heart failure were observed during the study period, but the mean plasma BNP level was high (Table 3). BNP is secreted by the heart in response to volume loading, though it has also been reported to increase with malnutrition [23]. The participants in this study were in the nutritional high-risk group, and undernutrition may have contributed to the elevated plasma BNP level. In addition, of the 13 participants, 7 had heart valve disease and 3 had a history of myocardial infarction. In particular, a participant with a plasma BNP level exceeding 5000 pg/ml before and after starting IDPN had aortic valve stenosis, asymptomatic myocardial ischemia, and atrial fibrillation. These may be the reasons for the high mean plasma BNP level in this study.

Diabetic patients on hemodialysis often experience hypoglycemia [24, 25], and even non-diabetic patients may experience hypoglycemia [26]. Hypoglycemia has been associated with increased risk of excess mortality in patients with chronic kidney disease [25]. Therefore, caution should be exercised in hemodialysis patients because asymptomatic hypoglycemia has been reported to occur during hemodialysis [27–29]. The optimization of glycemic control in diabetic patients on maintenance dialysis requires accurate assessment. Using 48-h continuous glucose monitoring, Kazempour et al. showed that blood glucose levels were significantly lower on dialysis days than on non-dialysis days and that the risk of asymptomatic hypoglycemia was highest within 24 h after dialysis [27]. The usefulness of FGM in dialysis patients has been reported [30], and the use of FGM in this study captured asymptomatic hypoglycemia in several cases. In addition, continuous glucose monitoring can also assess blood glucose fluctuations, which activate oxidative stress and are associated with atherosclerosis [31, 32]. In this study, IDPN using ENEFLUID® injection during hemodialysis improved the glycemic variability observed by FGM in dialysis patients who were in the nutritional high-risk group according to the NRI-JH. Glucose-free dialysates and low glucose concentration dialysates (80 mg/dl) remove 14–31 g of glucose per hemodialysis session [33, 34], increasing the risk of hypoglycemia during dialysis. Glucose concentrations of 100, 125, and 150 mg/dl are mainly used in dialysis solutions in Japan and, although the use of dialysis solutions containing glucose may be able to prevent hypoglycemia during dialysis [28, 35, 36], hypoglycemia cannot be completely prevented [36]. Furthermore, chronic undernutrition [37] and a lack of renal glycogenesis [38] are believed to contribute to the development of hypoglycemia. The participants in this study were in a group considered to be chronically undernourished, and IDPN with ENEFLUID® injection was judged to improve the glucose fluctuations and might have a positive impact on prognosis.

There are some limitations to this study. First, this single-arm study had a small number of patients and a short observation period. However, this was because the present study was a pilot study that mainly aimed to determine whether ENEFLUID® injection can be used safely in hemodialysis patients in the nutritional high-risk group. Also, this study was conducted with no control group because it would be ethically problematic not to provide appropriate nutritional management to high-risk patients in the control group. Second, dietary intake was not examined, and dialysis conditions such as dialysate composition and dialyzer varied from patient to patient. Further long-term evaluation is needed to establish the clinical impact of IDPN using ENEFLUID® injection on prognosis and survival in the high-risk group. Based on the results of this study, we are also currently planning to undertake a more detailed study with a control group in the medium-risk group according to the NRI-JH. Third, participants who were hospitalized or visited the emergency room during the observation period were not excluded from this study. Thus, we cannot eliminate the influence of illness or medical treatment during admission, such as antibiotics, but we also believe that this is an

unavoidable problem, as has been seen in other studies of dialysis patients with a high rate of hospitalization [39].

Conclusions

In this study, IDPN using ENEFLUID® injection, a standard amino acid solution, during hemodialysis could be safely continued in dialysis patients who were in the nutritional high-risk group according to the NRI-JH, although it did not significantly improve serum transthyretin levels between before and 12 weeks after the start of IDPN. Moreover, it showed the potential to ameliorate asymptomatic hypoglycemia during the hemodialysis session. Although the ESPEN guidelines [16] do not conclude that IDPN clearly improves nutritional outcomes compared with dietary counseling and ONS, IDPN may be a beneficial treatment for dialysis patients in the nutritional high-risk group according to the NRI-JH by improving glycemic variability.

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Author contributions
MH, HK, YS, and AS were responsible for the conception and design of the study. MH was the chief investigator and responsible for data analysis. RY and HK were responsible for data analysis. RY, AT, and DU were responsible for data acquisition. RY, MH, and HK were responsible for data interpretation and drafting the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this article.

Declarations

Ethics approval and consent to participate
The Ethics Committee of the Niigata University School of Medicine approved the study (approval number: 2020-0442). Written informed consent was obtained from each participant.

Consent for publication
Not applicable.

Competing interests
M.H., H.K., and I.N. have received lecture fees from Otsuka Pharmaceutical Co., Ltd. I.N. has received research funding from Otsuka Pharmaceutical Co., Ltd.

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