Revista de Nutrición Clínica y Metabolismo

Review article

Use of intradialytic parenteral nutrition: a review of the Renal Pathology Study Group of the Argentine Association of Enteral and Parenteral Nutrition

Uso de nutrición parenteral intradialítica: una revisión del Grupo de Estudio de Patología Renal de la Asociación Argentina de Nutrición Enteral y Parenteral

Uso de nutrição parenteral intradialítica: uma revisão do Grupo de Estudo de Patologia Renal da Associação Argentina de Nutrição Enteral e Parenteral

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Received: March 21, 2023. Accepted: June 17, 2023.
Posted online: June 18, 2023.
https://doi.org/10.35454/rncm.v6n4.528

Summary

The need for renal replacement therapy (RRT) in Argentina has increased by more than 30% in the last 15 years. The prevalence of malnutrition in this population is high and it is known as *protein-energy wasting* (PEW). The rapid diagnosis and treatment of PEW is essential since it is a strong predictor of morbimortality. Intradialytic parenteral nutrition (IDPN) is one of the options for its treatment, which is recommended after nutritional counseling, oral nutritional supplements, and enteral nutrition. The indication for IDPN should be individually evaluated, taking into consideration the advantages, disadvantages, contraindications and the barriers of its implementation. This review will cover these points for both adults and children.

Keywords: Malnutrition; renal replacement therapy; parenteral nutrition; hemodialysis.

Resumen

En los últimos 15 años se ha incrementado en más de un 30 % la necesidad de diálisis en Argentina. En esta población existe una alta prevalencia de desnutrición, la cual se conoce como *desgaste proteico energético* (DPE). Su diagnóstico y tratamiento oportuno es esencial ya que es un gran predictor de morbimortalidad. Dentro de las opciones de tratamiento se encuentra la nutrición parenteral intradialítica (NPID), la cual se recomienda luego de la realización de consejería nutricional; el uso de suplemento nutricional oral (SNO) y nutrición enteral (NE). La indicación de la NPID debe evaluarse individualmente teniendo en consideración los criterios de inicio, sus ventajas, desventajas y las contraindicaciones de su uso, como así también diferentes barreras que existen para su implementación. La presente revisión abordará dichos puntos tanto para la población adulta como pediátrica.

Palabras clave: desnutrición, terapia de reemplazo renal, nutrición parenteral, hemodiálisis.

Resumo

Nos últimos 15 anos, a necessidade de diálise na Argentina aumentou mais de 30%. Em esta população há uma alta prevalência de desnutrição, conhecida como desperdício energético-protéico (PEW). O seu diagnóstico e tratamento oportuno é essencial uma vez que é um grande preditor de morbilidade e mortalidade. Entre as opções de tratamento está a nutrição parenteral intradialítica (NPI), que é recomendada após orientação nutricional, o uso de suplementos nutricionais orais (SNO) e nutrição enteral (NE). A indicação da NPI deve ser avaliada individualmente, levando em consideração os critérios de início, suas vantagens, desvantagens e contraindicações para seu uso, bem como as diversas barreiras existentes para sua implementação. Esta revisão abordará esses pontos tanto para as populações adulta como pediátrica.

Palavras-chave: desnutrição, terapia renal substitutiva, nutrição parenteral,

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INTRODUCTION

The latest Argentina Registry of Chronic Dialysis, conducted in 2020, shows a total of 29,423 patients on dialysis throughout the country. Despite the value being 2.9 % lower than the previous year, there has been a 31.7 % increase in the last 15 years[1].

The term Protein-Energy Wasting (PEW) is used to refer to malnutrition caused by factors related to chronic kidney disease (CKD), such as the hypercatabolic state induced by uremia, anorexia, dietary restrictions, inflammation, comorbidities, and dialysis, among others[2]. PEW affects 20 % to 75 % of dialysis patients and is considered one of the major predictors of morbidity and mortality, negatively impacting the quality of life and increasing healthcare costs. Therefore, its early diagnosis and treatment are essential[3].

Diagnostic criteria for PEW include laboratory values (serum albumin, prealbumin, creatinine), body mass index (BMI), weight and muscle mass loss, and deficient dietary intake[2].

The intradialytic parenteral nutrition (IDPN) is one of the nutritional treatment options for PEW, which involves the administration of nutrients during each dialysis session through the venous drip chamber in the extracorporeal circuit. IDPN began to be used worldwide in the 1970s[4]. In contrast to alternative treatments, such as nutritional counseling, oral nutritional supplements (ONS) or enteral nutrition (EN), this treatment is more expensive and has been linked to adverse effects, including infections, hypoglycemia, fluid overload, electrolyte imbalances, and more[5].

Its impact on clinically relevant parameters remains a matter of debate. Consequently, international nutrition guidelines recommend its implementation only after patients on hemodialysis (HD) do not respond to the previously mentioned treatments[5-7]. However, IDPN is often used as the first step in nutritional support if there are difficulties in implementing ONS or EN. Currently, there is a lack of data regarding its use in Argentina, but varying prevalence has been observed in other countries, for instance, 50 % of healthcare centers in Australia do not employ IDPN[6, 7].

In pediatric patients, the severeness of malnutrition is associated with increased mortality, which supports the use of an intensified nutrition regime (such as IDPN) to reverse malnutrition[8-10]. This article aims to provide an updated scientific review and describe the limitations on the use of IDPN in Argentina, both in the adult and pediatric populations.

ANALYSIS AND DISCUSSION

Intradialytic parenteral nutrition implementation

The indications, initiation criteria, advantages, disadvantages, and contraindications of IDPN should be considered when evaluating its use for each individual case (Table 1). The initiation criteria vary according to different societies.

- The European Best Practice Guidelines[5] recommend the initiation in patients with malnutrition whose intake is > 20 kcal/kg and 0.8 g of protein/kg of ideal body weight per day. For lower intakes, they consider the use of total parenteral nutrition.
- The European Society for Clinical Nutrition and Metabolism (ESPEN)[11] suggests the initiation in malnourished patients or those at risk of malnutrition who have not previously responded to ONS or EN.
- The Spanish Society of Nephrology (SENEFRO) and the Spanish Society of Parenteral and Enteral Nutrition (SENPE)[12] recommend its use whenever ONS or EN are not possible, along with at least three of the following criteria:
  - albumin < 3.5 g/dL or prealbumin < 20 mg/dL for three or more months;
  - serum creatinine < 8 mg/dL for three or more months;

Table 1. Advantages, disadvantages, and contraindications of IDPN[4, 11-18]

Advantages	- It does not require adding another vascular access or placing a nasogastric tube - It provides significant amounts of proteins in a short period of time - Extra fluids and minerals are ultrafiltered during hemodialysis - It requires little effort from the patient and is usually well accepted - If its use manages to avoid hospitalization, costs are reduced, and quality of life improves - It does not depend on the patient's appetite
Disadvantages	- It cannot be used as an only source of nutrition since it does not provide all the nutrients required and is only administered during hemodialysis - It may not reverse malnutrition - It is more expensive than oral supplements and enteral nutrition - In patients with fluid overload, the extra fluid can be difficult to ultrafilter - It does not improve the patient's eating habit - It predisposes to a higher risk of infection, dysglycemia, postprandial hypotension, or hyperphosphatemia. *These can be avoided with proper monitoring and adherence to best practices*
Contraindications	- Allergy to any of the components (soybean oil or fish, egg, and peanut) - Hypertriglyceridemia (> 300 mg/dL)[19] - Inborn errors of amino acid metabolism - Inability to maintain a flow in the pump > 200 mL/min - Dialysis with a single needle - Patients on palliative treatment, whose life expectancy does not exceed the time necessary to see the changes that IDPN could produce or in cases where it cannot make significant improvements to their quality of life

IDPN: Intradialytic parenteral nutrition.

- weight loss exceeding 10 % of their usual weight or 20 % of their ideal weight within the past six months;
- loss of more than 10 % or 20 % of usual and ideal weight, respectively, in the last six months;
- BMI < 18.5 kg/m^2 or modified Subjective Global Assessment (SGA)/Malnutrition Inflammatory Score (MIS) indicating moderate to severe malnutrition (score C or 12);
- reduced food intake that does not meet caloric needs (25-28 kcal/kg/day);
- reduced food intake that does not meet protein needs (0.75 g/kg/day).

In patients with PEW and intakes lower than 20 kcal/kg/day or 0.8 g/kg/day, daily nutritional support (ONS or NE) is recommended instead of support administered only during dialysis sessions, such as IDPN[5]. However, obstacles to following treatment recommendations (such as the taste of ONS, adherence to prolonged consumption of if, resistance to EN, and the convenience of its use) have led to the early use of IDPN[6].

Refeeding syndrome

Refeeding syndrome is characterized by metabolic and electrolyte alterations resulting from the reintroduction and/or increased provision of calories after a period of decreased or absent caloric intake. Currently, there is no universal definition to ascertain its incidence and guide effective strategies for its detection, prevention, and treatment[19,20]. This leads to the risk of developing it being subjectively identified at the time of initiating feeding[19].

Although hypophosphatemia is considered the hallmark of this syndrome, the recommendations of the American Society for Parenteral and Enteral Nutrition (ASPEN) assign the same relevance to hypokalemia, hypomagnesemia, and thiamine deficiency for its development, considering the following diagnostic criteria[19]:

- A decrease in any 1, 2, or 3 of serum phosphorus, potassium, and/or magnesium levels by at least 10 % and/or organ dysfunction resulting from a decrease in any of these and/or due to thiamine deficiency, and
- occurring within 5 days of reinitiating or substantially increasing energy provision.

Based on this definition, ASPEN provides recommendations for its prevention and treatment, although it acknowledges that they may not apply to every population, such as those with renal insufficiency, as there is no evidence from randomized studies[19]. It should also be considered that hyperphosphatemia and hyperkalemia, which are common in this population, could mask

the syndrome[19], so a cautious implementation of any type of nutritional support is suggested in patients with severe malnutrition[20].

Intradialytic parenteral nutrition formulas

The formulas used for IDPN can be commercial ready-to-use solutions or compounded. It is recommended to use a more concentrated formula to reduce the risk of volume overload and administer it over the duration of an HD session. IDPN provides between 800 and 1200 calories from glucose, lipids, and amino acids (AA) per approximately 1000 mL[7, 13].

The formulation of compounded IDPN depends on nutrient compatibility and its maximum infusion rate, as well as the time of administration, which corresponds to the duration of the session (around 4 hours). A rapid administration of glucose and lipids (> 250 mL/hour of parenteral solution) could lead to adverse effects (Table 2)[14, 21, 22].

The caloric density of the formulas is approximately 1 kcal/mL[26, 27]. The amount of calories administered is limited by the hepatic glucose utilization of 4 mg/kg/min, which usually provides 15 kcal/kg[26].

Carbohydrates

The recommended dosage for each session is between 150 to 175 grams[27]. Various authors suggest that when higher glucose levels are required, for example, in patients with diabetes or with poor utilization of peripheral glucose, insulin should be co-administered within the compounded IDPN at a rate of 1 unit for every 10 grams of dextrose[13-15, 26-28]. However, this is not usually carried out and, in these cases, exogenous insulin is applied.

Proteins

The standard composition is 1.2 g/kg or 30-60 grams of AA, of both essential and non-essential AA[15, 26]. The amount received is limited to less than 150 grams per week, due to the losses of 4-8 grams of AA during each session, as well as the days with no dialysis[21]. Additionally, specialized AA, like glutamine and carnitine, can be added in parallel[27].

Glutamine is a conditionally essential AA that has pharmacological effects on cells of the immune system, the small intestine, and the colon. On the other hand, carnitine can enhance the removal of serum triglycerides by promoting mitochondrial uptake and metabolism of circulating fatty acids, thereby mitigating the risk of hypertriglyceridemia[27]. Nevertheless, in our country, their usage is infrequent due to their high costs.

Lipids

Lipids provide a significant amount of calories in a small volume[26]. To prevent hypertriglyceridemia, it is recommended to provide 20 to 40 grams of lipids during each dialysis session[28]. There is no conclusive data regarding the option of fatty acids. The role of polyunsaturated omega-3 (ω-3) fatty acids is uncertain in CKD, and there is insufficient evidence to recommend their use[11].

Table 2. Monitoring and treating potential adverse effects of IDPN[9, 23-25]

Component	Adverse effect	Frequency of measurement	Suggested management
Carbohydrates	Hyperglycemia (> 350 mg/dL)	Serum glucose: - First week of IDPN: before the session, one hour later, and at the end - After changes in dextrose flow - Monthly	- Decrease dextrose by 2 mg/kg/min - Administer insulin to maintain serum glucose below 200 mg/dL
Lipids	Hypertriglyceridemia > 250 mg/dL or a 50 % increase from the initial value before completing two weeks of IDPN	Serum triglycerides: - During the first and second week of treatment initiation - Monthly	- Decrease/discontinue the infusion of lipids - Evaluate the overall continuity of IDPN if lipids are already discontinued
	Hypersensitivity (allergy)	During the first week of lipid administration within the first 30 minutes of starting IDPN	

IDPN: Intradialytic parenteral nutrition.

However, considering that CKD carries a substantial burden of cardiovascular disease, fish oil and oleic acid could be used, or if standardized formulas are available, those are preferred with third-generation lipids (medium-chain triglycerides, soybean oil, olive oil, and fish oil)[16, 29-31]. The choice of one fatty acid over another will also depend on availability, financial resources, and the therapeutic nutritional properties required[27].

Phosphorus, potassium, and calcium

The presence of hyper-/hypophosphatemia, hyper-/hypokalemia, and hyper-/hypocalcemia is common in these patients. Ideally, a ready-to-hang or specially designed compounded bag for IDPN should not include these minerals. If necessary, it is preferable to supplement them based on serum levels or clinical manifestations resulting from deficiencies or excesses[11, 17].

Selenium and zinc

Routine supplementation is not suggested as there is limited evidence that it improves both nutritional and inflammatory status[16].

Water-soluble vitamins

Deficiencies may be suspected due to reduced intake and loss of nutrients resulting from dialysis treatment. As a result, some guidelines recommend the monitoring and supplementation of multivitamins, although there is no consensus on this approach. The United States (US) National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (NKF KDOQI) 2020 guidelines[16] suggest considering supplementation only when signs and symptoms are present, while the ESPEN Guidelines on Parenteral Nutrition: Adult Renal Failure[32] suggest doubling the dose to compensate for losses.

Fat-soluble vitamins

Their intake should be individualized due to their potential toxicity (Table 3)[16].

In conclusion, the routine addition of vitamin or mineral supplements in a compounded IDPN bag is not recommended, and supplementation should be done individually if necessary.

Administration

One of the advantages of IDPN is that the same access used for hemodialysis can be utilized to administrate the nutrients. This is due to the fact that blood vessels are not suitable for sustaining the high flow required for dialysis treatment; thus, it is necessary to create a vascular access point, known as an arteriovenous fistula, to facilitate long-term treatment[30]. In cases where this cannot be established, a prosthesis or catheter may be used, and in these situations, IDPN can also be administered.

Table 3. General composition of IDPN[12, 15, 21, 27]

Caloric density	1-1.2 kcal/mL
Carbohydrate (glucose)	150-175 g
Protein/AA	0.8-1.2 g/kg o 30-60 g total AA
Lipids	40-50 g
Electrolytes	Does not contain
Vitamins	Does not contain Addition only individualized
Phosphorus	Individualized
Volume	625-1000 mL
Osmolarity	1200-1600 mOsm/L

AA: amino acids; IDPN: Intradialytic parenteral nutrition.

It should be noted that in Argentina, a significant number of patients do not enter renal replacement therapy (RRT) on a scheduled basis, requiring treatment initiation through a temporary catheter. In 2020, the year the coronavirus disease (COVID-19) pandemic began in Argentina, 73.3% of patients entered dialysis with this access[33]. To the date, there is no published scientific evidence indicating that this type of access is a contraindication for the administration of IDPN. Furthermore, patients initiating unplanned RRT usually have deteriorated nutritional status and are likely to require some form of nutritional support.

The supplies required for IDPN administration include the bag, guide, infusion pump, sterile equipment for connection (gown, cap, mask, gloves), glucose monitoring test strip, and the dialysis machine[12, 14, 15, 21, 26]. The IDPN solution should be infused throughout the dialysis session using a volumetric infusion pump, not the gravity method[28]. The ultrafiltration rate should be adjusted, taking into account the volume provided by IDPN to avoid fluid overload[21].

The infusion of the IDPN should start when the dialysis machine pressure and the patient's control parameters are stable, around 15 minutes into the dialysis[21, 34]. The amount administered should not exceed 1000 mL

per session. When it comes to the rate of IDPN infusion, recommendations vary in the literature. Some authors suggest a gradual increase during the first week in order to reach 16 mL/kg/day[35]. Others recommend infusing at 125 mL/h in the first week and, then, from the second week onwards, at 250 mL/h, which coincides with the maximum infusion rate[36]. A different option is to reach one-third of the target volume in the first week, two-thirds in the second week, and the final third in the third week[21].

There is no unanimity regarding the method of administration, as it depends on the patient's clinical condition (fluid overload, refeeding syndrome, among others)[20].

Monitoring of complications and nutritional evaluation

In order to reduce complications associated with IDPN, various parameters should be monitored (Table 4). The literature suggests conducting laboratory tests, assessing the protein catabolism rate, measuring anthropometrics, and using SGA (Table 5)[26] for the nutritional follow-up.

Suspension of intradialytic parenteral nutrition

The literature recommends a minimum duration of the treatment of 4 to 12 months to obtain nutritional benefits[26]. This highlights the lack of consensus on the optimal duration of IDPN for observing improvements in nutritional parameters. In contrast, other authors[12] propose discontinuing in situations such as:

- Improvement in nutritional status according to:
  - Nutritional assessment (albumin > 3.8 g/dL, dry weight > 80 % of ideal weight).
  - Normal nutritional status or mild malnutrition according to SGA.
  - Increased oral intake: protein > 1 g/kg/day and calories > 30 kcal/kg/day.
- Complications or intolerance due to IDPN, or lack of improvement after six months of treatment.

Considerations in pediatric patients

HD carries a high risk of malnutrition due to low calorie and protein intake, food aversion, feeding intolerance, and the inherent protein catabolism associated with the disease, compounded by losses from dialysis[37]. Adequate nutrient administration is crucial for growth and development[37]. The following parameters are used to define it:

- Growth delay[38]:
  - Weight for age/sex <-1.88 standard deviation (SD);
  - Height for age/sex <-1.88 SD;
  - BMI < third percentile.
- Severe growth delay[39]:
  - Height for age/sex <-2.5 SD;
  - Height for age/sex < 1 percentile.

Table 4. Recommended monitorization to prevent complications in patients with IDPN[12, 14, 15, 21, 26]

Capillary blood glucose	During the dialysis session, maintaining stable values is suggested (cutoff points may vary in the literature, ranging from 120-150 mg/dL to 110-180 mg/dL) It is recommended to provide a carbohydrate intake of 15-30 grams 30 minutes before completing the IDPN administration to prevent hypoglycemia In patients with diabetes, special attention should be given to insulin administration timing. Using short-acting subcutaneous insulin analogs is encouraged to avoid post-dialysis hypoglycemia
Electrolytes	In the initial weeks of administering IDPN, strict monitoring of electrolytes is advised to maintain control over the internal environment
Pre-dialysis bicarbonate	Monthly for the control of acidosis
Pre-dialysis triglycerides	Monthly for the control of hypertriglyceridemia
Hepatic function	Measure liver enzymes monthly, and then individualize the monitoring

IDPN: Intradialytic parenteral nutrition.

Table 5. Recommended parameters to assess in patients on IDPN[26]

Laboratory	- Albumin or prealbumin to assess the impact of IDPN (every 1-3 months), always taking into consideration the CRP value - Cholesterol (every 1-3 months)
Anthropometric measurements	- Monthly monitor BMI, weight compared to their usual weight and ideal weight - Multifrequency bioimpedance or DEXA
Normalized protein catabolic rate (nPCR)	- Monthly
SGA	- Every 3-6 months (depending on the reference)

BMI: Body mass index; DEXA: Dual-energy X-ray absorptiometry; IDPN: intradialytic parenteral nutrition; nPCR: Normalized protein catabolic rate; CPR: C-reactive protein; SGA: Subjective global assessment. Taken from: Huarte-Loza E, et al. Dial Traspl. 2006;27(4):138-61[26].

Observational studies have found a higher risk of mortality in patients with severe growth delay[38] (approximately 35 % of children with CKD exhibit this condition in the pre-dialysis stage)[40].

Pediatric nutritional support

The initial treatment involves nutritional counseling and ONS[9, 41]. However, the progressive loss of appetite presents a considerable challenge in most cases, requiring alternative nutritional support, such as EN or IDPN. There are various criteria for initiating IDPN in this patient population (Table 6).

Table 6. Initiation criteria of IDPN treatment[23, 25, 42, 43]

Texas Children's Hospital Renal Dialysis Unit criteria
At least two of the following criteria must be present: - Weight loss > 10 % in three months - Inability to meet nutritional needs orally due to various reasons: Fluid restriction, poor oral tolerance, inability to use the gastrointestinal tract - Inability to meet requirements using enteral nutrition - Clinical signs of malnutrition - Serum albumin levels < 3.5 mg/dL
KDOQI 2009 Guidelines criteria
At least one of the following criteria must be present: - Children below the 5th percentile of BMI - Inability to meet nutritional requirements orally or through enteral means

BMI: body mass index; IDPN: intradialytic parenteral nutrition. KDOQI: Kidney Disease Outcomes Quality Initiative.

Although published studies have small sample sizes, positive effects have been observed following the implementation of IDPN, such as increased food intake after three months, higher BMI values, and significant changes in normalized protein catabolic rate (nPCR) at the beginning of therapy and at five months[23, 44, 45].

Formulation of intradialytic parenteral nutrition in pediatrics

Currently, there is no specific recommendation regarding the optimal composition of IDPN for pediatric patients. Therefore, recommendations are made considering the maximum nutrient limits for this population (Table 6)[19, 44, 46]. Furthermore, it is essential to monitor nutrient levels and potential adverse effects of IDPN, such as hyperglycemia, hyperlipidemia, and hypersensitivity (Table 7).

Table 7. Maximum nutrient limits for the pediatric population[9, 42, 44, 47]

Nutrient infused	Administration dose
Glucose	5-9 mg/kg/min
Lipids	1-2 g/kg/day
Protein	1.3 g/kg/day

Suspension of intradialytic parenteral nutrition

Once IDPN is discontinued, the use of EN/ONS should be continued to maintain a nutritional status, achieve adequate calorie intake, and support growth resumption[23, 43, 48].

CONCLUSION

The superiority of IDPN in terms of nutritional status and overall health compared to nutritional counseling and ONS has not been demonstrated. There are no studies comparing it with EN.

The advantages of its implementation, such as not requiring new access and its independence from the patient's appetite, among others, make IDPN an alternative treatment option in certain cases.

Future research should compare IDPN with each of the possible nutritional support options and assess the effectiveness of combining these treatments, aiming to achieve clinically relevant outcomes that can enhance recommendations.

KEY POINTS

- IDPN consists in administering nutrients during each dialysis session.
- Although IDPN is recommended following nutritional counseling, and despite the use of ONS and EN, this is not commonly practiced.
- Parenteral formulas typically provide between 800 and 1200 calories per session due to nutrient constraints and time limitations.
- It is advisable to maintain IDPN treatment for a minimum of four months, and in some cases, even up to 1 year, to realize nutritional benefits.
- To date, specific criteria for this topic in the pediatric population are not available.

Acknowledgments

We extend our gratitude to the AANEP Study Groups Committee, with special appreciation for Dr. Marisa Deforel, Lic. Elisa Messera, and Lic. Julia Rodríguez Bugueiro.

Conflict of interests

The authors affirm that they have no conflicts of interest.

Funding

The study did not receive any funding.

Authorship declaration

R. Philippi, V. Battistella, P. Navarro, MF. Salcedo, R. Sosa, J. Torres Rivas, M. Fischberg, and A. Gugliotti contributed to data acquisition, interpretation, and manuscript preparation. All the authors meticulously reviewed the manuscript, concurring to uphold the integrity and precision of the work. They have read and approved the final manuscript.

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