



Parenteral nutrition: how to prescribe your inputs

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Abstract

Parenteral nutrition (PN) is a vital therapeutic modality for a specific group of patients in need of nutritional support. The proper use of this complex therapy is capable of maximizing its clinical benefits, minimizing the potential risks of adverse events. In certain situations, the clinical lability in which the patient finds himself requires the prescription of customized parenteral formulas. Due to the number of components used in these solutions, the possibilities of Physico-chemical incompatibilities are common and represent a serious problem. For this, prescribers must be familiar with its composition process in order to guarantee a safe formula for infusion. The objective of this work is to present the various inputs (amino acids, carbohydrates, lipids, vitamins, trace elements, electrolytes, and drugs) commonly prescribed in PN formulas, as well as their possibilities of interaction for the formation of precipitates. The concept of osmolarity and its relationship with infusion sites (central or peripheral) will also be addressed. However, an excellent understanding of the different types of inputs used in PN formulas, and also of their physical-chemical interactions capabilities, associated with good clinical judgment in the individualization of these solutions, has reduced sources of errors and ensured greater safety and quality in this type. of intervention to patients.

Keywords: Nutrition. Parenteral formula. Infusion. Clinical guidelines. Inputs.

Introduction

Parenteral nutrition (PN) formulas are extremely complex solutions containing amino acids, dextrose, lipid emulsion, electrolytes, trace elements, vitamins, and/or drugs [1-3]. Among the incompatibility errors most commonly associated with simultaneous use in the

PN, the bag is the administration of insulin, electrolytes, and medications [3]. Factors frequently associated with most errors include poor knowledge about parenteral therapy, miscalculation of doses of prescribed inputs, and failure to recognize the change in the patient's clinical condition and organ function. In an effort to avoid these PN-related shortages, each formula should be balanced to the patient's metabolic condition [3].

Therefore, the energy requirement will fluctuate according to organic functions, disease state, metabolism, body composition, and medications in use [3,4]. For this, prescribers of this type of nutritional support must be familiar with the standard doses of each nutrient, knowing how to recognize the ideal moments to make use of extra additives in formulas [5].

Therefore, the present study aimed to describe the different types of inputs used in customized parenteral nutrition formulas, as well as to describe the phases of metabolism in acute disease, showing the ideal time to start nutritional support, and to suggest simple calculations for energy estimation, paying attention to constant metabolic changes in the patient's clinical condition, presenting the existing amino acid solutions and their particular characteristics, showing the basic protein requirements of adults in the clinical scenarios evidenced, describing the types of carbohydrate solutions most used and their complications, showing the importance of lipids in parenteral nutrition on the patient's inflammatory condition, as well as its side effects, types of emulsions with a brief application in clinical practice, and determine the daily water requirements, as well as the electrolytes and trace elements of each patient, present the concentrations and propose Limitations of electrolytes and each macronutrient to promote a stable and safe 3-in-1 formula, define the concept of osmolarity, indicating its influence on the use of peripheral parenteral nutrition, and discuss the safety of concomitant infusion of drugs

(most common) in formulas of PN.

Methods

Study Design

The rules of the Systematic Review-PRISMA Platform (Transparent reporting of systematic reviews and meta-analysis-[HTTP://www.prisma-statement.org/](http://www.prisma-statement.org/)) were followed.

Data sources and research strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): “*nutrition, parenteral formula, compounding, infusion, clinical guidelines, inputs, aminoacids, carbohydrates, lipids emulsion, safety*”. The research was carried out from June 2021 to January 2022 and developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar. Also, a combination of the keywords with the booleans "OR", "AND", and the operator "NOT" were used to target the scientific articles of interest.

Study Quality and Bias Risk

The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. Two independent reviewers carried out research and study selection. Data extraction was performed by reviewer 1 and fully reviewed by reviewer 2. A third investigator decided on some conflicting points and made the final decision to choose the articles.

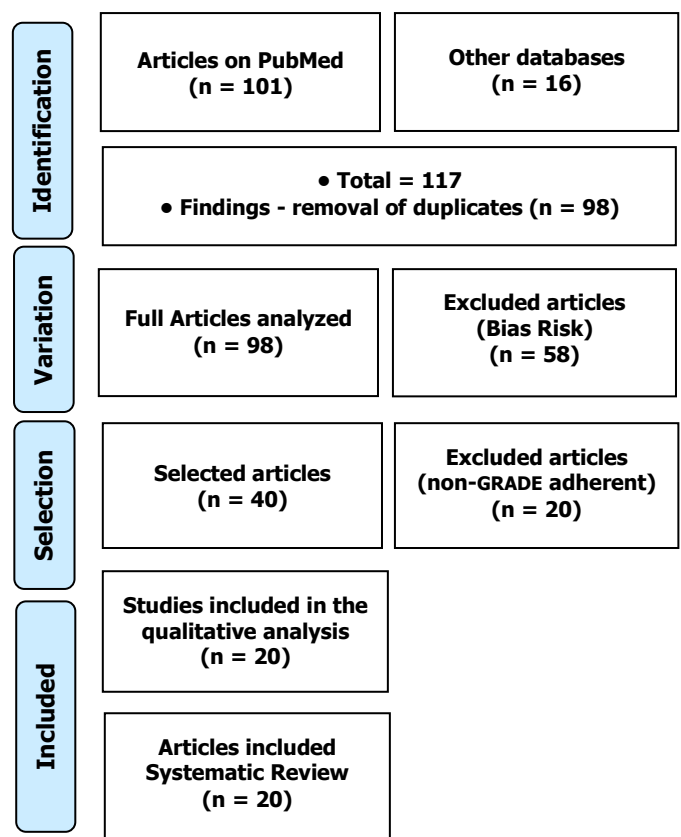
Results and Development

After the selectivity of articles and literary findings, a total of 117 studies were analyzed, with only 20 medium and high-quality studies selected, according to the rules of the GRADE, and with bias risks that do not compromise scientific development, based on the Cochrane instrument (**Figure 1**).

Energy needs and start of PN

Intestinal failure can be defined as the inability of enterocytes to absorb nutrients necessary for the normal functioning of the body [5]. These situations can be found in some clinical cases such as high intestinal fistulas or high output, severe and prolonged paralytic ileus, intestinal obstruction, severe diarrhea, short bowel syndrome, malabsorptive diseases, digestive hemorrhages, etc. In all these scenarios, both the arrival and the adequate absorption capacity of nutrients by the

Figure 1. Article selection (Systematic Review).



enterocytes are compromised, thus indicating the need for parenteral nutritional support.

Situations that contraindicate the use of PN are usually associated with a phase of metabolic instability. Unlike a healthy person in fasting, in which the body adapts in the best possible way using fatty acids as a source of energy and conserving body proteins, another who has suffered acute insult will not adapt well to fasting. Therefore, in the presence of fasting with acute stress (severe tissue damage), there will be no adaptive response in order to spare proteins. The catabolic response to an acute injury is intense, the body increases the production of defense cells and acute-phase proteins to fight the offending agent and repair tissue damage. This response was didactically divided by Cuthbertson (1980) into two stages called the hyperdynamic phase (ebb phase) and hypermetabolic phase (flow phase) [6,7].

Thus, in the first moments after the initial insult (24 to 48 hours - ebb phase), we have the period of greatest metabolic instability, in which the patient may present with uncontrolled glycemic control, severe acidosis, hyperlactatemia as well as increasing doses of drugs. vasoactive. During this period, any type of nutritional support, including parenteral support, is contraindicated, since there is no way to maintain the oxidation of nutrients in states of low perfusion, lower

transport, and oxygen consumption. After stabilization of the clinical picture, the period of hypermetabolism (flow phase) begins, which is when nutritional support is indicated [7].

Respecting its contraindications, and with the diagnosis of intestinal failure, PN should be started. Therefore, it is necessary to calculate the patient's energy needs. Ideally, this measurement could be performed using indirect calorimetry (gold standard), which is not always possible in clinical practice. In this way, the formulas that allow the calculation of energy expenditure are the tools used. Classically, the energy calculation can be performed using the Harris-Benedict equation without using the injury and thermal factors or using the Pocket Formula (25-35 kcal/kg/d). However, we still lack a formula that can predict all the factors inherent to the treatment of each patient [8].

For these reasons, episodes of hypo and hyperalimentation are not uncommon during PN therapy. In the first case, the patient will have consequences of negative energy balance and subsequent malnutrition, while in the latter, it causes an increase in diet-induced thermogenesis, CO₂ production, and hepatic fat deposition. Not only the excessive administration, in a global way, but also the administration of certain macronutrients can harm the patient, as is the case with the excessive administration of carbohydrates: hyperglycemia, glucosuria, increased synthesis, and deposition of fat, hepatic steatosis, and elevation of the respiratory quotient [9].

The use of permissive malnutrition (underfeeding) is discussed, if the reduction of the caloric supply can bring benefits or, at least, avoid the iatrogenesis of hyperalimentation, increase insulin sensitivity and reduce inflammation. This concept applies only to patients who are not malnourished and objectively is characterized by the later introduction of parenteral nutrition [7].

More important than establishing the energy required to be offered to the patient is recognizing the metabolic and inflammatory fluctuations that occur during the period of parenteral nutritional support. We know that after an initial insult, the patient develops systemic inflammatory response syndrome (SIRS), and its degree of intensity depends on innate (genetics, age) and acquired variables (nutritional status, habits, intensity of tissue damage). Concomitant to the onset of SIRS, we have a compensatory anti-inflammatory response syndrome (CARS). In the CARS state, we have an immature innate cellular response, with low antigen presentation. It presents as diffuse apoptosis, but mainly of lymphocytic and epithelial cells of the gastrointestinal tract, deactivation of neutrophils and

monocytes, proliferation of suppressor T cells, alteration of the TH1 and TH2 phenotype, decrease in lean body mass. The relationship between these two phenomena (SIRS-CARS) on the patient's current illness will determine the patient's prognosis for death from multiple organs and system dysfunction (DMOS) or cure [7,8].

There is still a state considered "mixed", such as persistent inflammatory-immunosuppression catabolism syndrome (PICS) that usually occurs after a very intense initial insult (eg, a big burn) or successive ones (eg: pneumonia, after a surgical procedure). Risk factors for the development of PICS are severe trauma, necrotizing pancreatitis, large burn (a burned surface area greater than 30%), major surgery complicated with sepsis. PICS can be recognized in patients who present with: prolonged hospitalization (greater than 14 days), the elevation of C-reactive protein (greater than 150µg/dL), immunosuppression (lymphocyte count <800 cells/mL, and catabolic state (weight loss greater than 10% or BMI less than 18, reduction in serum albumin less than 3g/dL, reduction in prealbumin to less than 10mg/dL) [7,8].

A bimodal evolution for DMOS is observed: patients who develop SIRS without an infectious etiology usually progress to it early, whereas those with CARS induced by injuries and infection unrelated to the initial insult and with SIRs progress to late DMOS. Thus, it is recommended to use a smaller amount of calories at the beginning of nutritional therapy, increasing the amount progressively with the objective of reaching the target need in a variable period, depending on the tolerability and clinical evolution of each case [7]. However, considering these data, we can consider that the beginning of PN will depend on the diagnosis of intestinal insufficiency, metabolic status (ebb/flow phase), and calculation of the estimated energy requirement. For the continuation of the same, the clinician must be aware of the inflammatory condition (SIRS/CARS/PICS) in which the patient is and which will be closely related to his metabolic status and tolerability of PN according to the estimated energy target during the period of hospitalization.

Amino acids

The main objective of parenteral nutrition is to promote sufficient energy requirements to maintain the integrity of vital organs [9]. In the absence of amino acids, protein synthesis will be profoundly compromised, generating cellular nucleotide failure and, consequently, the entire organic system. Amino acids are essential for protein production and can be classified as: essential

(AAE), non-essential (AANE), and conditionally essential (AAE). The latter become as important as the AAE in certain clinical conditions, as is the case, for example, with the use of glutamine, arginine, and cysteine.

In an adult with normal metabolism, the expected protein requirement is 0.8 g/kg/day to maintain healthy body functions. In situations of catabolic stress, this need may be increased, ranging on average from 1.2 to 1.5g/kg/day or even from 2.0 to 2.5g/kg/day in exceptional cases (obese and severe burns). It should still be noted that each gram of infused amino acid provides 4kcal of energy after its oxidation. In order to optimize protein synthesis appropriate to the amount of AA infused, we must be aware of the energy inputs from a non-protein source used in PN. Thus, for low-stressed patients (hospitalized inwards), we maintain a ratio of grams of nitrogen per non-protein kilocalories (gN/kcal non-AA) that can range from 1/110 - 1/180 [9,10].

In those stressed patients (in the intensive care unit), this ratio should be closer, between 1/70 - 1/100. To find out the amount in grams of nitrogen offered to the patient, simply divide the value in grams of AA infused into the PN by 6.25 (ie, 16% of the weight of the AA). Another noteworthy relationship for promoting protein synthesis is the AAE/NAANE ratio, which should remain between 0.66 to 1.0 [9].

Indications and Contraindications

The amino acid solution is an indispensable component in PN since the absence of this macronutrient is directly related to the homeostasis of the patient's nitrogen balance. Another indication is the ability of these solutions to perform a buffering effect when used in association with glucose solutions, making these PN formulas more stable. Some clinical situations may contraindicate the use of standard amino acid solutions, such as those born with inborn errors of amino acid metabolism (eg, phenylketonuria, maple tea urine disease, cystinuria) or those with severe use disorders. of amino acids (eg liver failure) [10].

Amino Acid Solutions

Crystalline amino acid solutions are available on the market in concentrations that can vary from 3.5 to 20%, with different aminograms according to each purpose to be used. Many of these solutions can be accompanied by electrolytes and discrete amounts of carbohydrates, and the prescribing clinician should be aware of these changes in their calculation of nutritional needs [10]. No single amino acid solution is capable of ideally promoting all amounts of essential and non-essential amino acids required by the patient's clinical

condition. This is due to the poor individual solubility capacity of each amino acid, making the aqueous medium unstable for infusion into the patient.

In most clinical situations we will use a standard amino acid solution, in which concentration can vary from 10% to 20%. The choice between one and the other will depend on the patient's hemodynamic condition in being able to receive more or less volume. In clinical practice, 10% of formulas are used. These solutions are tailored to meet the protein needs of a healthy adult. However, this standard amino acid solution may be inappropriate in some clinical scenarios, such as neonates, liver and kidney disease.

In this last condition (renal failure), there is a solution of amino acids customized for this profile on the market. It contains an aminogram based on the exclusive use of AAE and histidine. This amino acid solution was based on the established principle to treat patients with chronic kidney disease through a low-protein diet and AAE supplement [10]. Because of the underlying differences in the metabolic response between chronic and acute kidney disease, this AA solution might not meet the protein requirements needed by the patient. The benefit of this modified amino acid solution over the standard one remains controversial, particularly in acute renal failure. Therefore, this type of modified solution has rarely been used, only in those very individualized situations in which clinical judgment shows a greater risk of dialysis treatment than the use of a standard amino acid parenteral formula [10].

Known as Fisher's solution, this formulation was modulated for patients with liver disease complicated with encephalopathy. Its standard concentration is 8%, with high amounts of branched-chain amino acids and low amounts of aromatic amino acids. The basis for formulation emerges from the theory about the pathophysiology of hepatic encephalopathy as well as the production of false neurotransmitters. Patients with hepatic encephalopathy have elevated plasma concentrations of aromatic amino acids (AAA) due to decreased hepatic metabolism and low plasma concentration of branched-chain amino acids (AACR) due to peripheral metabolism. The reduction in the AACR - AAA ratio favors the brain uptake of AAA that competes with AACR across the blood-brain barrier. AAAs derive from neuroamines (phenylethylamine, tyramine, phenylethanolamine, octopamine, serotonin, and tryptamine) that are elevated in the blood and central nervous system and are associated with hepatic encephalopathy [10].

Furthermore, patients with hepatic encephalopathy are often malnourished. The traditional approach to

nutritional intervention in patients with hepatic encephalopathy has been protein restriction. However, when the diet is restrictive, malnutrition and its additional complications further compromise liver failure. Thus, this approach has not been well accepted. Most patients with liver disease are able to receive the standard amino acid solution. In those patients with hepatic encephalopathy, particularly grades III and IV, 8% Fisher's solution should be considered. This last approach is still discussed in the scientific community, and the latest meta-analyses that showed this benefit had very heterogeneous samples [11].

Solutions aimed at the pediatric public try to circumvent the immaturity of the metabolism, since certain amino acids are considered non-essential for adults, is essential for children. The most notable inactive metabolic pathway is the conversion of phenylalanine to tyrosine and the transsulfuration pathway. When standard amino acid solutions are administered to this population, aberrant plasma concentrations of amino acids have been observed, including high concentrations of methionine, phenylalanine, and low concentrations of tyrosine, cysteine, and taurine [10]. In this way, these formulations seek a balance between plasma amino acids, especially among infants in the first month of life. Studies comparing the standard AA solution with those customized for this population showed greater weight gain and nitrogen balance in the postoperative period in the intervention group. The concentration of these solutions varies between 6 to 10% tends to have higher concentrations of glutamic acid, aspartic, taurine, leucine, and arginine; while lower alanine, glycine, methionine, and valine.

Glutamine

Glutamine is the most abundant free non-essential AA in the human body. It is synthesized predominantly in skeletal muscle. In some catabolic stress situations, low glutamine levels are associated with a worse prognosis. Thus, glutamine was postulated as a conditionally essential amino acid. However, the latest meta-analyses have shown a greater benefit in its parenteral use and in situations of severe trauma, major burns, and surgical patients [12].

Standard amino acid solutions contain a small amount of glutamine, due to its low solubility or instability in aqueous media. For this reason, commercial glutamine solutions are available in the form of 20% L-alanyl-glutamine dipeptide. This solution has been safer for use in custom PN. Its standard dose is usually 0.3 to 0.5 g/kg/day of glutamine or up to 20%

of the patient's protein requirements. The prescribing clinician must be aware that for every 20g of this dipeptide we have 13.46g of L-glutamine and 8.2g of L-alanine. It is still important to note that when associated with PN solution, the concentration of glutamine should not exceed 1-1.5% due to the risk of forming precipitates [9].

Carbohydrates

Carbohydrate is the main non-protein energy source used in PN. It can be used in several ways: glucose, fructose, maltose, glycerol, and xylitol, for example. They may arise in the human body bound to proteins (proteoglycans), as amino sugars (glucosamine), or in complex forms as a composite of a structural matrix. As stated in the nomenclature, carbohydrates are composed of the molecule carbon (C) and water (H₂O).

However, the use of PN is accompanied by a more rigorous glycemic control, due to the concomitant use with carbohydrates (in this case, glucose). Therefore, regulation of the serum glucose level plays an important role and is influenced by several factors: glucose infusion rate, oxidation capacity, gluconeogenesis, and glycogenolysis capacity in the liver and muscle. Therefore, the prescribing clinician of PN must be aware of the patient's metabolic and clinical condition, knowing how to use the ideal dose and type of carbohydrate in his PN formula. The main characteristics of the carbohydrates used in PNS will be described below [13].

Glucose

It is the most used carbohydrate source in PN. Used intravenously as glucose monohydrate (3.4kcal/g) or anhydrous (3.85kcal/g). These commercial glucose solutions can vary their concentrations between 5 and 70%, and their choice will depend on the volume, hemodynamics, and central or peripheral use of the parenteral nutrition formula [13]. In situations where PN will be infused in a peripheral route, it is sought not to reach a concentration greater than 12.5% due to its high osmolarity [10]. Another benefit of glucose solutions is their acidic pH, which can range from 3.5 to 5.5, counterbalancing the alkaline pH of amino acid solutions, making the pH of the final solution more biocompatible for infusion into the patient.

The biggest limiting factor when using this carbohydrate source, besides osmolarity, is the development of hyperglycemia during parenteral nutritional therapy. In general, 60% of non-protein energy is supplied in the form of carbohydrates, with

4g/kg/day (2.8mg/kg/min) being its upper limit. It is preferable to maintain an infusion rate between 3.0-3.5 g/kg/day (2.1-2.4mg/kg/min). In those hypercatabolic patients, as is the case with critically ill patients, endogenous glucose production is not able to be suppressed by a higher infusion of carbohydrates or lipids. In these patients, the risk of hyperglycemia is increased and is associated with infections. Therefore, it is recommended that at the beginning of parenteral nutritional therapy, low amounts of glucose are infused, at a rate of 1 - 2g/kg/day, maintaining strict glycemic control with the use of regular insulin according to the capillary glycemia found. This rule can also be applied to other situations such as sepsis, diabetes, elderly people, and those using steroid therapy [13].

In those patients in which uncontrolled glycemic control (glycemia greater than 200mg/dL) is the rule, requiring high doses of regular intravenous insulin (greater than 6u.i./h) may be necessary to reduce the pre-established glucose dose. Another way to improve glycemic control would be the suspension of the glucose solution from the formula (not recommended for stability reasons) or the association of another non-insulin-dependent carbohydrate (glycerol, fructose, and xylitol, for example) [13].

Fructose

Fructose is an important carbohydrate in the regular diet and can be partially metabolized in the body independently of insulin. In the past, fructose was often used to provide hypercaloric nutrition to critically ill or diabetic patients in order to prevent the complications of hyperglycemia without the use of insulin. Nowadays, its use has been rare, since the recommended dose of carbohydrates has been lower, as well as the need for the total energy value [13]. Infusion of fructose solution may be associated with serious, life-threatening side effects, such as patients with undiagnosed hereditary fructose intolerance, lactic acidosis, hyperuricemia, and hypophosphatemia. It is not an ideal carbohydrate to use, since not all tissue is able to use it as an energy source. For these reasons, its routine use in nutritional therapy is not recommended [13].

Xylitol

It is an alcohol sugar that partially depends on insulin secretion and can be metabolized in the pentose cycle. Either way the infusion of xylitol results in lower concentrations of glucose and administration. It can be found accompanying some amino acid solutions. It may be associated with major complications such as lactic acidosis, lower ATP production, hypophosphatemia,

liver, and kidney failure. Routine use is not recommended [13].

Glycerol

Glycerol, a sugar alcohol that promotes 4.32 kcal/g, is a non-protein caloric source that can be used in parenteral nutrition. Found in 3% solutions, with or without amino acids and electrolytes. This product was created with the intention of being applied to patients in the postoperative period and in the short term. Its benefit over standard formulations is the lower incidence of hyperglycemia and insulin use [10].

Lipids

During parenteral nutritional therapy, the use of lipids, as well as carbohydrates, provides energy from non-protein sources. They are sources of high energy content (1g corresponds to 9kcal), as well as present in an osmolar emulsion and with a pH very close to the physiological one. Among other advantages, the association of lipids in PN bags reduces the need to use carbohydrates as a non-protein energy source, contributing to better glycemic control and avoiding the risk of hepatic steatosis. Lipid emulsions are also important to meet the basic demand for essential fatty acids and have lately been used to modulate the inflammatory state of the patient [14].

The dominant lipid in these emulsions are triglycerides (esterified glycerol molecule

with three fatty acids). Its chemical, physical and metabolic properties are determined by the characteristics of its fatty acids (FA). Based on the number of carbon atoms, FA molecules can be classified into chains: short (less than 8 carbon atoms), medium (8 to 10 carbon atoms), intermediate (11 to 15 carbon atoms), and long chains. (greater than 15 atoms); These molecules can be either saturated (no double bond in the AG molecule), monounsaturated (only one double bond), or polyunsaturated (more than one double bond in the AG molecule) [14].

All these characteristics play an important role in human metabolism, especially under catabolic clinical scenarios (eg, sepsis, postoperative, severe acute respiratory distress syndrome). While saturated fatty acids act primarily as an energy source, polyunsaturated fatty acids play an important role in the structural composition of lipid membranes. Among the latter, we have the long-chain fatty acids of the n-6 series (gamma-linoleic acid and metabolites) and n-3 series (alpha-linolenic acid and metabolites), which cannot be synthesized by our body and, for this reason, considered essential fatty acids. They are important components of

the cell membrane and markedly affect its various properties such as fluidity, the activity of integrated proteins and receptors. They are also a source of pro-inflammatory cytokine precursors through arachidonic acids, such as linoleic acid (n-6 series), which promote increased vascular reactivity and platelet aggregation; or anti-inflammatory cytokines through eicosapentaenoic acid (n-3 series) promoting avascular and platelet process antagonistic to n-6 series fatty acids [14].

Although rare in recent years, essential fatty acid deficiency can occur, especially in those cases in which there is a hypermetabolic state associated with the use of a 2:1 PN formula for long periods (greater than 14 days). Fatty acid insufficiency syndrome (SIAG) manifests as platelet dysfunction, hair loss, delayed healing, dry, scaly skin that is refractory to the use of moisturizers. To avoid SIAG, a minimum lipid infusion of 2 to 4% linoleic acid and 0.25 to 0.5% linolenic acid of the total calories offered to the patient is recommended, which should be done continuously in children and intermittently in adults (2 to 3 times a week) when opting for PN 2:1 formulas [4,10,14].

Indications And Contraindications

The infusion of lipid emulsions is indicated for PN lasting longer than 14 days in adults and longer than 07 days in children, in order to avoid SIAG. There are contraindications to its use in situations in which the patient has severe hyperlipidemia, severe metabolic acidosis, coagulopathies (eg, stage III severe disseminated intravascular coagulopathy - DIC), and a history of allergy to soy, egg (the latter due to the presence of lecithin and egg phosphatide in mixed emulsions of LCT/MCT at 10% or pure LCT) and fish (in the case of emulsions rich in omega 3).

Every patient using a lipid infusion in their PN prescription should receive monitoring of triglyceridemia (TAG) levels. Lipid infusion is contraindicated when its levels are greater than 1000 mg/dl at any time during treatment [14]. In cases where there is an intermittent infusion of the emulsion, TAG values are acceptable up to 250 mg/dL, when the laboratory collection is within 4 hours after the end of the infusion. In those patients in which we use a 3:1 PN formula (continuous infusion of lipid), the lipid dosage should be reduced or suspended if TAG values exceed the range of 400mg/dL [3].

Lipid Emulsions In General

The lipid emulsions available for use in our market have concentrations ranging from 10 (1.1kcal/mL) to 20% (2.0kcal/mL). They can be found in the form of

soybean oil (n-6 series polyunsaturated fatty acid) containing or not: olive oil (monounsaturated fatty acid), fish (n-3 series polyunsaturated fatty acid), and coconut oil (middle chain). The choice of these emulsions will depend on the patient's clinical situation as well as their specific contraindications [10]. Just as there is a need for a minimum infusion of this ingredient to avoid SIAG, we must also be aware of its maximum dose. Adults usually receive doses from 0.5 to 1.0 g/kg/day up to a maximum of 2.5 g/kg/day, while in children it is usually used between 2 to 3g/kg/day and can reach up to 4g/kg/day [10]. In this last group of patients, due to their enzymatic immaturity, doses of 0.5-1.0g/kg/day should be started, progressing with increments of the same value per day as tolerated by the patient [10].

Fatty acids are mainly oxidized in hepatocytes, myocardium, and skeletal muscle. A lipid supply greater than the maximum lipid oxidation rate, which is estimated to be between 1.2 - 1.7mg/kg/min, can lead to lipid overload syndrome (SSL). Symptoms of SSL are similar to SIRS and severe sepsis such as fever, hepatosplenomegaly, thrombocytopenia, jaundice, acute lung injury (acute respiratory distress syndrome - ARDS), bleeding disorders, metabolic acidosis, pulmonary hypertension, hypoalbuminemia and hypertriglyceridemia [14].

In the case of critically ill patients with ARDS, the lipid oxidation capacity may be more impaired than expected. Schuner et al. (2002) demonstrated in their study that rapid lipid infusions (less than 06 hours) were related to a worse metabolism of prostaglandins, with an increase in pulmonary shunt and lower oxygenation index, therefore, infusions between 12 to 24 hours are recommended in these cases [15]. Hyperlipidemia may be a limiting factor for the use of lipids in PNs. For this reason, emulsions with a low phospholipid/triglyceride ratio present at 20% concentrations are preferable to 10%. This fact is especially important in children, in whom the association of excessive amount of phospholipid with worsening of the lipemic profile was seen [10].

Specific Lipid Emulsions

Soybean oil emulsion: rich in polyunsaturated fatty acids (PUFA, around 60% of the total FA), with a ratio of linoleic acid (n-3 series) to linolenic acid (n-6 series) of approximately 8:1. For this reason, these emulsions are more associated with an increase in the levels of IL-6 and C-reactive protein, especially in postoperative periods and critical illness (predisposes to an inflammatory state). They are also associated with a higher consumption of vitamin E, and it is always

necessary to supplement this (10 IU of alpha-tocopherol 2 to 3 times/week) when using this emulsion [14,15].

Mixed Emulsions of Soybean Oil and Medium Chain Triglycerides (TCL/MCT): are divided with 50% soy oil (TCL) and 50% with coconut oil (TCM). The advantage lies in the lower amount of PUFAs in this emulsion (less pro-inflammatory activity) [16], however, it maintains the same linoleic acid to linolenic acid ratio of 8:1 [10,14]. Compared to TCL, TCM is not dependent on carnitine transferase to enter the mitochondria, presenting a more effective metabolic profile, especially in situations of increased stress (critical patients), when this enzyme usually has its activity more depressed. Some studies refer that the use of mixed emulsions of LCT/MCT would have a slight advantage on the nitrogen balance when compared with emulsions of pure soybean oil [17].

Emulsions with mixed soybean oil and olive oil: have a ratio of olive oil to soybean oil of 4:1, containing a high concentration of monounsaturated oleic acid and biologically active vitamin E. The ratio of linoleic acid to linolenic acid is 9:1, with a much lower concentration of PUFA than the aforementioned emulsions. On inflammatory activity, olive oil has an inert effect, and may be an individualized option in chronic and acutely inflamed patients. This emulsion has gained space in long-term PN administrations (longer than 06 months) when compared to soybean oil, since it showed less catheter-related infection, thrombosis, number of hospitalized days and better liver function [18].

Fish oil emulsions: has been much studied in critically ill patients, since they are characterized by their hyper-inflammatory condition, immune dysfunction and the presence of organ failure [19]. So, in this context, fish oil lipid emulsions could act as an immunomodulatory agent, since it is rich in n-3 series PUFA with alpha-linolenic acid and followed by eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), generating anti-inflammatory precursors and containing the exaggerated effect of SIRS [14]. In addition to these facts, fish oil lipid emulsions has gained popularity for patients with hepatic dysfunction caused by PN, not only as a supplement to soybean oil in the prevention, but also as a treatment for this disease [20]. When used in parenteral formula, doses of 0.1 to 0.2g/kg/day are recommended, maintaining an infusion of 0.1g/kg/h and starting 24 to 48 hours after admission to the ICU [19]. The coagulogram, serum level of platelets, triglycerides and blood pressure should be monitored during its use, as well as supplementing the patient with vitamin E (15 - 29mg/100mL of ELOP).

Furthermore, a systematic review and meta-analysis study by Manzanares et al. (2014) [18] showed

a trend towards lower mortality and duration of mechanical ventilation in patients using lipid emulsion with fish oil. However, this meta-analysis failed to gather clinical data strongly enough to generate a routine recommendation for the use of this oil. Therefore, the use of fish oil in PN should be indicated individually and strategically. Emulsion of soybean oil, MCT, olive oil and fish: presenting a 30:30:25:15 quantitative ratio of lipids, at a concentration of 20% and at a dose of 0.125g/kg/h (time of 6 hours) has been related to a slight hypertriglyceridemia with rapid clearing after the break, when compared to soy emulsion. Some studies have pointed out that this emulsion may be related to a shorter hospital stay, when used in postoperative periods with 5 days of treatment. This emulsion has also been used as a strategy in patients with hepatic dysfunction caused by PN [14].

Water, electrolytes, trace elements, and vitamins

Water: the water needs of a healthy adult normally vary between 20 to 40mL/kg/day, while in children: 100 - 150mL/kg/day. To avoid dehydration in the patient on PN, the difference between the total volume of water calculated and the PN solution must be added. However, this rule is not usually practical, since the water requirement of patients in PN is very variable, that is, it depends on the clinical situation in which the patient is, and medical evaluation at the bedside is essential. The clinician should also be aware of the extra fluids to PN received, as is the case of dilutions performed in antibiotics, sedatives, vasoactive drugs, etc [6].

Electrolytes: the supply of these by the PN is also very variable and depends on the current clinical condition of the patient. Current recommendations take into account the daily electrolyte requirements of healthy adults. They are: sodium (1-2mEq/kg), potassium (1-2mEq/kg), phosphorus (20-40mmol/day or 01mmol for each 100kcal), magnesium (8-20mEq), chloride (50-250mEq or according to the need to maintain PN pH). Given these values, the prescriber must adapt these needs to the patient's current condition, being aware of the expected serum variation of electrolytes, as well as their estimated body loss in the coming hours; and evaluating the possibility of these ions interacting with each other in the solution, making the PN formula unfeasible [4].

Trace elements: also follow standard requirements, based on healthy adults. Are them: chromium (10-15mcg/day), copper (0.3-0.5mg/day), iron (1-1.5mg/day or 25 - 50mg/month), manganese (60-100mcg/day), selenium (20-60mcg/day) and zinc

(2.5-5mg/day). The clinician should be aware of some scenarios in which the demand for these elements needs to be reduced, such as manganese and copper in patients with hepatobiliary disease that inhibit their excretion. The presence of these elements in other PN inputs should also be taken into account [4,6]. Trace elements are usually grouped (except iron) in a ready-to-use ampoule, with standard doses for adult and pediatric patients, and can be added to customized PN or carried out separately when using previously ready formulas [4]. In the latter case, a standard trace element ampoule must be diluted in 250mL of 5% glucose solution, infused between 4 and 12 hours. Some elements can be supplied separately, such as iron, zinc, and selenium.

Vitamins: as well as trace elements, are supplied on the market in ampoules with doses predetermined and not always ideal for use in adults and children. For this reason, the prescriber must pay attention to the daily demand for vitamins, adapting the dose to the patient's clinical condition (eg, severely malnourished patients should receive thiamine prophylaxis due to the risk of Wernick's syndrome; while major burns with vitamin C, zinc and copper for better healing; in renal injury, reduce the dose of vitamin A) [6]. Some of the vitamins can be supplied separately, such as thiamine, ascorbic acid, vitamin K and folic acid. If the multivitamin solution does not contain vitamin K, it must be supplied separately once a week. Daily vitamin requirements in healthy adults for PN are: thiamine (6mg), riboflavin (3.6mg), niacin (40mg), folic acid (600mcg), pantothenic acid (15mg), pyridoxine (6mg), cyanocobalamin (5mcg), biotin (60mcg), ascorbic acid (200mg), vitamin A (3,330IU), vitamin D (200IU), vitamin E (10IU), vitamin K (150mcg) [4].

Stability of parenteral nutrition

The combination system of amino acids, dextrose, lipid emulsion, electrolytes, vitamins, and trace elements as a single element (3 in 1 system) for infusion into the patient is widely used in many hospital and home PNs. The combination of all these inputs has a high potential for chemical and physico-chemical interactions, which can result in short-term problems with PN bag stability, putting the patient's life at risk [2]. Of these, the most threatening is the formation of precipitates that exceed a diameter of 5 microns, since when they fall into the bloodstream they can obstruct the pulmonary capillaries leading to massive pulmonary embolism [4].

Physicochemical incompatibilities, including solid and liquid precipitates, can occur in PN. In the first

(solids), they come mainly from the interaction between phosphorus and calcium salts. To maintain a stable relationship between these ions in the PN formula, a calcium/phosphorus ratio of 2.6 mEq/mMol, or 1.7-2.0mg/mg, must be maintained. One can also try to keep the product of the multiplication of the amount of calcium in mEq by phosphorus in mMol less than 150mEq•mMol/L of PN [7]. Another way to improve stability is to give preference to using calcium gluconate over calcium chloride. The formation of solid precipitates can also occur with alkalizing agents in the formula, as is the case with bicarbonate reacting with calcium. To avoid this reaction, we can use acetate, its alkalizing equivalence being the same as bicarbonate (1mEq of acetate equals 1mEq of bicarbonate) [4].

The presence of phase separation in the PN bag (3-in-1 formulas) should also be recognized as an incompatibility. The formation of these precipitates, now in liquid form, is due to the separation of the lipid emulsion from the other macronutrients in the bag [4]. The instability of the lipid emulsion occurs when there is an interaction between ions, variation in ionic strength, and changes in pH occurring in the aqueous phase of the solution [2]. Any decrease in the pH value will change the electronegativity (zeta potential) making the emulsion unstable and consequent "lipid breakdown" (phase separation) [2]. For the PN formula to remain stable, it is ideal to maintain a pH close to 6.9. It should be noted that excess dextrose acidifies the formula, while amino acids act as buffering agents for dextrose, keeping the pH more stable and thus tending to maintain the lipid emulsion coalescing. Electrolytes, especially the positive divalent (calcium and magnesium) and trivalent (iron) ions, when in excess, are capable of neutralizing the negative charges on the surface of the lipid particles, causing the loss of the electrostatic and mechanical barrier created by the emulsifying agents (phosphatides of egg yolk) followed by "lipid breakdown". To avoid this last phenomenon, cation concentrations must be maintained: monovalent (sodium and potassium) between 0-150mEq/L, divalent (magnesium and calcium) between 4-20 mEq/L, and trivalent (ferric ions in iron dextran) of 0 -10mEq/L. As trivalent ions have a high potential to create instability in the formula, their use in the PN bag should be avoided as much as possible [2].

On the disposition of macronutrients, Driscoll et al (2006) revealed that to keep 3-in-1 formulas stable, in general, they must have minimum concentrations of 10% dextrose, 4% amino acids, and 2% lipids; in addition to cations in the concentrations and proportions mentioned above and with the exclusion of trivalent ions [2].

Peripheral parenteral nutrition and osmolarity

Osmolarity is a measure of the osmotically active particles in a solute (osmoles) per liter of solution. It is actively influenced by the number of amino acids and dextrose used in the solution. The quantification of its value is especially important when using peripheral parenteral nutrition (PPN) infusion. The administration of PPN has the advantage of avoiding complications related to the use of central venous catheters, however, it is limited by the number of macronutrients used and the need to use high volumes, to avoid high osmolarity values. Thus, the most significant complication when using PPNs is the appearance of thrombophlebitis, which can have an incidence of up to 30% in 6 days [2].

Many determinants have already been tested to establish a PPN bag that can avoid this complication, such as the use of lipid-rich formulas, use of heparin, corticosteroids, and varying degrees of osmolarity. There is consensus in the literature that a maximum osmolarity value of up to 900 mOsm/L should be admitted, with an infusion of up to 100 mm/h to have a good tolerance to PPN. Regarding the other factors, its use is still controversial [2].

Use of medications in parenteral nutrition

In some situations, due to excessive water balance and/or absence of other venous access, the PN solution has been used as a vehicle for infusion of non-nutrient drugs. Among them, the most used: are insulin, heparin, and furosemide. The main purpose of using insulin in PN is to improve glycemic control in these patients. As a rule, the dose of 0.1IU per gram of dextrose used in the PN formula is applied. If the patient presents with capillary blood glucose levels above 150mg/dL, before the infusion of PN, the initial dose should be 0.15UI/g of dextrose, while for values greater than 300mg/dL, the indication should be reassessed. to start the PN [4]. Insulin used in PN can undergo adsorption by the PN bag and thus present erratic infusion as prescribed.

Unfractionated heparin has been used to prevent catheter thrombosis and thrombophlebitis in PPN. Its use in the bag must be very judicious, since it favors the separation of phases and the appearance of precipitates, mainly in 3 in 1 formula. When used, its maximum concentration must be 1 IU/mL. As for the use of furosemide, few incompatibilities have been described. However, the routine use of non-nutrient drugs in parenteral nutrition formulas is not recommended, due to the high probability of drug-nutrient interaction in the pouch and the appearance of

precipitates. When in unusual situations, the PN formula must be evaluated together with a qualified pharmacist, to avoid physicochemical incompatibilities and instability of the formula [2].

Conclusion

Parenteral nutritional support is essential for the maintenance of organ systems in the face of the diagnosis of intestinal failure. Its formula is complex, using several inputs. Its start should be indicated in the hypermetabolic phase (flow phase) estimating the energy expenditure by the Harris-Benedict or Pocket formulas. For its continuation, attention should be paid to the inflammatory state (SIRS/CARS/PICS) with which the patient evolves and which will be closely related to the metabolic state. Thus, it will be possible to couple the estimate of energy expenditure with tolerability of PN, avoiding periods of hyper or hypofeeding. However, the PN infusion will be safe for the patient as long as it respects the patient's metabolic requirements, as well as the ideal choice of its various supplies, is adjusted to the individual's clinical condition, and adapting it to the formula stability criteria.

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