

Solutions Preparing for Total Parenteral Nutrition and Influences on their Stability

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Abstract: In the article contribution is discussed the usability of standard or individual solutions for parenteral nutrition of septic patients in intensive care. The indications for the usage of solutions with their constitution and affects on the patient's condition are presented. Special emphasis is put on the processes of solution preparation and the nutrition regimen of septic patients.

Key – words: biology, parenteral nutrition, types of solutions, solution preparation, solution stability, solution usability and septic patients

1 Introduction

Total parenteral nutrition (TPN) means patient's nutrition through infusion system into the central or peripheral vein blood system. The aim of artificial nutrition, either enteral or parenteral is to lower the loss of proteins and to protect the organism from the consequences of starvation. Poor nutrition threatens health and prolongs the recuperation period.

When the patient is hospitalized is not pay enough attention to his/her diet nor the assessment of the nutrition. Good nutrition of the patient effects the outcome of the recuperation process, on healing of the wounds, the possibility of infection lowers and the possibility of complications during the operation diminishes.

During hospitalization the plan for further healing is prepared, together with the nutrition plan [2]. As soon as the patient is capable of consuming food, is decided for peroral nutrition [2].

When the patient is not capable of consuming food perorally due to different pathologies, is prescribed enteral food consumption, which has precedence over parenteral food because of being cheaper, lighter, safer and bearing lower chances of metabolic problems or infections. Besides this it enables physiological functioning of the digestive system [2].

Total parenteral nutrition is advised when is expected that the patient will not be able to consume food perorally or enterally for more than 5 days and

when the patient is undernourished (has been previously underfed).

The solutions for perfect parenteral nutrition are applicated into peripheral or central vein system.

Currently, more and more attention is given to monitoring the solution stability for perfect parenteral nutrition which includes fat emulsions. Its aim is to reach solution stability for a longer period of time. The pharmaceutical company Pharmacia & Upjohn has developed a computer program PrePARE™ [3], which includes incompatibility of solutions and thus diminishes possible mistakes.

2 Ingredients of total parenteral nutrition

The ingredients of total parenteral nutrition are [4]: amino acids, glucose, fats, electrolytes, vitamins, elements in traces, water.

There are more and more new pharmaceutical products which are used as ingredients for parenteral nutrition:

- solutions containing amino acid glutamine (Glamin®, Dipeptiven®),
- highly energetic fat emulsions (30% Intralipid®), which are used with a patient who demands diminished volume of infused fluid by using less concentrated solutions,
- electrolyte solutions (Calcijex®).

2.1 Amino acids [5]

When choosing the solution for total parenteral nutrition, must be first of all consider the needs for nitrogen.

$$\text{Nitrogen balance} = \frac{\text{Protein synthesis}}{\text{Protein decomposition}} \quad (1)$$

Under different conditions, such as sepsis, trauma and postoperative conditions, the secretion of nitrogen is extremely increased, which leads into negative nitrogen balance and exhaustion of one's own protein stocks. [1]. When excretion of nitrogen is 10-15 g per day, it is to be replaced by sufficient amounts of amino acids with which are covered all possible losses of body proteins and reach positive nitrogen balance. If it comes to exceptional protein catabolism (excretion of 20 – 30 g per day), it is impossible to reach a positive nitrogen balance.

For the optimal usage of infused amino acids it is necessary to cover the energy needs by non-protein sources (carbohydrates and fats).

The needs for amino acids are classified according to patient categories:

- MILD STRESS – normal/basic needs: 0.7 to 1.0 g amino acids or 0.15g nitrogen/kg body mass (MB)/day.
- NORMAL STRESS – slightly increased needs: 1.0 to 1.5 g amino acids or 0.2g nitrogen/kg body mass (MB)/day.
- SEVERE STRESS – strongly increased needs: 1.5 to 2.0g amino acids or. 0.3g nitrogen/kg body mass (MB)/day.

2.2 Non-protein energy sources

Energy needs are fulfilled with carbohydrates and fat emulsions. Balanced nutrition with solutions of carbohydrates and fat emulsions enables optimal consumption of received amino acids. The energy received in the form of carbohydrates and fats, is non-protein energy source.

To calculate the energy needs (EN) is used the so called Harris – Benedict equation [6]:

Men:

$$EP=66.47+(13.75 \times BM)+(5.00 \times BH)-(6.76 \times A) \quad (2)$$

Women:

$$EP=665.10 + (9.65 \times BM)+(1.85 \times BH) - (4.68 \times A) \quad (3)$$

BM.....body mass expressed in kg

BH.....body height expressed in cm

A.....age expressed in years.

For the majority of patients is used approximate evaluation of energy needs, which is 105 to 126 kJ/kg BM/day.

Carbohydrates provide a large amount of energy. The most commonly used carbohydrate is glucose, while other (xilitol, sorbitol, levulose) are less represented. Normal needs for glucose are 3 to 5 g/kg of body mass per day. Glucose consumption is approximately 320 g under normal (physiological) conditions: on average the brains need 250g, blood cells and kidneys 45g, muscles 20g, fat tissues 2g glucose daily.

When preparing solutions for total parenteral nutrition is used glucose solutions of different concentrations, as listed in the table 1.

Table 1: Glucose solutions of different concentrations, energy value and the level of osmolality.

Concentration (ut/vol)	Energy kJ/l (kcal/l)	The level of osmolality (mosm/kg)
5%	796 190	278
10%	1591 380	555
20%	3182 760	1110
50%	7955 1900	2775
70%	11137 2660	3885

Fat emulsions consist of soy oil, egg yolk phospholipids serve as an emulgator. They contain different amounts of glycerol.

Fat emulsions are body suppliers of the necessary essential fat acids, such as linol, linolenic and arachidonic acids, at the same time they are a rich energy source, their energy value is 37.7 kJ.

Fat acids oxidize into acetyl CoA, which enters the cycle of tricarbon acids or they are metabolized in liver to ketons, which are also an energy source.

Fat emulsions have a special place in total parenteral nutrition. They can be used as carriers of healing substances which dissolve poorly in water (amphotericin B, etomidate, diazepam, propofol) and in fat dissolving vitamins [7].

Defining stability and compatibility of 10% and 20% fat emulsions shows that all solutions in use are stable for 48 hours at 2 - 8°C [8].

2.3 Electrolytes

Solutions for total parenteral nutrition contain natrium, calium, magnesium, calcium, and phosphate chloride and acetate ions. Although general rules for measurement of electrolytes during total parenteral nutrition exist, it is often necessary to follow the electrolyte balance. [4, 5, 8].

Prescribed daily electrolytes requirements for adults are normally added to solutions for total parenteral nutrition. Their function is evident from table 2 [4].

Table 2: Daily electrolytes requirements for adults and their function

ELEKTROLYTE	FUNCTION	DAILY REQUIREMENT S (mmol)
NATRIUM	The main extracellular cation	60 – 100
CALIUM	The main intracellular cation, acid-base balance regulation, neuromuscular contractility	60 – 100
MAGNESIUM	cofactor in enzyme systems, neuromuscular contractility	5 – 10
CALCIUM	Mineralization of bones and teeth, neuromuscular contractility	5 – 7.5
PHOSPATE	The main intracellular anions, acid-base balance regulation, highly-energetic phosphates	20 - 45
CLORID	The main extra cellular anion, acid-base balance regulation	Dependant on acid-base balance 60 – 100

2.4 Vitamins [5]

Vitamins are the basis for maintenance and normalization of metabolic functions. In fat dissolvable vitamins are stored in the organism, thus the deficit and its consequences do not appear fast. On the other hand, vitamins which are water soluble should be added already from the beginnings of total parenteral nutrition. Some producers add solubilizers to the vitamins which are fat-soluble, in the presence of which retinol is absorbed in large quantities on infusion bags or infusion system [1].

2.5 Elements in traces (oligoelements)

Pharmaceutical products with oligoelements, which are on the market, assure complete and balanced composition of essential elements in traces for adult patients with increased requirements for oligoelements.

The most important among the oligoelements which are added into solution for total parenteral nutrition are: zinc, copper, iron, chrome, molybdenum, manganese, selenium.

Many of them are also cofactors in enzyme processes. During starvation period the deprivation of oligoelements only occurs after a few months, with burned patients or those with extensive injuries even before, which is mainly true for zinc.

Copper ion presence protects from the decay of ascorbic acid. We are to avoid synchronized

application of iron and ascorbic acid, which leads to brown precipitate. Some oligoelements can enter interaction with different amino acids (e.g. copper with cysteine).

2.6 Water [4]

Water is dispersing medium for different chlorides and a possible medium for transmit to cells. It is also evacuation way for the products which are created in metabolism, via excretion organs (kidneys, intestines, etc.)

Water is a constituent part of organism and represents 45% to 75% of the whole body mass of adults and 70% to 80% with children.

Basic requirements are calculated:

$$\text{ml water/day} = 1500 \text{ ml} + 20 \cdot (\text{body mass} - 20) \text{ or } 30 \text{ to } 35 \text{ ml/kg body mass per day}$$

Water requirements of a 70kg person are 2500 ml/24 h.

More factors affect the basic daily water requirements of organisms [4]:

- increased body temperature,
- abnormal loss through digestion process (vomiting, diarrhea),
- increased anabolism (starvation),
- increased water loss through damaged skin with burned patients,
- heart or kidney failure,
- medication therapy,
- external factors (humidity, temperature).

3 Starting point for defining condition of patient's nutrition [2]

The following methods are mainly used to define condition of patient's nutrition:

- **Anthropometric methods:** body mass, body height, under-skin fat, calves size, middle arm size.
- **Biochemical tests: albumin, transferin or prealbumin in serum.** *Albumin* is a good indicator of over nutrition and metabolism, but not with badly affected patients. It is no accurate with septic patients; because the albumins are reduced due to other reasons (e.g. reduced liver synthesis ability). Slightly different indicators are *transferin* and *prealbumin*, because they have shorter division time. If there is a lack of iron for absorption, the amount of transferin is reduced. If the amount of prealbumin increases, it declares a positive nitrogen balance.
- **Nitrogen balance** is the most common clinical method. The daily protein intake is measured;

we subtract excretion through urine and add 2 - 4g due to gastro-intestinal system.

- **Indirect and direct calorimetry** – are the methods used to count metabolic needs according to used oxygen, excreted carbon dioxide and body temperature.
- **Skin reaction to antigen.** Not satisfactory nutrition usually is usually connected with worsen patient's immune system, thus can be assess immune system. This is incorrect data about patient's over nutrition, but it is very important for prognosis.

4 Solution stability

Fat emulsion of different manufacturers differs severely in composition, effectivity and stability in solutions of total parenteral nutrition [9].

Possible causes for the differences are:

- the source of active ingredients,
- procedures of cleansing the active substances,
- manufacturing process.

The appearance of physical instabilities of emulsion systems can be defined by different criteria.

Forms of instability can be:

- **REVERSABLE:**
 - merging of droplets – flocculation, aggregation;
 - sedimentation;
 - collection of droplets on the surface – flotation, »creaming«.
- **IREVERSIBLE:**
 - merging of droplets – coalescence.

4.1 Flocculation (aggregation)

Droplets of dispersed phase are joined into larger aggregates, but they do not mix. Flocculation depends on [10]:

- intensity of interaction between droplets,
- ratio in phase volumes,
- concentration of electrolytes,
- ion emulor presence

The classic theory **DLVO** (**D**eryagin, **L**andau, **V**erwey, **O**verbeek) takes into account two kinds of interaction:

- van der Waals attractive forces, V_A ,
- Electrostatic repelling forces between electrical double layers, V_R .

Sources of both forces are independent, so the contribution of each can be calculated separately, the collective potential of interaction, V_T , equals the sum of both contributions:

$$V_T = V_A + V_R \quad (4)$$

The value of common potential considering the distance between droplets determines stability of the system. Equation is valid only when droplets are monodisperse. With flocculation the majority of the systems can be easily redispersed by shaking.

4.2 Coalescence

Coalescence is induced when two droplets that have sufficient energy to mix get close to one another which leads to creation of increasingly bigger drops. The possibility of coalescence depends on the thickness of emulsifier film, distance and forces present between the droplets (van der Waals, electrical, entropic) [10].

4.3 Flotation and sedimentation

If the density of droplets of dispersed phase are different from the density of dispersed medium, the droplets due to the effect of the gravitational forces and in accordance to Stokes equation either drop to the bottom (sedimentation) or gather on top of the substance (flotation).

$$v = \frac{2r^2(\rho_1 - \rho_2)g}{9\eta} \quad (6)$$

vvelocity of sedimentation

rradius of dispersed phase droplets

ρ_1density of dispersed phase

ρ_2density of dispersion medium

ηviscosity of dispersion medium

Flotation and sedimentation are undesirable in pharmaceutical substances, because homogeneity of the substance is necessary for proper administration.

4.4 Formation of precipitate

The most common cause for precipitate formation in solutions for total parenteral nutrition is presence of calcium phosphate, which surfaces when are added potassium sulphate and calcium chloride and exceed product of solvability of calcium phosphate [1].

The process of formation of calcium phosphate is more intensive when calcium is in chloride form, and less when it is organically bound in the form of gluconate or glucuronate.

The factors that influence the formation of precipitate are:

- calcium concentration,

- phosphate concentration,
- temperature,
- sort of calcium salt,
- concentration of amino acids and their structure,
- pH value of the solution,
- Glucose concentration.

Amino acids in solution for total parenteral nutrition form solvable complexes with calcium and phosphate and by doing that decrease the amount of unbound calcium.

4.6 Solution preparation procedure

Solution stability for total parenteral nutrition is influenced by the order of added individual ingredients. Procedure is as follows:

- Solution from the ampoule is added, that contains oligoelements and solution of electrolyte without phosphate to the solution of amino acids.
- Solutions of electrolytes containing phosphates to the glucose solution are added.
- Obtained solutions are transferred to infusion bag for total parenteral nutrition.
- Water and fat soluble vitamins are joined and transferred to fat emulsion.
- Fat emulsion with vitamins is transferred to infusion bag for total parenteral nutrition.
- The prepared contents of infusion bag are slightly shaken.
- All of the described procedures must be executed in aseptic conditions.

4.7 Package

Package has an important influence on solution stability for total parenteral nutrition. The most suitable materials for the manufacturing of the infusion bags are copolymer of ethylene and vinyl acetate (EVA).

Currently infusion bags and infusion systems are sterilized by being exposed to gamma radiation the appropriate radio isotope source or electron current, which are transmitted by an appropriate particle accelerator. Referential absorbed dosage for that method of final sterilization is 25 kGy.

Packaging for simple infusion solutions was until recently hydrolytic class I glass, that was first replaced by hard plastic. The deficiency of both is, that the liquid used is replaced by the surrounding air, which was a common cause of contamination.

All infusion bags (EVA) are air free and compressible, so there is no air intrusion and so the content contamination is prevented.

5 TPN at septic patient

Sepsis is the most common and the most serious complication, which is connected with the use of catheter [11].

When placing central vein catheter into the central vein, skin bacteria often transit and infect the outside part of the catheter surface. In some cases infection might occur in the lumen of the catheter. Infection of central vein catheter is most commonly caused by Gram positive bacteria (especially metycilin resistant *Staphylococcus aureus*) and coagulates-negative *staphylococcus*.

Standard therapy of the infection, connected to central vein catheter, requires change of the catheter and its placement at the uninfected area, where solution of suitable antibiotic is placed.

The base for treating sepsis is prevention of infection! Because of that the most common therapy for treating sepsis is by antibiotics.

Sepsis is defined by 4 phases, with certain clinical signs and parameters evident from the table 3 [6].

Metabolic changes at sepsis show themselves in extremely increased level of oxidation protein.

Table 3: Sepsis phases with clinical signs

CLINICAL SIGNS	PHASE A	PHASE B	PHASE C	PHASE D
Skin changes	Skin reddens	Skin reddens or becomes pale	Yellowish, pale	Cold or gray-blue
Changes in temperature	high	Extremely high	Normal to reduced	Reduced
Breathing	Hyperventilation	Hyperventilation	Patient is short winded, catching breath	reduced
Encefalopaty (stage)	0	1	2	coma

With septic patient can be said that catabolism of body proteins is highly increased, which results in negative nitrogen balance.

Fat emulsion is main source of energy in spite of increased production of endogen glucoses.

Insulin resistance confirms creation of sepsis.

Main cause for metabolic disruption with septic patient is attributed to cytokines (tumors, necrosis factors, interleukins, and interferon).

Studies [12] indicate that overfeeding, especially overdose of protein intake have negative effect on survival at experimental animal (septic) model. Literature states that solution for total parenteral nutrition intended for a septic patient has to provide:

- ENERGY: 105 to 126 kJ /kg BM/day, which means
 - glucoses intake: 5.76 g/kg BM/day

- protein intake: 1.5 g/kg BM/day

6 TPN in intensive therapy

Patient's nutrition is one of the basic therapeutically approaches, which does not count as a resuscitation procedure, however is very important to start with it at the right time. Especially patients in intensive therapy are often undernourished or are in intensive catabolic state.

Total parenteral nutrition [13] is indicated when patient cannot be fed physiologically that is through the gastrointestinal system.

Nutrition is being executed via intro vein catheters, which are placed centrally or peripherally, in way that all the nutrition ingredients needed by the patient can be delivered: amino acid, carob hydrates, fats, electrolytes, minerals, elements in traces, vitamins and water.

Average daily use of patient's energy is 105 to 189 kJ/kg BM, depending on patient's condition.

When beginning with total parenteral nutrition the main goal is to achieve nitrogen balance, energy needs can be covered later on when patient is more stable.

7 Conclusion

When preparing solution for complete parenteral nutrition we have to provide chemical and physical compatibility of ingredients and system stability.

In final solutions all the necessary ingredients for total parenteral nutrition are present; their compatibility is proven. They differ by:

- nitrogen contents,
- liquid volume,
- energy value,
- electrolytes contents,
- ingredient ratio,
- prescribed method of application (central, peripheral approach).

There is found out the importance of adequate selection of ingredients for total parenteral nutrition on results of the treatment: improves the healing of wounds, there is less possibility for sepsis and after operative complication. Complications are reduced with a correct approach to the healing: antibiotics are added directly to the TPN solution (ingredients compatibility is verified) and that applies lesser amount of stress to the patient by not injecting him multiple times.

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