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Parenteral Feeding with Fat Emulsions of Patients in the Intensive Care Unit: Understanding What, When and How: A Literature Review

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Abstract: One of the key problems in the departments of anesthesiology and intensive care is the energy deficit in patients. To resolve this, critically ill patients are prescribed parenteral nutrition, which contains fat emulsions. It is known that essential fatty acids in fat emulsions can exhibit both pro-inflammatory (linoleic acid) and anti-inflammatory (linolenic acid) effects. In order to reduce the impact on the immune system, it is recommended to use alternative fat emulsions, as this can provide better clinical results. The first generation of fat emulsions consisted of soybean oil, but it has been proven that it can increase the risk of purulent-septic complications. The second generation of fat emulsions contains medium-chain triglycerides, the metabolism of which can lead to acidosis, so their use is limited, especially in patients with diabetes mellitus. Third-generation fat emulsions contain olive oil, which reduces the risk of thrombosis, is considered immunoneutral and less sensitive to lipid peroxidation. The fourth generation of fat emulsions includes fish oil, which has anti-inflammatory properties and can reduce the length of stay of patients in critical condition. It is most promising to use balanced fats, among which Omega-3 Fatty Acids, is commonly used in Nigeria. It has been proven that for patients in need of parenteral nutrition, fat emulsions are an integral part of it, and patients in critical condition are recommended to use fat emulsions containing fish oil. However, it is recommended to assess the initial level of triglycerides before prescribing. In view of the above, it can be concluded that lipids provide the needed fatty acids that affect important processes of the body, including metabolism, immune response, blood clotting. Alternative fat emulsions may be a better source of energy, also exhibiting antioxidant effects and less suppression of immunity.

Keywords: intensive care, parenteral nutrition, fat emulsions, lipid, Omega-3 Fatty Acids.

Introduction

Energy deficit is a common and serious problem in intensive care units (ICU), which is associated with an increase in the frequency of complications, length of hospital stays and mortality [1, 2]. Parenteral nutrition (PN) in combination with enteral nutrition (EN), or independent complete PN, can improve the delivery of nutrients to critically ill patients [1]. Indications for PN - there are indications for the use of fat emulsions [2]. Lipids are more high-calorie sources of calories (when 1 g of fat is oxidized, 9.4 kcal/g) than amino acids (4 kcal/g) or glucose (4.1 kcal/g). Lipids are not only the main source of calories in the PN feeding to prevent or correct energy deficiency energy, but also provide the delivery of essential High calorie content of fat emulsion(FE) in a small volume of injected solution, this also provide non-protein energy needs of the body. According to the recommendations (ESPEN, 2009), intravenous administration of lipid emulsion is carried out in a dose of 0.7 to 1.5 g/kg for 12-24 hours [4].

Indispensable (essential) are called FAs that the liver is unable to synthesize. These FAs include ω-3 (α-linolenic) and ω-6 (linoleic) polyunsaturated fatty acids. In the process of their metabolism, less saturated long-chain fatty acids are formed, such as arachidonic acid (ω-6), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

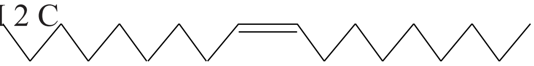
FAs are classified on the basis of several different characteristics, including the length of the carbon chain, the presence and position of double bonds in the chain and their configuration. Depending on the chain length, fatty acids are divided into: short –chain ((< 6 atoms of carbon) medium-chain (6-12 atoms of carbon) medium- H2C are ω-3, ω-6 and ω-9).

The number indicates the position of the double bond in relation to the methyl end of the molecule, which is called the ω carbon. For many years, the focus remained the question of the adverse effects of the use of lipids on the treatment outcomes of patients in critical condition. This is associated with impaired immune defense, altered inflammatory reactions and the development of infectious complications in critically ill patients [1].

It is worth to note that the purpose of PF containing fat emulsion (FE) should be based on available clinical data of a particular patient and the pathophysiology of the disease [2]. In critical conditions, fat metabolism changes, and these changes must be taken into consideration when managing patients in the ICU. In some cases, it is necessary to evaluate not only the energy component of FE, but also the potential impact on organ function and component of systemic inflammatory reaction [3].

Stearinic acid (18:0)COOHchain triglycerides (MCT), long-chain (□14 atomsof carbon) – long-chain triacylglycerol (LCT). Fat- acids, the chain of which consists of 20 or more atoms of carbon, sometimes called fatty acids with very long chain. FAs can be divided into saturated and unsaturated.

H 2 C



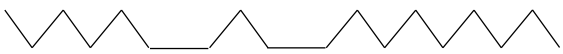
COOH

Oleic acid (18:1 Δ-9)

H 2 C Linoleic acid (18:2 Δ-6)

Saturated FAs do not have double bonds (Fig. 1), unsaturated FAs are divided into monounsaturated (one double bond - oleic acid 18:1) and polyunsaturated fatty acids

COOH



(PUFAs): two (linoleic acid 18:2) or more double bonds (α-linolenic acid 18:3). According to the position of the double bond in the carbon chain of PUFAs, as a rule, they distinguish three families: omega-3, omega-6 and omega-9 (which are also called A-Linolenic acid (18:3 Δ-3)

H2C COOH

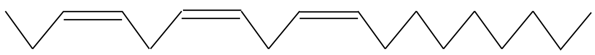


Fig. 1. Structure of long-chain (18-carbon) fatty acids

Using fat emulsions as a component of PN in intensive care unit have been a subject of discuss in developing countries for a decade now. The guidelines currently do not recommend the use of arginine, glutamine, and omega-3 fatty acids in the general critically ill patient population. [4, 5]. FAs can influence inflammatory and immune processes by affecting the structure of cell membranes by functioning modifying the profile of inflammatory mediators and changes in the genetic structure.

The influence of lipid emulsions on the functioning of the immune system and inflammatory processes in critically ill patients' ICU is another important controversial area [6]. The pro-inflammatory and anti-inflammatory effects of linoleic acid (18:2 ω-6) and α-linolenic acid (18:3 ω-3), respectively, are due to the metabolism of essential FAs.ω-6 and ω-3 FAs which are metabolized by two different pathways, but uses the same enzymes with a preference for ω-3 > ω-6 > ω-9.In the metabolism linoleic acid (ω-6) arachidonic acid (20:4 ω-6) is formed. The arachidonic acid metabolizes in the cyclooxygenase pathway of prostaglandins($PG_{2th\ series}$) and thromboxane of the 2 series ($TX_{2th\ series}$) and continues in the lipoxygenase pathway – leukotrienes of the 4th series($LT_{4th\ series}$). Thus, arachidonic acid is converted into eicosanoids, this interfere with inflammatory processes and potentially suppressing cellular immunity in the critically ill patients.

Usage of ω-6 fat emulsion for intravenous administration (FEIV) as part of PN in critically ill patients provides pro-inflammatory effect, affecting the reduction proliferation and activity of lymphocytes, decreased chemotaxis and phagocytosis of neutrophils, chemotaxis and proliferation of monocytes, de- creased function of NK cells and NK T-lymphocytes, activated by lymphokines, increased release pro-inflammatory mediators (IL-1, IL-6, IL-8,TNF, PAF, TXB2, CRP, MCP-1, NFkB) and adhesion molecules (ICAM-1, CD11a, CD18, CD44), development apoptosis [12].Conversion of linolenic acid (ω-3) to eicosatetraenoic acid (and further to docosahexaenoic acid) competes with the conversion of linoleic acid to arachidonic acid, and since the same enzymes are used, an excess linoleic acid can inhibit biosynthesis thesis of DNA and RNA [7].Metabolism of eicosatetraenoic acid proceeds in the cyclooxygenase pathway of prostaglandins ($PG_{3th\ series}$) and thromboxane 3 series ($TX_{3th\ series}$), the lipoxygenase pathway – leukotrienes of the 5 series ($LT_{5th\ series}$), which provide anti-inflammatory effect.

Some authors postulates that ω-3 FAs in the composition of PN reduces the proliferation of T-lymphocytes and promotes apoptosis of T-helpers, causes synthesis of less active eicosanoids, reduces the release of pro-inflammatory mediators and molecules adhesion, inhibits proliferation of lymphocytes and monocytes, chemotaxis, adhesion and migration of leucocytes [12].To reduce the impact of lipid emulsions on the immune system, it is recommended to replace part of soybean oil (ω-6) with less biological active components, such as coconut oil (medium-chain FAs, MCT), olive oil (ω-9 monounsaturated FAs), fish oil (ω-3 PUFAs) [12]. These alternative fatty emulsions for intravenous administration are metabolized by different pathways, which can lead to smaller pro-inflammatory effects and lesser suppression of immunity [9].

Thus, many ICU patients are already in a compromised state, such patients may potentially have better clinical outcomes when receiving one of the alternative of FEIVs to reduce consumption of potentially pro-inflammatory ω-6 FAs, which is more than 50% of the fatty profile acids in soybean oil.

PURPOSE OF THE WORK:

To substantiate the indications, safety and effectiveness of the use of multicomponent fatty emulsions in parenteral nutrition of critically ill patients in the ICU.

In current medical practice several generation of fatty emulsion are used for parenteral feeding in the ICU, the first generation was manufactured 1957 and used 1961, this consisted of a long-chain chain neutral triglyceride of soybean oil (soybean oil, SO) and contained a large amount ω-6 FAs. Soybean oil is a valuable source of essential fatty acids: linoleic (ω-6) and α-linolenic(ω-3 of plant origin). However, from-it is known that lipid emulsions based on soybean oils can cause oxidative stress [10].

The FAs contains double bonds located through the CH group are most susceptible to the action of oxygen free radical. It is from this CH-group, a radical (oxidation initiator)an electron is donated which in turn, the lipid containing the acid, into a free radical. High content of ω-6 PUFAs in the most commonly used lipid emulsions. Some authors considered that soybean oil has a disadvantage due to their pro-inflammatory potential, which can lead to poor results [11].Mateu-de Antonio J. et al (2008) conducted a retrospective observational study, which demonstrated that fat emulsions based on soya oil with a high content of linoleic acid in PP may increase the risk of purulent-septic complications [12].

Although currently available standard soybean oil-based VEVs meet the needs of most patients undergoing PP, over time the concept of PP has evolved to change the composition of the first-generation fat emulsion by deliberately reducing the content of ω-6 fatty acids, which has led to effectiveness and safety for patients in critical condition.

This problem initiated the development of emulsions in which part of the ω-6 fatty acid component is replaced by less biologically active fatty acids, such as coconut oil (rich in medium-chain saturated fatty acids) or olive oil (rich in monounsaturated oleic fatty acids).

Second-generation VEVs began to be used in Europe since 1984, characterized by a content of containing 50:50 (by weight) of a physical mixture of long- chain triglycerides of soybean oil and medium chain triglycerides .Medium chain triglycerides (MCT) are derived obtained from refined coconut oil or kernel palm oil, are a good and safe source of energy. It is accepted that the oxidation of fatty acids is promoted by carnitine, which carries fatty acids in the form of acyl carnitine to the mitochondria. To date, it is widely recognized that carnitine does not play a significant role in the transport of MCT. It is believed that MCTs enter mitochondria, bypassing the carnitine transport system. MCTs are not a substrate for the synthesis of pro- inflammatory mediators, are stable in peroxidation conditions, have additional effect on protein metabolism and function reticuloendothelial system, they do not affect inflammatory mediators, adhesion molecules, lymphocyte and monocyte proliferation, chemotaxis, adhesion and migration of leukocytes [12].

Metabolism of medium chain fatty acids in the liver stimulates ketogenesis and can lead to acidosis. In view of this ketogenic effect the use of medium chain triglycerides should be limited in patients with diabetes and in clinical conditions with acidosis or ketosis.

Third generation VEVs came into used 1990s, it consists of 80% olive oil and 20% soybean oil by weight (Clinoleic). This reduced the "load" of ω-6 fatty acids by 75% from the baseline of soybean oil-based VE.

This composition promotes physiological metabolism of fats, and the kinetics of triglycerides and is comparable to natural chylomicrons, which is confirmed by clinical studies [13].Olive oil helps preserve mixture for PP and favorably affects blood glucose levels [14], it has advantages in terms of reducing the risk of cancer, reduces the risk of thrombosis by reducing platelet aggregation [15].

Fat emulsions for PP based on olive oil is well tolerated by patients in critical condition. In another study it was noted that ω-9 oleic acid is an immunoneutral fatty acid that is not involved in the formation of pro-inflammatory mediators, does not cause immunosuppression or immunosuppression [16]. This ω-9 VEVV, has a minimal effect or no on lymphocyte proliferation, NK cells and granulocyte activity. The release of chemokines and the number of adhesion molecules are reduced, there is a weak effect on the production of eicosanoids and a weak susceptibility to peroxidation. Olive oil in PP does not affect the release of pro-inflammatory mediators, proliferation of lymphocytes, monocytes, chemotaxis, adhesion and migration of leukocytes [12].

Fuhrmana B. et al (2006) suggested that monounsaturated fatty acids with one double bond derived from olive oil may be less susceptible to lipid peroxidation than ω 6 and ω-3 PUFAs with multiple double bonds [17].According to Ennaliza Salazar et al, (2019) The advantages of alternative VEVs in non- critical patients are doubtful [18].

In most comparative studies on using alternative intravenous lipid emulsions and traditional ones conducted in critically ill patients shows that on the 5th day of intensive care admission, there was a significant decrease in CRP levels with alternative therapy compared to traditional VE.

In other to reduce the undesirable effects, is the introduction of fish oil (ω-3) to lipid emulsions of soybean oil in ICU patients, this fatty acid has biological activity different from that of ω-6 PUFAs, so these emulsions can affect positively affect the immune- mediated conditions [19].

Fourth generation IVLEs include fish oil (FO) alone or in combination with one or more oils used in previous generations. The work of Philip C. Calder (2020) emphasizes that although soybean oil consists of 53% of linoleic acid, it also contains ω-3 fat acids, reduced the average length of stay in the intensive care unit (10 RCTs; 1.95 days, 95% CI 0.42 –3.49; P = 0.01) and reduced the length of stay in the hospital (26 RCTs; 2.14 days, 95% CI 1.36–2.93; P <0.00001).

The risk of sepsis (9 RCTs) was reduced by 56% in those who received PN enriched with ω-3 fatty acids (OR 0.44, 95% CI 0.28-0.70; P=0.0004).In patients with severe acute pancreatitis fatty acids (8%α-linolenic acid), studies shows that nutritional support by PN with a ratio of ω 6: ω-3 fatty acids is approximately 7:1. However, it is important to note that difference between ω-3 fatty acid of plant origin using a three- chamber bags enriched with ω-3 fatty acids, as this rapidly restored the level of total protein and blood album in, while fatty acid from origin from marine sources (e.g. fish)α-linolenic acid normalizes the neutrophil-leukocyte index[20].

IVLEs containing ω-3 fatty acids based on fish oil, have high biological activity compared to MCT and olive oil,is not only a nutrient and but an alternative source of energy, and has anti- inflammatory properties, also has important pharmacological benefits [21, 22].

Adding DHA and EPA to lipid emulsions has an obvious positive effect on cells membranes and inflammatory processes, beneficially affect blood lipids, coagulation blood, liver metabolism, endothelial function and cardiovascular diseases [23, 24].Lipid emulsions containing fish oil, may likely reduce the length of stay of patients in critical condition (ESPEN, 2009).

Systematic review with meta-analysis and sequential analysis studies conducted on parenteral nutrition, enrichedω-3 fatty acids compared to standard PN in hospitalized patients showed significant advantages in terms of liver enzyme levels (aspartate aminotransferase, alanine aminotransferase and gamma-glutamyl transferase), and higher levels of antioxidant α-tocopherol, as well as there were lower levels of inflammation markers, such as TNF-α.

Using IVEs containing ω-3 fatty acids based on fish oil, had a beneficial effect on coagulation and significantly improved the fatty acid profile with increasing levels of ω-3 fatty acids, DHA and EPA[25]. It has been shown that the relative risk (OR) of infection (24 RCTs) was 40% lower when PN enriched with ω-3 fatty acids than with standard PN (OR 0.60, 95% confidence interval [CI] 0.49–0.72; P <0.00001).

Patients, who received ω-3 PN, enriched with fatty acids recorded lower levels of leukocytosis and increasing level of blood lymphocytes and pronounced reduction in the level of CRP in the blood [26].

In meta-analysis, conducted William Manzanares et all (2013) showed that alternative IVLEs for critically ill patients can reduce overall mortality, reduce days of ventilation and ICU stay [27].The work of Philip C. Calder et al (2020) shows that a high level of exogenous intake of ω-6 fatty acids can worsen biphasic immuno- inflammatory reactions in traumatic stroke (Fig. 2), this is characterized by increased formation of inflammatory mediators and then transition to immunosuppressive state[28]. The presence of ω-3 fatty acids docosahexaenoic and eicosapentaenoic acids in the composition of PN can improve this situation.

Anti-inflammatory effect of fish oil ω-3 fatty acids is due to: Reduction of leukocyte chemotaxis, decreased expression of adhesion molecules and reduction of interaction of leukocytes with the endothelium .Reduction of the production of eicosanoids from arachidonic acid. Reduction of the production of endocannabinoids, containing arachidonic acid, increased production of "weak" eicosanoids from EPA. Increased production of anti-inflammatory endocannabinoids, contain-containing DHA and EPA. Reducing the production of inflammatory cytokines and decreased reactivity of T cells.

In a studies it was stated that it is necessary to avoid lipid emulsions based entirely on soybean oil for parenteral feeding, lipid emulsions in which linoleic acid and α-linolenic acid can be partially replaced with medium-chain triglycerides, olive oil and fish oil, providing EPA and DHA. The properties of the lipid emulsion should be considered as a result of the action of all its components.

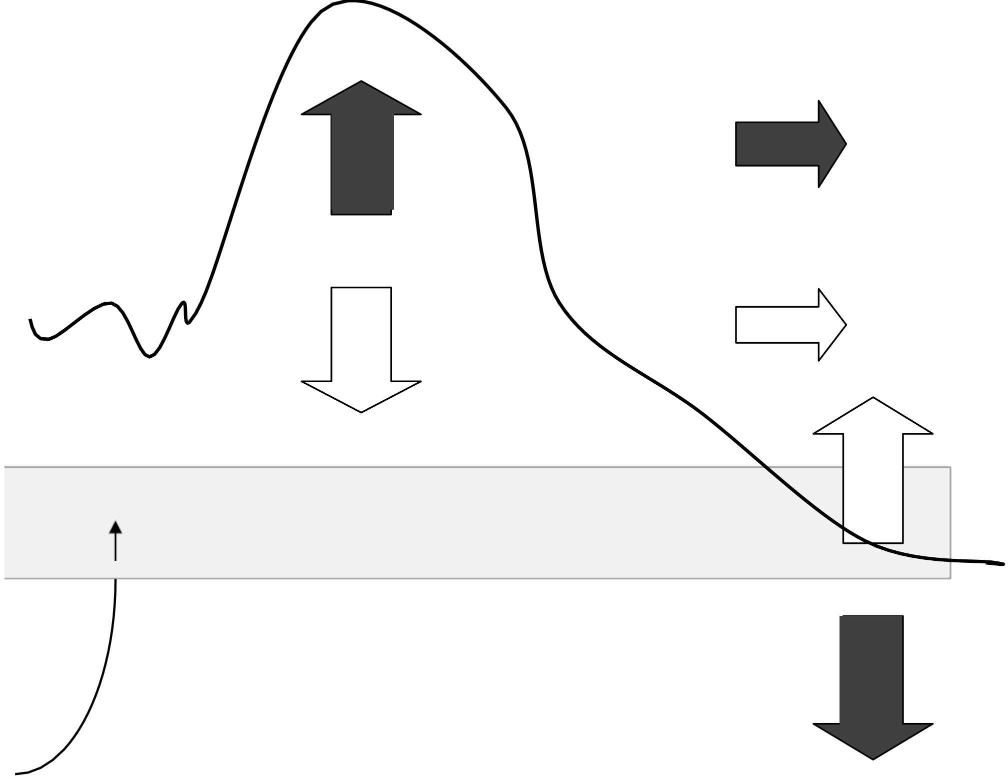
This alternative of lipid-emulsions may be especially relevant for critically ill patients with hyper metabolic process and in a pronounced inflammatory process, also in severe massive surgical procedures, multi injured patients, burns and sepsis [29, 30].

Pharmacoeconomic assessments of the comparison of lipid emulsions containing ω-3 fatty acids with standard lipid emulsions in critical and surgical populations have shown that intravenous administration of lipid emulsions containing ω-3 fatty acids isa cost-effective strategy for patients requiring PN.

A number of studies have shown that absolute concentrations of some polyunsaturated FAs are more important than their ratio in determining their biological effects [].The most promising at this stage of PN development is the development and implementation in clinical practice of the so-called "balanced" fats. They contain in their composition fractions of MCT, LCT triglycerides and ω-3 FAs from fish oil .In most countries, the component is a three-chamber bags for parenteral nutrition in different trade name.

HYPERINFLAMMATION

In important to note that in case of excess of inflammatory process where eicosanoids, cytokines, oxygen radical and adhesion molecules



IMMUNO SUPPRESSION

Figure 2. Development of a two-phase immune-inflammatory response to traumatic stroke (Philip C. Calder, Dan L. Waitzberg, Stanislaw Klek, Robert G. Martindale, 2020)

And excess of immunosuppressive cytokines, traumasuppression of T-cell functionwhen prescribing PP, is important to use solutions fish oil (94%).

With most recent available clinical data, systematic reviews and meta-analyses for hospitalized adult surgical patients who require PP [41]adult surgical patients who require PP, lipids are an integral part of it, fat emulsions containing fish oil(94%) during the first week of PP. The intravenous dose of lipids should not exceed 1.5 g/kg/day. It is recommending 0.1–0.2 g of fish oil/kg/day in the form of lipid emulsions containing fish oil (93%).There is no evidence that lipids containing fish oil increases the risk of coagulopathy or bleeding. It is recommended that before prescribing PF to assess all patients baseline TG levels in serum.

In surgical patients from the low risk group, it is recommended to consider the possibility of early initiation of PP, if it is expected that the patient will not be able to reach 50–60% of the planned energy and protein within the first 5 days, and early is important start of PP in pediatric patients. To minimize potential risks associated with PP, a higher degree of standardization of the PP process is recommended. Studies and guidelines recommends considering the possibility of using commercially available multi-chamber bags or combined bags, depending on local experience and economic considerations.

CONCLUSIONS

Lipids are the main source of non-protein energy this reduces reduce the amount of carbohydrates that needs to be introduced as part of nutritional support. They are building blocks for cell membranes and supply essential FAs, allow the delivery of fat-soluble vitamins. LCs differ in chain length, as well as in the presence, number and position of double bonds. These factors can affect the properties of fatty acids, affecting processes such as metabolism, inflammation, immune response, oxidative stress, blood clotting, organ functions and wound healing.

Oil-based alternative IVFE may have less pro-inflammatory effect, less immunosuppression and more anti- oxidant properties than standard IVFE on soybean oil base, and may potentially be a better alternative source of energy with high risk of malnutrition

nutrition, if enteral or oral nutrition is contraindicated or insufficient. In surgical patients, the main indication for PP is intestinal failure sufficiency. Although EP is considered the first line of treatment severe pancreatitis, if the patient requires PP, lipids are an integral part of this PP.

There are sufficient scientific data clinical trials, systematic reviews and meta-analyses to demonstrate that IVFE containing fish oil have advantages over standard IVFE (without fish oil) when used in adult surgical patients who require PP.

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