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Mini Review

Oxidative stress: the dark side of soybean-oil-based emulsions used in parenteral nutrition.

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Abstract

Soybean-oil based lipid emulsion have been used for parenteral nutrition since 1980's decade. These kind of pharmaceutical formulations represent an important energy source to critically ill patients. But it has been demonstrated that soybean-based-lipid emulsions induce a hyperlipidemic state and oxidative stress, which represent the major complications of these energy sources. The aim of the present work was to review the state of the art on lipid emulsions and its relationship with oxidative stress, and associated diseases.

INTRODUCTION

Energy deficit is a common and serious problem in intensive care units and is associated with increased rates of complications, length of stay, and mortality. Parenteral nutrition (PN) can improve nutrient delivery to critically ill patients [1].

Early PN formulations consisted primarily of high concentrations of glucose and amino acids in order to provide adequate calories [2] and were often associated with a number of complications. Prolonged use of these formulations was associated with essential fatty acid deficiency because they did not provide linoleic acid (LA; 18:2 ω-6) or α-linolenic acid (ALA; 18:3 ω-3), which are not synthesized by the body and must be obtained from the diet. The incorporation of lipids into PN formulations has addressed many of these issues. Lipids provide a more energy-dense source of calories (approx. 9 kcal/g) than either amino acids (4 kcal/g) or dextrose monohydrate (3.4 kcal/g)[3]. Parenteral lipid emulsions derived from soybean oil are the most extensively evaluated formulations in preclinical and clinical studies and have demonstrated efficacy and safety in delivering vital nutrition to critically ill patients [1].

The majority of early lipid emulsions, which were first included in PN during the 1960s, were derived from soybean oil, which contains a high concentration of both LA and ALA [4]. However, studies published during the 1970s and 1980s found that soybean-oil- and cottonseed-oil-based lipid emulsions were associated with a number of adverse immunological effects [5].

On the other hand, the high number of double bonds in ω-6 and ω-3 polyunsaturated fatty acids (PUFA) provides targets for lipid peroxidation (LPO), and these oxidized fatty acids may therefore be associated with an increased risk of oxidative stress (OS) [6]. Recently, high levels of LPO, a depletion of antioxidant enzymes, and atherosclerosis development were observed by our

group in animals supplemented with Lipofundin® MCT/LCT 20% [7-10]. The present work offers an overview of the state of the art about lipid emulsions and its consequences on redox disruption and the subsequent OS.

Oxidative stress

Release of reactive oxygen species (ROS), which consist of oxygen free radicals and other chemical entities, can deplete antioxidant systems resulting in the development of OS. When ROS are generated in elevated quantities they are able to promote cell injury [11]. Most oxidant species are generated during mitochondrial respiration [12], although other reactions or sources also contribute to ROS formation. These agents are scavenged by endogenous antioxidant systems that include superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), and small molecules such as glutathione (GSH) and vitamins [13].

ROS, such as superoxide anion ($O_2^{\bullet-}$) and hydroxyl radical ($^{\bullet}OH$), avidly interact with proteins, lipids, and nucleic acids and, thereby, irreversibly destroy or alter the function of target molecules. In fact, ROS have been increasingly recognized as major contributors to various pathological processes in nearly all biological organisms that use O_2 [14]. Fifty years ago, Harman proposed the "free radical theory" of aging, a fundamental life process, speculating that endogenous oxygen radicals are generated in cells and result in a pattern of cumulative damage leading to aging [15]. Despite substantial gaps that persist, aerobic metabolism and the corresponding generation of ROS remain the most widely accepted cause of aging and aging-related chronic diseases in humans, such as neurodegeneration, cardiovascular diseases, and cancer [16].

Lipid emulsions-induced hyperlipidemia

It has been demonstrated that soybean-based-lipid emulsions induce a hyperlipidemic state [17, 18] and OS [8, 19]. Hyperlipidemia is considered as an elevation of lipids in the bloodstream, and these lipids include fats, fatty acids, cholesterol, cholesterol esters, phospholipids, and triglycerides [20].

Today in most of the developed and developing countries, hyperlipidemia and atherosclerosis represent the leading cause of cardiac illness and deaths [21]. In 1984 it was demonstrated for the first time that there is a link between high serum cholesterol levels and risk to coronary heart disease [20]. Hypercholesterolemia has been associated with OS that results from the increased production of ROS or impairment of antioxidant systems [22, 23].

Considerable experimental and clinical data suggest that elevated serum levels of total and LDL-cholesterol are associated with impaired endothelial function [24]. Hypercholesterolemia increases the expression of endothelial adhesion molecules [25], and platelet aggregation and adhesion, as well as augmenting vasoconstriction [26]. The oxidized lipids, especially LDL, promote an inflammatory phenotype in vasculature [27]. In cholesterol-fed rabbits there is an induction of $O_2^{\bullet-}$ generation, which in turn reacts with nitric oxide ($^{\bullet}NO$) forming the powerful oxidant peroxynitrite ($ONOO^-$)[28].

The investigations of Hailer and Wolfram first showed that Lipofundin® and Intralipid®, two soybean-oil-based lipid emulsions, induce a hyperlipidemic state in humans [17, 18]. After, Riemens and coworkers also demonstrated that Lipofundin® administration induced an increase of TG and non-HDL-cholesterol in healthy men one week after a single intravenous injection, while a decrease of HDL levels was observed [29]. Recently, our group has demonstrated that Lipofundin® induces a significant increase of total cholesterol, triglycerides, LDL- and HDL-cholesterol after 8 days of treatment [8]. Our data also reaffirmed the observations of Jellinek and coworkers, which first showed that Lipofundin is able to induce atherosclerotic lesions in rabbits [30].

On the other hand, hypertriglyceridemia is one of the common complications of Lipofundin use during parenteral nutrition [31]. Triglycerides are considered an independent risk factor for cardiovascular disease (CVD). When triglycerides are elevated, lipoprotein metabolism is altered, which increases CVD risk. Patients with elevated TG and low HDL are at particularly high risk of CVD [32]. TG are often associated with other CVD risk factors, such as obesity, insulin resistance, diabetes mellitus, low HDL-cholesterol, lifestyle factors, and changes in lipoprotein size and density [33].

Numerous changes in lipoprotein metabolism have also been noted with high TG levels. Evidence suggests that TG-rich lipoproteins, including VLDL, IDL, and chylomicrons, are all atherogenic [34]. The TG-rich lipoproteins can penetrate the arterial wall, promoting atherosclerosis. In addition, the presence of high TG levels causes the production of small, dense LDL particles and HDL particles, which increase atherogenicity [35, 36].

Approach to minimize the oxidative stress

In an effort to address concerns associated with the soybean-oil-based lipid emulsions, alternative sources of FA were investigated [37]. Much of this research focused on minimizing complications to which

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critically ill patients are particularly susceptible, including OS, alterations in cell-mediated immunity, inflammation, and thrombosis.

A key consequence of oxidative stress is LPO, where ROS react with the double bond of unsaturated lipids, producing unstable lipid peroxides that may cause cell death [38]. For this reason, the antioxidant α-tocopherol (vitamin E) is sometimes added to PUFA rich lipid emulsions in clinical practice.

Another approach to minimize OS is the partial replacement of PUFA-rich oils with alternative fatty acids, such as oils rich in medium-chain triglycerides (MCT; derived from coconut oil containing medium chain fatty acids such as capric acid), which are more resistant to oxidative damage [1].

Metabolism of MCT differs from that of long-chain triglycerides (LCT). Unlike longer-chain fatty acids, MCT require little carnitine for mitochondrial entry, and it has been suggested that their more rapid breakdown may impart an increased production of ketones in critically ill patients [39]. However, this is thought to be a transient phenomenon that is reversible upon discontinuation of MCT infusion and rarely causes clinical problems. However, formulations containing MCT should not be used in patients who develop ketosis or acidosis in the intensive care units setting [1].

It has been suggested that monounsaturated FA (MUFA; often derived from olive oil, which also provides antioxidants) with only one double bond, such as oleic acid (OA; 18:1 ω-9), may be less susceptible to LPO than ω-6 and ω-3 PUFA with several double bonds. In vitro studies indicated that cells treated with OA or olive oil were associated with less mitochondrial ROS production than cells treated with certain PUFA (e.g., DHA) or a soybean-oil-based lipid emulsion [40]. In a preclinical rodent study, lipid peroxidation was lower among mice administered OA or olive oil by gavage than among mice administered PUFA (*i.e.*, linoleic acid or docosahexanoic acid) or fish oil [41]. In children requiring PN, a lipid emulsion containing 80% olive oil led to lower concentrations of certain lipid peroxides than a soybean-oil-based lipid emulsion [1].

CONCLUSIONS

Parenteral lipid emulsions derived from soybean oil are the most extensively evaluated formulations in preclinical and clinical studies and have demonstrated efficacy in delivering vital nutrition to critically ill patients. But one of the lipid emulsion associated-major complications is the OS induction. Recently, newer lipid emulsions that utilize partial substitution of soybean oil with MCT, olive oil or fish oil either alone or in combination have demonstrated potential benefits in terms of reduced impacts of OS and other complications. However, ongoing research to further characterize and compare the biologic properties of lipids given parenterally must be carried out, in order to determine the most effective for each individual patient.

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COMPETING INTERESTS

The author stated no conflicts of interest.

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