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Original article

Does the type of parenteral lipids matter? A clinical hint in critical illness

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SUMMARY

Background & aims: An altered lipid profile is common among intensive care unit (ICU) patients, but evidence regarding the impact of different fatty acid (FA) emulsions administered to patients requiring parenteral nutrition (PN) is scarce. This study aimed to compare the plasma triglycerides (TG) response to two types of commercial lipid emulsions: a structured mixture of long- and medium-chain triglycerides (LCT/MCT) or LCTs with n-9 FA (LCT+) in ICU patients.

Methods: In this retrospective observational study conducted in a multidisciplinary ICU: two groups were defined by the type of emulsion used. Inclusion criteria were: consecutive patients on PN staying ≥4 days with one TG determination before commencing PN and at least one during PN. Recorded variables included energy intake, amount and type of nutritional lipids, propofol dose, glucose and protein intake, laboratory parameters, and all drugs received. Hypertriglyceridemia (hyperTG) was defined as TG >2 mmol/L.

Results: The dynamic impact of the emulsion was analyzed in 187/757 patients completing the inclusion criteria (112 LCT/MCT and 75 LCT+). The demographic variables, severity indices, diagnostic categories, and outcomes did not differ between the two groups. Seventy-seven patients (41%) presented hyperTG. Both groups received similar daily energy (1604 versus 1511 kcal/day), lipids (60 versus 61 g/day), and glucose intake (233 versus 197 g/day). There was no increase of TG concentration in those receiving the LCT/MCT emulsion compared to those receiving the LCT+ emulsion (0 and 0.2 mmol/L, respectively, $p < 0.05$).

Conclusion: LCT/MCT emulsions are associated with a less pronounced increase of plasma TG levels than LCT+ emulsions.

1. Introduction

Critical illness is characterized by nutritional and metabolic disorders, resulting in increased muscle catabolism, fat-free mass loss, hyperglycemia, and hypertriglyceridemia (hyperTG) [1,2]. In patients with contraindications to enteral feeding or insufficient enteral feeding, parenteral nutrition (PN) is the standard of care [3]. Intravenous lipids are a vital component of PN as an important source of energy because they maintain integral components of cell membranes and prevent the development of essential fatty acid deficiency [4,5]. It has been demonstrated that PN is frequently associated with overfeeding and its deleterious consequences such as hyperglycemia, hyperTG, liver steatosis, endocrine dysfunction, impairment of immunity, infections, and increased mortality [3,6,7]. The association between PN and morbidity is multi-factorial and has often been suggested to be linked to the fat emulsions used [3,8,9]. Although the evidence for this suggestion has never been conclusive, many centers limit the use of fat emulsions, especially when hyperTG is present [3,6,9].

The first available lipid emulsions contained only long-chain triglycerides (LCTs) [10] and metabolic disorders related to their use have been published, and efforts at further developing and optimizing lipid emulsions have focused on replacing part of the LCTs with medium-chain triglycerides (MCTs) [11]. Indeed, the fatty acids (FAs) composing emulsions do influence the clinical responses, depending on their chemical structure. Compared with

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LCTs, MCT-based emulsions are cleared more rapidly from the plasma [8,12]. Other benefits of MCTs include their less pronounced tendency for deposition in tissues and their favorable effect on protein metabolism [11,13]. Further advances include the development of lipid emulsions containing structured triglycerides, which are metabolized even more efficiently than LCTs and MCTs [13]. As an alternative to the physical mixture of MCT and LCT emulsions a mixture of medium-chain and long-chain fatty acids can be obtained by interesterifying the different fatty acids to create a mixed triglyceride molecule called a structured triglyceride (STG). Olive oil-based emulsions in which 60% of the LCTs consist of mono-unsaturated fatty acid (n-9 FA) were then developed [14] with the latter having a theoretical limited impact on lipid metabolism. In the most recent emulsions developed, the LCTs and MCTs are progressively replaced by other fatty acids, particularly omega-3.

Having observed an increasing incidence of hyperTG after changing the commercial parenteral lipid emulsion in our intensive care unit (ICU), this study aimed to compare the metabolic responses to commercial PN solutions containing the LCT n-9 FA (LCT+) versus structured LCT/MCT lipids in critically ill patients.

2. Methods

This retrospective observational study was approved by the ethics committee of the Canton of Vaud and was conducted over a 50-month period (November 2008 to December 2013) in a 32-bed adult mixed ICU. Inclusion criteria were as follows: consecutive patients on PN staying $\geq$4 days and <18 days with one TG determination before commencing PN and at least one during PN. Exclusion criteria were as follows: less than 3 days of continuous PN or if TG levels were not determined after/before and during PN administration. HyperTG was defined as a plasma TG level >2 mmol/L, according to the current guidelines of the American Heart Association [15]. Patients were grouped according to the type of lipid in the PN (see below).

2.1. Patient data

Patient data included age, admission weight, body mass index (BMI), type of admission (surgical or medical), severity of disease (SAPSII), and mortality during the ICU and hospital stay. All data were collected during the stay in order to have a dynamic view and to establish a temporal relationship with the type of lipid emulsion used. Nutritional data included intravenous and enteral energy, with details of the quantity of lipids, carbohydrates, and proteins. The cumulative energy intake included nutritional (i.e., enteral nutrition (EN) and PN) and non-nutritional energy intake (i.e. propofol and dextrose 5% perfusions). Laboratory data included the levels of alanine transaminase, aspartate transaminase, albumin, pancreatic amylase, direct and indirect bilirubin, gamma-glutamyl transferase, alkaline phosphatase, procalcitonin, prealbumin, and C-reactive protein.

2.2. Study periods

This study was divided into 2 periods. During the first period (2008–2011), the predominant commercial solution was a structured mix of 64% LCT/36% MCT, made from soja and coco oil respectively, emulsion (Structokabiven®, Fresenius Kabi, Oberdorf, Switzerland); while an 100% LCT emulsion, made from 80:20 mix of olive and soybean oil, was used from 2011 (Olimel 5.7%®, Baxter AG, Volketswil, Switzerland). Some patients also received the CHUV local-compounded PN in our Service of pharmacy called ALISIA (ALImentation aux Soins Intensifs Adultes), which is an ICU patient adapted, concentrated (1230 mL), low-fat (20% of energy as LCT/MCT mix), high-protein (25% energy), and high-glucose solution (55% energy) [16,17]. This solution is recommended when PN lasts >3 days. The compositions of these solutions are shown in Table 1.

2.3. Nutritional management

Nutritional requirements were based on the ESPEN guidelines [3] evolved over time as follows: energy targets were 25–30 kcal/kg/day (medical and surgical conditions) during the first period, and they decreased to 20–25 kcal/kg/day during the second period (with downregulation in elderly and obese patients). During the first and the second period there was a switch of the commercial PN. Indirect calorimetry was recommended after 1 week. The protein target was 1.2–1.3 g/kg/day, and continuous EN was encouraged. Combined EN and PN was considered when EN was insufficient, otherwise, PN was restricted to gastrointestinal failure. Lipid profile monitoring was an integral part of the ICU nutrition protocol (blood sampling three times weekly at 6 a.m. for determination of TG and C-reactive protein levels). Non-nutritional intake was taken into account when devising final feeding regimen, and the sedation protocol was based on ESICM recommendations [18], discouraging the use of high-dose propofol (>4 mg/kg/h) while integrating daily sedation pauses. Overfeeding was defined as $\geq$28 kcal/kg in the absence of indirect calorimetric determination based on the large multicenter Spanish ICU study including 725 patients receiving either EN or PN [19].

2.4. Laboratory analysis

All analyses were performed on a Cobas 8000 modular analyzer (Roche Diagnostics, Switzerland), except for prealbumin, which was determined on an Integra instrument (Roche Diagnostics, Switzerland). Enzymatic methods were used to determine TG levels (GPO-PAP), and an immunoturbidimetric assay was used for the determination of albumin and C-reactive protein. Pancreatic amylase was determined by an immunoinhibition assay, and an electrochemical immunoassay was used for procalcitonin antigen detection. The hospital's Laboratory of Clinical Chemistry is ISO 15189:2012 certified.

2.5. Data collection and analysis

Data were extracted from the clinical information system (CIS) MetaVision (iMDSoft®, version 5.45.5403, Tel Aviv, Israel). The CIS was customized to provide detailed composition information and quantities of the enteral and parenteral feeding solutions, including the respective amounts of LCTs and MCTs [20]. It was customized to show the total energy with detailed information including non-nutritional substrate intake.

The data and results are presented as medians and interquartile ranges or as number of subjects and percentage. Two-way analysis of variance and linear regression were used for analysis with the software programs R language (R Foundation, version 2.10.0) and JMP V5.1 (SAS Institute, Cary, NC, USA). Statistical significance was considered at the level of $p < 0.05$.

3. Results

During the study period, 10,656 patients were admitted to the ICU, of whom 757 (7%) were on PN and eligible for the study based on the length of stay. Altogether, 228 patients (30.1%) presented at least one episode of hyperTG during their time on PN, but there was no significant difference between the LCT/MCT and LCT+ groups ($p = 0.53$). Only 187 patients could be analyzed for dynamic TG

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