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Parenteral nutrition providing a restricted amount of linoleic acid in severely burned patients: a randomised double-blind study of an olive oil-based lipid emulsion *v*. medium/long-chain triacylglycerols

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It has been claimed that lipid emulsions with a restricted linoleic acid content can improve the safety of total parenteral nutrition (TPN). The tolerability of TPN and its effects on the metabolism of fatty acids were assessed in this prospective, double-blind, randomised study comparing an olive/soyabean oil long-chain triacylglycerol (LCT) with a medium-chain triacylglycerol (MCT)/LCT; 50:50 (w) based lipid emulsion in two groups (O and M, respectively; eleven per group) of severely burned patients. After resuscitation (48–72 h), patients received TPN providing 147 kJ/kg per d (35 kcal/kg per d) with fat (1·3 g/kg per d) for 6 d Plasma fatty acids, laboratory parameters including liver function tests, and plasma cytokines were assessed before and after TPN. Adverse events encountered during TPN and the clinical outcomes of patients within the subsequent 6 months were recorded. With both lipid emulsions, the conversion of linoleic acid in its higher derivatives (di-homo-γ-linolenic acid) improved and essential fatty acid deficiency did not appear. Abnormalities of liver function tests occurred more frequently in the M (nine) than in the O (three) group ($P=0{\cdot}04$, Suissa–Shuster test). Seven patients (four from group O and three from group M) died as a consequence of severe sepsis 3–37 d after completion of the 6 d TPN period. When compared with the surviving patients, those who died were older ($P=0{\cdot}01$) and hyperglycaemic at baseline ($P<0{\cdot}001$), and their plasma IL-6 levels continued to increase ($P<0{\cdot}04$). Although fatty acid metabolism and TPN tolerability were similar with both lipid emulsions, the preservation of liver function noted with the use of the olive oil-based lipid emulsions deserves confirmation.

Burns: Parenteral nutrition: Lipid emulsion: Olive oil: Liver function tests

Burn trauma is one of the most severe physiological insults and thus consistently produces one of the most devastating responses to metabolic stress. Although a patient's early outcome is predominantly related to the extent of burn as well as age and comorbidities (Zawacki *et al.* 1979; Tobiasen *et al.* 1982), nutritional strategies may facilitate recovery with a possible reduction in death rate (Montegut & Lowry, 1993; Pelaez *et al.* 1997). Although no clear specific nutritional recommendations have been decreed for burn patients (Deitch, 1995), the nature and quantity of nutritional intake are of critical choice in these patients, who are concomitantly hypermetabolic, inflamed and immunosuppressed, and are therefore highly sensitive to the risk of sepsis (Alexander, 1990; Barlow, 1994).

Several reports have demonstrated that an excessive lipid intake may adversely affect the immune system and clinical outcome in critically ill patients (Garcia-de-Lorenzo & Culebras, 1992; Battistella *et al.* 1997; Weissman, 1999), including severely burned patients (Garrel *et al.* 1995). This relationship between high fat intake and impaired immune response has arisen from studies mainly implicating soyabean oil-based lipid emulsions because they are the most commonly used lipid source (Nordenstrom *et al.* 1979; Seidner *et al.* 1989; Freeman *et al.* 1990; Kinsella *et al.* 1990; Calder & Newsholme, 1992; Sadeghi *et al.* 1999; Eritsland, 2000; Garnacho-Montero *et al.* 2002). Soyabean oil-based lipid emulsions are particularly rich in *n*-6 PUFA, namely linoleic acid (LA, 18 : 2*n*-6), and are consequently suspected of causing an imbalanced production of prostaglandins and other eicosanoids (Hageman *et al.* 1983; Spielmann *et al.* 1988; Kinsella *et al.* 1990), with the potential risk of worsening the pre-existing immunosuppressed and inflammatory state of critically ill patients (Sparkes, 1997; Schwacha & Chaudry, 2002).

Alternatives to standard soyabean oil-based lipid emulsions are those with restricted LA content. A lipid emulsion that has recently become available is based on a mixture of olive oil and soyabean oil (4:1, W:G), and is characterised by its low content of LA (18 % of total fatty acids) and its high content of oleic acid, an *n*-9 MUFA (63 %). Clinical studies have already confirmed the nutritional and metabolic efficacy of this lipid emulsion, as well as its good global safety in different situations: from short-term total parenteral nutrition (TPN) in critically ill patients (Rossle *et al.* 1992; Reimer *et al.* 2001) and pre-term infants (Gobel *et al.* 2003) to longer periods of home parenteral

Abbreviations: AA, arachidonic acid; ICU, intensive care unit; LA, linoleic acid; LCT, long-chain triacylglycerol; MCT, medium-chain triacylglycerol; TPN, total parenteral nutrition; ULN, upper limit of normal.

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nutrition in adults (De Francesco *et al.* 1999; Vahedi *et al.* 1999; Thomas-Gibson *et al.* 2004) and paediatric patients (Goulet *et al.* 1999).

To confirm the potential interest in this low LA-content lipid emulsion in critically ill patients, we performed a prospective double-blind trial in severely burned patients. To estimate the role of a restricted LA supply, a comparison was carried out with another lipid emulsion also characterised by its low LA content (26 % of total fatty acids; Lipofundina (B. Braun, Melsungen, Germany); 50:50 medium-chain triacylglycerol/long-chain triacylglycerol (MCT/LCT)). Use of this intravenous lipid emulsion is widely documented in many clinical circumstances, and it is routinely used in the intensive care unit (ICU).

Table 1. Composition of intravenous lipid emulsions

Per 100 ml	ClinOleic 20 %	Lipofundin MCT/LCT 20 %
Soyabean oil LCT	4 g	10 g
Olive oil LCT	16 g	–
MCT	Reimer *et al.* 2001;	10 g
Egg phospholipids	1·2 g	1·2 g
Glycerol	2·25 g	2·5 g
PUFA	4 g	6 g
MUFA	13 g	2 g
Saturated fatty acids	3 g	12 g
Linoleic acid/total fatty acids	18 %	24 %

MCT, medium-chain triacylglycerols; LCT, long-chain triacylglycerols.

Methods

The protocol was approved by the Committee on Human Rights in Research of the University Hospital 'La Paz' and was in accordance with regulations of European Good Clinical Practice.

Patients and study design

Adult patients with severe burns (Abbreviated Burn Severity Index ≥ 7; Tobiasen *et al.* 1982) admitted to ICU were included, TPN usually being indicated for a duration of 5–7 d according to actual practice in the same centre (Herruzo-Cabrera *et al.* 1995). TPN was justified by the high energy requirements and a formal contraindication to enteral nutrition. Before receiving TPN, patients were resuscitated for a period of less than 3 d with Ringer's lactate or saline infusions associated with frozen plasma (Warden *et al.* 1973).

Patients were not included if they had pre-existing pathologies such as AIDS, chronic renal disease (creatininaemia >2 mg/dl), hepatic dysfunction (bilirubin above twice the upper limit of normal (>2 ULN), alanine aminotransferase or aspartate aminotransferase >4 ULN, or prothrombin time <50 %), lipid disorder (triacylglycerols >250 mg/dl) or any contraindication to the components of TPN. Patients who had been sedated with propofol were excluded because of its lipid emulsion excipient. All patients received similar wound-care treatment, including wound excision and skin-grafting of deep second- and third-degree wounds, mechanical ventilation, analgesia and antibiotic therapy.

Patients were enrolled into this prospective, controlled, double-blind, randomised, monocentre study according to: (1) the centre's capacity for recruitment; (2) reference to previous clinical studies comparing the effect of olive-oil based and soyabean oil-based lipid emulsions on patients' plasma fatty acid profile as the primary criterion of efficacy.

Parenteral nutrition

Patients were randomly assigned into one of the two groups to receive exclusive parenteral nutrition (TPN) with either ClinOleic 20 % (Baxter, Maurepas, France; group O) or Lipofundina MCT/LCT 20 % (B. Braun; group M) for 6 d. The constituents of the two lipid emulsions are presented in Table 1.

The nutritive admixture was prepared daily in a designed formula by usual hospital practices, delivered in blind-labelled plastic bags and continuously infused for 24 h through a central catheter. To ensure that nutrition support was isoenergetic and iso-nitrogenous between groups, TPN (per kg usual body weight per d) contained a total of 147 kJ with 0·25 g N delivered as Synthamin (Baxter). Lipids were administered at 1·3 g/kg usual body weight per d, and glucose at 4·3 g/kg usual body weight per d, providing 40 % and 60 % of patients' non-protein energy supply, respectively. Vitamins (Cernevit; Baxter, Maurepas, France), trace elements (Addamel; Fresenius Kabi, Bad Homburg, Germany) and electrolytes (Na, K) were prescribed according to individual need.

Plasma phospholipid fatty acid profiles

Samples were taken before the first lipid infusion (D1) and 4–8 h after the last one (D6). Samples were preserved at -20°C in tubes containing 2 ml plasma in 0·4 ml solution containing butylated hydroxytoluene (1 g/l absolute ethanol) as an antioxidant. Plasma phospholipid fatty acids were measured as previously described by Driss *et al*. by using GLC on a Carlo Erba Chromatograph (Erba & Sciences, Paris, France) equipped with a polar column (Omegawax Supelco Inc, Bellafonte, PA, USA) and a flame ionisation detector (Driss *et al.* 1988). The levels (%) of each saturated fatty acid, MUFA and PUFA were determined. The arachidonic acid (AA):LA, sum of LA upper derivatives (Σn-6, C $>$ 18 + 18 : n-6) to LA, and 20 : 3n-6:AA ratios were calculated as reflecting the activities of δ6- and δ5-desaturases. Triene/tetraene (20 : 3n-9:20 : 4n-6) and n-3 : n-6 ratios were established as respective estimates of essential fatty acid deficiency (Holman, 1960) and cell membrane fluidity and immune function (Peck, 1994).

Clinical and biological safety indices

All patients were monitored for TPN intake, adverse events including septic events, and biochemical parameters including serum albumin, C-reactive protein, fibrinogen, glucose, urea, creatinine, Na, K, Cl^-, haematology (haemoglobin, blood cell count, platelets) and lipids (total cholesterol, triacylglycerols) from the initial period to D6. Plasma concentrations of 'pro-inflammatory' (IL-6, TNFα) and 'anti-inflammatory' (IL-1 receptor antagonist, IL-10) cytokines were quantitatively determined at D1 before the first lipid infusion and at D6, 4–8 h after the end of the last one, by ELISA (Quantikine; R&D Systems Europe, Abingdon, Oxfordshire, UK).

Because liver function tests are considered to be critical safety parameters during the parenteral infusion of lipids (Cavicchi *et al.* 2000), we performed a detailed analysis of these parameters. Abnormalities were interpreted according to the following rule(s):

1. Cholestasis: when a value above the ULN occurred during treatment and was observed for at least two parameters from conjugated bilirubin, alkaline phosphatases and γ-glutamyl transpeptidase.
2. Cytolysis: when a value >2 ULN of aspartate aminotransferase and/or alanine aminotransferase occurred during treatment.

Adverse events and clinical outcome

Septic events, multiple organ dysfunction score, duration of ventilation, morbidity, mortality and length of stay in ICU and in hospital were recorded during the double-blind period of treatment and by follow-up assessment after 6 months.

Statistical analysis

The results are expressed as means with their standard errors. SAS (SAS Institute Inc, Cary, NC, USA) for Windows was used for the analyses. A baseline (D1) comparison was made across treatments for clinical and laboratory characteristics of patients. For quantitative criteria, non-parametric methods were used. Comparisons between groups were assessed by the Wilcoxon rank sum test, the Wilcoxon signed rank test being used for intra-individual differences between D6 and baseline (D1).

For liver function test abnormalities, an exact unconditional test, the Suissa–Shuster's unconditional test, was applied (Suissa & Shuster, 1985). This test was preferred to a χ^2 test or a Fisher's exact test because the Fisher's exact test is known to be very conservative with small sample sizes, and the conditions for applying a χ^2 test were not fulfilled (less than five for some cells/occurrences).

The analyses were conducted on the intention-to-treat group, and the level of significance was set at $P \leq 0{\cdot}05$.

Results

Patient groups at baseline

Having collecting their informed consent, twenty-two patients were included (eleven in each group). They had all been healthy before the burn injury. The two groups did not differ in age, BMI, gender ratio, total burned surface area or need for mechanical ventilation at baseline (Table 2). Some liver abnormalities were found in both patient groups (cholestasis: one case in group O; cytolysis: two in group O *v.* one in group M). Baseline laboratory characteristics did not differ statistically between groups, except for a higher mean leucocyte count in group M.

Parenteral intake

During the double-blind period, the average daily amount (per kg per d) of administered parenteral lipids as well as intakes of N and glucose were similar in the two groups (Table 3). The use of concomitant medications, including vitamins, trace elements, plasma substitutes, plasma protein fractions and blood and related products was not significantly different between the groups (data not shown).

Table 2. Patient characteristics at baseline for groups of patients randomised to receive olive-oil (O) or medium-chain/long-chain triacylglycerol (M) based lipid emulsions

(Mean± SEM or *n*)

	Group O (*n* 11)		Group M (*n* 11)		
	Mean	SEM	Mean	SEM	*P*
Age (years)	49·1	4·6	39·9	5·1	NS
BMI (kg/m^2)	24·4	0·8	24·7	1·1	NS
Gender (male/female) (*n*)	8/3		6/5		NS
Inhalation trauma (*n*)	7		9		NS
Delay from thermal injury (d)	2·1	0·2	2·4	0·2	NS
Abbreviated Burn Severity Index	8·7	0·5	8·7	0·5	NS
Total burned surface area (%)	38·5	4·0	37·4	4·9	NS
Glucose (mg/dl)	102·9	6·2	109·0	7·2	NS
Blood white cells ($\times 10^3/\mu$l)	7·74	1·05	11·44	1·13	0·018

NS, $P>0{\cdot}05$ by the Wilcoxon rank sum test for all parameters, except for gender and inhalation trauma.

Plasma phospholipid fatty acids

Changes in plasma phospholipid fatty acids from D1 to D6 were not statistically different between groups, except for oleic acid, which increased significantly in group O compared with group M ($P<0{\cdot}001$; Table 4).

Plasma levels of LA decreased significantly in both groups (−5·06 (SEM 0·65), $P=0{\cdot}004$, and −2·52 (SEM 0·91), $P=0{\cdot}05$, in groups O and M, respectively). This variation was associated with a statistically significant decrease in AA level (−1·32 (SEM 0·43), $P=0{\cdot}01$, and −2·52 (SEM 0·91), $P=0{\cdot}03$, in groups O and M, respectively). Nevertheless, the conversion of LA to its C20–C22 derivatives was actually maintained, as illustrated by the evolution of the AA:LA ratio, which remained unchanged, and the ratio between the sum of LA upper derivatives and LA, which increased significantly ($P=0{\cdot}03$ in both groups). The rise

Table 3. Parenteral intakes during the study period for groups of patients administered parenteral nutrition including olive oil (O) or medium-chain/-long-chain triacylglycerol (M) based lipid emulsions

(Mean± SEM)

	O (*n* 11)		M (*n* 11)		
	Mean	SEM	Mean	SEM	*P*
Treatment duration (d)	5·1	0·6	6·0	0·0	NS
Lipid infusion duration (h)	21·4	0·8	22·8	0·2	0·012
N (g/kg per d)	0·24	0·00	0·24	0·00	NS
Glucose (g/kg per d)	4·9	0·1	4·8	0·1	NS
Lipid (g/kg per d)	1·3	0·0	1·3	0·0	NS
Volume (ml/d)	2336	141	2490	93	NS
Non-protein energy (kJ/kg per d)	129·7	1·6	129·7	1·2	NS
Total energy (kJ/kg per d)	154·9	1·6	154·9	1·6	NS
Lipid (% of non-protein energy)	37·0	0·5	37·4	0·6	NS
Glucose (% of non-protein energy)	63·0	0·5	62·6	0·6	NS

NS, $P>0{\cdot}05$ by the Wilcoxon rank sum test for all parameters.

Table 4. Changes in plasma phospholipid fatty acid profiles* for groups of patients administered parenteral nutrition including olive oil (O) or medium-chain/long-chain triacylglycerol (M) based lipid emulsions (Mean ± SEM)

	O (*n* 9)					M (*n* 11)					
	D1		D6			D1		D6			
	Mean	SEM	Mean	SEM	*P*†	Mean	SEM	Mean	SEM	*P*†	*P* between groups
Oleic acid 18 : 1*n*-9 (%)	12·5	1·0	18·4	1·0	0·004	10·7	0·6	12·1	0·4	NS	0·000
Linoleic acid 18 : 2*n*-6 (%)	22·5	0·8	17·5	1·2	0·004	24·3	0·8	21·8	1·1	0·053	0·081
Di-homo-γ-linolenic acid 20 : 3*n*-6 (%)	2·0	0·1	3·6	0·3	0·004	2·1	0·1	3·9	0·3	0·002	NS
Arachidonic acid: 20 : 4*n*-6 (%)	7·7	0·5	6·4	0·5	0·007	8·2	0·5	7·1	0·5	0·032	NS
Ratio of C20 : 4*n*-6:C18 : 2*n*-6	0·3	0·0	0·4	0·1	NS	0·3	0·0	0·3	0·0	NS	NS
(Sum of *n*-6, C > 18 + C18 : 3*n*-6)/C18 : 2*n*-6	0·5	0·0	0·7	0·1	0·027	0·4	0·0	0·6	0·1	0·032	NS
Ratio of 20 : 3*n*-6:20 : 4*n*-6	0·3	0·0	0·6	0·0	0·004	0·3	0·0	0·6	0·1	0·002	NS
Ratio of arachidonic acid: 20 : 3*n*-9:20 : 4*n*-6	0·0	0·0	0·1	0·0	0·007	0·0	0·0	0·1	0·0	0·002	0·015
Ratio of sum *n*-3:sum *n*-6	0·39	0·03	0·29	0·02	0·004	0·35	0·03	0·27	0·01	0·006	NS

NS, $P > 0.05$ by the Wilcoxon rank sum test for all parameters.
*The plasma concentration of each fatty acid expressed as the percentage of total phospholipid fatty acids was measured as described by Driss *et al.* (1988).
† Wilcoxon signed rank test for intra-group comparisons over time.

in di-homo-γ-linolenic acid (C20 : 3*n*-6) level in both groups ($P = 0.004$ and $P = 0.002$ in groups O and M, respectively) also contrasted with the fall in AA. In addition, the triene:tetraene ratio, although increasing in both groups, remained mainly below the threshold of 0·2 in all patients, indicating that the patients did not develop essential fatty acid deficiency. Conversely, *n*-3 : *n*-6 ratios were decreased in both groups ($P = 0.004$ and $P = 0.007$ in groups O and M, respectively).

Nutritional and inflammatory status

The change in the patients' nutritional and inflammatory parameters, including plasma cytokines, did not differ statistically between groups (Tables 5 and 6).

Liver function tests

After the 6 d period of infusion, abnormal values were more frequent in group M (Table 7). Markers of cholestasis occurred during TPN in three out of nine patients in group O, compared with nine out of eleven patients in group M. This difference was statistically significant between the two groups ($P = 0.04$, Suissa–Shuster test). Markers of cytolysis were also associated with cholestasis in two group O and three group M patients.

The comparative analysis of clinical and laboratory characteristics of the groups of patients with and without liver function abnormalities (twelve *v.* ten, respectively) showed that there were no statistical differences for age, gender ratio, BMI, Abbreviated Burn Severity Index, parenteral intake or incidence of sepsis. Also, the baseline of and changes in plasma glucose, phospholipid fatty acid profiles and inflammatory parameters including cytokines were not significantly different when comparing patients who had liver abnormalities with the remaining patients.

Other laboratory parameters

Plasma lipid changes did not differ statistically between the two groups (Table 5). Plasma triacylglycerols increased between 1 and 2 ULN in three patients in each group and above 2 ULN in one patient from group M. Total cholesterol was either within the normal range at baseline, or was below normal in two patients from each group. It remained stable or normalised over time in all cases except for two patients in group M, who showed a decrease. (Paired data are missing for two patients from group O.)

Hyperglycaemia occurred or increased in both groups, between 1 and 2 ULN in five group O *v.* three group M patients, and above 2 ULN in three group O *v.* two group M patients. There was no statistical difference between groups regarding changes in all other routinely assessed laboratory parameters (data not shown).

Adverse events and clinical outcome

During the 6 d period of TPN, septicaemia or documented infections of the lungs or burn area were diagnosed in six patients from each group.

After the completion of TPN, seven patients died from multiple organ failure during their stay in ICU (from 4 to 37 d after the last infusion of TPN, occurring in four patients from group O, including one case of a premature end at D2, and in three patients from group M). No other death was observed during the 6-month

Table 5. Change in plasma of lipids, nutritional and inflammatory parameters during parenteral nutrition for groups of patients administered parenteral nutrition including olive oil (O) or medium-chain/long-chain triacylglycerol (M) based lipid emulsions

(Mean ± SEM)

	O (*n** 9)					M (*n** 11)					
	D1		D6			D1		D6			
	Mean	SEM	Mean	SEM	*P*§	Mean	SEM	Mean	SEM	*P*§	*P* between groups
Total proteins (mg/dl)	4·0	0·3	4·9	0·3	0·008	4·0	0·2	5·1	0·2	0·009†	NS
Albumin (mg/dl)	2·4	0·2	2·4	0·1	NS	2·5	0·2	2·5	0·2	NS†	NS
Triacylglycerols (mg/dl)	115	15	185	30	0·012	124	14	193	28	0·014†	NS
Total cholesterol (mg/dl)	112	7	121	6	0·047	127	10	125	8	NS	NS
Glycaemia (mg/dl)	104	8	211	49	0·012	109	7	163	31	0·006	NS
Haemoglobin (g/dl)	11·5	0·8	10·1	0·5	NS	12·4	0·4	10·6	0·3	0·032	NS
C-reactive protein (mg/dl)	11·5	1·1	11·7	2·5	NS†	12·1	1·2	11·1	1·8	NS‡	NS
Fibrinogen (mg/dl)	596	42	742	42	0·039	651	43	750	42	0·024	NS
Platelets (10^9/μl)	114	11	291	37	0·004	140	21	351	37	0·001	NS

NS, $P > 0{\cdot}05$ by the Wilcoxon rank sum test for all parameters.
* Number of patients in each group with available sample for a paired analysis.
†*n* 8 and ‡*n* 10 for a paired analysis.
§ Wilcoxon signed rank test for intra-group comparisons over time.

follow-up. For each death, a pre-existing severe sepsis as defined by Bone (1992) was identified as a direct causative event.

When comparing the patients who died (*n* 7) with those who did not (*n* 15), patients did not differ at baseline in terms of BMI, Abbreviated Burn Severity Index, inflammatory parameters, triacylglycerols, total cholesterol and serum albumin values (Table 8). Their parenteral intakes were not statistically different. For the seven patients who died, the burn was associated with an inhalation trauma, but this characteristic of thermal injury severity (German *et al.* 1997) did not make them statistically different from the other patients. Conversely, they were statistically different from the patients who lived (*n* 15) on three characteristics: age; hyperglycaemia at baseline; change in plasma cytokine levels. Indeed, the individuals who died were older and significantly more often hyperglycaemic (>110 mg/dl) at baseline. The relative risk of mortality in the 6 months following the thermal injury was about 8·5 times higher for patients who were hyperglycaemic at baseline (RR = 8·5; 95 % CI 2·3, 31·2). Considering the cytokine analysis, IL-6 evolved differently, its level continuing to increase in the group of patients with fatal sepsis while decreasing in the other patients.

Change in multiple organ dysfunction score, duration of ventilation (11·0 (SEM 3·6) *v.* 13·0 (SEM 4·9) d), length of stay in ICU (32·9 (SEM 3·2) *v.* 41·8 (SEM 5·6) d) and in hospital (57 (SEM 4·6) *v.* 64·9 (SEM 8·2) d) were not statistically different between groups O and M.

Discussion

Profound alterations in fatty acid metabolism following burn injury have been reported (Cetinkale & Yazici, 1997, Pratt *et al.* 2001) and consequently represent a fundamental process in the genesis of the post-injury immunosuppressive and hyper-inflammatory state. In particular, plasma and cell membrane levels of phospholipid LA and of LA's higher derivatives, including AA, fall early, this being characterised by a prolonged and progressive deterioration during at least the first 2 weeks following thermal injury. The changes in fatty acid profile are greatest around 7–10 d after the burn and occur concomitantly with the highest impact on immunity and on the production of inflammatory mediators (Pratt *et al.* 2002).

This is the first time that the effects of parenteral nutrition on fatty acid metabolism in thermally injured patients have been studied and reported. This study was exploratory in nature because an olive-oil based lipid emulsion has never previously been compared with an MCT/LCT lipid emulsion in critically ill patients. The choice of MCT/LCT as a comparator was made as this was the referenced lipid emulsion in the study centre. It is better justified than a high LA-content lipid emulsion with potentially deleterious effects on immunity and inflammation. In the present study, the comparative assessment of the two lipid emulsions with restricted LA content confirms both a similar improvement over time of fatty acid metabolism (LA elongation to di-homo-γ-linolenic acid) and their global safety in severely burned patients.

Consistent with previously published data, there was at D6 (corresponding to 7–9 d after thermal injury) a decrease in LA and AA, possibly explained in part as the consequence of series 2 prostaglandin biosynthesis from AA oxidative metabolism (Karlstad *et al.* 1993). However, we found in both groups a statistical increase in the sum of *n*-6 higher derivatives, the AA:LA ratio and the level of di-homo-γ-linolenic acid (C20 : 3*n*-6), the immediate precursor for series 1 prostaglandins, which are considered as anti-aggregatory, anti-inflammatory eicosanoids. These findings can be interpreted as reflecting the beneficial effect on LA metabolism of a reduced LA-content lipid emulsion despite the sustained inflammatory response observed in severely burned patients.

Although no significant difference in global safety was found between lipid emulsions, a statistically higher number of patients experienced liver function abnormalities with MCT/LCT, raising concern regarding the tolerability of this lipid emulsion or suggesting a better preservation of liver function with an olive/soyabean oil lipid emulsion.

It has been previously reported that liver function can be impaired in severely burned patients (Herndon *et al.* 1987). Early hepatic changes result from shock and hypovolaemia, but more significant changes occur later as a result of sepsis and other complicating factors (Friedman & Deppe, 2002). In addition, liver function abnormalities are very common in parenterally fed

Table 6. Change in plasma cytokines (pg/ml) during parenteral nutrition for groups of patients administered parenteral nutrition including olive oil (O) or medium-chain/long-chain triacylglycerol (M) based lipid emulsions

(Mean± SEM)

	O (*n** 9)							M (*n** 11)							
	T0		D6		D6 – T0			T0		D6		D6 – T0			
	Mean	SEM	Mean	SEM	Mean	SEM	*P*†	Mean	SEM	Mean	SEM	Mean	SEM	*P*†	*P* between groups
TNF-α	160	59	73	25	−87	38	0·023	63	12	47	9	−16	16	NS	NS
IL-10	27	11	11	2	−16	11	NS	17	5	12	3	−5	5	NS	NS
IL-6	139	51	51	32	−87	66	NS	55	11	38	14	−17	6	0·025	NS
IL-1 receptor antagonist	2969	1210	1304	227	−1665	1155	NS	1110	112	1281	198	171	183	NS	NS

NS, $P > 0{\cdot}05$ by the Wilcoxon rank sum test for all parameters.
* Number of patients in each group with available sample for a paired analysis.
† Wilcoxon signed rank test for intra-group comparisons over time.

Table 7. Distribution of abnormal values of liver function parameters before and after parenteral nutrition and according to their severity for groups of patients administered parenteral nutrition including olive oil (O) or medium-chain/long-chain triacylglycerol (M) based lipid emulsions

	O (*n** 9)						M (*n* 11)					
	T0			D6			T0			D6		
	>ULN	>2 ULN	>5 ULN	>ULN	>2 ULN	>5 ULN	>ULN	>2 ULN	>5 ULN	>ULN	>2 ULN	>5 ULN
Alkaline phosphatases	1			2	1					6	1	
γ-GT†		1		1	3	2				1	5	3
Conjugated or total bilirubin	2	1		2			5	1		3	1	
Aspartate aminotransferase	1	2	1	5			1	1		4	2	
Alanine aminotransferase	1	1		1	3		1			6	1	1

> ULN, an abnormal value between once and twice the upper limit of the normal range; >2 ULN, an abnormal value between twice and five times the upper limit of the normal range; >5 ULN, an abnormal value above five-fold the upper limit of the normal range.
* Number of patients in each group with an available sample.
† γGT, two sets of data missing at D6 for group O; in both cases, other markers of cholestasis were normal.

Table 8. Comparison between patients with fatal sepsis *v.* others for groups of patients administered parenteral nutrition including olive oil (O) or medium-chain/-long-chain triacylglycerol (M) based lipid emulsions

(Mean ± SEM or *n*)

	Fatal sepsis (*n* 7)		Patients staying alive (*n* 15)		
	Mean	SEM	Mean	SEM	*P*
Group membership (O/M)	4†/3		7†/8		NS
Total burn surface area (%)	42	7·5	36	3·0	NS
Abbreviated Burn Severity Index	9·57	0·69	8·33	0·33	NS
Inhalation trauma (*n* (%))	6 (86 %)		10 (67 %)		NS
Age (years)	57·1	6·12	38·6	3·45	0·012
Hyperglycaemia* at baseline (*n* (%))	5 (71 %)		0 (0 %)		0·001
Glycaemia change (mg/dl) (D6 − D1)	129·5	65·0	55·5	21·5	NS
C-reactive protein at baseline (mg/dl)	126	13·2	118	8·9	NS
Fibrinogen at baseline (mg/dl)	691	58	612	31	NS
IL-6 at baseline (pg/l)	174	117	103	33	NS
IL-6 % change (pg/l) (D6 − D1)	77	110	−62	9	0·035

NS, $P > 0{\cdot}05$ by the Wilcoxon rank sum test for all parameters.

* Glycaemia > upper limit of normal, which is 120 mg/dl.

† Including one case of premature death at D1.

patients, although they usually occur during prolonged TPN (Capron *et al.* 1983; Garcia-de-Lorenzo, 1983; Beau *et al.* 1994; Alpers, 2001). In the present study, whereas several causal factors could be suggested (patient characteristics, severity of burn injury, sepsis), none has been specifically identified to explain the difference in the occurrence of these abnormal hepatic changes.

From an analysis of previous clinical studies, ClinOleic's hepatic tolerability has thus far been revealed as being at least equivalent to that observed with soyabean oil-based emulsions (Bouletreau *et al.* 1996; Masini *et al.* 1996; De Francesco *et al.* 1999; Goulet *et al.* 1999; Vahedi *et al.* 1999; Thomas-Gibson *et al.* 2004). Moreover, several experiments carried out in rats have shown the following benefits when using ClinOleic. First, it has been demonstrated that ClinOleic does not have a significant effect on biliary secretion, unlike soyabean oil emulsions (Ythier-Moury *et al.* 1990). Second, Garnacho *et al.*, in a model of Gram-negative bacteraemia, have recently compared ClinOleic with MCT/LCT and soyabean oil-based LCT lipid emulsions. The mononuclear phagocyte system functions were better preserved with the olive oil-enriched lipid emulsion. Bacterial clearance from the animals' liver, spleen and lungs was significantly impaired in animals parenterally fed with the other two emulsions when compared with the control group of orally fed animals (Garnacho-Montero, 2002).

Concerning MCT/LCT, experimental studies have also provided advantageous findings. It has been proposed that MCT preserve gut permeability and the pathological liver changes induced by lipopolysaccharide (Kono *et al.* 2003). On the other hand, this is not the first time that a deterioration in liver function has been reported with the use of this lipid emulsion (Beau *et al.* 1995) although no convincing explanation has been given to support this observation. In addition, short infusions of MCT/LCT lipid emulsions in human subject have been shown to increase total lipid and cholesterol concentration in the bile and increase gallbladder bile lithogenicity in patients with (Pakula *et al.* 1999) and without (Rubin *et al.* 1992, 1996) gallstones. A recent study performed on septic patients who required TPN showed that MCT/LCT infusion, when compared with soyabean oil emulsions, led to an increase in plasma triacylglycerols and total and free cholesterol (Charcon Castro *et al.* 2000). Finally, it must be remembered that lipid emulsions manufactured differently appear to induce different side-effects even when the basic ingredients are the same (Chambrier *et al.* 1999).

Sepsis continues to be a significant cause of mortality after the acute phase of major burns (McManus *et al.* 1985). In the current trial, the number of septic complications, with their high level of mortality, is consistent with previous observations and is partly explained by the high Abbreviated Burn Severity Index scores and frequency of patients with inhalation trauma (German *et al.* 1997).

In the current study, other mortality risk factors of the post-burn period have been either validated (age, change in cytokines) or elicited (hyperglycaemia after the resuscitation period and pre-existing before starting TPN). In accordance with the recent trial of Van den Berghe *et al.* (2001), which confirmed that hyperglycaemia of even a moderate level could increase mortality risk in ICU patients, we have shown an 8·5-fold increase in relative risk of mortality in the 6 months following thermal injury for patients who were hyperglycaemic before starting TPN. In these patients, hyperglycaemia is better explained by thermal injury and its related stress rather than by solutions of glucose infused into some of them. Concerning the potential capacity of MUFA-enriched emulsions to improve glucose homeostasis (Rocca *et al.* 2001), a 6 d period was probably too short to demonstrate any effect.

Finally, a few studies have investigated the effect of intravenous lipid emulsions upon cytokine production. These studies mainly aimed to demonstrate the immunosuppressive effects of soyabean oil-based lipid emulsions and the potential role of alternative lipid emulsions such as MCT/LCT (Bellinati-Pires *et al.* 1993; Waitzberg *et al.* 1997), structured lipids (Wanten *et al.* 2000), fish oil (Morlion *et al.* 1996) or olive oil-based lipid emulsions (Granato *et al.* 2000; Moussa *et al.* 2000). The results of the present trial are in accordance with current knowledge:

1. The levels of pro- and anti-inflammatory cytokines tend to decrease but are still high within 10 d following severe burns (Guo *et al.* 1990; Drost *et al.* 1993; Endo *et al.* 1996; Yamada *et al.* 1996; Carsin *et al.* 1997).

2. The change in IL-6, with a persistent increase in the patients who died, is proving to be a reliable predictor of fatality, as previously shown (Ueyama *et al.* 1992; Kowal-Vern *et al.* 1994; Papini *et al.* 1997).

In conclusion, the use of parenteral nutrition with lipid emulsions with a restricted LA content is efficient in reversing the impairment in essential fatty acid metabolism usually seen in severely burned patients. The difference found in terms of changes in hepatic parameters would be an advantage for the olive oil/soyabean oil-based lipid emulsion, making it a good alternative for the parenteral nutrition of severely burned patients.

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