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ORIGINAL ARTICLE

Pulmonary lesions and total parenteral nutrition in children admitted to a pediatric intensive care unit

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Abstract

Objective: To describe lung injuries in autopsied pediatric patients (neonates through 15 years old) subjected or not to total parenteral nutrition, in an intensive care unit.

Methods: Sections from six paraffin-embedded lung fragments, from 114 children were studied by routine staining. Demographic, clinical and therapeutic data were retrieved from the records. Statistical analysis was performed using Statistical Package for the Social Sciences.

Results: The 114 patients were divided in two groups: 50 who were treated with total parenteral nutrition with lipid emulsion and 64 who did not receive total parenteral nutrition. The two groups did not differ in gender (p = 0.654), age (p = 0.682) or body weight (p = 0.175), but duration of hospital stay (p = 0.000), prematurity (p = 0.008) and treatment with blood products (p=0.009) were all higher in the group treated with total parenteral nutrition. All patients received mechanical ventilation during hospitalization. Chi-square comparisons showed that diffuse alveolar injury (p=0.022), pulmonary fibrosis (p = 0.019), pneumocyte hyperplasia (p = 0.004), microthromboembolism (p = 0.047) and thrombophlebitis (0.033) all exhibited a significant relationship with total parenteral nutrition. However, a multivariate analysis by logistic regression, taking into account prematurity and duration of hospital stay, demonstrated that total parenteral nutrition was an independent factor only with respect of pulmonary fibrosis.

Conclusion: Although lung injuries were significantly more frequent in children who had received total parenteral nutrition, it was impossible to conclude that the lipid infusion had a direct relationship with these injuries, because prematurity and duration of hospital stay were significant co-factors.

J Pediatr (Rio J). 2005;81(2):155-61: Parenteral nutrition, parenteral, lung, pathology.

Introduction

Several studies have suggested that the intravenous fat emulsions used for total parenteral nutrition (TPN) are associated with the genesis of some of the lung injuries suffered by critical patients, with emboli of fat in the lumen of arteries[1-3] and capillaries[1,2,4-7] being reported in addition to deposits in the cytoplasm of alveolar macrophages,[1,2,4,7-9] alveolar epithelial cells,[9] septal macrophages, bronchial cartilage chondrocytes and other interstitial cells.[10]

Injuries described as associated with or consequent on these fatty emboli and deposits, include nodular lesions,[11] pulmonary infarct,[8] granulomatous inflammatory reaction in the lumen and wall of pulmonary artery branchings,[12-14] pulmonary hypertensive vascular disease with hypertrophy of small arteries and proliferation of foamy cells creating saliencies into the vascular lumen.[2]

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A review of the literature shows that the majority of papers consists of reports of lung injuries after TPN lipid infusion, and of samples predominantly made up of newborns. Additionally, the number of cases in each of these observations was low and comparison groups were not included. Attention is drawn to the absence of systematic studies of the occurrence of lung injuries and their possible association with TPN lipid infusions. In this article the lung injuries observed in a series of autopsies of patients who died in an Intensive Care Unit will be described. The patients were aged up to 15 years and a group that received lipid infusion during total parenteral nutrition will be described together with a group that did not.

Methods

Study sample

Three hundred and one (25.7%) of the 1,172 children admitted to the Pediatric Intensive Care Unit at the *Hospital Infantil Nossa Senhora da Glória* in Vitória, Espírito Santo (Brazil) between January 1998 and December 2001 suffered fatal outcomes. In 114 (37.9%) of these cases permission was granted by parents for autopsy, which was performed within 12 hours of death. Of the autopsied patients, 50 had been on parenteral nutrition with lipid infusion and 64 did not receive parenteral nutrition as part of their therapy while in hospital. The study included all autopsies with no exclusion criteria.

Total parenteral nutrition

The solution contained a lipid emulsion at 20%, amino acids at 10% and micronutrients, administered intravenously in Y, continuously for 24 hours, by infusion pump, together with venous liquids composed of glucose solution, sodium chloride at 20%, potassium chloride at 10% and potassium phosphate at 10%. Calcium gluconate at 10% and magnesium sulphate were administered separately in bolus intravenously. In order to reduce the effect of lipid peroxidation by light, photosensitive equipment was used. Maximum lipid infusion for all patients was 0.17 g per kilo per hour and heparin was not added to the total parenteral nutrition solution.

The lipid emulsion used for TPN (Lipofundin®, B. Braun Melsungen AG, Germany) was composed of soy oil, long-chain triglycerides (LCT), with predominantly unsaturated fatty acids, medium-chain triglycerides (TCM) primarily caprylic acid (60%) and capric acid (40%), lecithin from eggs, glycerol, sodium oleate, α-tocopherol, linoleic acid and α-linoleic acid. The initial lipid dose was 0.5 g per kilo per day with daily increases of 1 g/kg up to a maximum of 3.5 g/kg. The laboratory test results for cholesterol and triglycerides remained within limits for normality throughout the procedure in all cases. In certain cases it was necessary to infuse the parenteral nutrition via the same line as other medications. Ninety-four children had a central venous catheter inserted.

Autopsy

Autopsies were performed at the Pathological Anatomy Laboratory of the *Hospital Infantil Nossa Senhora da Glória, Vitória (ES)*. All were complete and for each patient, in addition to anatomopathological diagnoses, information was recorded on lung weight, characteristics and number of pulmonary lesions and presence or absence of deep venous catheter and its complications.

Six lung fragments were removed from each patient, including samples from the central portion, the parahilar area and the peripheral area. The fragments were paraffin embedded and stained with hematoxylin and eosin and, when necessary, with special methods (Gomori trichrome staining and PAS). The histopathological analysis of these fragments was performed at the Pathology Laboratory of the *Hospital Infantil Nossa Senhora da Glória*. The histopathological analysis procedure was reviewed by two investigators, one of them from the Infectious Diseases Research Center at the *Universidade Federal do Espírito Santo*.

Demographic and clinical patient data

Information was obtained from medical records on age, sex, weight, length of hospital stay, treatment and clinical diagnosis. Treatment details recorded were related to the infusion of vasoactive drugs, use of blood products and the lipid emulsion dosage. In order to calculate the lipid dose the TPN solution infusion start and end times were taken from prescription and nursing records. Since all of the patients had had more than one clinical diagnosis, the principal diagnoses were considered or the diagnoses that included other diseases. The most common were: sepsis, heart failure, acute kidney failure, asphyxia and prematurity. The diagnosis of sepsis was based on the criteria proposed by the *American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference* (ACCP/SCCM, 1992),[15] and modified by Hayden[16] and maintained by Levy et al.[17] For diagnoses of congestive heart failure acute kidney failure criteria described by Bernstein[18] and Bergstein, respectively, were used.[19] Perinatal asphyxia was defined using the score proposed by Apgar[20] and the gestational ages of the newborns, appearing on all medical records for this sample patients, was assessed by the New Ballard Score.[21]

Statistical analysis

For the statistical analysis, the Statistical Package for the Social Sciences (SPSS 11.0 Inc. Chicago, IL, USA) software package was employed. Differences in proportions (frequencies) were calculated using the chi-square statistic, with correction for continuity if applicable. Continuous variables were compared with the Kolmogorov-Smirnov test and the test of adequate comparison was applied depending on type of variable distribution. Values were considered significant at $p < 0.05$, with all tests being two-tailed. Multivariate analysis by logistic regression was employed to test the inter-relation of co-factors with TPN in the origin of the lung injuries observed.

The study was approved by the Committee for Ethics in Research at the *Universidade Federal de Minas Gerais*, hearing ETIC 116/03.

Results

Data on age, sex, length of hospital stay, body weight, clinical diagnosis, use of vasoactive drugs and blood products for the 114 children, subjected or not to TPN, are summed up in Table 1. The groups are similar with respect of these variables, with the exception of length of hospital stay and prematurity.

All of the patients had required mechanical pulmonary ventilation with inspired oxygen fractions above 60% in order to maintain oxyhemoglobin saturation above 90%.

Lipid doses varied from 0.5 to 3.5 g/kg/day (mean: 1.95; SD: 0.89 g/kg/day; median: 2 g/kg/day) and TPN duration varied from 1 to 34 days (mean: 7.37; SD: 7.46 days; median: 5 days).

The main macroscopic injuries observed (pneumothorax, hydrothorax, pleural petechiae, serous secretion in the bronchi, ulcers in bronchial mucosa, infarcts and collapsed areas) did not differ significantly with respect of TPN use.

The principle microscopic injuries are listed in table 2, split by TPN use. Figure 1 shows some of the most relevant microscopic features of the injuries observed.

Statistically significant relationships with infusion of total parenteral nutrition were observed with interstitial pulmonary lesions compatible with diffuse alveolar damage ($p = 0.022$), pneumocyte hyperplasia ($p = 0.004$) and septal pulmonary fibrosis ($p = 0.019$). Acute respiratory distress syndrome (ARDS) was more common in the group that received parenteral nutrition, and the difference was at the limit of statistical significance ($p = 0.053$). Statistically significant relationships between TPN and vascular damage was observed for microthromboembolism ($p = 0.047$) and thrombophlebitis ($p = 0.03$). However, when a multivariate analysis by logistic regression was performed taking into account prematurity and length of hospital stay, which differed significantly between the two groups, it was shown that TPN was an independent factor only for fibrosis (Table 3).

Thrombotic damage had characteristics of recent or past formation with intravascular recanalization. Diffuse alveolar damage had identical histological characteristics to that observed in premature newborns with hyaline membrane disease or in patients who have developed acute respiratory distress syndrome. In some cases alveolar damage was focal and restricted to certain isolated areas.

In certain patients unidentified foreign bodies were observed in the intravascular space. Many vessels exhibited intraluminal or intramural calcification or this was observed

Table 1 - Age, sex, time of hospital stay and clinical diagnosis, use of vasoactive drugs and blood products in children under parenteral nutrition or not, and submitted to necropsia in the *Hospital Infantil Nossa Senhora da Glóri*a, in Vitória (ES)

Variables	**Total parenteral nutrition**		**p**
	Yes (n = 50)	**No (n = 64)**	
Sex n (%)			
Male	28 (56.0)	32 (50.0)	
Female	22 (44.0)	32 (50.0)	0.654
Age (days)			
Median (IQ25-75%)	36 (3.0-319.7)	88 (4.0-493.5)	0.682*
Weight (g)			
Median (IQ25-75%)	3,600 (1,975.0-7,732.5)	4,555 (9,3162.5-9,812.5)	0.175*
Time of hospital stay (days)			
Mediana (IQ25-75%)	10 (5.7-15.5)	2.5 (1.0-4.7)	0.000*
Clinical Diagnose n (%)			
Sepsis	40 (80.0)	41 (64.1)	0.098
Pneumonia	21 (42.0)	18 (28.1)	0.177
Prematurity	13 (26.0)	4 (6.2)	0.008
Congenital cardiopathy	10 (20.0)	15 (23.4)	0.832
Enteritis	6 (12.0)	4 (6.3)	0.457
Kidney failure	5 (10.0)	7 (10.9)	1.000
Heart failure	3 (6.0)	3 (4.7)	1.000
Asphyxia	1 (2.0)	7 (10.9)	0.138
Treatment			
Vasoactive drugs	47 (94.0)	59 (92.2)	0.995
Blood products	48 (96.0)	49 (76.6)	0.009

* Two-tailed Mann-Whitney test (bicaudal). Other comparisons made with χ^2 test, with continuity correction if applicable.

Table 2 - Interstitial pulmonary lesions and alveolar lesions in children under total parenteral nutrition or not, submitted to necropsia in the *Hospital Infantil Nossa Senhora da Glória*, Vitória (ES)

Variables	Total parenteral nutrition		
	Yes (n = 50)	No (n = 64)	p
Interstitial and alveolar lesions			
ARDS *	10 (20.0)	4 (6.3)	0.053
Pulmonary congestion	11 (22.0)	22 (34.4)	0.216
Septal congestion	2 (4.0)	6 (9.4)	0.456
Diffuse alveolar damage	17 (34.0)	9 (14.1)	0.022 †
Pulmonary edema	6 (12.0)	6 (9.4)	0.884
Pulmonary infarct	1 (2.0)	1 (1.6)	1.000
Pulmonary fibrosis	9 (18.0)	2 (3.1)	0.019 †
Pulmonary hemorrhagie	29 (58.0)	31 (48.4)	0.409
Pneumocyte hyperplasia	11 (22.0)	2 (3.1)	0.004 †
Pulmonary hypertension	11 (22.0)	7 (10.9)	0.177
Lymphocytic interstitial infiltrate	6 (12.0)	6 (9.4)	0.884
Vascular lesions			
Foreign body	7 (14.0)	2 (3.1)	0.074
Vascular granulomas	8 (16.0)	6 (9.4)	0.434
Intravascular megakaryocyte	7 (14.0)	11 (17.2)	0.838
Microthromboembolism	24 (48.0)	18 (28.1)	0.047 †
Thromboflebitis	5 (10.0)	–	0.033 †
Intravascular calcification	7 (14.0)	4 (6.4)	0.284
Endothelial growth	2 (4.0)	–	0.371
Intimal proliferation	3 (6.0)	–	0.163

* ARDS = acute respiratory distress syndrome.
† Considering prematurity and time of hospital stay, the multivariate analysis by logistic regression showed that only pulmonary fibrosis remained significant as for total parenteral nutrition.

adhering to the wall of the blood vessel. Granulomas with multinucleated giant cells were observed in vessel walls, close to foreign bodies and had a statistically significant relation with the period of time for which lipid emulsions were used infused in the total parenteral nutrition ($p = 0.01$). In five patients septic thrombophlebitis and thromboembolism were observed, caused by *Candida* or *Staphylococcus aureus*.

Discussion

Among the 114 patients in the study sample, the TPN group was made up of 22 newborns and 28 children (babies, toddlers, schoolchildren and adolescents). This is a numerically significant sample and, in addition to newborns, it contains a large number of older children. The group of 64 children who had not been given TPN included 25 newborns and 39 children (babies, toddlers, schoolchildren and

Table 3 - Multivariate analysis by logistic regression with significant difference as for total parenteral nutrition, considering prematurity and time of hospital stay. Values represent p

Co-fatores	Variables: Diffuse alveolar damage	Fibrosis	Pneumocyte hyperplasia	Microthrom-boembolism	Throm-boflebitis
TPN	0.319	0.022	0.115	0.871	0.973
Prematurity	0.720	0.710	0.344	0.115	0.788
Time of hospital stay	0.976	0.984	0.008	0.487	0.751

TPN = total parenteral nutrition.

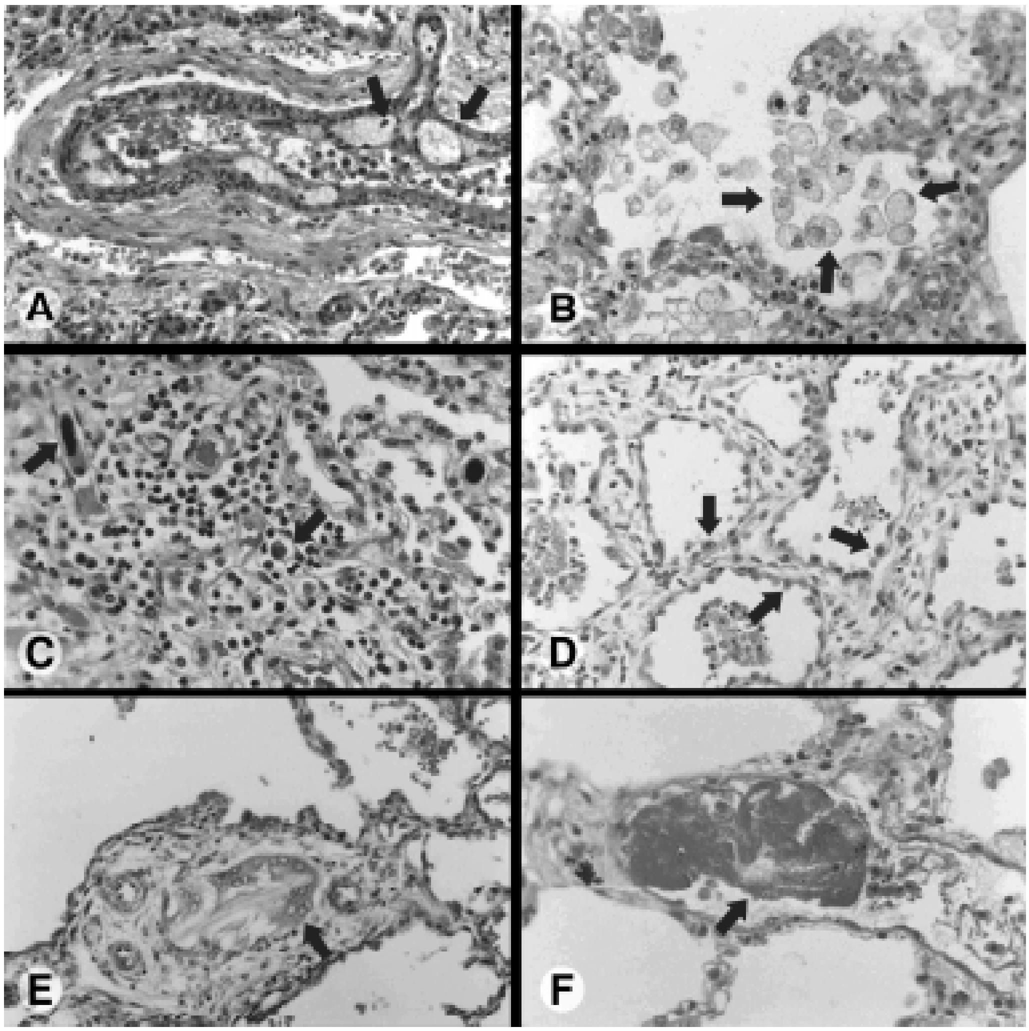

Figure 1 - Some of the most relevant microscopic aspects of the injuries observed

adolescents). In this respect the two samples are comparable, with the same being true for age, sex, weight and clinical diagnoses. However, the samples exhibited significant differences with respect of length of hospital stay and the presence of prematurity, more common among the TPN group. These differences may constitute a bias when the results are analyzed. This does not invalidate the sample, but requires caution in analyzing certain comparisons between the results observed, even after the multivariate analysis by logistic regression has been performed taking account of those variables with significant differences between the groups.

The frequency of lung injuries observed macroscopically did not have any significant difference between the TPN and no TPN groups. This observation is to be expected since the injuries observed were those that are found in critical patients with systemic inflammatory syndromes. The lipid infusion does not appear to cause any injuries with specific macroscopic characteristics. Harman & Ragaz[22], in experiments with rabbits subjected to severe dehydration reported: petechial hemorrhages, hemorrhagic suffusions in the pleura and pulmonary parenchyma, septal pulmonary fibrosis and atelectasis after infusion of homologous fats. These injuries are observed in the lungs of patients with ARDS, especially if the patient remains in the intensive care unit for a long time.

The microscopic alterations observed were those described in classic ARDS, which accompanies shock and systemic inflammation. Nevertheless, certain injuries were significantly more common in the TPN group when the comparison took account only of the use of TPN. Nevertheless, it became obvious by means of multivariate analysis that prematurity and length of hospital stay were important factors in the origin of these injuries. Only fibrosis was independently related to TPN.

The use of mechanical pulmonary ventilation and of oxygen at concentrations above 60% for ventilation are factors that aggravate these injuries.[23,24] However, all of the patients had received these treatments when in hospital and the medical records did not contain the ventilation period before the children were transferred to the unit. As length of hospital stay was significantly greater for the TPN group and since all patients were put on mechanical ventilation while in the unit, without doubt the TPN group were ventilated for longer even without knowing the duration before admission.

The prevalence of microthromboembolism was 36.8% and significantly greater in the group that had received total parenteral nutrition (48%; p = 0.047). This is probably the first report on the prevalence of pulmonary microthromboembolism in children admitted to an Intensive Care Unit. The elevated prevalence of pulmonary microthromboembolism in this sample could be related to : (a) the clinical condition that led to the child receiving intensive care, especially sepsis; (b) interactions between drugs and parenteral nutrition, encouraging lipid precipitation; (c) trauma from external heart massage, leading to embolization of bone marrow; and (d) the presence of deep venous catheters.

It is probable that sepsis was not a significant factor in the frequency of thromboembolism among the patients given TPN. In fact the frequency of thromboembolism for these patients did not differ significantly between the subsets with or without sepsis (data not shown).

Septic emboli with bacterial or fungal colonization (*Candida*) were observed in five patients, all in the TPN group. The endothelial lesions induced by lipids infused with the parenteral nutrition can encourage both thrombosis and colonization by microorganisms.

The formation of fatty microemboli may encourage the formation of thrombi, which may explain, in part, the greater frequency of microthromboembolism observed in the patients who had received TPN. *In vivo* experimental studies of perfused rat lungs have demonstrated such endothelial damage induced by the intravenous infusion of lipids.[25,26] Another study has demonstrated an increase in thromboxane production in the lungs of patients who received lipid infusion in TPN, which favors thrombosis.[27]

There are other aspects of the present study that should also be taken into account. All of the patients were submitted to treatment with multiple drugs with the potential for interaction with the lipids of the infusion encouraging their aggregation and thrombotic potential.[28] Cardiac massage was used with all patients and is also an important factor in the genesis of emboli represented by fragments of myeloid tissue.[29] It was not possible to characterize the presence of bone marrow embolus in the lung fragments examined from the thromboembolism cases.

Intravenous catheters are considered an important risk factor for pulmonary embolism.[30,31] In the sample studied, the frequency of thromboembolism was not significantly related with the use of deep venous catheters, even in the TPN group (thromboembolism present in 35/94 with venous catheter and 7/20 without venous catheter; p = 0.533).

Intrapulmonary megakaryocytes were common (15.8% of 114 autopsies), but there was no significant difference between the TPN and no TPN groups (p = 0.838). These cells are found in normal lungs and intrapulmonary migration may have occurred after an insult.[32] They can also be found in association with microthromboembolism, ARDS and disseminated intravascular coagulation.[33] The statistical analysis showed that these associations were not significant in the present study.

In conclusion, the observations made of the study sample demonstrate that although certain lung injuries were more frequent in the group treated with total parenteral nutrition, the multivariate analysis showed that TPN, in isolation, does not appear to have a direct relation with these injuries.

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