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ENDOTOXAEMIA, PULMONARY COMPLICATIONS, AND THROMBOCYTOPENIA IN LIVER TRANSPLANTATION

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Summary

Plasma endotoxin was measured in 64 patients undergoing primary liver replacement. Endotoxin concentrations increased during the anhepatic phase of the operations, and remained high for several days. Although the severity of endotoxaemia did not correlate with duration of the anhepatic phase, there was a correlation between endotoxaemia and the need for perioperative platelet transfusions, ventilator dependency postoperatively, and one-month case-fatality.

Introduction

Common complications after orthotopic liver transplantation (OLT) are coagulopathy, cardiovascular instability, respiratory distress syndromes, and multiple organ failure; these abnormalities also occur in animals with endotoxaemia that have not had a transplant.[1–4] Using a quantitative blood endotoxin assay,[5,6] we have shown a correlation between endotoxaemia and pulmonary failure in man.[7] We have now used this assay to see whether there is an association between endotoxaemia after OLT and the development of pulmonary complications or thrombocytopenia.

Patients and Methods

Patients

36 men and 28 women (mean age 46 years, range 18–66) had primary OLT between March 7 and July 31, 1988. None of the patients had had preoperative bacterial infections or massive intraoperative bleeding due to technical mishaps. Samples of systemic venous blood were collected preoperatively, at the end of the anhepatic phase of the operation but before platelet transfusion, and on the 1st, 3rd, and 7th postoperative days. The 64 recipients were divided into two groups: group A consisted of patients whose endotracheal tube could be removed within 5 days (n = 32); group B consisted of those who needed longer ventilatory support (30) or who died within 5 days (2). 6 patients in group B had a retransplantation within 7 days. The two groups did not differ with respect to underlying diseases, medical urgency as judged prospectively,[8] or age and sex distribution. 3 patients in each group were on ventilators preoperatively.

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Platelet replacement during OLT was guided by thrombelastographic monitoring.[9] In most cases, 1 unit of platelets was given with each unit (200 ml) of fresh frozen plasma and 250 ml of crystalloids. Platelets were not given until the end of the anhepatic phase.

Endotoxin Assay

Systemic venous blood was drawn in a pyrogen-free disposable syringe, anticoagulated with heparin (10 units/ml), centrifuged immediately at 1000 *g* for 10 min to remove platelets, and stored at −80°C. For the colorimetric limulus assay,[6] 0·32 mol/l perchloric acid, 0·18 mol/l sodium hydroxide, and 'Toxicolor' (lyophilised amoebocyte lysate from *Tachypleus tridentatus* and synthetic chromogenic substrate Boc-Leu-Gly-Arg-*p*-nitroanilide; Seikagaku Kogyo, Tokyo, Japan) with "tris"-hydrochloric acid buffer (pH 8·0) were used. The standard curve was plotted with *Escherichia coli* 0111:B4 endotoxin (Westphal type; Difco Laboratories, Detroit, Michigan) in distilled water. The value of plasma endotoxin concentrations from 24 healthy volunteers was always less than 10 pg/ml.

Student's *t* test was used to analyse the data.

Results

The mean preoperative endotoxin concentrations of the two groups were similar and were within the normal range. Intraoperative endotoxaemia developed at the end of the anhepatic phase in most of the patients of both groups (fig 1). The severity of endotoxaemia did not correlate with the duration of the anhepatic intervals (fig 1)—range 41–173 min, mean 104·8 (SEM 5) for group A and 108·5 (3·7) for group B. Endotoxaemia was more severe in group B patients who eventually required prolonged ventilatory support (fig 2). Significant differences between groups A and B were maintained for the next 3 days as the endotoxin concentration gradually decreased (fig 2).

43 patients received platelet transfusions because of coagulopathy and thrombocytopenia. More transfusions were given (intraoperatively and during the next 24 h) to patients in group B than to those in group A—mean 13·3 units (1·8) *vs* 4·6 (1·0), $p < 0·01$. There was a positive correlation between the number of units transfused and endotoxin concentrations at the end of the anhepatic phase (fig 3).

8 of the 64 patients died within a month; 7 could not be extubated until death. The other patient died suddenly on the 11th postoperative day from rupture of a splenic artery aneurysm: convalescence up to this time had been satisfactory. Diffuse pulmonary infiltrates developed in 6 of the group B patients before death.

Discussion

Most of the endotoxin that enters the blood stream is detoxified in the liver.[10–12] During the anhepatic phase of liver transplantation endotoxin entering the circulation from intestinal bacterial flora[10,13,14] or infectious foci can accumulate in the blood stream. In laboratory animals endotoxaemia leads to a rapid decrease in the number of platelets in peripheral blood.[4] Thus, the positive correlation between the volume of platelet transfusion needed perioperatively and the endotoxin concentrations at the end of the anhepatic phase in the present study was not surprising. Similarly, the correlation of high endotoxin with pulmonary complications was as expected from animal experiments[1–3] and our previous report in human beings.[5]

The role of endotoxin in human disease is poorly understood, partly because the lethal dose even in the target organs varies with the animal species.[15,16] Additionally, there have been

difficulties[17,18] with the qualitative assay that was previously available.[19] The chromogenic substrate method developed by Iwanaga et al[20] in 1978 paved the way to a sensitive quantitative assay of endotoxin.[5,6] Study of patients with liver transplants may indicate how endotoxin triggers such diverse processes as pulmonary oedema,[1,3] and also shock[2] and coagulopathy.[4]

Acknowledgments

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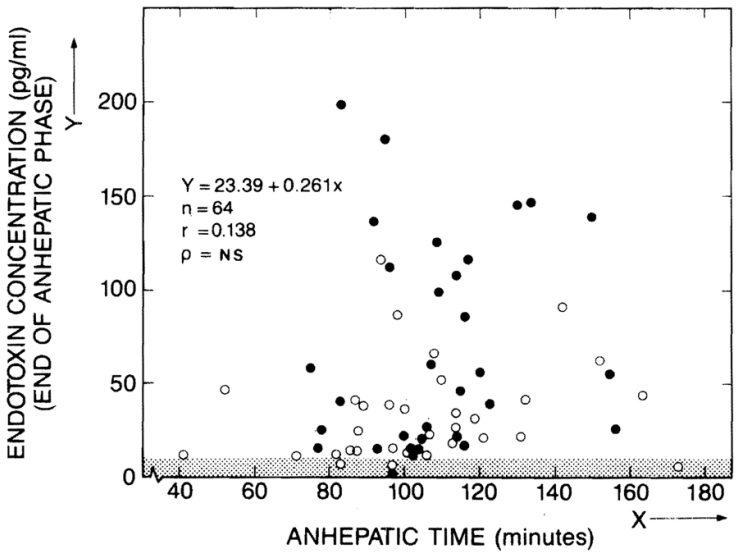

Fig 1. Relation of plasma endotoxin to duration of anhepatic phase

○ = group A; ● = group B; NS = not significant.

Shaded area is normal endotoxin range.

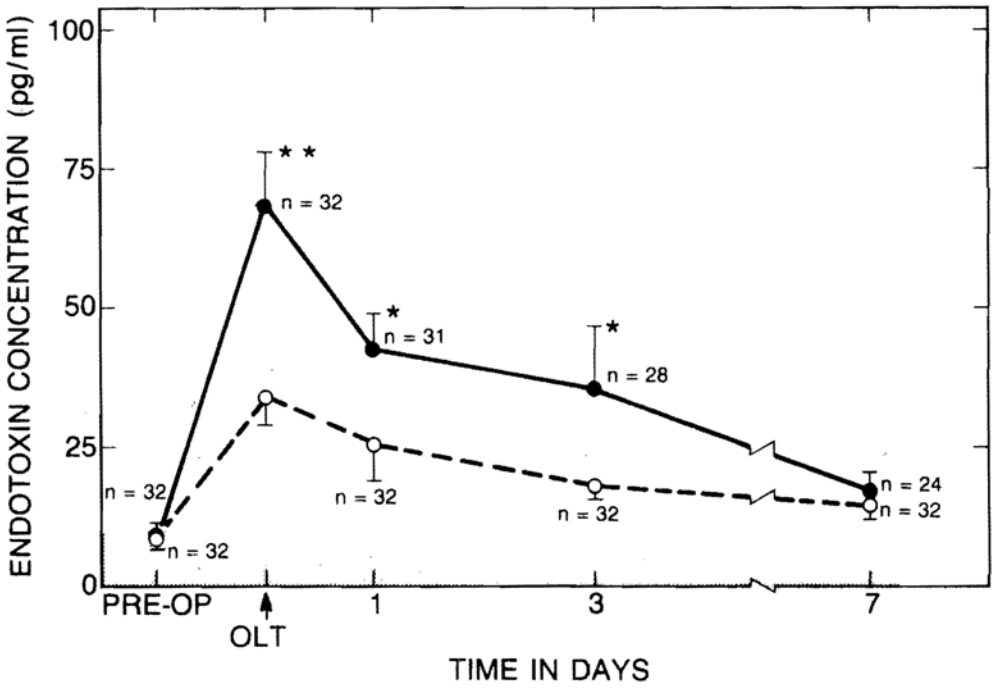

Fig 2. Endotoxin concentrations in group A (----), and group B (——)
★p < 0·05; ★★p < 0·01.

*p < 0·05; **p < 0·01.

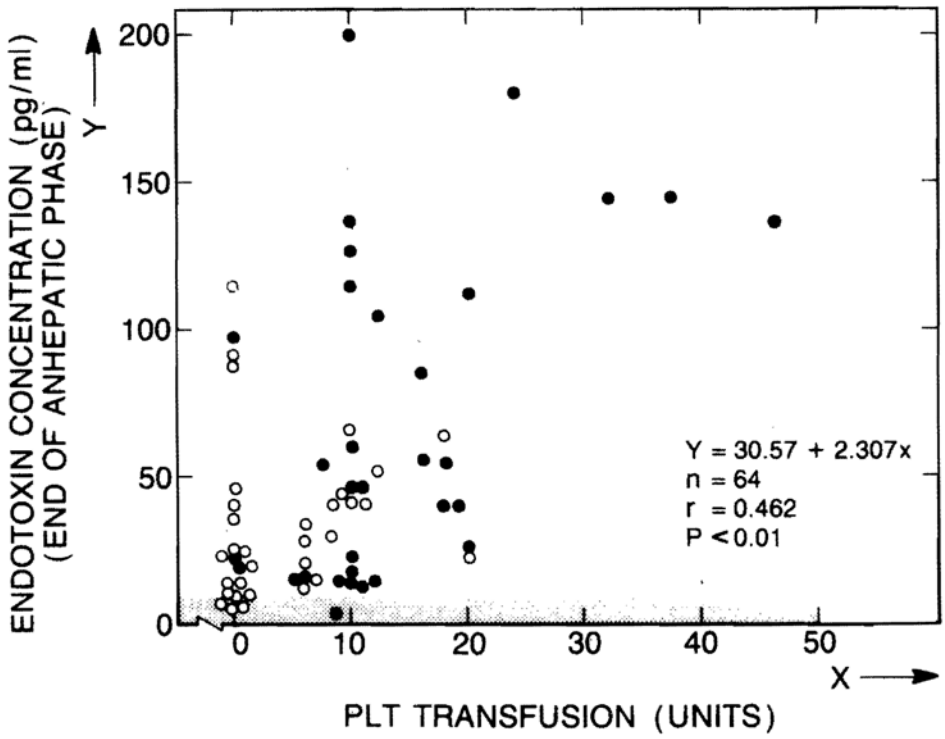

Fig 3. Relation of plasma endotoxin to platelet transfusions
PLT = platelet.