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Relevance of two-stage total hepatectomy and liver transplantation in acute liver failure and severe liver trauma

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Abstract Emergency liver transplantation frequently is the only life-saving procedure in cases of acute liver failure. It remains unclear whether emergency hepatectomy with portocaval shunt followed by liver transplantation as a two-stage procedure should be performed in cases in which a donor organ is not yet available. It has been stated that "toxic liver syndrome" could be treated by means of this strategy. From 1990 to 1995 we performed emergency hepatectomies in eight cases of acute liver failure or traumatic liver rupture with exsanguinating bleeding. In six cases we were able to perform a subsequent liver transplantation. Five of the six patients who underwent an emergency hepatectomy died. Emergency hepatectomy led to a significant increase in epinephrine dosage until the transplantation was performed. Only after transplantation did the need for epinephrine therapy decrease. The need for oxygen support did not change during the entire observation period. Plasmatic coagulation was stabilized by substitution, showing significantly higher values at 24 h after transplantation than at 48 h before transplantation. Fibrinogen increased significantly after transplantation in this group of patients. The experiences gathered at our clinic, however, do not show advantages that would allow a recommendation of emergency hepatectomy and subsequent liver transplantation as a two-stage procedure except for situations of severe and uncontrollable hepatic bleeding. Considering the progressive destabilization of our patients, fast procurement of donor organs seems to be of imminent importance for the outcome.

Keywords Liver transplantation · Emergency hepatectomy · Intensive care · Outcome · Toxic liver syndrome

Abbreviations *HELLP Hypertension · Elevated Liver tests · Low Platelets*

Introduction

Acute liver failure can affect patients without known pre-existing liver disease [4, 6, 13, 14, 21] and results in mortality rates of between 40% and 85%, as generally reported [23, 30]. The most important causes of acute liver failure are the hepatitis B and C viruses [2, 18, 29, 33, 34]. Intoxication constitutes another important cause [3].Until now, there is no specific treatment for acute liver failure. If the clinical course is unfavorable, liver transplantation is the only therapeutical option [7, 16, 19, 22, 28]. The decision to perform a liver transplantation is based on such factors as age and the clinical condition of the patient as well as the progression of the clinical symptoms [10, 17].

Extended liver resections with insufficient postoperative liver function or impaired postoperative blood supply are other causes that can lead to acute liver fail-

ure. For these patients, liver transplantation remains the only therapeutical measure. It is very difficult to foresee whether a postoperative liver failure is reversible, and the decision to perform a liver transplantation can frequently only be made very late. This problem regularly leads to a poorer outcome after liver transplantation [1, 7, 10].

In cases of severe liver injury and liver rupture, mortality is caused by hemorrhage. Additionally, the required blood transfusion can result in consumption coagulopathy. Especially in cases of injuries of hepatic veins or partial branches, mortality rates of even over 70% are reported [8].

Should the indication for liver transplantation be given in one of these cases, there is still the problem of maintaining the recipient stable until a donor organ becomes available. Only by achieving this goal does a transplantation have a chance of being successful.

For cases of acute liver failure or graft failure that lead to either "toxic liver syndrome" or hepatic trauma resulting in exsanguinating hemorrhage, Ringe et al. have recommended early hepatectomy and portocaval shunt. Concomitantly, an urgent donor organ request should be made. Until the arrival of a suitable liver, the patients remain anhepatic [23, 24].

In the present study, we report on our experience with emergency hepatectomy followed by liver transplantation (two-stage procedure) among patients with acute liver failure and severe liver trauma. The aim of this retrospective work was to determine whether emergency hepatectomy before liver transplantation leads to a measurable improvement of the clinical condition of patients while anhepatic and whether this procedure results in a better outcome.

Patients and methods

From 1990 to 1995 we performed an emergency hepatectomy in eight cases of acute liver failure at the Department of General Surgery of the University of Essen (Table 1). In none of these cases was a donor organ available at the time of hepatectomy.

The indications for transplantation are summarized in Table 2. For five patients, the indication for hepatectomy was severe bleeding caused by liver rupture. Three of these patients suffered a traumatic rupture, and in two cases bleeding was caused by HELLP syndrome (*H*ypertension, *E*levated *L*iver tests, *L*ow *P*latelets). In one patient, a carbon tetrachloride intoxication (CCl_4) had induced an extended liver necrosis. Two patients developed liver necrosis secondary to operations of the biliary system or the portal vein.

All patients were treated by means of a portocaval shunt, and an urgent liver request was made to Eurotransplant at the same time. During the anhepatic phase, patients received hemofiltration and plasma separation treatment at the surgical intensive care unit.

At the time of hepatectomy and/or notification of Eurotransplant, all patients showed multiple organ failure with anuria, cardiocirculatory insufficiency, and the need for artificial ventilation. Among the patients with nonbleeding liver failure, hepatic coma was observed.

Table 1 Mortality rate and demographic data for six of eight patients after emergency orthotopic transplantation and prior emergency hepatectomy as two-stage procedure

Death while on waiting list	2 of 8 patients
Mortality rate of remainder after transplantation	5 of 6 patients
Sex ratio m/f	3/3
Age	33 ± 4.7 years
Waiting time	20 ± 8.3 h

Table 2 Causes of acute liver failure leading to the indication for emergency liver transplantation

Cause of acute liver failure	Number of patients
Hemorrhage	
Trauma	3
HELLP syndrome	2
Liver necrosis	
Intoxication	1
Postoperative	2

The clinical and chemical parameters between indication and 24 h after transplantation were studied. Besides outcome (mortality rate), the following parameters were investigated: (1) epinephrine dosage, (2) inspiratory fraction of oxygen, (3) diuresis, (4) thromboplastin time, (5) fibrinogen, and (6) thrombocyte count.

The data were evaluated through one-way analysis of variance or Kruskal-Wallis one-way analysis of variance on ranks to indicate significant differences between the groups. Data were considered statistically significant if P values were less than 0.05. Results are presented as mean ± SEM.

Results

Outcome

Two of the eight patients died of uncontrollable bleeding before a donor organ became available. In one case it was a patient with HELLP syndrome (anhepatic for 18 h). The other patient suffered a traumatic liver rupture. This patient arrived at our hospital after an emergency clamping of the liver hilus without portal-venous release had been performed more than 2 h before. The patient, who had to be considered anhepatic at arrival, died 9 h later at our intensive care ward.

For the remaining six cases, Eurotransplant was able to provide suitable organs that arrived 20 ± 8.3 h after notification. The mean anhepatic phase lasted for 17.6 h (9–22 h). In all cases, the histological evaluation of the liver necrosis confirmed the indication for emergency liver transplantation.

Five of the six patients that underwent transplantation after emergency hepatectomy died postoperatively

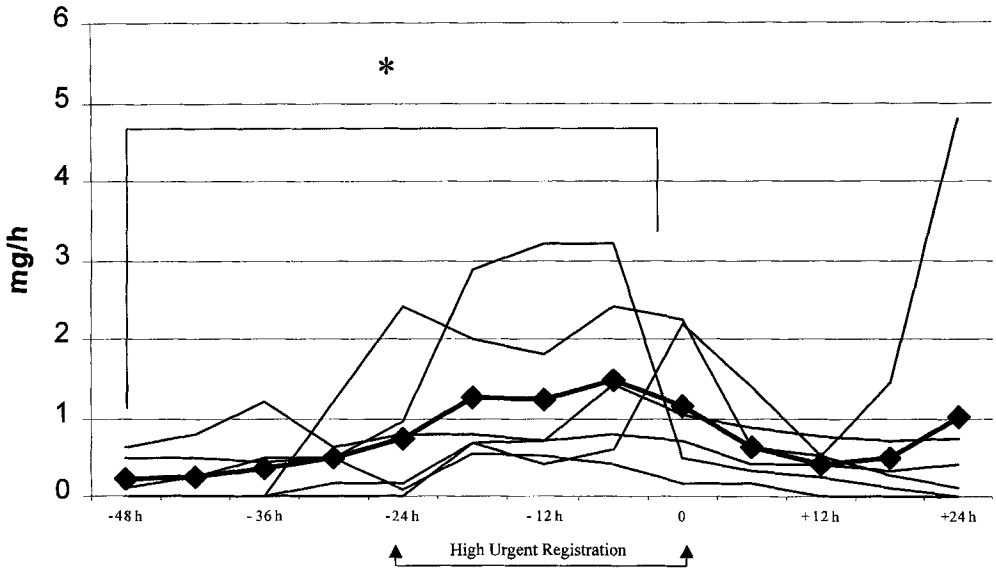

Fig. 1 Epinephrine therapy of patients with two-stage orthotopic liver transplantation ($n = 6$). *$P < 0.05$; *black diamonds* indicate mean epinephrine dosage

Table 3 Causes of death after emergency liver transplantation and prior emergency hepatectomy as two-stage procedure

Cause of death	Number of patients
Primary nonfunction	1
Sepsis/Multiple organ failure	3
Cardiac consequences of intoxication	1

(Table 3). One patient showed primary nonfunction, and multiple organ failure was refractory to any therapy. He died 2 days after transplantation. In one patient, who underwent transplantation after a severe abdominal trauma with liver rupture, severe peritonitis developed 3 weeks after transplantation. The favorable clinical course after transplantation changed dramatically. The patient also developed multiple organ failure. The cause of peritonitis was an extended ischemia of the small bowel; however, the origin of this complication remained unclear. A small bowel resection did not improve the deteriorated clinical status, and the patient died 36 h after surgical revision due to multiple organ failure. Two patients died as a consequence of sepsis (8 and 12 weeks, respectively, after transplantation) in spite of initial stabilization and good organ function. The patient with carbon tetrachloride intoxication died 5 days after transplantation due to intoxication-induced cardiac complications. At the time, graft function was good.

One patient with HELLP syndrome and four resuscitation episodes prior to hepatectomy was discharged from the hospital 3 months after transplantation. Now, 6 years after transplantation, the general condition is good and showing normal liver function [12].

Cardiocirculatory parameters

The mean epinephrine dosage before hepatectomy was 0.48 mg/h (0–0.96 mg/h); after hepatectomy, 0.72 mg/h (0–0.96 mg/h); and in the anhepatic phase it increased significantly in relation to the dosage before hepatectomy to 1.44 mg/h (0.52–3.2 mg/h; $P < 0.05$). It was not till after transplantation that the need for epinephrine therapy decreased. There were no statistical differences between the patients with exsanguinating hemorrhage and those without bleeding (Fig. 1).

Besides the increased need for catecholamine therapy, these patients needed continuous substitution of fluid. A pre-existing positive fluid balance progressed in all patients after hepatectomy. Although the patients showed an initial recovery from diuresis after hepatectomy, they developed anuria within the course of the anhepatic phase (Fig. 2).

Respiratory parameters

The need for oxygen support did not change during the entire observation period. Until transplantation, the patients required a mean inspiratory oxygen fraction of 0.5 (0.3–0.8) (Fig. 3).

Coagulation

Plasmatic coagulation was stabilized by substitution, showing significantly higher values at 24 h after transplantation than at 48 h before transplantation (the mean thromboplastin time ranged from 31% to 63%; $P < 0.05$), but there were no significant movements in

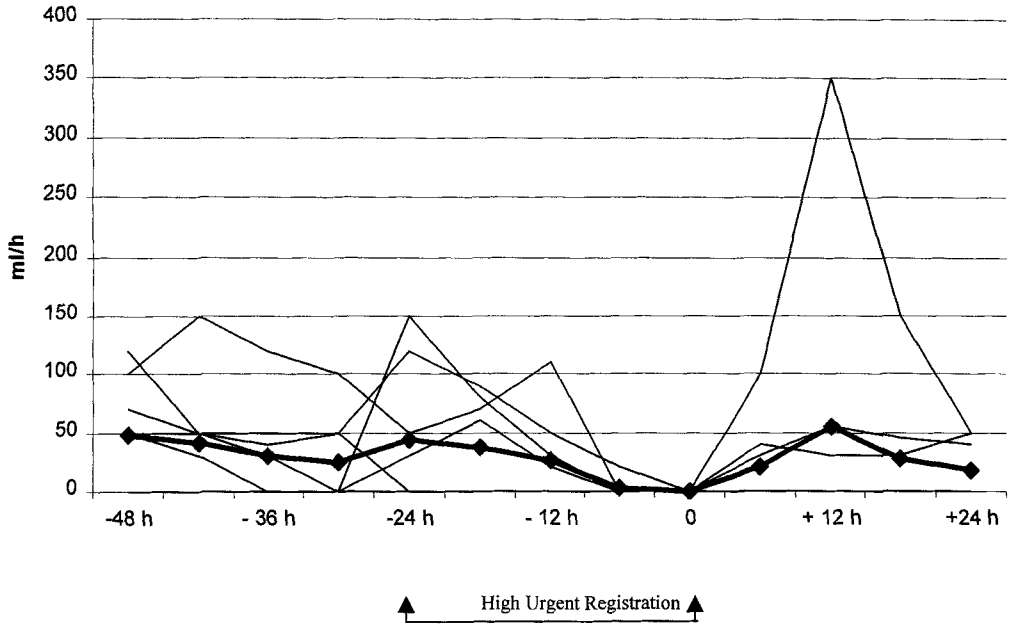

Fig. 2 Hourly diuresis of patients with two-stage orthotopic liver transplantation ($n = 6$); *black diamonds* indicate mean hourly diuresis

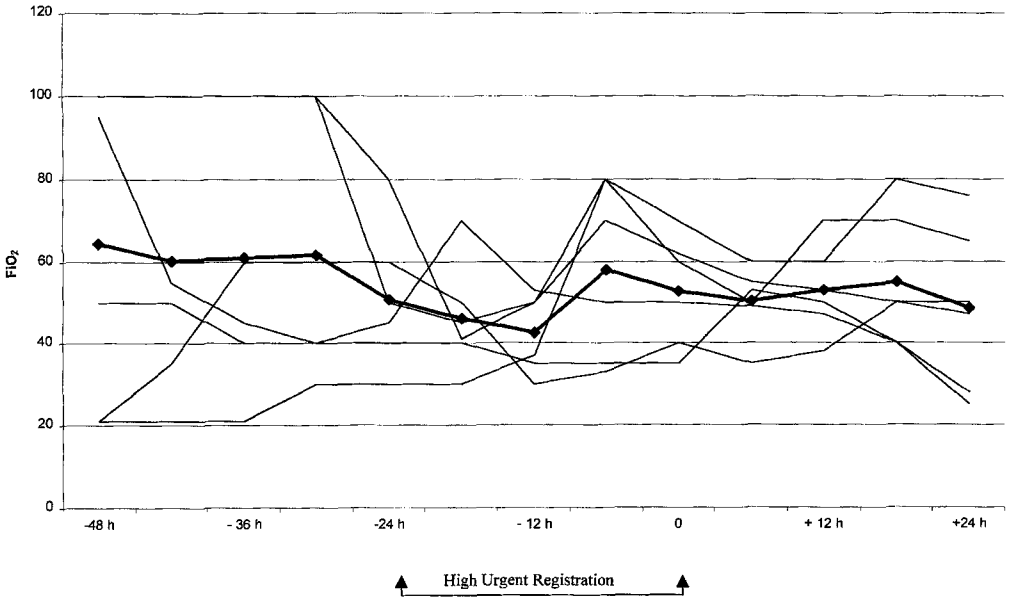

Fig. 3 Inspiratory oxygen fraction of patients with two-stage orthotopic liver transplantation ($n = 6$); *black diamonds* indicate mean FiO_2

the Quick value with the time of transplantation taken as reference point (Fig. 4). Fibrinogen increased significantly after transplantation in this group of patients (from 156 mg/dl at transplantation to 326 mg/dl at 24 h after transplantation; $P < 0.05$) (Fig. 5). A continuous decrease of thrombocytes could be observed (139,000/ml^3 to 42,400/ml^3), which did not improve after transplantation (Fig. 6).

Discussion

The indication for liver transplantation due to acute liver failure has increased of late [5, 6, 17, 26], and outcome could be improved because of several factors [1, 10, 16, 17, 19, 20, 22, 31]. The most common causes of acute liver failure are fulminant hepatitis (A, B, C, G?) [2, 29, 33], acute decompensation of chronic liver diseases without cirrhosis (Budd-Chiari syndrome, veno-occlusive disease, some cases of Wilson's disease), and traumatic as well as nontraumatic liver rupture (HELLP syndrome)

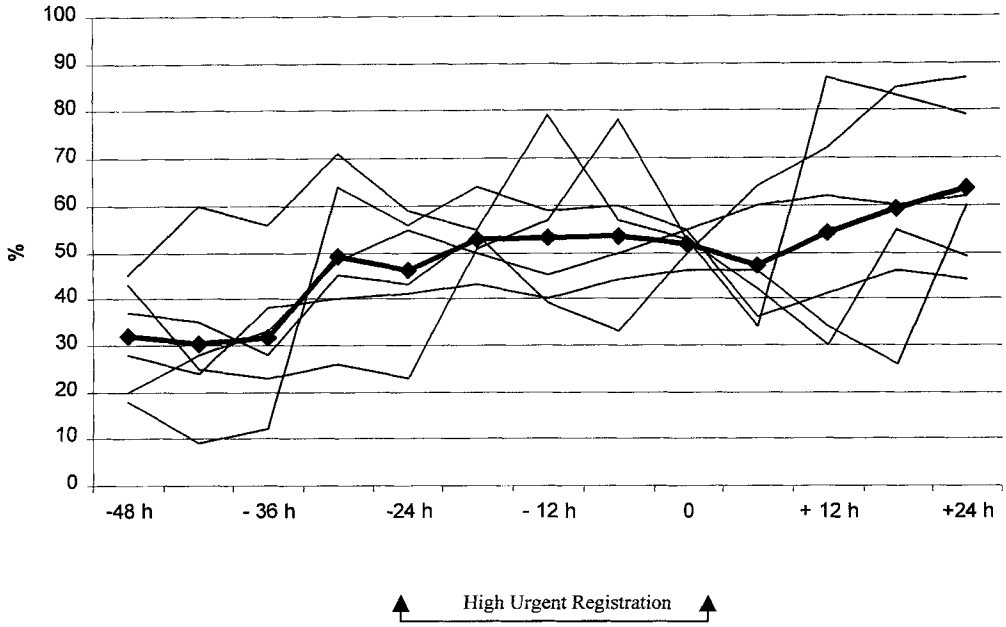

Fig. 4 Thromboplastin time (Quick) of patients with two-stage orthotopic liver transplantation ($n = 6$); *black diamonds* indicate mean Quick

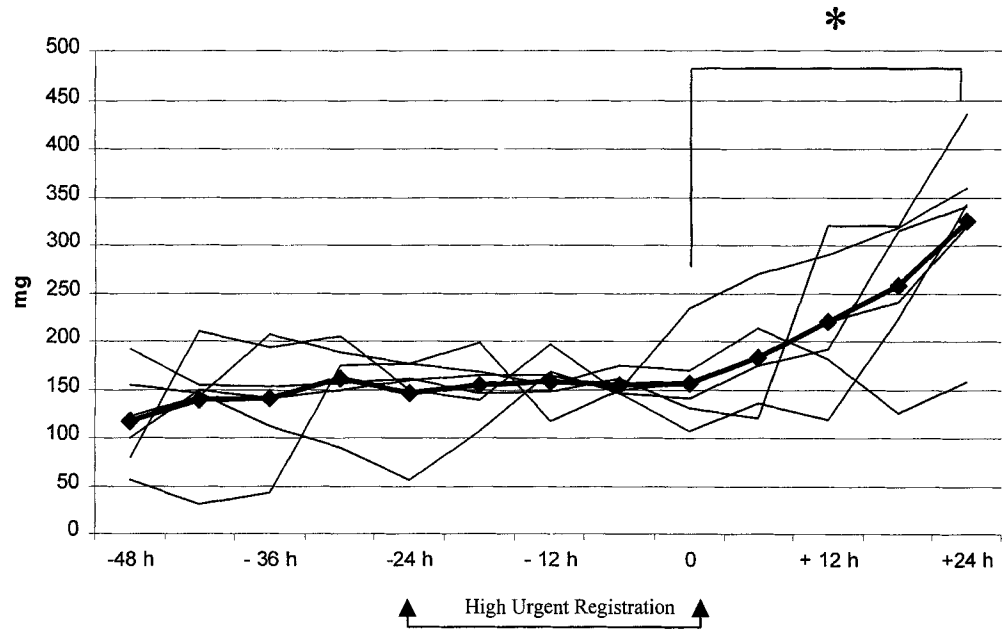

Fig. 5 Fibrinogen of patients with two-stage orthotopic liver transplantation ($n = 6$). *$P < 0.05$; *black diamonds* indicate mean fibrinogen

[23, 25, 30]. Besides early donor organ request and adequate intensive care therapy [18, 32, 35], Ringe et al. have proposed stabilizing patients with acute liver failure by explanting the diseased organ until a donor organ becomes available [24]. Initially this procedure was recommended for cases of traumatic liver rupture with exsanguinating bleeding from the liver parenchyma. Another indication was seen in cases of "toxic liver syndrome," defined as multiple organ failure on the basis of liver failure. By eliminating the source of toxins, other organs would be given the possibility to recover. Ringe et al. summarized: "If this procedure is done in time, there is a good chance to rescue patients with liver transplantation even after a prolonged anhepatic period" [24].

In some cases of exsanguinating hemorrhages from destroyed liver parenchyma, there is no doubt about the fact that bleeding can only be brought under control through removal of the organ. It is also known that an anhepatic phase of up to 40 h can successfully be bridged under intensive care therapy [9, 15, 28]. The in-

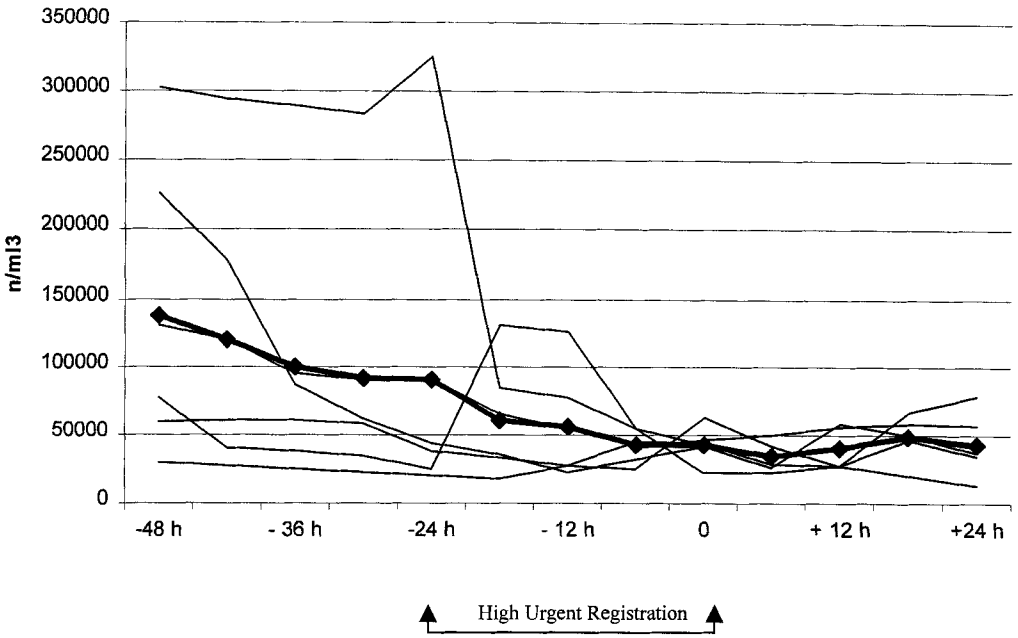

Fig. 6 Thrombocyte count of patients with two-stage orthotopic liver transplantation ($n = 6$); *black diamonds* indicate mean thrombocyte count

dication, however, to perform an emergency hepatectomy in the case of acute liver failure remains controversial. It is very difficult to foresee which group of patients could benefit from this maneuver.

In our cohort, the clinical condition of the patients that underwent hepatectomy due to acute liver failure did not improve as was initially expected. They even showed a higher need for epinephrine therapy once the organ was removed. It was not until after transplantation that they returned to preoperative levels. Additionally, the function of the other organs (lung, kidney) did not show significant changes during the observation period either. Thus, the possible benefit of emergency hepatectomy could not be objectified by means of intensive care parameters.

The outcome deserves special consideration. Indeed, five of the six patients died within the clinical course of the two-stage liver transplantation. In one case, the cause of death could not be attributed to the liver transplantation, but to cardiac consequences of a carbon tetrachloride intoxication. Another two patients died 2 and 3 months after transplantation due to sepsis, although they showed good initial function of the graft. Another patient with good initial organ function died of multiple organ failure he developed 3 weeks after transplantation. Only one patient showed initial nonfunction of the organ and died 2 days after transplantation. In summary, after two-stage hepatectomy and liver transplantation, five of six patients either survived the initial course after liver transplantation or died of causes not directly related to the procedure.

We see an indication for emergency hepatectomy in cases of exsanguinating hemorrhages from destroyed liver parenchyma. In cases of acute liver failure with "toxic liver syndrome," there are the two possible therapeutic options of (1) performing an early hepatectomy even if a donor organ is not yet available and trying to stabilize the patient by means of intensive care treatment or (2) performing a hepatectomy once a donor organ becomes available and hoping that primary graft function will lead to sufficient stabilization. The future will show whether bioartificial liver support systems are able to compensate for the loss of hepatic function and thus improve the outcome of acute liver failure. However, despite potential merit, these devices have not yet been able to show improvement in the outcome of patients with acute liver failure. Also, some major safety issues remain to be resolved, in particular the risk of transmission of unknown zoonoses to man [11, 27].

Furthermore, the so-called toxic liver syndrome needs to be studied in greater detail to define objective parameters that will allow precise identification of this clinical situation. Probably only then will it become possible to determine which patients might benefit from a two-stage procedure.

So far, the experiences at our clinic did not show the expected advantages of a two-stage procedure, although the relatively low number of patients has to be considered. Finally, we believe fast donor organ procurement to be of imminent importance for the outcome of these emergency situations.

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