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Should retransplantation still be considered for primary non-function after liver transplantation?

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Abstract. Primary non-function (PNF) of a transplanted liver is a postoperative condition characterized by absence of hepatic recovery due to various insults during harvesting, preservation or revascularization. Until recently early retransplantation (RTx) has been considered the policy of choice. Results of RTx for PNF are unsatisfactory (1-year survival rates ranging from 0 to 34 %). The management of PNF by medical care without RTx with a recovery rate of 80 % and a 1-year actuarial survival rate of 50 % is reported for a series of 33 consecutive liver transplants. The guidelines for the medical care management are given and the results are discussed.

Key words: Liver transplantation – Retransplantation, liver

Primary non-function (PNF) of a transplanted liver is a postoperative condition characterized by absence of hepatic recovery due to various insults during harvesting, preservation or revascularization [3, 10, 16, 20, 22, 28, 30–32, 34]. Its incidence in several series has been shown to range from 7 to 36 %, probably due to different definition criteria employed and great variability of the donor pool [3, 10, 20, 22, 28, 34]. The therapeutic approach to this condition has been the object of discussion. Until recently early RTx has been considered the policy of choice and patient survival has been related to the availability of a suitable organ [21, 26, 30–32].

Unsatisfactory results of RTx for PNF (1-year survival rates ranging from 0 to 34 % [26, 28, 31] and current application of critical care techniques to acute liver failure have changed the approach to PNF, and have lead us to a conservative management without RTx. We report on our series of liver transplants in which PNF was managed by this approach.

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Patients and methods

A total of 33 consecutive liver transplants were performed in 32 patients from 1987 to 1991 at the Catholic University of Rome. Donor acceptance criteria and graft preservation modalities, reported in detail elsewhere [4] are summarized in Table 1. Recipient characteristics have recently been reviewed [2, 7].

Criteria used for the definition of PNF are shown in Table 2, together with those for primary dysfunction (PDF) according to other authors [16, 31].

Supportive management

In the case of PNF, supportive management consisted of both liver function support and extra-liver organ support.

Liver function support consisted of efforts to ensure:
A. optimal perfusion and oxygenation by invasive haemodynamic monitoring, stable haemoglobin level (> 10 g/dl), optimization of pulmonary exchanges, pharmacological support with inotropic drugs, when necessary, and prostaglandins PGE_1 (0.5 μg/kg per h) to diminish hepatic vascular resistance;
B. adequate protein supplementation by monitoring and prompt correction of coagulation disorders administering fresh frozen plasma, fibrinogen, antithrombin III and cryoprecipitates, and by maintenence of adequate albumin and vitamin co-factor levels;

Table 1. Donor acceptance criteria and graft preservation modalities

Donor criteria
– age < 50 years
– SBP > 90 mm Hg
– mechanical ventilation < 5 days
– serum Na < 160 mEq/l
– AST and/or ALT < 100 UI/l
– serum bilirubin < 2 mg/dl
– PT > 45 %
– dopamine infusion < 10 gamma/kg per min
– no major surgery
– no cardiac arrest
– appearance at laparotomy (color and palpation)
Graft preservation modalities
– use of UW solution (26/33)
– CIT < 10 hours
– WIT < 70 min

Table 2. Recovery after perioperative injury

Primary dysfunction
- ALT and AST peak 2000–5000 IU/l
- biliary output < 100 ml/day
- low-grade coagulopathy
Primary nonfunction
- ALT and AST peak > 5000 UI/l
- bilirubin peak > 20 mg/dl
- no bile production (at least 5 days)
- severe coagulopathy
- relevant neurological impairment
- lactacidaemia
- ± renal failure
- ± haemodynamic instability

C. artificial nutrition by high glucose and nitrogen content with branched chain amino acids, proscription of aromatic amino acids and low fat supplementation;
D. limitation of intestinal toxic production (lactulose, topically active antibiotics, plasmapheresis).

Extra-liver organ support consisted of:
A. slow withdrawal from mechanical ventilation by pressure support, CPAP;
B. prevention of renal failure by high urinary output using volume, diuretics, dopamine, proscription of nephrotoxic antibiotics and avoidance of high cyclosporin levels;
C. reduction of infectious risk by antibiotic and antimycotic prophylaxis, selective bowel decontamination, aspecific immunoprophylaxis and low grade immunosuppression.

Results

In 32 first transplant patients we observed five cases of PNF (15.6%) and five cases of hepatic liver dysfunction (15.6%) according to the criteria previously defined. In addition, another case of PNF was seen in our only retransplant carried out because of hepatic artery thrombosis; this case, in which we used unsuccessfully a donor with suboptimal characteristics due to the urgency, was not included in the study.

Early results showed that four of out five patients (80%) recovered in a period ranging from 4 to 9 weeks using critical care procedures. The fifth patient died in the second postoperative week due to evolution towards multiple organ failure. Late results showed that one patient of the four died in the second postoperative month from pulmonary aspergillosis, although he was experiencing continuous improvement in liver function. At the time of writing three out of four patients were alive and well at 55, 27, 22 months. Survival trends are represented in Fig. 1, where the group of patients with PNF is compared with the group without PNF (including those with PDF). Actuarial survival rates at 1 year were, respectively, 50 and 69%. In spite of the 19% gap, the difference is not signficant due to the small number of patients (Mantel-Cox, $P = 0.258$; Breslow, $P = 0.143$).

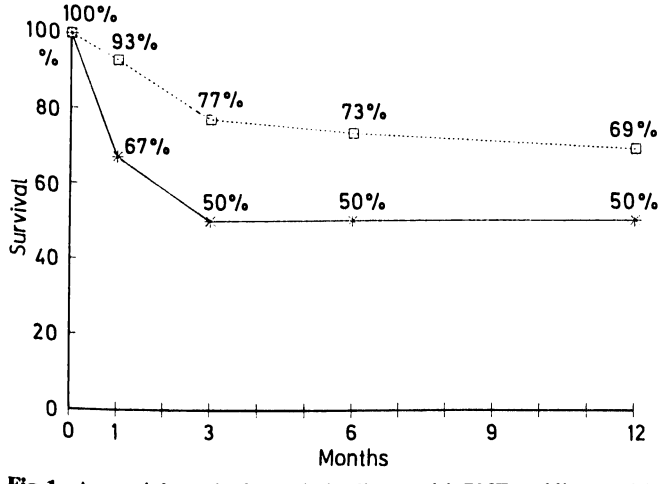

Fig. 1. Actuarial survival trends for livers with PNF and livers without PNF. □, Normal function; *, primary non-function. Liver Transplantation, Catholic University, Rome, Italy

Discussion

In the recent past RTx was the policy of choice for graft failure due to chronic rejection, technical complications and PNF [21, 26, 30–32]. Particularly in the case of PNF, a new liver was usually sought before even attempting an aggressive drug therapy. At present this approach is changing because of the poor results of RTx in this condition, the improving medical management of acute hepatic failure [1, 6, 18] and the lower donor/recipient ratio.

Reasons for failure of the RTx procedure in PNF should be identified in the highly compromised conditions of patients with severe PNF (liver failure and severe extrahepatic organ compromise) that make a second operation unsuccessful in relation to both intraoperative and postoperative trauma.

Worldwide reconsideration of RTx for PNF is underway [21, 26]. Probably the drive in this direction has been the continuous improvement in critical care procedures for liver failure. Among these we consider of great and probably the greatest importance the clinical introduction of prostaglandins. Prostaglandin PGE_1, initially used for acute hepatic failure [1], has subsequently proved useful for PNF [15, 16]. The close monitoring of the coagulation pattern seems also to be relevant and the recent introduction of measurement and supplementation of antithrombin III may be useful [23]. Monitoring of coagulation has provided a guideline for the selective reintegration of proteins lacking from hepatic synthesis with the effect of avoiding both haemorrhagic complications (cerebral and abdominal) and disseminated intravascular coagulation, which may evolve in multiple organ failure. Fresh frozen plasma administration together with albumin supplementation is also useful to ensure adequate intravascular colloid osmotic pressure by replacing other missing proteins of hepatic synthesis. Parenteral nutrition is fundamental to compensate the great caloric expenditure due to hepatic cell regeneration [19, 27]. It seems especially important to supply high concentrations of branched chain and non-aromatic amino acids [19]. The use of lactulose, intestinal antibiotics and, in selected cases, plasmapheresis are effective in diminishing production and removing toxic substances [9].

In addition other extra-liver organ support procedures that have proved beneficial, are:
A. respiratory care with prolonged mechanical ventilation (pressure support, CPAP) to ensure optimal oxygenation, to diminish respiratory work and to control acid–base equilibrium [23]

B. prevention of renal failure by absolute proscription of potentially nephrotoxic antibiotics and by avoidance of high cyclosporin levels
C. reduction of the infectious hazard by non-specific immunoprophylaxis and by selective bowel decontamination [33]. (In this context it is fundamental to maintain the patient at a low immunosuppressive level.)

From the start of our liver transplant programme we chose to attempt a critical care approach for patients with PNF in consideration of the large experience of our team in the management of liver failure in patients with multiple organ failure, cirrhosis, trauma and sepsis [8, 13, 14]. This policy was also justified by the donor shortage in Italy [29]. We have reported herein our results that show the soundness of this choice as represented by an 80% recovery rate after PNF and 50% actuarial survival of this group.

In conclusion, the treatment of PNF is the subject of discussion, but there are two options: retransplantation, which should be done as early as possible, but has been shown to give bad results and to cause organ wastage [26, 28, 31], or supportive management, which, when unsuccessful, precludes late RTx due to multiple organ compromise. Patients are lost also with medical management, but fewer than die as a consequence of surgical trauma added to the critical conditions in RTx, as our small series demonstrates. Various indexes have been proposed to predict the occurrence and severity of PNF from intraoperative or early postoperative parameters [5, 11, 12, 17, 24, 25]; these may be useful to indicate the optimum therapeutic approach.

A wider acceptance of supportive management of PNF would probably lead to a new definition of subgroups that may benefit from medical care and the identification of cases with a worse prognosis in whom supportive management as well as retransplantation would have little success.

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