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Feasibility of a New Technique of Reperfusion in Liver Transplantation

Background: Poor initial graft function secondary to reperfusion remains a major problem in liver transplantation. Retrograde reperfusion, a new method of reperfusion during liver transplantation was introduced in our center. We evaluated this technique in a retrospective study and compared the results concerning primary graft function with a historical control group.
Methods: In the study group 56 liver transplantations were performed in piggy-back technique with retrograde reperfusion. In the historical control group 21 patients underwent liver transplantation in standard technique with standard reperfusion.
Results: Fifty (twenty) out of 53 (21) patients were alive and well on day 8 after liver transplantation. On day 1 after liver transplantation, mean aspartate aminotransferase was 221 U/L in the study group and except of 3 patients (6,6%) with hepatic artery thrombosis no primary nonfunction appeared. In the control group on day 1 after liver transplantation mean aspartate aminotransferase was 327 U/L and three patients (14,2%) had primary nonfunction.
Conclusions: Our retrospective study demonstrates that retrograde reperfusion via the caval vein and antegrade reperfusion via the portal vein is feasible; it lowered postoperative liver enzyme values and improved initial liver function after LTX. Further careful evaluation will be necessary to verify these findings.

Key words:
liver transplantation, reperfusion, primary nonfunction, surgical technique

Neue Reperfusionstechnik bei Lebertransplantation

Hintergrund: *Die unzulängliche initiale Organfunktion nach der Reperfusion bleibt ein wesentliches Problem der Lebertransplantation. Daher haben wir in unserem Zentrum die Retrograde Reperfusion eingeführt. In einer retrospektiven Studie vergleichen wir die Ergebnisse dieser Technik mit einem historischen Kollektiv.*
Methoden: *In der Studiengruppe haben wir bei 56 Lebertransplantationen die Piggy-back-Technik mit retrograder Reperfusion angewandt. In der Kontrollgruppe sind 21 Patienten in Standardtechnik mit Standard-Reperfusion lebertransplantiert worden.*
Ergebnisse: *50 (20) der 53 (21) Patienten erlebten (in gutem Zustand) Tag 8 post operationem. Am Tag nach der Transplantation betrug in der Studiengruppe die mittlere Aspartataminotransferase 221 U/L, bei 50 Patienten funktionierte die Leber initial - lediglich bei drei Patienten (6,6%) versagte sie wegen einer Arterienthrombose die Primärfunktion. In der Kontrollgruppe lag*

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die mittlere Aspartataminotransferase bei 327 U/L, und drei Patienten (14,2%) erlitten eine primäre Nichtfunktion.
Folgerungen: *Unsere retrospektive Studie zeigt, daß die retrograde Reperfusion via vena cava und die antegrade Reperfusion via vena portae realisierbar sind; die neue Technik verminderte die postoperativen Leberenzyme und verbesserte die initiale Leberfunktion. Eine weitere sorgfältige Evaluation ist erforderlich, um die Befunde zu verifizieren.*

Schlüsselwörter:
Lebertransplantation, Reperfusion, Primärfunktion, chirurgische Technik

Introduction

Transplantation has become the most appropriate treatment for end-stage liver failure, but it requires exposure of the graft to ischemia and reperfusion. Each graft sustains damage during hypothermic storage and subsequent normothermic reperfusion [1]. Primary graft dysfunction secondary to injury by ischemia and reperfusion remains a major problem with regard to morbidity and mortality in clinical liver transplantation (LTX). Up to one-fifth of the patients [2] suffer from poor initial liver function due to severe hepatocyte damage, with concomitant borderline synthetic and metabolic activity. This leads either to primary nonfunction as described in approximately 6% of LTX [3] or to slow recovery [4].
In patients with poor initial graft function, an increased incidence of acute allograft rejection and graft loss during the first month after LTX has been observed [5]. Furthermore, the primary function of the graft plays an important role in long-term survival of liver transplants. It was shown [6] that initially good and fair function of the liver grafts resulted in a significantly better long-term survival compared with grafts with initially poor function or primary nonfunction.
Improving primary graft function and reducing reperfusion injury would be an important step toward ameliorating the results in LTX. Since Starzl described the first LTX, different kinds of reperfusion have been tried; we present a new approach. At our center, we perform LTX with piggy-back-technique and without veno-venous bypass. A new method of reperfusion during LTX was introduced. We evaluated this technique in a retrospective study covering the last 4 years and present the feasibility in comparison with a historical control group.

Materials and Methods

Patients

In the study group, from July 1998 to March 2003, 56 consecutive LTX in 53 recipients (13 female, 55 [26-70] years old) were performed. In the historical control group, from September 1989 to July 1998, 21 consecutive LTX were performed in 21 patients (17 male, 4 female; average age 48 years, range 22-63 years). Indications for liver transplantation were hepatitis B and/or C (16/4), alcoholic cirrhosis (16/9), hepatocellular carcinoma (9/3), primary biliary cirrhosis (2/3), α-1-antitrypsin deficiency (3/1), autoimmune hepatitis (1/0), Wilson`s syndrome (3/1), hemochromatosis (1/0), primary sclerosing cholangitis (1/0) and polycystic disease of the liver (1/0).

Donor and Harvesting

Donor age was 41 (17-70) / 34 (18-56) years. The average ASAT value was 27 (3-120) / 17 (6-44) U/L. Fourteen / four donors were from other centers and 34 /17 were local. The donor liver was harvested using standard techniques. University of Wisconsin (UW) solution was used in 36/19 cases (75.3%/90.5%) and histidin-tryptophan-ketoglutarat (HTK) solution in 12/2 cases (24.7%/9.5%).

Surgical Technique

In the study group, LTX was performed in piggy-back technique with retrograde reperfusion. Therefore, after completing the piggy-back anastomosis, the caval vein was declamped immediately and retrograde low pressure reperfusion of the graft with low oxygenated venous blood was established. Significant venous backflow via the portal vein appeared immediately after declamping the piggy back anastomosis. Subsequently, portal anastomosis was performed using a running suture. Venous backflow via the portal vein was sucked into a cell saver device. In order to provide optimal retrograde liver perfusion, no clamping of the donor liver portal vein was done. After completing portal anastomosis, the recipient portal vein was declamped immediately. During arterial anastomosis, the transplanted liver was antegradely perfused via the portal vein. After completing hepatic artery anastomosis, declamping of the hepatic artery was done and arterial perfusion started. No backtable or in-situ-flushing except the described reperfusion technique was performed.
In the control group, LTX was performed in standard technique using veno-venous bypass and standard reperfusion technique.

Patient Monitoring

The integrity of hepatocytes after LTX was monitored by the aspartate aminotransferase (ASAT) values on days 1, 3, 5 and 8. Good graft function was defined as ASAT max < 1000 U/L, fair function as ASAT 1000-2500 U/L, and poor early graft function was defined as peak ASAT >2500 U/L. Poor early graft function causing a repeat liver transplant or death within 14 days was called primary nonfunction. The synthetic function of the liver was assessed by prothrombin time.

Results

In the study group, 50 out of 53 patients (94.34%) were alive and well on day 8

after LTX. One patient died during hepatectomy of heart failure, one patient died of pulmonary artery embolism on day 3 after LTX and one patient died after preexisting portal vein thrombosis on day 2 after LTX. Retransplantation was indicated and performed in 3 patients due to hepatic artery thrombosis.

Ischemic and anastomosis times are displayed in table 1 as well as reperfusion times. Liver enzymes, bilirubin, prothrombin time and antithrombin III on days 1, 3, 5 and 8 after LTX showed favourable values and are displayed in table 2. Mean ASAT value on day 1 after LTX was 221 U/L. Except in the 3 patients presenting with hepatic artery thrombosis, primary nonfunction or poor early graft function did not occur. Two patients (4.4%) had fair function and all the others had good primary graft function.

In the control group, 20 out of 21 patients (95.24%) were alive and well on day 8 after LTX. One patient died of pulmonary artery embolism on day 2 after LTX. Retransplantation was indicated and performed in 1 patient due to primary nonfunction.

Ischemic and anastomosis times are displayed in table 1. Liver enzymes, bilirubin, prothrombin time and antithrombin III on days 1, 3, 5 and 8 after LTX are displayed in table 3. Three patients (14.2%) had primary nonfunction; one of them died 3 weeks after LTX. Three patients (14.2%) had fair primary graft function, the others had good function.

Tab. 1: Ischemic, anastomosis and reperfusion times

Times	**Study group Minutes**	**Control group Minutes**
Cold ischemic time	288 ± 49	275 ± 45
Warm ischemic time	85 ± 21	n.a.
Cavo-caval anastomosis time	23 ± 7	41 ± 13
Portal vein anastomosis time	20 ± 8	25 ± 9
Hepatic artery anastomosis time	33 ± 11	31 ± 11
Time of retrograde reperfusion	26 ± 8	0
Time of antegrade reperfusion	33 ± 11	0

Cold ischemic time: from the beginning of donor liver perfusion until insertion of the liver into the recipient. Warm ischemic time: from the insertion of the liver into the recipient until the hepatic artery anastomosis was opened. Cavo-caval anastomosis time: from the insertion of the liver until declamping of the caval vein. Portal vein anastomosis time: from declamping of the caval vein until declamping of the portal vein. Hepatic artery anastomosis time: from declamping of the portal vein until declamping of the hepatic artery. Retrograde reperfusion time: from declamping of the caval vein to declamping of the portal vein. Antegrade reperfusion time: from declamping of the portal vein to declamping of the hepatic artery.

Tab. 2: Liver enzymes, bilirubin, prothrombin time and antithrombin III on days 1, 3, 5 and 8 after liver transplantation in the study group (mean values)

	POD 1	**POD 3**	**POD 5**	**POD 8**
ASAT U/L	221	74	34	15
ALAT U/L	168	131	92	59
GGT U/L	35	91	119	98
Bilirubin mg/dl	2.6	1.8	2.1	1.9
Prothrombin time %	74	92	90	95
Antithrombin III %	63	75	88	92

Abbreviations: ASAT - aspartate aminotransferase; ALAT - alanine aminotransferase; GGT - χ-glutamyltransferase

Tab. 3: Liver enzymes, bilirubin, prothrombin time and antithrombin III on days 1, 3, 5 and 8 after liver transplantation in the control group (mean values).

	POD 1	**POD 3**	**POD 5**	**POD 8**
ASAT U/L	327	176	87	28
ALAT U/L	239	151	141	108
GGT U/L	50	65	78	91
Bilirubin mg/dl	3.7	3.0	2.9	3.6
Prothrombin time %	53	66	68	72
Antithrombin III %	62	70	80	82

Abbreviations: ASAT - aspartate aminotransferase; ALAT - alanine aminotransferase; GGT - χ-glutamyltransferase

Discussion

Liver transplantation is a highly successful treatment for end-stage liver disease. Although severe preservation and reperfusion injury may heal within 3 to 4 weeks, it can seriously compromise the early postoperative course and lead to an increased incidence of complications. Although the techniques for LTX have become standardized, there is still disagreement on how to reperfuse the liver during LTX. We present a new method of reperfusion, consisting of retrograde reperfusion via the caval vein and antegrade reperfusion via the portal vein. With this method our patients had low postoperative liver enzyme values with a mean ASAT of 221 U/L. In our experience, retrograde reperfusion is highly effective for evacuating the perfusion fluid from the transplanted liver. Furthermore, we hypothesize that low pressure perfusion with low oxygenated blood reduces the production of free oxygen radicals. Improvement of initial graft liver function by retrograde reperfusion during LTX might provide substantial benefits for the graft recipient: immediate clotting, rapid elimination of metabolites and toxic agents, and earlier recovery.

We observed that patients with the highest liver enzymes had no or poor venous reperfusion. Patients with good reperfusion had good primary graft function. Thus we suppose that the better the reperfusion, the lower the postoperative liver enzyme values.

We compared the results with this new method of reperfusion with the results of a historical control group. The donors and the recipients in these two groups differ. The donors for the control group were younger and the quality of the liver was better. In the control group, cold ischemic time was shorter than in the study group. The recipients in the control group were younger. The two groups are not directly comparable, but it was shown that the technique with retrograde reperfusion is feasible without deterioration of the results. Although donors and recipients in the control group were in better condition than in the study group, the results for the study group were better (table 2 and 3). Concerning the degree of cellular damage, there was a slight difference between the two groups. In the study group, the mean ASAT value on day 1 after LTX was 221 U/L versus 327 U/L in the control group. One week after LTX, mean ASAT levels were normal in the study group and slightly elevated in the control group. There was a significant difference in synthetic function: On day 1 after LTX, mean prothrombin time was 74% but by the end of the first week had normalized (95%). Synthetic liver function in the control group was worse. Mean prothrombin time on day 1 after LTX was 53% and on day 8 it was 72%.

This study showed the feasibility of a new technique of reperfusion in LTX. If this method could be confirmed in further studies, it would have some advantages for patients after LTX. Primary nonfunction, early postoperative morbidity and mortality could be decreased and long-term function of the graft could be ameliorated. With the technique of retrograde reperfusion, more marginal donor livers could be accepted for LTX. The number of liver transplantations could be increased and mortality on the waiting list decreased.

Our retrospective study demonstrates that retrograde reperfusion via the caval vein and antegrade reperfusion via the portal vein is feasible; it lowered postoperative liver enzyme values and improved initial liver function after LTX. Further careful evaluation will be necessary to verify these findings. We propose a prospective, randomized, open, multicenter trial to validate the retrospective single-center results.

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