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ORIGINAL ARTICLE

Outcomes after identical and compatible orthotopic liver transplantation for fulminant hepatic failure: a single center experience in UK

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Summary

To analyze the outcomes between identical and compatible liver transplantation (OLT) for fulminant hepatic failure (FHF) from September 1984 to November 2005. The patients were divided in three groups; group 1 (identical), group 2 (compatible) and group 3 (incompatible), according to the donor-recipient blood type matching. We analyzed several outcomes regarding mortality, patient and graft survival, incidence of acute graft rejection during the first postoperative month (30 days), incidence of biliary complications and indications of re-transplantation. We also analyzed the relationship of Coomb's positive test with postoperative hemolysis to all the above mentioned factors. During the study period, 168 males and 112 females underwent their first OLT for FHF, with 37.1% overall mortality and 42.1% overall graft failure rate. The results between group 1 (203 patients) and group 2 (73 patients) were comparable. A statistically significant difference was recorded in 1 year and overall graft survival between group 1 and group 2 ($P = 0.049$ and log-rank $= 0.035$ respectively). Coomb's positive test did not influence the outcomes. OLT in FHF can be safely carried out whether the donor organs are identical or compatible. Hemolysis (Coomb's positive test) after identical or compatible OLT does not influence the outcomes.

Introduction

Organ transplantation causes immunological alterations in the recipient treated with life-long immunosuppressive therapy. The liver is a privileged organ with a relatively low risk of hyperacute rejection due to its resistance to antibody-mediated injury [1–3].

ABO blood group incompatibility in OLT is considered in the literature as a relative contraindication [1], because of the presence of preformed isoagglutinins in recipient serum against the donor A or B antigens which may cause hemolysis, acute renal failure, disseminated intravascular coagulation, hypotension, increased icidence of biliary and/or vascular complications and multiorgan failure with substantial morbidity and mortality [4–12]. Fulminant hepatic failure (FHF) represents 9% of all OLTs in Europe [13]. Successful management after OLT due to FHF depends on the condition of the patient before transplant and the technical and immunological aspects of the transplant itself.

The four ABO blood groups are not proportionally distributed within any population and the blood group of donor and recipient might not be similar. Therefore, patients with rapid deteriorating hepatic disease such as FHF, are candidates for receiving an ABO compatible-non identical (comp) or an incompatible (incomp) graft [13].

In this study, we review our experience and analyze the outcomes after identical or compatible OLT for FHF in the last 21 years.

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Materials and methods

Prospectively collected data on patients with FHF who underwent their first OLT between September 1984 and November 2005 was retrospectively analyzed. Patients were divided into group 1 (ABO identical), group 2 (ABO compatible but nonidentical) and group 3 (ABO incompatible), according to the donor-recipient ABO-type matching.

We recorded the incidence of the primary liver disease causing FHF and analyzed overall mortality, overall graft failure, incidence of histologically proven acute graft rejection during the first postoperative month (30 days), incidence and etiology of re-transplantation, incidence of short term (3 months postoperatively) and long term (more than 3 months postoperatively) biliary complications (biliary leaks, biliary strictures, biliary obstructions), recipient and graft 1 month (30 days), 1 year, 5 year and overall survival during the study period in these groups of patients. We also analyzed independently the relationship between a positive Coomb's test in the postoperative period to all the above mentioned factors. Coomb's test was done and it was positive in patients who had hemolytic episode postoperatively, with droping of hemoglobin more than 2 g/dl and rising of LDH more than 100 U/l, without evidence of hemorrhage (Coomb's positive group). We have to mention that these patients were Coomb's negative preoperatively. The rest of the patients of the study group were included in the Coomb's negative group.

Fisher's test for correlation and Kaplan–Meier method for actuarial survival were used for the statistical analysis. ''Statistical Package for the Social Sciences'' version 12 for Windows (SPSS, Chicago, IL, USA) was used for the above analysis. A P level less than 0.05 was considered significant.

Results

Demography

Between September 1984 and November 2005, 280 patients underwent first OLT for FHF; 168 were females (60%) and 112 males (40%) with median age 38 years (16–66 year). Group 1 consisted of 203 recipients (72.5%), group 2 of 73 recipients (26.1%) and group 3 of 4 recipients (1.4%). The distribution of each group and the demography are shown in Table 1. Interestingly the patients in group 3 were identified in the first 7 years of the study period.

Table 1. Patients distribution and demography.

No. of patients (total)	280
Group 1	203
Group 2	73
Group 3	4
Sex	
Male	112
Female	168
Age (years)	
Mean	38.76
Median (range)	38 (16–66)

Etiology

Unknown origin hepatitis (due to insufficient data cases with non A-non B hepatitis and hepatitis C are included in this term) was the major etiological diagnosis in 139 out of 280 patients (49.6%); paracetamol induced hepatic failure in 58 patients (20.7%); sub-acute hepatic necrosis in 30 patients (10.7%); nonparacetamol drug induced hepatic failure in 25 patients (8.9%); fulminant hepatitis B in nine patients; fulminant Wilson's disease in eight patients; acute Budd-Chiari syndrome in five patients, fulminant hepatitis A in two patients; four patients developed FHF due to other miscellaneous causes. The distribution of the primary liver diagnoses is shown in Table 2.

Outcomes

Overall mortality was 37.1% (34% in group 1, 45.2% in group 2, 50% in group 3, $P = 0.155$) and overall graft failure occurred in 42.1% (38.9% in group 1, 49.3% in group 2 and 75% in group 3, $P = 0.121$). Retransplantation was carried out in 8.2% (23 cases), (15 cases in group 1, six cases in group 2 and two cases in group 3, $P = 0.047$). These operations were carried out in the first postoperative month in group 3. The reason for regrafting in groups 1 and 2 was chronic rejection in eight cases, hepatic artery thrombosis in seven cases, massive hemorrhagic necrosis in two cases, while graft ischemia, primary nonfunction, secondary biliary cirrhosis, and severe acute rejection were the reasons in one case each. Ten patients in group 1 and five patients in group 2 were retransplanted during the

Table 2. Aetiology of fulminant hepatic failure in the study group.

Etiology	No. of patients
Unknown origin hepatitis	139
Subacute necrosis	30
Acute Budd-Chiari	5
Fulminant hepatitis B	9
Paracetamol-induced hepatic failure	58
Nonparacetamol hepatic failure	25
Fulminant Wilson's disease	8
Fulminant hepatitis A	2
Fulminant miscellaneous	4

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first year post-transplant, while five patients in group 1 and one patient in group 2 were retransplanted after the first year post-transplant ($P = 0.623$). Biliary complications recorded in 54 cases (40 cases in identical and 14 in compatible group, $P = 1$). Early biliary complications were recorded in 19 patients in group 1 and in eight patients in group 2 ($P = 0.818$) and included thirteen biliary leaks, ten biliary anastomotic strictures, three nonanastomotic strictures and one biliary obstruction. Late biliary complications were recorded in 21 patients in the identical group and in six patients in the compatible group ($P = 0.817$); 23 of them were anastomotic biliary strictures and four were biliary obstructions.

Insufficient data was the reason to exclude the first 7 years of the study period from the Coomb's analysis. Therefore the study group for this analysis included 219 patients instead of 280. A positive direct Coombs test occurred in 44 patients who experienced a postoperative hemolytic episode; 29 patients were in group 1 and 15 patients were in group 2 ($P = 0.172$). The Coomb's negative group included 135 patients in group 1 and 40 patients in group 2.

During the first postoperative month 123 episodes (43.9%) of acute rejection were recorded (89 episodes in group 1, 32 episodes in group 2 and two episodes in group 3, $P = 1$).

The 1-month patient survival was 81.1% (83% in group 1, 76.7% in group 2, 75% in group 3, $P = 0.381$) and graft survival at 1 month was 78.2% (80.3% group 1, 74% in group 2, 50% in group 3, $P = 0.153$). The 1-year patient survival was 66.8% (70% in group 1, 57.5% in group 2, 75% in group 3, $P = 0.120$) and 1-year graft survival was 62.9% (66.5% in group 1, 53.4% in group 2, 50% in group 3, $P = 0.098$).

The 5-year patient survival (not all the patients were included) was 63% (64.8% in group 1, 57.4% in group 2 and 75% in group 3, $P = 0.588$) and graft survival at 5-year was 59% (62.7% in group 1, 51.9% in group 2, 25% in group 3-not all the patients were included, $P = 0.143$).

When we excluded from the analysis the group 3 (small number of patients) there was statistically significant difference only in graft 1-year survival between group 1 and group 2 ($P = 0.049$). All the above mentioned data is shown in Table 3.

In order to avoid any bias from the long study period in the analysis, we divided this interval in three equal periods A, B and C and we compared the outcomes between identical and compatible groups The difference in the studied factors between group 1 and group 2 in each period did not reach statistical significance (Table 4).

Overall patients and graft survival analysis

The small number of patients let us to exclude group 3 from the survival analysis (Table 3).

There was not statistically significant difference between group 1 and group 2 in the overall patients survival in the study period (134 patients survived in group 1 and 40 patients in group 2, log rank = 0.105) (Fig. 1).

There was statistically significant difference in the overall graft survival between group 1 and group 2 in the whole study period (124 surviving grafts in group 1 and 37 grafts in group 2, log-rank = 0.035). Interestingly the difference in overall graft survival became statistically significant after 100 months post-transplant (Fig. 2).

When the same analysis was done in each of the above mentioned periods A–C, there was statistically significant difference between the period A and the periods B, C in the overall patients and graft survival (log-rank = 0.001 and log-rank = 0.012 respectively). The only statistically significant difference between group 1 and group 2 was recorded in the overall graft survival analysis in the period 3 (log-rank = 0.018) (Table 4).

Table 3. Analysis of the studied parameters between each group of patients.

Studied parameters	Group 1, *n* (%)	Group 2, *n* (%)	Group 3, *n* (%)	*P*-value	*P*-value*
Acute rejection	89 (43.8)	32 (43.8)	2 (50)	1	1
Patient 1-month survival	168 (82.8)	56 (76.7)	3 (75)	0.381	0.295
Graft 1-month survival	163 (80.3)	54 (74)	2 (50)	0.153	0.318
Patient 1-year survival	142 (70)	42 (57.5)	3 (75)	0.120	0.061
Graft 1-year survival	135 (66.5)	39 (53.4)	2 (50)	0.098	0.049
Patient 5-year survival	92 (64.8)	31 (57.4)	3 (75)	0.588	0.214
Graft 5-year survival	89 (62.7)	28 (51.9)	1 (25)	0.143	0.170
Overall mortality	69 (34)	33 (45.2)	2 (50)	0.155	0.092.
Overall graft failure	79 (38.9)	36 (49.3)	3 (75)	0.121	0.130
Retransplantation rate	15 (7.4)	6 (8.2)	2 (50)	0.047	0.800

*Group 3 was excluded from the analysis. Only in 1-year graft survival the difference between group 1 and group 2 was statistically significant.

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Table 4. Analysis of the studied parameters between periods.

Studied factors	A		B		C				
	Group 1 (%)	Group 2 (%)	Group 1 (%)	Group 2 (%)	Group 1 (%)	Group 2 (%)	A vs. B (*P*)*	A vs. C (*P*)*	B vs. C (*P*)*
Periods									
Acute rejection	51.3	44.4	38.9	42.9	45.9	44.4	0.258	0.741	0.413
Pateint 1-month survival	64.1	61.1	86.7	85.7	87.8	77.8	0.001	0.003	0.847
Graft 1-month survival	56.4	55.6	85.6	82.1	86.5	77.8	<0.001	<0.001	1
Patient 1-year survival	56.4	38.9	75.6	67.9	80	64	0.004	0.003	0.873
Graft 1-year survival	51.3	38.9	71.1	60.7	78.5	60	0.008	0.003	0.539
Patient 5-year survival	48.7	38.9	72.2	67.9	61.5	62.5	0.001	0.307	0.442
Graft 5-year survival	46.2	38.9	70	60.7	61.5	50	0.003	0.319	0.453
Overall mortality	64.1	66.7	33.3	39.3	18.9	37	<0.001	<0.001	0.102
Overall graft failure	66.7	66.7	42.2	46.4	20.3	40.7	0.044	<0.001	0.007
Retransplantation rate	7.7	5.6	11.1	10.7	2.7	7.4	0.587	0.460	0.074

*Only *P* level is mentioned.

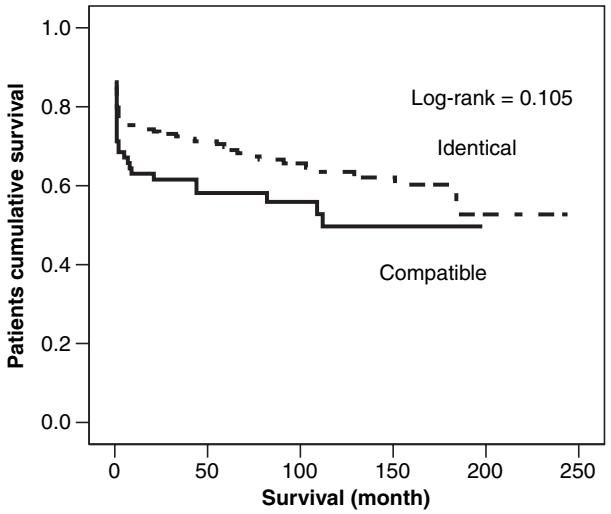

Figure 1 Kaplan–Meier overall patients survival curve.

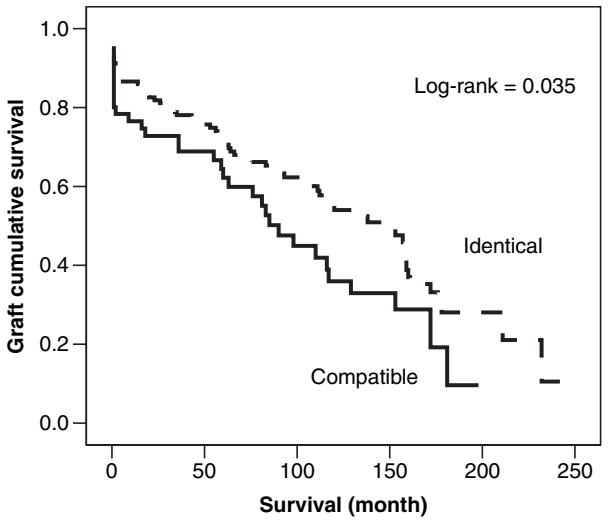

Figure 2 Kaplan-Meier overall graft survival curve.

Coomb's test analysis

When positive Coomb's test was considered as the independent variable, there was no studied factor which reached statistically significant difference in the analysis (Table 5). There was not statistically significant difference between Coomb's positive and Coomb's negative patients in the overall patient and graft survival (Table 5).

Discussion

Fulminant hepatic failure is a common indication for OLT in highly urgent liver transplantation patients waiting-list [14]. OLT is the preferred method of treatment in FHF, although overall mortality and graft failure are high.

The small incompatible group and therefore our limited experience do not allow us to exclude safe conclusions from the analysis of this group. We decided to concentrate on the analysis of the results in the other two groups of patients and also to mention the results in group 3 in order to give a detailed picture of our experience in the treatment of FHF. Bjoro *et al.* [13], showed that an ABO-compatible donor was a negative independent significant factor of patient survival after highly urgent liver transplantation, although the authors remarked on the high number of deaths from extrahepatic causes and the lower number of retransplantations in

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Table 5. Comparison of the outcomes between coomb's (+)ve and coomb's (–)ve groups.

Studied parameters	Coomb's (+)ve group (*n*)	Coomb's (–)ve group (*n*)	*P*-value
Acute rejection	23	70	0.173
Patient 1-month survival	39	149	0.637
Graft 1-month survival	39	146	0.49
Patient 1-year survival	31	124	0.697
Graft 1-year survival	31	116	1
Patient 5-year survival	19	78	1
Graft 5-year survival	19	73	0.658
Overall mortality	16	49	0.275
Overall graft failure	18	59	0.382
Retransplantation rate	3	14	1
Overall patients survival	28	126	0.310*
Overall graft survival	26	116	0.749*

*Kaplan–Meier test was used.

that group of patients. In the same study there was a significantly higher survival rate in patients receiving ABO-identical organs compared with ABO-compatible organs. Data from European Liver Transplantation Registry in 2002 (European Liver Transplantation Registry, available at: http://www.eltr.org/publi/results, accessed in August 11, 2002) did not demonstrate any difference in survival between identical and compatible groups of recipients in acute liver failure; similar results demonstrated in our study. In our study although overall mortality was also high, mainly influenced by the results in period I (Table 4), it was less in the ABO-identical group during the study period. This difference was not statistically significant between ABO-identical and ABO-compatible OLTs.

In one study [13] the authors did not demonstrate statistically significant difference in graft survival between identical and compatible groups of patients. Reding *et al.* [15] reported that the difference in graft survival between identical and compatible OLT in their study was not statistically significant. Aladaq *et al.* [16] reported no significant difference between identical and compatible OLTs in patient and graft survival; the study group included elective and urgent OLTs. Smith *et al.* [17] published that nonidentical OLT was a factor that increased the odds of graft failure. In our study statistically significant difference was recorded between the identical and compatible groups of recipients in 1-year and overall graft survival. The analysis of the fact that the difference in overall graft survival reached statistical significance almost 10 years post-transplant (Fig. 2), requires further study including donor and recipient parameters and chronic rejection fully detailed data.

Bjoro and colleagues [13] demonstrated a strikingly higher retransplantation rate in ABO-identical compared to ABO-compatible transplants. In our study, hepatic artery thrombosis and chronic rejection were the major causes for regrafting, while more recipients in group 1 were retransplanted. In another study the main reasons for retransplantation were chronic rejection, hepatic artery thrombosis and primary nonfunction [18]. ABO compatibility was a statistically significant factor in hepatic artery thrombosis in the study of Stange *et al.* [19]. Blood group related antigens are known to be expressed on the surface of the erythrocytes and on the epithelial cells of large bile ducts as long as 150 days post-transplant. Therefore the biliary epithelium of hepatic allograft is more susceptible to immunologic injury after nonidentical OLT [20]. Biliary complications in our group were not statistically significant different between groups 1 and 2. Biliary stricture was the most frequent late biliary complication. We could not find any studies in the literature comparing the incidence of biliary complications and the reasons for retransplantation between identical and compatible OLT.

Although we found better results after the first 7 years of the study; we showed that this fact did not influence the results of our analysis between group 1 and group 2 of recipients. We believe that this difference can be attributed to the greater experience, to the refinement of the transplantation technique and to the improvement of the intensive care and of the immunosuppressive regimens and protocols, since our policy for the treatment of patients with FHF has not been changed.

Acute graft rejection in the first postoperative month is a short-term immunological risk for ABO-incompatible organs [1,21,22]. The existence of anti-donor isoagglutinins in recipient serum can induce a progressive antibody-mediated humoral endothelial injury, which in severe cases leads to interstitial hemorrhage, obstruction of the microvascular level, and ischemic necrosis of the hepatic graft. Reinforced immunosuppression has been used in this type of patients [15] and alternatives such as splenectomy, preoperative or postoperative plasma exchange have also been reported [23] although such strategies are not risk free [24,25]. In our study there was not statistically significant difference in the treated episodes of histologically proven acute rejection between the three groups of patients.

In 1971, Beck and colleagues first described the passive transfer of viable lymphocytes with the capability of producing antibodies [3]. Since then the model of graft-derived antibodies from passenger lymphocytes directed to host antigens and producing isohemagglutinins after solid organ transplantation has been widely accepted [7,8,26,27]. Hemolytic anemia after organ transplantation is more frequently encountered in proportion to the lymphoid mass transplanted [26,27]. Ramsey reported that the frequencies of hemolytic antibodies and hemolysis

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after liver transplantation were 40% and 29% respectively [7]. Reliable parameters in predicting which patients will develop red cell antibodies or hemolysis have not yet been established [28]. Hemolysis is a type of graft versus host disease (GVHD) and Coomb's test, if it is not immediately positive, will be positive within 1–2 days [28–30]. In cases of hemolysis the incidence of Coomb's negative test is rare [31]. The differential diagnosis of hemolysis following transplantation also includes passive transfer of antibody to the recipient following red cells, plasma and platelet transfusions, minor incompatiblity from other than ABO and Rh systems and drug induced hemolytic anemia [29,32]. In minor Rh-incompatible solid organ transplantation, previous donor sensitization may predict GVHD anti-Rh induced hemolysis [7,33]. Some published studies in selected patients have suggested prophylactic transfusion of donor type red cells perioperatively and postoperatively [7,27,29,33]. In cases of severe hemolysis corticosteroids, plasma and red cells exchange have also been recommended [3,27,34].

In our study the proportion of patients with hemolytic episode and Coomb's positive test was lower than it has been previously reported [4,6,7,28]. In Coomb's positive group, the serum antibodies were detected in 11th postoperative day in median. A Rh-unmatched OLT was carried out in 15 out of the 44 Coomb's positive cases. There was not statistically significant association of any of the studied parameters with Coomb's positive test, in this group of patients. The increased number of Coomb's positive test in group A might be related to minor unmatched OLT (nine cases of Rh unmatched OLT recorded in this group). The Coomb's negative group included also patients who experienced drop of hemoglobin and rise in serum LDH lower than our criteria. This test was not done in these cases as that episode was clinically insignificant and the cause of the drop of hemoglobin combined with a possible Coomb's positive test was not profound.

In conclusion, we believe that our results support the policy of OLT in FHF with the first identical or compatible available donor. Hemolysis (Coomb's positive test), after ABO or Rh-unmatched OLTs is usually a self limiting form of GVHD and according to our experience does not influence the outcomes in FHF.

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