Transpl Int (1998) 11 [Suppl 1]: S 164–S 167

R. J. Porte
R. J. Ploeg
B. Hansen
J. H. van Bockel
J. Thorogood
G. G. Persijn
J. Hermans
O. T. Terpstra
and the
European Multicentre
Study Group[1]

Long-term graft survival after liver transplantation in the UW era: late effects of cold ischemia and primary dysfunction

R. J. Porte · J. H. van Bockel · O. T. Terpstra
Department of Surgery, Leiden University Hospital, The Netherlands

R. J. Ploeg (✉)
Department of Surgery, University Hospital Groningen, PO Box 30.001, 9700 Groningen, The Netherlands Tel. 31-50-361 2896; Fax 31-50-361 3873
e-mail r.j.ploeg@chir.azg.nl

B. Hansen · J. Thorogood · J. Hermans
Department of Medical Statistics, Leiden University Hospital, The Netherlands

J. Thorogood · G. G. Persijn
Eurotransplant Foundation, The Netherlands

[1] For contributors see Acknowledgements

Abstract The use of University of Wisconsin (UW) solution in liver transplantation (LTX) has significantly prolonged preservation times and facilitated semielective transplant procedures. Despite this advantage potential risk factors related to the donor, recipient, or cold storage method will persist in the UW era and detrimental effects will be reflected by primary dysfunction (PDF) after LTX. Concern has been voiced about the maximum period of UW preservation in LTX and various cold ischemia times (CIT) are mentioned. To evaluate the effect of UW solution in LTX, a prospective European multicenter study was initiated in 1988 and short-term results have been reported previously. This report focuses on the long-term effects and survival of prolonged preservation with UW solution and primary function after LTX. Three hundred and fifteen LTXs were performed in 288 patients in participating European centers. Complete follow up of at least 6 years was available for 296 grafts in 277 patients. Effects of donor, preservation, and recipient risk factors on PDF including primary non-function (PNF) and initial poor function (IPF) were evaluated. Next, the effect of risk factors on graft survival (GS) was analyzed including the long-term impact of PNF and IPF using multivariate analyses and the Kaplan-Meyer method. PDF occurred in 15.2% (45/296) with PNF in 7.8% and IPF in 7.4%. Patients with IPF had a 34% lower GS at 3 months those with immediate function (IF; 58% vs 91%; $P < 0.001$). This difference persisted up to 6 years for patients with IPF with a 39% GS vs 72% after IF ($P < 0.001$). Median CIT was significantly longer in grafts with PNF compared to IPF or IF ($P = 0.03$). Long-term GS, however, was significantly influenced at a lower CIT threshold with a 6-year GS for CIT $\leq$ 16 h of 67%, compared to a CIT > 16 h of 51% ($P = 0.02$). Other independent risk factors for the 6-year survival rate were re-LTX, ABO incompatibility, and recipient diagnosis of acute hepatic failure. In conclusion, liver patients with PNF, but not with IPF, have a significantly lower CIT. IPF is associated with a significantly lower 3 month GS compared to IF, but this difference of 34% does not further increase during a 6-year follow up. Although a short term follow up (3 months) shows that with UW solution CIT up to 18 h has no adverse effect on GS, the 6-year data clearyl suggest that CIT should be kept to less than < 16 h to avoid tetrimental effects on lang-term GS after LTX.

Key words Liver transplantation · UW solution · Primary dysfunction · Cold ischemia time · Long-term survival

Introduction

Over the last decade results in organ transplantation have improved tremendously. Achievements especially in the filed of graft preservation and immunosuppression have contributed greatly to this effect [1, 2]. A milestone was the introduction of the University of Wisconsin (UW) solution developed by Belzer and his group in 1987 [3]. In several experimental and clinical studies it was demonstrated that the use of UW solution allows longer cold ischemia times with better graft preservation and posttransplant function than when Euro-Collins and similar solutions are used [4–8]. The advantages of UW solution have been longer preservation times with semielective liver transplant procedures and the possibility of reduction or splitting of the liver graft on the back table [6, 7, 9].

Although the initial experience with UW solution showed that livers could safely be cold stored for as long as 24 h [7, 9], it has recently been speculated that the extension of the ischemia time is still a risk factor that may effect posttransplant liver function and survival [10–12]. Primary dysfunction, including primary non-function and initial poor function, remains a serious complication after liver transplantation [10, 13]. Proper timing of retransplantation is important and requires more insight in to risk factors to prevent the risk of graft failure as early as possible.

To evaluate the effects of preservation with UW solution and prolonged cold ischemia times on patient and graft survival and graft function after liver transplantation, we initiated a prospective European multicenter study. This study was part of a European multicenter study on UW solution in kidney [14], pancreas [15], and liver transplantation. A large number of donor, procedure-related, preservation, and recipient factors was assessed to determine their effect on graft function as well as on graft and patient survival. This report focuses on the long-term survival and effects on prolonged preservation with UW solution and primary dysfunction after liver transplantation.

Patients and methods

Recipient population

Between 1988 and 1989, 21 European liver transplant centers participated in this study which was at that time coordinated by the Department of Surgery of the Leiden University Hospital in close collaboration with Eurotransplant. A total of 315 liver transplants were performed in 288 patients. Of these, 275 were first transplants and 41 retransplantations. Four out of 41 retransplantations were secondary transplantations and 14 out of 41 retransplantations were replacements of a liver that had been transplantated before the study period. Data on patient and graft variables were collected prospectively during the first 14 days on a day to day basis and then during the first 3 months after transplantation. Long-term graft and patient survival data were obtained from the European Liver Transplant Registry. Complete follow up of at least 6 years was available for 296 liver transplants in 277 patients.

Donor population

Characteristics of the liver donor and donor operation were accumulated. Livers were procured using a standardized technique [16, 17] in 63%, whereas "the rapid flush technique", described by Starzl et al. [18] was used in 37%. In general, 2 l of UW solution (4 °C) were infused through the aorta and 1 l was used as a portal flush to achieve rapid core cooling. After removal, the livers were flushed on the back table. Flush out of the gall bladder and common bile duct with UW solution was strongly recommended to our participating centers.

Recipient operation and care

Recipient hepatectomy and transplantation were performed using standardized techniques as previously described [2]. Prior to revascularization, the liver was either flushed with 500–1000 ml of lactated Ringer's solution with 5% albumin or blood reperfused from the recipient, depending on the Center's preference. The postoperative immunosuppressive regimen consisted of cyclosporine, prednisone, and azathioprine, according to the individual center protocol.

End point

Graft failure was defined as non-life-sustaining function of the liver requiring immediate retransplantation or leading to death. For graft survival the end point was graft failure, while patients who died with functioning grafts were censored at the time of death. Initial poor function was defined as AST > 2.000 IU/l and a prothrombin time > 16 s on postoperative days 2–7, as proposed by Ploeg et al. [13].

Statistical analysis

Estimates of patient and graft survival were obtained by the Kaplan-Meier method. The effect of variables on patient and graft survival was analyzed by both uni- and multivariate analyses. P values of less than 0.05 were considered significant.

Results

Overall patient survival at 3 months was 83% and after 6 years 63%. Overall graft survival was 75% after 3 months and 56% after 6 years. The median cold ischemia time of livers with immediate function after transplantation was 9.5 h versus 9.4 h in livers which suffered from initial poor function. In grafts with primary non-function, a median cold ischemia time of 14.5 h was seen ($P = 0.03$). Primary dysfunction occured in 15.2% (45/296) after liver transplantation; primary non-function was present in 7.8% and initial poor function in 7.4%. Calculating the effect of initial graft function on

graft survival liver transplants with immediate function had a 3-month graft survival of 92% and a 6-year graft survival of 72%. Grafts with primary non-function had by definition, a 0% graft survival. The livers with initial poor function had a 58% graft survival at 3 months and only a 39% graft survival after 6 years which is significantly lower than for livers with immediate function ($P < 0.0001$).

Next, the effect of cold ischemia time on graft survival was assessed. When cohort analysis was performed at the level of a 12-h cut-off point, no effect could be seen on graft survival comparing livers preserved for more than 12 h versus those who were cold stored for less than 12 h. For the 3-month follow-up period no significant effect of cold ischemia time on graft survival was seen for up to 18 h preservation time ($P = 0.057$). The 6-year follow-up analysis, however, showed at the level of 16 h a distinct cut-off point. Those livers preserved for less than 16 h had a 67% 6-year graft survival whereas those preserved for longer than 16 h had a 6-year graft survival of 46%. ($P = 0.013$). When the cohort analysis was extended to 17, 18, an 19 h cold ischemia time, the P value remained significant at the level of $P = 0.01$. When other variables were included in this analysis using a Cox's regression model, blood group incompatibility, recipient sex, recipient age, donor age, and cold ischemia time were the only independent predictors of graft survival after first liver transplantation.

Discussion

This paper reports on the results of a prospective study on UW solution in liver transplantation within an international organ-sharing system. The perspective of this study is not omited to the results of a single institution but it also reflects the quality of shared donor livers according to the allocation policy for livers in Europe. UW solution has now been used as a preservation solution for liver transplantation for over 10 years. Many procedures have peen performed after UW preservation without major complications despite longer preservation times. Nevertheless, with longer cold ischemia times more ischemia/reperfusion injury is likely that is detrimental to the graft function and graft survival and could increase antigenicity. Despite this vast experience the major question of the optimal length of preservation with UW solution in liver transplantation had not been answered. Our long-term analysis shows that primary dysfunction has a significant effect on survival after liver transplantation. Liver grafts with primary non-function but not initial poor function have a significant longer cold ischemia time. It remains to be seen whether this is a true cold ischemia time effect or whether interference with other variables is also responsible for this outcome. Initial poor function is an important clinical entity which leads to inreased morbidity, mortality, and a higher retransplantation rate. In our study initial poor function was associated with a significantly lower 3-month und 6-month graft survival than in liver transplants with immediate function. The difference in graft survival which was 34% lower in those livers which had suffered from initial poor function than those with immediate function, occurred in the first months after transplantation; however, it did not increase further during the 6-year follow up.

Next, we found that there is a definite effect on the length of cold ischemia time on graft survival. Follow-up analysis after 3 month indicates that preservation times up to 18 h with UW preservation are without adverse effects on graft survival. Long-term data with a 6-year follow-up, however, indicate that cold ischemia time should be kept to less than 16 h to avoid detrimental effects on graft survival. We realize that cut-off points for preservation times should not be viewed as sole indicators of future graft function. Nevertheless, the indication of an optimal safe graft preservation time should help the decision of the individual clinician facing a multitude of individual donor and recipient factors. Preservation time is on many occasions the only factor that we can truly control ourselves. With many other risk factors present, the cold ischemia time should obviously be as short as possible to prevent primary dysfunction. Ischemia/reperfusion injury with primary dysfunction possibly activates antigenicity and the chance of chronic transplant dysfunction after liver transplantation. It is also very questionable whether cold storage followed by reperfusion is the first step toward graft failure. It is possible that the very unphysiological phase of brain death could predispose to dysfunction of the liver after preservation and transplantation. In this respect, first results of a pilot study performed in our institution show that activation and upregulation during brain death causes dysfunction of the liver which is aggrevated by cold ischemia (Van der Hoeven et al. in press).

The results of this study underline the fact that the outcome after liver transplantation is influenced by multifactorial events. The introduction of UW solution has greatly improved liver graft preservation and allowed the increase of cold ischemia times. Nevertheless, preservation remains a risk factor and it is questionable whether the cold storage method will allow longer preservation times with the solutions we are currently using in liver transplantation. In this respect a parallel to kidney transplantation should be drawn. In kidney transplantation pulsatile machine preservation has remained superior as regards outcome compared to cold storage preservation. It appears not unrealistic to state that further improvements to liver preservation could be made by exploring the possibilities of machine preservation for the liver.

Acknowledgements We thank all investigators in the participating centers. Without their contributions this prospective study could not have been realized. The European Multicentre Study Group (liver) consisted of the following centers and clinicians. Austria: Medizinische Universität Klinik, Vienna (F. Piza, F. Mühlbacher, R. Steininger, P. Götzinger, P. Wamser). Belgium: Cliniques Universitaires St. Luc, Brussels (J. Otte, B. DeHemptinne, M. Jansen, F. Roggen); Hôpital Erasme, Brussels (J. Lambilliotte, M. Gelin, B. van Haelewijck); Université de Liège, Liège (M. Meurisse, P. Honore, M-H. Delbouille). France: Hôpital Paul Brousse, Villejuif (H. Bismuth, R. Adam, D. Castaing); CHU Pontchaillou, Rennes (B. Launois, J. Champion); Hôpital Jean Minjoz, Besancon (M. Gillet, G. Mation). Germany: Universitätsklinikum Rudolf Virchow, Berlin (P. Neuhaus, W. Bechstein, D. Horch); Universitätsklinik, Essen (F. Eigler, J. Erhard, W. Niebel, R. Abel); Johann Wolfgang Goethe Universitätsklinik, Frankfurt (D. Ernst, B. Markus, C. Allers); Universitätskrankenhaus Eppendorf, Hamburg (B. Kremer, C. Broelsch, W. Schreiber, C. Clausen, B. Hollenrieder); Medizinische Hochschule, Hannover (R. Pichelmayr, B. Ringe, G. Gubernatis, B. Heigel); Rupert Karls Universitätsklinik, Heidelberg (G. Otte, E. Frey, M. Jungmann); Chrisitan Albrechts Universität, Kiel (B. Kremer, I. Robiller, G. Schütt); Klinikum Rechts der Isar, Munich (R. Siewert, W. Adolf, C. Schulz); Ludwig Maximilians Universitätsklinikum, Munich (W. Land, E. Pratschke, C. Schultz); Westfälische Wilhelms Universität, Münster (B. Buchholz, K-H. Dietl, B. Högemann, M. Mauritz); Eberhard Karls Universität, Tübingen (W. Lauchart, E. Eichmann). The Netherlands: Academisch Ziekenhuis, Groningen (M. Slooff, G. den Butter, P. Peeters, J. Kranenburg, I. Saan). Sweden: Karolinksa Institute, Huddinge (C. Groth, B. Ericzon). Switzerland: Inselspital Bern (J. Lerut). Study coordination: Department of Surgery, Leiden University Hospital; R. Ploeg (coordinator), M. Groenewegen and P. Langendijk (data management), J. Thorogood (Eurotransplant/Department of Medical Statistics), J. Hermans and B. Hansen (Department of Medical Statistics).

References

1. Maddrey WC, Van Thiel DH (1988) Liver transplantation: an overview. Hepatology 8: 948
2. Starzl TE, Iwatsuki S, Van Thiel DH, et al (1982) Evolution of liver transplantation. Hepatology 2: 614
3. Wahlberg JA, Love R, Landegaard L, Southard JH, Belzer FO (1987) Seventy-two-hour preservation of canine pancreas. Transplantation 43: 5
4. Cofer JB, Klintmalm GB, Howard TK, Morris CV, Husberg BS, Goldstein RM, Gonwa TA (1990) A comparison of UW with Eurocollins preservation solution in liver transplantation. Transplantation 49: 1088
5. Furukawa H, Todo S, Imventarza O, Wu YM, Scotti C, Day R, Starzl TE (1991) Cold ischemia time versus outcome of human liver transplantation using UW solution. Transplant Proc 23: 1550
6. Stratta RJ, Wood RP, Langas AN, et al (1990) The impact of extended preservation on clinical liver transplantation. Transplantation 50: 438
7. Todo S, Nery J, Yanaga K, Podesta L, Gordon RD, Starzl TE (1989) Extended preservation of human liver grafts with UW solution. JAMA 261: 711
8. Olthoff KM, Millis JM, Imagawa DK, et al (1990) Comparison of UW solution and Europ-Collins solutions for cold preservation of human liver grafts. Transplantation 49: 284
9. Kalayoglu M, Sollinger HW, Stratta RJ, et al (1988) Extended preservation of liver for clinical transplantation. Lancet i: 617
10. Adam R, Bismuth H, Diamond T, et al (1992) Effect of extended cold ischaemia with UW solution on graft function after liver transplantation. Lancet 340: 1373
11. Furukawa H, Todo S, Imventarza O, et al. (1991) Effect of cold ischemia time on the early outcome of human hepatic allografts preserved with UW solution. Transplantation 51: 1000
12. Padburry RT, Attard A, Mirza DF, et al (1994) Extended preservation of the liver with UW solution. It is justifiable? Transplantation 57: 1490
13. Ploeg RJ, D'Alessandro AM, Knechtle SJ, et al (1993) Risk factors for primary dysfunction after liver transplantation: a multivariate analysis. Transplantation 55: 807
14. Ploeg RJ, Bockel JH van, Langendijk PTH, et al (1992) Effect of preservation solution on results of cadaveric kidney transplantation. Lancet 340: 129
15. Hartgrink HH, Bockel JH van, Hansen B, et al (1995) Effect of blood group and HLA matching on pancreas graft survival with the use of UW solution. Transpl Int 8: 366
16. Starzl TE, Hakala TR, Shaw BW Jr, et al (1984) A flexible procedure for multiple cadaveric organ procurement. Surg Gynecol Obstet 158: 223
17. Starzl TE, Iwatsuki S, Esquivel CO, et al (1985) Refinements in the surgical technique of liver transplantation. Semin Liv Dis 5: 349
18. Starzl TE, Miller C, Broznick B, Makowka L (1987) An improved technique for multiple organ harvesting. Surg Gynecol Obstet 1656: 343