LIVER TRANSPLANTATION 12:196-198, 2006

EDITORIAL

Preservation Solutions in Liver Transplantation: What Are the Options?

Bijan Eghtesad, Federico Aucejo, John J. Fung
Department of General Surgery, Liver Transplantation, Cleveland Clinic Foundation, Cleveland, OH

Received October 21, 2005; accepted October 21, 2005.

See Article on Page 226

Alexis Carrel took the initial steps in the area of organ preservation by successfully preserving an artery for several days using chilled Locke's solution, although this effort was largely overshadowed by his work in vascular surgery and organ transplantation. With the increased interest in clinical organ transplantation in the 1960s, the transplant community soon realized the need for preservation solutions and techniques to procure and store organs in "as-optimal" condition and to provide maximally safe times to transport organs to potential recipients. This became achievable by; 1) preventing graft damage in the donor by decreasing warm ischemia time; 2) minimizing cellular changes during the cold storage time; and 3) minimizing reperfusion injury to the organ after restoration of the blood supply in the recipient.

Induction of hypothermia to reduce metabolic requirements of the organ is the mainstay of all clinically utilized preservation methods. Simple surface cooling with ice slush in the donor was used by Moore,[1] while Starzl[2] introduced the concept of core cooling by flushing abdominal organs by cold solution through an aortic cannula. The development of machine perfusion by Belzer[3] and simple cold storage by Collins[4] in the late 1960s were the original options in the rapidly expanding field of organ preservation and transplantation and are still in use today.

Belzer and coworkers conceptualized the use of impermeant molecules, added to the preservative solution, with the goal to prevent cell swelling during hypothermic storage, which were incorporated into the preservation solution developed at the University of Wisconsin (UW, also known as Viaspan) in the mid-1980s.[5] With the burgeoning liver transplant activity in the United States in the 1990s, UW soon became the gold standard for preservation of the liver and other intraabdominal organs.[6] However, in spite of the clinical success of the solution, several alternative solutions have been introduced and utilized in liver allograft preservation with potential benefits.

Histidine-tryptophane-ketoglutarate (HTK) solution was originally developed for cardiac preservation and was subsequently utilized in organ transplantation. Its preservative function is also based on a principle of different buffers and electrolyte composition, i.e., extracellular-based electrolyte composition with low potassium content, compared to UW solution. The use of HTK in liver transplantation can be traced to European efforts in the late 1980s, where it was shown to be efficacious and safe in liver preservation when compared to UW.[7,8] The solution was not utilized in the United States until 2002, when it was first used at the University of Pittsburgh in cadaveric and living donor liver transplantation.[9] The lower viscosity of HTK and potentially better penetration in the microcirculation of liver prompted the program to use HTK with the main focus to evaluate long-term outcome of liver transplantation and biliary problems, especially in the setting of non-heart-beating donation after cardiac death donors. In addition, the expansion of the living donor program, utilizing a piggyback venous reconstruction, benefited from the low potassium content, obviating the need for in situ flush prior to revascularization.[10,11]

In this issue of *Liver Transplantation*, Mangus et al.[12] compared HTK vs. UW in a large series of cadaveric adult liver transplantations at Indiana University. They examined the outcome of 174 livers preserved with HTK and compared the results with a historical control

Abbreviations: HTK, histidine-tryptophan-ketoglutarate; **UW**, University of Wisconsin.

Address reprint requests to Bijan Eghtesad, M.D., General Surgery and Liver Transplantation, The Cleveland Clinic Foundation, 9500 Euclid Avenue/Desk A-110, Cleveland, Ohio 44195. Telephone: 216-444-9898; FAX: 216-444-9375; E-mail: eghtesb@ccf.org

DOI 10.1002/lt.20698
Published online in Wiley InterScience (www.interscience.wiley.com).

group of 204 patients who received livers preserved with UW. Both groups of recipients were similar in age, gender, and primary disease. Median cold ischemia time in both groups was the same and primary nonfunction was reported in 1% of the patients (1.5% UW and 0.5% HTK). Biochemical values after liver transplantation were similar in both groups at day 30, although a higher day 1 level of transaminases and total bilirubin level was noted in the HTK-preserved allografts. The 1-, 6-, and 12-month patient and graft survivals were the same in both groups. With similar outcome, when the authors looked at the volume of the preservative flush used and price of the solutions utilized, they found HTK to be cheaper ($422/donor) and thus economically attractive, especially for high-volume liver transplant programs.

This outcome is similar to the data from the University of Pittsburgh presented at the American Transplant Congress in 2003.[13] They compared 84 liver transplants preserved with HTK with a control group of 169 UW preserved livers. These groups were matched with age and gender of donors and recipients and had similar primary liver disease and cold ischemia time. They reported similar rates of primary nonfunction and graft dysfunction in both groups. In contrast to speculation that HTK would be inferior to UW in liver transplantation for extended preservation, the Pittsburgh group found no difference in outcome for graft preserved for more than 14 hours of cold ischemia time. Both groups had similar biochemical values on days 1 and 7 after transplant and at 1 month. Patient survival at 1 month and graft survival at 1 yr was slightly higher in the HTK group but this did not reach statistical significance.

A higher rate of late biliary complications has been reported in the UW-preserved livers when compared to HTK-preserved organs, in both cadaveric and living donor liver transplantation[10,14]; however, in the present report by Magnus et al.,[12] this issue was not addressed. Possible explanations for the lower incidence of biliary complications may be attributed to greater penetration of the HTK solution through the small capillary system supplying the bile ducts due to the lower viscosity of the solution, especially at lower temperatures, and/or lack of macroaggregate formation of adenosine crystals and plastic byproducts in the solution, which may cause occlusion of small capillaries at the time of perfusion.[15,16]

The use of expanded criteria donors, included donation after cardiac death (non-heart-beating) donors has recently increased across the United States. Unfortunately, higher rates of primary nonfunction and late biliary complications are still a major problem with this class of donor. Prolonged cold ischemia time is known to have a major impact on the outcome.[17] There is a theoretical benefit of a solution with lower viscosity, which may better penetrate into the microcirculation, especially in the setting of cardiac arrest. The present report by Mangus et al.[12] does not indicate whether any of the livers used were from donation after cardiac death (non-heart-beating) donors. The Pittsburgh group compared the outcome of 8 livers from donation after cardiac death (non-heart-beating) donors preserved with HTK and 15 livers preserved with UW. The HTK group had no primary nonfunction compared with 3 in the UW group. In addition, the rate of long-term biliary complications was more in the UW group but did not achieve statistical significance because of small numbers.[13]

The economical impact of the use of HTK is one of the main benefits noted in the paper by Mangus et al.[12] They conclude that their organ procurement organization, based on 160 donors per year, could roughly save about $67,000 per year by using HTK compared to UW, with similar outcomes. This cost-savings issue was also published by a Hong Kong group when they used HTK instead of UW in their living donors ($137.6/donor).[10] A report from the Center for Organ Recovery and Education (Western Pennsylvania Organ Procurement Organization) also mentioned a savings of $73,000-137,000 based on 160 donors per yr (Brian Broznick, personal communication, July 2002).

The report by Magnus et al.[12] is important because it confirms the European experience that HTK solution is comparable to the gold-standard UW solution in preservation of liver allografts with comparable outcomes and because is it associated with significant cost savings, especially at the significantly lower volumes of HTK used in this study, as compared to the European experience. However, the use of HTK in donation after cardiac death (non-heart-beating) donors, its impact on the rate of primary nonfunction, and the long-term biliary complications using HTK will require a large-scale controlled trial.

In addition, new preservation solutions, such as Celsior, which combines the buffering properties of HTK and the impermeants of UW, should also be evaluated based on preservation capacity, incidence of biliary strictures, and cost.[8]

REFERENCES

1. Moore FD, Smith LL, Burnap TK. One stage homotransplantations of the liver following total hepatectomy in dogs. Transplant Bull 1959;6:103-107.
2. Kaupp HAJ, Starzl TE. The use of an external bypass during experimental total hepatectomy. Surgery, 1960;48: 330-331.
3. Belzer FO, Ashby BS, Dunphy JA. 24-hour and 72 hour preservation of canine kidneys. Lancet 1967;7515:536-538.
4. Collins GM, Bravo-Sugarman M, Terasaki PI. Kidney preservation for transplantation. Lancet 1969;7632:1219-1222.
5. Jamieson NV, Sundberg R, Lindell S, Laravuso R, Southard JH, Belzer FO. Successful 24–30 hour preservation of the canine liver: a preliminary report. Transpl Proc 1988;20:945.
6. Todo S, Nery S, Yanaga K, Podesta L, Gordon R, Starzl TE. Extended preservation of the human liver grafts with UW solution. JAMA 1989;261:711.
7. Gubernatis G, Pichlmayr R, Lamesch P, et al. HTK-solution (Bretschneider) for human liver transplantation. First clinical experiences. Langenbecks Arch Chir 1990;375:66-70.
8. Erhard J, Lange R, Schere R, Kox WJ, Bretschnider HJ,

Gebhard MM, et al. Comparison of histidine-tryptophan-ketoglutarate (HTK) solution vs. University of Wisconsin (UW) solution for organ preservation in human liver transplantation. A prospective, randomized study. Transpl Int 1994;7:177-181.

9. Eghtesad B, Fontes P, Cacciarelli TV, Jain AK, Sindhi R, Geller D, et al. Comparison of histidine-tryptophan-ketoglutarate (HTK) solution vs. University of Wisconsin (UW) solution for organ preservation in liver transplantation. Hepatology 2002;36(Pt 2):Abstract 2052.
10. Chan SC, Liu CL, Lo CM, Fan ST. Applicability of histidine-tryptophan-ketoglutarate solution in right lobe adult-to-adult live donor liver transplantation. Liver Transpl 2004;10:1415-1421.
11. Testa G, Malago M, Nadalin S, Treprow B, Paul A, Frilling A, Broelsch C. Histidine-tryptophan-ketoglutarate versus University of Wisconsin solution in living donor liver transplantation: results of a prospective study. Liver Transpl 2003;9:822-826.
12. Mangus R, Tector AJ, Agarwal A, Vianna R, Murdock P, Fridel JA. A comparison of histidine-tryptophan-ketoglutarate solution (HTK) and University of Wisconsin solution (UW) in adult liver transplantation. Liver Transpl 2005:12: 226-230.
13. Eghtesad B, Broznick B, Patel K, Malek S, Cacciarelli T, Jain A, et al. Comparison of histidine-tryptophan-ketoglutarate (HTK) solution versus University of Wisconsin (UW) solution for organ preservation in liver transplantation. Am J Transpl 2003;5:Abstract 1172.
14. Canelo R, Hakim NS, Ringe B. Experience with histidine-tryptophan-ketoglutarate versus University of Wisconsin preservation in transplantation. Int Surg 2003;88:145-151.
15. Walcher F, Marzi I, Schafer W, Flecks U, Larsen R. Undissolved particles in UW solution cause microcirculatory disturbances after liver transplantation in the rat. Transpl Int 1995;8:161-162.
16. Tullius SG, Filatenkow A, Horch D, Mehlitz T, Ruetzel-Sleke A, Pratschke J, et al. Accumulation of crystal deposits in abdominal organs following perfusion with defrosted University of Wisconsin solution. Am J Transpl 2002;2: 627-630.
17. Abt P, Crawford M, Desai N, Markmann J, Olthoff K, Shaked A. Liver transplantation from controlled non-heart-beating donors: an increased incidence of biliary complications. Transplantation 2003;75:1659-1663.
18. Nardo B, Beltempo P, Bertelli R, Montalti R, Vivarelli M, Urbani L, et al. Comparison of Celsior and University of Wisconsin solutions in cold preservation of liver from octogenarian donors. Transplant Proc 2004;36:523-524.