Platelet Transfusions Have a Negative Impact on Liver Transplant Survival

The impact of intraoperative transfusion of platelets and red blood cells on survival after liver transplantation. *de Boer MT, Christensen MC, Asmussen M, van der Hilst CS, Hendriks HG, Slooff MJ, et al.* Anesth Analg 2008;106:32-44.

Abstract

Background: **Intraoperative transfusion of red blood cells (RBC) is associated with adverse outcome after orthotopic liver transplantation (OLT). Although experimental studies have shown that platelets contribute to reperfusion injury of the liver, the influence of allogeneic platelet transfusion on outcome has not been studied in detail. In this study, we evaluate the impact of various blood products on outcome after OLT. *Methods*: Twenty-nine variables, including blood product transfusions, were studied in relation to outcome in 433 adult patients undergoing a first OLT between 1989 and 2004. Data were analyzed using uni- and multivariate stepwise Cox's proportional hazards analyses, as well as propensity score-adjusted analyses for platelet transfusion to control for selection bias in the use of blood products. *Results*: The proportion of patients receiving transfusion of any blood component decreased from 100% in the period 1989-1996 to 74% in the period 1997-2004. In uni- and multivariate analyses, the indication for transplantation, transfusion of platelets and RBC were highly dominant in predicting 1-yr patient survival. These risk factors were independent from well-accepted indices of disease, such as the Model for End-Stage Liver Disease score and Karnofsky score. The effect on 1-yr survival was dose-related with a hazard ratio of 1.377 per unit of platelets ($P = 0.01$) and 1.057 per unit of RBC ($P = 0.001$). The negative impact of platelet transfusion on survival was confirmed by propensity-adjusted analysis. *Conclusion*: This retrospective study indicates that, in addition to RBC, platelet transfusions are an independent risk factor for survival after OLT. These findings have important implications for transfusion practice in liver transplant recipients.**

COMMENTS

In 1968, Starzl and his group[1] reported on platelet changes following liver transplantation. In the 1980s, a debate arose concerning whether to give platelets for thrombocytopenia or to transfuse platelets only for uncontrollable bleeding episodes. In 1988, Plevak et al.[2] suggested that thrombocytopenia resulted from sequestration of platelets in the newly grafted liver and that intraoperative transfusion of platelets would possibly not prevent thrombocytopenia. In 1994, Porte et al.[3] confirmed that sequestration of platelets occurred in the liver after transplantation. In 1997, Richards et al.[4] reported that post–liver transplantation thrombocytopenia was due to an increased rate of platelet consumption associated with the magnitude of liver transplant surgery. In 1999, Chatzipetrou et al.[5] studied 541 liver transplant patients and reported on a correlation among thrombocytopenia, massive platelet transfusions, and poorer patient and graft survival.

For this present review, de Boer et al. examined the influence of allogeneic platelet transfusion on the outcome of liver transplantation. The authors pointed out what might be a logical observation, that the necessity of giving blood or blood product transfusions may simply be a surrogate marker for sicker patients who naturally have a higher death rate. However, the authors used propensity score–adjusted statistical analysis in an attempt to limit the influence of confounding factors related to both blood transfusion and outcome. The study group consisted of 422 adult patients receiving their first liver transplant in the program from 1989 to 2004. The investigators' platelet transfusion policy was never dictated solely by laboratory values; platelets were transfused during times of excessive blood loss with platelet levels below 50×10^9/L not controllable by other measures. The propensity-adjusted hazard ratio for 1 unit of platelets negatively associated with 1-year patient survival was 2.613 (95% confidence interval, 1.315-5.192; $P = 0.012$). As the authors emphasize, their retrospective study did not prove causality between platelet transfusion and poor outcomes.

Also using propensity analysis, Khan et al.[6] reported that even though critically ill medical patients who received transfusions were older and had higher acute physiologic and chronic health evaluation (APACHE) III scores, transfusions with platelets and other blood products in these patients was associated with an increased risk for acute lung injury and death. Chang et al.[7] suggested that the presence of thrombocytopenia identifies a subgroup of liver transplant patients susceptible to early major fungal infections and subsequent death.

Thrombocytopenia does reflect the severity of the postoperative course and is frequently found after liver transplantation.[8] In deciding to give a platelet transfusion, one must balance the immediate benefit with the long-term effect on survival. Nascimbene et al.[9] recently found that treatment with high-dose intravenous im-

Abbreviations: APACHE, acute physiologic and chronic health evaluation; CMV, cytomegalovirus.

DOI 10.1002/lt.21486
Published online in Wiley InterScience (www.interscience.wiley.com).

munoglobulins resulted in resolution of thrombocytopenia in more than 70% of their study patients. More studies are needed on this critical issue.

REFERENCES

1. Hutchison DE, Genton E, Porter KA, Daloze PM, Huguet C, Brettschneider L, Groth CG, Starzl TE. Platelet changes following clinical and experimental hepatic homotransplantation. Arch Surg 1968;97:27-33.
2. Plevak DJ, Halma GA, Forstrom LA, Dewanjee MK, O'Connor MK, Moore SB, et al. Thrombocytopenia after liver transplantation. Transplant Proc 1988;29:630-633.
3. Porte RJ, Blauw E, Knot EA, de Maat MP, de Rjuiter C, Minke Bakker C, et al. Role of the donor liver in the origin of platelet disorders and hyperfibrinolysis in liver transplantation. J Hepatol 1994;21:592-600.
4. Richards EM, Alexander GJ, Calne RY, Baglin TP. Thrombocytopenia following liver transplantation is associated with platelet consumption and thrombin generation. Br J Haematol 1997;98:315-321.
5. Chatzipetrou MA, Tsaroucha AK, Weppler D, Pappas PA, Kenyon NS, Nery JR, et al. Thrombocytopenia after liver transplantation. Transplantation 1999;67:702-706.
6. Khan H, Belsher J, Yilmaz M, Afessa B, Winters JL, Moore SB, et al. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. Chest 2007;131:1308-1314.
7. Chang FY, Singh N, Gayowski T, Wagener MM, Mietzner SM, Stout JE, et al. Thrombocytopenia in liver transplant recipients: predictors, impact on fungal infections, and role of endogenous thrombopoietin. Transplantation 2000;69:70-75.
8. Ben Hamida C, Lauzet Y, Rézaiguia-Delclaux S, Duvoux C, Cherqui D, Duvaldestin P, et al. Effect of severe thrombocytopenia on patient outcome after liver transplantation. Intensive Care Med 2003;29:756-762.
9. Nascimbene A, Iannacone M, Breando B, De Gasperi A. Acute thrombocytopenia after liver transplant: role of platelet activation, thrombopoietin deficiency and response to high dose intravenous IgG treatment. J Hepatol 2007;47:651-657.

Have You Seen a Liver Transplant Patient with a Cytomegalovirus-Associated Ophthalmologic Complication?

Cytomegalovirus-associated chorioretinitis after liver transplantation: case report and review of the literature. *Egli A, Bergamin O, Müllhaupt B, Seebach JD, Mueller NJ, Hirsch HH.* Transpl Infect Dis 2008;10:27-43.

Abstract

A cytomegalovirus (CMV) donor positive/recipient negative liver transplant recipient developed CMV syndrome with presumed colitis 2 weeks after discontinuing the standard 3 months of valganciclovir prophylaxis. Treatment with intravenous ganciclovir (GCV) reduced, but did not clear, CMV replication. A CMV UL97 mutation (M460V) conferring GCV resistance was identified. Reduction of immunosuppression was followed by rapidly rising lymphocyte counts as well as by clearance of CMV viremia and of clinical symptoms. However, bilateral chorioretinitis was diagnosed 2 weeks later and treated with foscarnet and cidofovir. Then, right eye vitritis occurred necessitating vitrectomy due to a partially rhegmatogeneous retinal detachment. Because chorioretinitis-vitritis after rising lymphocyte counts and clearance of CMV viremia was strongly suggestive of an immune reconstitution syndrome (IRS)-like disease, we investigated CMV-specific T-cells in the peripheral blood available during follow-up. We found strong $CD8^+$ but only low $CD4^+$ T-cell responses (4.77% vs. $< 0.1\%$) to the CMV immediate early pp72, while responses to CMV-lysate or CMV-pp65 ($CD4^+ < 0.01\%$; $CD8^+ < 0.01\%$) were low. Over 16 weeks of follow-up, pp72-specific $CD8^+$ responses declined, while responses to pp65 gradually increased ($CD4^+$ 0.16%; $CD8^+$ 0.76%) indicating a slowly adapting CMV-specific cellular T-cell response. Review of 12,653 published liver transplant patients identified only 14 (0.1%) reported cases of CMV-associated chorioretinitis at a median 41.7 weeks post transplant. CMV-associated ophthalmologic complications late post transplantation may possibly involve 2 different entities of cytopathic retinitis and IRS-like chorioretinitis-vitritis.

COMMENTS

According to this literature review by Egli et al., not many liver transplant physicians have treated patients with chorioretinitis resulting from cytomegalovirus (CMV) infection. This report summarizes 101 studies from 1987 to 2007. In 12,653 liver transplant recipients, 25.6% had CMV replication, 21% had CMV syndrome, 10.6% had CMV organ invasive disease, and only 14 patients (0.1%) had CMV chorioretinitis. CMV chorioretinitis occurred at 101 ± 127 weeks following transplantation, which was substantially later than the occurrence of the other CMV diseases.

In an earlier article, Eid et al.[1] reported on all cases of CMV retinitis after hematopoietic stem cell and solid organ transplantation at the Mayo Clinic from 1990 to 2000. CMV retinitis was diagnosed in 14 eyes of 9 patients who had received kidney (n = 5), liver (n = 2), heart (n = 1), and autologous hematopoietic stem cell transplants (n = 1). The mean time to diagnosis was 9 months (range 4 months to 13 years). Four (44%) of the patients had concomitant pneumonitis or hepatitis. All patients received induction therapy with intravenous or oral ganciclovir (n = 8) or foscarnet (n = 1) for a median of 43 days, which was followed by maintenance therapy with intravenous or oral ganciclovir for a median of 88 days. At follow-up examination, visual acuity was found to be improved in 4 eyes, stable in 4 eyes, and worsened in 6 eyes. The authors concluded that CMV retinitis is a highly morbid infectious complication in which early intervention is crucial to prevent irreversible vision loss.

In an extensive review of retinal complications in solid organ or bone marrow transplant patients, Chung et al.[2] found 11 cases of CMV retinitis in 1198 transplant patients examined by their institution's ophthalmology department. In all patients with CMV retinitis, the presenting symptom was a decrease in vision or the presence of floaters. Onset ranged from 32 to 1812 days (mean 341 days) following transplantation. Only 2 pa-

tients had extraocular CMV infection preceding the CMV retinitis. For treatment, intravenous ganciclovir was given to all patients for 2 weeks to 4 months, and some patients received intravitreal ganciclovir. The retinitis improved rapidly and resolved gradually to leave a thin scar. Final visual acuity was ≥20/50 in 7 eyes. Four eyes showed visual acuity of 20/400 or worse because of macular involvement. The authors concluded that a transplant patient with loss of vision needs prompt diagnosis and aggressive treatment.

The rarity of CMV-associated ophthalmic complications in liver patients can induce low vigilance in transplant physicians. Even though CMV-associated ophthalmic complications seldom occur after liver transplantation, an emergency ophthalmology consultation is prudent for any transplant patient who reports a change in vision, whether or not there is CMV infection. Delay could result in devastating complications.

REFERENCES

1. Eid AJ, Bakri SJ, Kijpittayarit S, Razonable RR. Clinical features and outcomes of cytomegalovirus retinitis after transplantation. Transpl Infect Dis 2008;10:13-18.
2. Chung H, Kim KH, Kim JG, Lee SY, Yoon YH. Retinal complications in patients with solid organ or bone marrow transplantations. Transplantation 2007;83:694-699.

How Do You Perform Your Hepatic Arterial Anastomosis? Traditional or Straight?

Comparison of two techniques of arterial anastomosis during adult cadaveric liver transplantation. *Lorenzin D, Adani GL, Comuzzi C, Sainz-Barriga M, Benzoni E, Bresadola V, et al.* Transplant Proc 2007;39: 1879-1880.

Abstract

Arterial complications are a major source of morbidity and mortality after orthotopic liver transplantation (OLT). The incidence of hepatic artery thrombosis (HAT) ranges from 1.6% to 8%, with a mortality rate that ranges from 11% to 35%. We have described herein a technique of arterial anastomosis aiming to perform the anastomosis as straight as possible to avoid any kinking, redundancy, or malposition of the artery when the liver is released in its final position. We compared this technique with the traditional technique of arterial anastomosis using an aortic Carrel patch, namely, 198 OLT (group A) with the traditional technique and 117 OLT (group B) with the modified technique. An aorto-hepatic bypass was necessary in 25% of the cases in group A and in 21% of the cases in group B ($P = .33$). Vascular anomalies were present in 20% of cases in group A and in 27.5% in group B ($P = .14$). Fourteen cases (7%) of HAT developed in group A versus 0 cases in group B ($P = .003$). In group B, we experienced 2 (1.7%) late arterial stenoses that were successfully treated using percutaneous transluminal angioplasty. The 14 cases of HAT occurring in group A were successfully managed using immediate surgical revascularization with graft salvage in 6 cases (43%), whereas the remaining 8 cases needed urgent retransplantation. We suggest that a technique of arterial anastomosis aimed at avoiding kinking, redundancy, or malposition of the artery may be a viable option to reduce the risk of HAT after OLT.

COMMENTS

In this article, Lorenzin et al. present a new technique for hepatic arterial anastomosis during liver transplantation that is employed to make the anastomosis as straight as possible to avoid any kinking, redundancy, or malposition of the artery. In Lorenzin et al.'s new "straight" approach, the anastomosis is made as straight as possible between the donor proper hepatic artery at the level of the stump of the gastroduodenal or splenic artery (without an aortic cuff) and the recipient common hepatic artery at the level of the gastroduodenal artery. The authors compare this technique to what they label the traditional approach using the donor's aortic Carrel patch and the common hepatic artery of the recipient at the level of the gastroduodenal artery.

Lorenzin et al. performed the traditional approach from 1996 to 2002 in 198 liver transplants and used their new straight approach from 2003 to 2006 in 117 liver transplants. Vascular anomalies were present in 20% of patients in the traditional group and in 27.5% of patients in the "straight" group. In patients undergoing the traditional approach, any accessory left gastric artery was preserved, and a right hepatic artery coming from the superior mesenteric artery was anastomosed to the stump of the splenic artery. In the "straight" group, any accessory left gastric artery was ligated (reported by the authors as accomplished without any postoperative problems), and the aberrant right hepatic artery was anastomosed to the stump of the gastroduodenal artery. All anastomoses in both groups were performed with a double running suture using 6-7 or 8/0 prolene with the aid of 4× surgical loupes.

To evaluate hepatic artery flow, all patients underwent daily ultrasound for 7 days and thereafter when clinically indicated. All episodes of hepatic artery thrombosis were confirmed by selective hepatic angiography. The traditional group had 14 (7%) occurrences of hepatic artery thrombosis versus 0 in the straight group, and this was significant ($P = 0.003$). The straight group experienced 2 occurrences (1.7%) of arterial stenosis more than 6 months following transplantation.

In the traditional approach, use of the Carrel patch avoids narrowing the anastomosis; however, this does occasionally lead to excess vessel length, forming a gentle loop when done properly. Most surgeons who use the traditional approach would say they are able to avoid kinking and malposition of the artery. The main point of using the straight approach is that when the liver is in its final position, there is less redundancy or looping of the shorter artery than in the traditional approach. As Lorenzin et al. suggest, the technique producing the best hemodynamic flow will result in the lower incidence of thrombosis.

Boozari et al.[1] used color Doppler ultrasound to

study the influence of arterial anastomosis on hepatic hemodynamics and overall survival in 224 liver transplant patients. Using systolic and diastolic arterial velocities, resistance indexes, and other parameters, these investigators reported on the results of 5 different techniques of arterial anastomosis. The technique most similar to the straight approach connected the branch patch between the donor's common hepatic artery and the recipient's gastroduodenal artery and encompassed 139 (62.1%) of the anastomoses. The method most similar to the traditional approach attached the branch-patch aorta to the recipient's level of the splenic artery and included 26 (11.6%) of the anastomoses. A comparison of the straight and traditional approaches found no difference in systolic arterial velocities. For diastolic arterial velocities, the straight approach produced significantly higher velocities at 18.98 ± 8.1 cm/second ($P = 0.029$) than the traditional approach at 12.2 ± 6.4 cm/second. Likewise, the resistance index was significantly lower ($P = 0.018$) in the straight approach (0.69 ± 0.09 cm/second) compared to the traditional approach (0.77 ± 0.06 cm/second). Most importantly, there was no difference in the 5- and 10-year survival rates between the 2 approaches (90% and 81% for the straight approach versus 100% and 95% for the traditional approach, respectively). Of the 5 study groups, the group with the lowest survival was that of patients who received more than 1 anastomosis.

Whichever approach a surgeon prefers, further excellent studies such as this by Lorenzin et al. are required to prove which technique is best.

REFERENCES

1. Boozari B, Nashan B, Hecker H, Kubicka S, Klempnauer J, Strassburg C, et al. The type of arterial anastomosis influences hepatic hemodynamics and overall survival in liver graft recipients. Ultraschall Med 2007;28:587-592.

The Cost of Liver Transplant Complications

Incremental costs of post–liver transplantation complications. *Ammori JB, Pelletier SJ, Lynch R, Cohn J, Ads Y, Campbell DA, et al.* J Am Coll Surg 2008; 206:89-95.

Abstract

Background: **Complications after liver transplantation are common and expensive. The incremental costs of adult posttransplantation liver transplantation complications and who pays for these complications (center or payor) is unknown. *Study Design*: We reviewed the medical and financial records (first 90 postoperative days) of all adult liver transplant recipients at our center between July 1, 2002, and October 30, 2005 (N=214). The association of donor, recipient, and financial data points (total costs, reimbursements, and profits) was assessed using standard univariable analyses. The incremental costs of complications were determined with multiple linear regression models to control for the costs inherent to donor and recipient characteristics. *Results*: Univariate analyses demonstrated that both total hospital costs and reimbursements were substantially increased in patients with several different complications. Multiple linear regression analysis, controlling for recipient (age, gender, race, and laboratory Model for End-Stage Liver Disease [MELD]) and donor factors (donor risk index), noted that increased hospital costs and hospital reimbursements were independently associated with laboratory MELD (incremental costs of $3,368 and $2,787, respectively, per MELD point) and pneumonia ($83,718 and $68,214, respectively). A negative profit margin for the medical center was independently associated with peritonitis ($21,760). Commercial insurance was associated with no changes in total costs when compared with public insurer, but it was associated with decreased reimbursement and profit. *Conclusions*: The incremental costs of complications in liver transplantation are high for both the medical center and payor, but medical center profits are not affected substantially. The payor bears the financial burden for post-liver transplantation complications.**

COMMENTS

Cost concerns have been associated with liver transplantation since the National Institutes of Health Consensus Conference on Liver Transplantation in 1983.[1] A huge part of the cost of liver transplantation is variable, depending on the occurrence of post–liver transplant complications.

In 1997, Brown et al.[2] reported that 27% of liver transplantation patients experienced surgical complications requiring a return to the operating room during the initial hospitalization, which resulted in markedly increased costs and length of hospital stay. In 1999, Whiting et al.[3] reported that patients developing major bacterial or fungal infections that prolonged the length of stay incurred drastically increased costs. In 2002, Taylor et al.[4] reported that for Canadian adult liver transplant recipients, postoperative cytomegalovirus infection, reoperation, and biliary complications were associated with increased costs. Other surgical units have shown that reducing postoperative complications markedly reduces costs.[5] However, a conflicting report found that preoperative risk factors and surgical complexity, as evaluated on 6 nontransplant surgical services, were more effective predictors of hospital costs than surgical complications.[6]

In this review, Ammori et al. analyze the incremental costs of post–liver transplantation complications and explore who pays for these complications. From July 1, 2002 until October 30, 2005, the authors evaluated 214 donor and recipient combinations for donor, operative, and recipient characteristics along with graft and patient outcomes, including transplant-specific complications. Financial data were collected on physician procedural fees (surgeons, gastroenterologists, intensivists, interventional radiologists, and nephrologists), facility fees, and reimbursements for each patient. The financial data collection period was the date of transplantation to 90 days following the transplant.

Analysis was conducted via activity-based cost accounting. Univariable analysis revealed that complications that increased hospital costs included peritonitis (+$75,433; $P < 0.001$), hepatic artery thrombosis (+$71,069; $P = 0.035$), reoperation (+$70,339; $P < 0.001$), bloodstream infection (+$64,680; $P < 0.001$), acute renal failure ($51,978; $P = 0.002$), pneumonia (+$50,572; $P < 0.001$), inferior vena cava stenosis (+$46,507; $P = 0.039$), urinary tract infection (+$43,290; $P = 0.007$), any infection (+$42,870; $P < 0.001$), and biliary complications (+$34,606; $P = 0.001$). Multivariable analysis of recipient characteristics revealed a hospital cost increase of $3368 for each increase in laboratory Model for End-Stage Liver Disease points. Univariable analysis of insurer costs showed that higher reimbursements were associated with peritonitis, urinary tract infections, pneumonia, bloodstream infections, acute renal failure, any infection, reoperation, and biliary tract infections. In assessing medical center profit margin, the only complication significantly associated with a negative profit margin was peritonitis ($24,232; $P = 0.03$). Ammori et al. concluded that surgical complications are expensive for both the medical center and payors, but payors bear the largest financial burden. This conclusion has been supported by a nontransplantation surgical review, which also stated that the greater financial burden of postoperative complications falls on health care providers.[7]

Several quality initiatives to lower complications—both hospital-directed and nationally based—have been and will be proposed to ultimately lower costs. As we strive to prevent posttransplantation complications, we must keep in mind, as noted by Ammori et al., that the real cost of complications is borne by patients and their families. Any quality initiative that is implemented will help them the most.

REFERENCES

1. National Institutes of Health Consensus Development Conference Statement: Liver Transplantation—June 20-23, 1983. Hepatology 1984;4:107S–110S.
2. Brown RS Jr, Ascher NL, Lake JR, Emond JC, Bacchetti P, Randall HB, Roberts JP. The impact of surgical complications after liver transplantation on resource utilization. Arch Surg 1997;132:1098-1103.
3. Whiting JF, Martin J, Zavala E, Hanto D. The influence of clinical variables on hospital costs after orthotopic liver transplantation. Surgery 1999;125:217-222.
4. Taylor MC, Greig PD, Detsky AS, McLeod RS, Abdoh A, Krahn MD. Factors associated with the high cost of liver transplantation in adults. Can J Surg 2002;45:425-434.
5. Dimick JB, Chen SL, Taheri PA, Henderson WG, Khuri SF, Campbell DA Jr. Hospital costs associated with surgical complications: a report from the private-sector National Surgical Quality Improvement Program. J Am Coll Surg 2004;199:531-537.
6. Davenport DL, Henderson WG, Khuri SF, Mentzer RM Jr. Preoperative risk factors and surgical complexity are more predictive of costs than postoperative complications: a case study using the National Surgical Quality Improvement Program (NSQIP) database. Ann Surg 2005;242:463-471.
7. Dimick JB, Weeks WB, Karia RJ, Das S, Campbell DA Jr. Who pays for poor surgical quality? Building a business case for quality improvement. J Am Coll Surg 2006;202:933-937.

James D. Perkins, M.D., Special Editor
Liver Transplantation Worldwide
University of Washington Medical Center
Seattle, WA