ORIGINAL ARTICLE

Effect of Intraoperative Blood Transfusion on Patient Outcome in Hepatic Transplantation

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Objective: To evaluate the effect of intraoperative transfusion of red blood cells (RBCs) on patient and graft survival.

Design: A retrospective study.

Setting: A tertiary care referral center.

Patients: Between January 1, 1992, and December 31, 1994, medical records from 225 adult patients who underwent primary liver transplantations were analyzed.

Results: Overall patient survival was 90% at 1 year and 86% at 3 years, while graft survival was 89% at 1 year and 85% at 3 years. The following factors were associated with patient and graft survival: age, sex, medical condition at the time of transplantation, and intraoperative transfusion of RBCs. When these factors were subjected to a multivariate analysis, all were independently associated with survival. Fifty-four recipients (24%) underwent transplantation without intraoperative transfusion of RBCs, while 171 recipients (76%) received at least 1 U of RBCs intraoperatively. Recipients who did not receive transfusion of RBCs had higher patient and graft survival rates than patients who did receive RBCs. By multivariate analysis, transplantation without intraoperative transfusion of RBCs no longer remained statistically significant, and only sex and the patient's medical condition were independently associated with patient and graft survival. Patient and graft survival decreased if 5 or more U were transfused, but transfusion of 5 or more U was not independently associated with survival by multivariate analysis.

Conclusions: Increased transfusion requirement for RBCs was independently associated with patient and graft survival. While transplantation without transfusion of intraoperative RBCs was associated with superior patient and graft survival, these effects were overridden by patient sex and medical condition at the time of transplantation.

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IMPROVEMENTS IN patient selection, surgical techniques, postoperative management, and immunosuppression for orthotopic liver transplantation (OLT) have led to patient survival approaching 80% at 1 year.[1] While attempts have been made to identify factors affecting patient and graft survival, no set of uniform predictive variables has been described.[2-5] The effect of intraoperative blood loss and transfusions on survival after liver transplantation has been assessed by several different centers, with most data showing a correlation between blood use and postoperative morbidity and mortality rates.[2,3,6-8] During a 3-year period, a substantial proportion of our adult patients underwent OLT without intraoperative transfusion of red blood cells (RBCs). These patients were compared with recipients who received at least 1 U of RBCs intraoperatively to determine the effect of not giving patients RBC transfusions on patient and graft survival rates after OLT.

RESULTS

In the present study, the overall patient survival rates were 90% at 1 year and 86% at 3 years, and graft survival rates were 89% at 1 year and 85% at 3 years. Patient and graft survival for patients undergoing OLT with and without intraoperative transfusion of RBCs are shown in **Figure 1**. Transplant recipients who did not receive RBCs intraoperatively had significantly higher patient and graft survival compared with transfused recipients ($P = .01$ and $P = .03$, respectively). However, the following factors were also associated with patient survival: age ($P = .04$), sex ($P = .005$), and the patient's medical condition ($P = .002$). When these factors, along with whether a patient was trans-

PATIENTS AND METHODS

Between January 1, 1992, and December 31, 1994, a total of 334 OLTs were performed at California Pacific Medical Center, San Francisco. Pediatric recipients (82 transplants) and retransplantations (27 transplants) were excluded from this study, leaving a total of 225 adult primary OLT patients for analysis. There were 105 female and 120 male patients, respectively. The mean age for the entire group was 49.5 years, 47.4 years for those patients who did not receive RBC transfusions, and 50.2 years for those who did receive RBC transfusions. Techniques for procuring and transplanting the donor liver have been described elsewhere.[9-11] The mean (±SD) cold ischemia preservation times in the transfused and nontransfused groups were 11.6 ± 0.2 and 10.7 ± 0.4, respectively. The difference was not statistically significant. The 225 OLTs were performed by the following techniques: 169 piggyback (75%), 36 standard with venovenous bypass (16%), and 20 standard without venovenous bypass (9%). Recipients were divided into 2 groups based on intraoperative RBC transfusion requirement. The transfused group included 171 recipients (76%) who received at least 1 U of RBCs intraoperatively, while 54 recipients (24%) received no RBCs (either packed cells or salvaged blood) intraoperatively (nontransfused group). Cell saver was not used in patients requiring less than 30 U of blood. For the effect of RBC transfusion on patient and graft survival, the groups were arbitrarily divided into 3 groups: intraoperative transfusion of 0 (54 patients), 1 to 4 (64 patients), and 5 or more (107 patients) U of RBCs, respectively. The transfused group included 171 recipients (76%) who received at least 1 U of RBCs intraoperatively.

STATISTICAL ANALYSIS

The influence of the following variables on patient and graft survival after OLT were determined by univariate analysis: age, sex, primary diagnosis, medical condition at the time of transplantation, previous abdominal surgery, transjugular intrahepatic portosystemic shunts, preoperative prothrombin time, intraoperative RBC requirement, cold ischemia time, and operative time. The patient's condition at the time of transplantation was based on Child's classification and United Network for Organ Sharing (UNOS) status. Patient and graft survival were also calculated for the transfused and nontransfused groups. Variables that had a substantial effect on patient and graft survival by univariate analysis were entered into a proportional hazards regression analysis along with transfused and nontransfused recipients to determine whether transfusion of packed RBCs was independently associated with survival or whether confounding variables were present.

Univariate analysis was performed by the Mann-Whitney nonparametric test. Patient and graft survival were determined using a log rank (Mantel-Cox) test and Kaplan-Meier cumulative survival plot. A proportional hazards model was used to control for any intergroup differences based on the aforementioned variables found to have a substantial effect on survival. Factors that were significant in univariate (Mann-Whitney) tests ($P < .05$) were considered in a multivariate proportional hazards regression model. Backward stepwise selection was used to find a group of factors that best influenced outcome. In the first step, all factors that had a significant effect on outcome as determined by univariate analysis were considered. At each step, the factor with the largest P value for significance was removed until only those factors with $P < .05$ remained. These remaining factors were then considered to be those that were statistically significant in predicting outcome. Statistical software (S-PLUS, Version 3.2, StatSci, Division of MathSoft Inc, Seattle, Wash) was used to perform the logistic regression analysis.

fused intraoperatively, were subjected to stepwise multivariate analysis, intraoperative transfusion of RBCs was not significant and only age ($P = .03$), sex ($P = .004$), and patient's medical condition ($P = .003$) remained significant (**Table 1**). The results of similar univariate and multivariate analyses for graft survival are given in Table 1. Men had poorer survival than women and survival was worse for critically ill patients (status 1 and 2a based on current UNOS classification).

When survival rates were examined, patient and graft survival decreased if 5 U or more were transfused ($P = .006$ and $P = .01$, respectively) (**Figure 2**). When subjected to multivariate analysis along with age, sex, and patient's medical condition, transfusion of 5 U or more was not independently associated with patient or graft survival (**Table 2**).

Transfusion of packed RBCs, when examined as a continuous variable, was found to influence patient and graft survival by univariate analysis ($P < .001$). When subjected to multivariate analysis, blood transfusion as a continuous variable remained significant for both patient ($P = .008$) and graft ($P = .03$) survival, along with age, sex, and the patient's medical condition (**Table 3**). **Figure 3** shows relative survival as a function of amount of RBC transfusion and demonstrates decreasing survival with increasing transfusion requirement.

When causes of patient and graft loss were examined, only 1 patient died (primary nonfunction) and 1 patient lost a graft (hepatic artery thrombosis) in the nontransfused group. Twenty-nine recipients in the transfused group died, and 45% (13 patients) died of septic complications, including generalized sepsis, endocarditis, aspergillosis, and bacterial pneumonia. The remaining causes of death were cancer (5 patients), cardiovascular disease (3 patients), trauma (3 patients), intraoperative cardiac arrest (2 patients), primary graft nonfunction (2 patients), natural causes (2 patients), and recurrent disease (1 patient). Causes of graft loss in the group included biliary strictures, hepatic artery thrombosis, and primary graft nonfunction, 1 patient each.

COMMENT

Several centers have examined factors that influence patient and graft survival after OLT, but no consensus exists as to which variables accurately predict outcome after OLT.[2-7] According to these studies, factors that have increased the risk of death or graft loss for patients

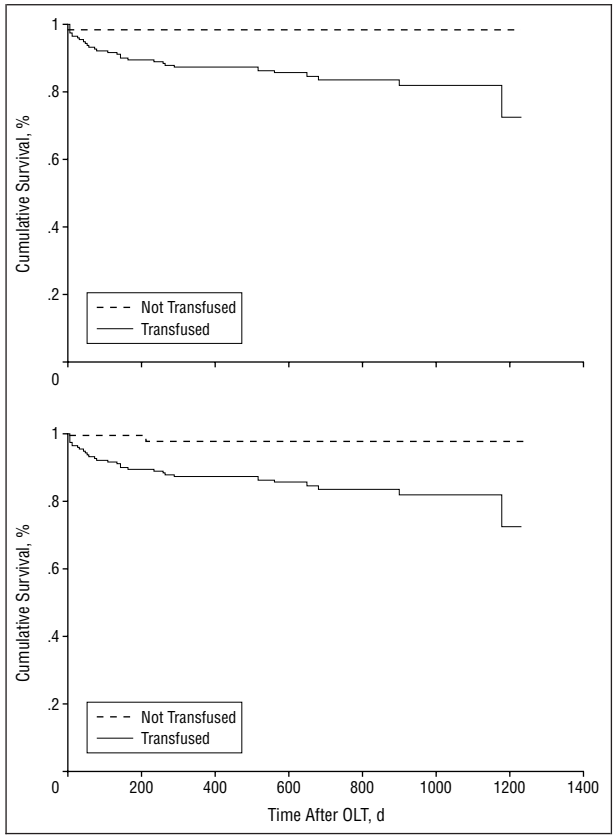

Figure 1. *Patient survival (top) and graft survival (bottom) by intraoperative transfusion of red blood cells in 225 orthotopic liver transplantations (OLTs). The differences in patient survival (*P *= .01) and graft survival (*P *= .3) between recipients transfused and not transfused intraoperatively were statistically significant.*

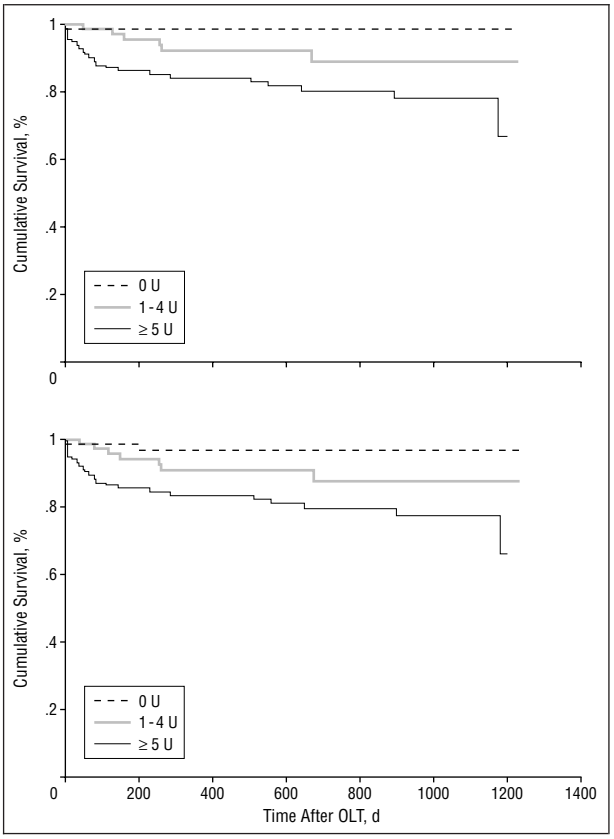

Figure 2. *Patient survival (top) and graft survival (bottom) by intraoperative transfusion of red blood cells (RBCs) in 225 orthotopic liver transplantation (OLT) recipients. The differences in patient survival (*P *= .006) and graft survival (*P *= .01) between recipients transfused 0 U and 5 or more U of RBCs intraoperatively was statistically significant.*

Table 1. Variables Influencing Patient and Graft Survival After OLT in Recipients Receiving No RBCs vs 1 Unit or More of RBCs Intraoperatively*

Variable	Univariate Analysis	Multivariate Analysis
Patient survival		
0 vs ≥1 U RBCs	.01	.17
Age	.04	.03
Sex	.005	.004
Patient's medical condition	.002	.003
Graft survival		
0 vs ≥1 U RBCs	.03	.30
Sex	.008	.005
Patient's medical condition	.002	.002

Table 2. Variables Influencing Patient and Graft Survival After OLT in Recipients Receiving Less Than 5 vs 5 Units or More of RBCs Intraoperatively*

Variable	Univariate Analysis	Multivariate Analysis
Patient survival		
<5 vs ≥ 5 U RBCs	.004	.12
Age	.04	.02
Sex	.005	.005
Patient's medical condition	.002	.006
Graft survival		
<5 vs ≥5 U RBCs	.01	.20
Sex	.008	.006
Patient's medical condition	.002	.01

**OLT indicates orthotopic liver transplantation; RBCs, red blood cells.*
P *values were calculated using proportional hazards regression analysis.*

undergoing OLT vary and include UNOS status, Child's classification, fulminant hepatic failure, ABO incompatibility, compromised renal function, and infection before transplantation. In addition, some studies have reported a detrimental effect of intraoperative blood loss and massive transfusion requirements after liver transplantation.[2,3,7,8] In a previous study, we conducted an analysis of several factors on the need for blood transfusion.[12] These factors were recipient's age at the time of transplantation, sex, Child's classification, UNOS status, preoperative hematocrit, prothrombin time, partial thromboplastin time, platelet count, and fibrinogen level. In addition, other factors examined were primary liver disease, year of transplantation, history of abdominal surgery, transjugular intrahepatic portosystemic shunt placed prior to transplantation, use of venovenous bypass technique for transplantation, cold ischemia time, and operative time. The univariate

Table 3. Variables Influencing Patient and Graft Survival After OLT, Analyzing Transfusion of RBCs as a Continuous Variable*

Variable	Univariate Analysis	Multivariate Analysis
Patient survival		
RBC transfusion	.0001	.39
Age	.04	.02
Sex	.005	.003
Patient's medical condition	.002	.003
Graft survival		
RBC transfusion	.0001	.61
Sex	.008	.004
Patient's medical condition	.002	.005

**OLT indicates orthotopic liver transplantation; RBCs, red blood cells.*
P *values were calculated using proportional hazards regression analysis.*

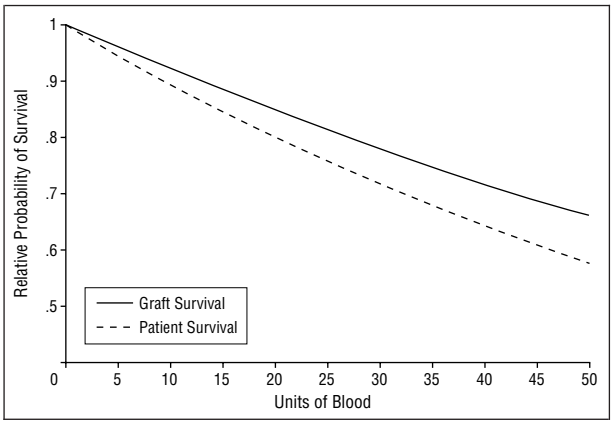

Figure 3. *Relative probability of patient and graft survival based on transfusion requirements when analyzed as a continuous variable.*

analysis showed the following factors to be associated with OLT without blood transfusions: Child's classification, UNOS status, lack of previous right upper quadrant surgery, preoperative hematocrit, prothrombin time, activated partial thromboplastin time, piggyback technique, operative time, adult recipient status, and year of transplantation. A regression analysis showed that UNOS status (healthier patients required less blood), preoperative hematocrit, piggyback technique, operative time, and year of transplantation remained independently associated with OLT without transfusion of RBCs.[12] Unfortunately, donor information was not available for the analysis.

The present study examined the effect of OLT without transfusion of any RBCs on patient and graft outcome. A significant improvement was noted in both patient and graft survival when recipients underwent OLT without intraoperative transfusion of RBCs. However, other factors, rather than the presence or absence of intraoperative blood transfusions, appear to have a more substantial effect on outcome. Male sex and severity of the patient's medical condition (patients in an intensive care unit) had a negative influence on patient and graft survival. This finding is in agreement with UNOS scientific registry data, which have shown that sex and patient's medical condition affect both patient and graft survival.[1,12]

Why OLT without RBCs transfusion was not independently associated with superior patient and graft survival may be related to several factors. Previous studies demonstrating an adverse effect of transfusion requirements on outcome were conducted during an earlier era of OLT and examined the effects of massive intraoperative transfusion of blood and blood products.[2,3,8] A more recent study also divided patients into a group of "bleeders" who received 10 U or more of RBCs.[7] The present study compared patients receiving no RBCs with a group who received at least 1 U of RBC intraoperatively, and the study population did not contain a large proportion of bleeders. In fact, 50 patients (29%) in the transfused group received 3 U of packed RBCs or less intraoperatively (mean 5.7 U, median 4.0 U, range 1-67 U). The small number of RBCs required intraoperatively in the present study is probably due to technical improvements in performing OLT. Even when a group of recipients who received 5 U or more of RBCs was examined, an independent association with survival was not seen. Because many patients in the transfused group received few RBCs, the detrimental effect of massive transfusions in the few patients who required it were most likely masked by the remaining patients receiving only a few units of RBCs.

When cutoff points were not employed and blood transfusion was examined as a continuous variable, it did have an independent association with survival. The concept that increased blood loss, and hence, a greater transfusion requirement during the transplantation, affects survival agrees with other data.[2,3,7] Although blood loss is not the only factor that influences survival, it does point to the need for attention to detail during the procedure.

Previous studies have reported a high mortality rate secondary to infectious complications in general,[13,14] and particularly in patients who have received blood transfusions.[7] Almost half the deaths in the present study involved septic complications, similar to the previous studies. In addition, all deaths due to sepsis occurred in the group that received transfusions, and the mean intraoperative RBC transfusion requirement for these patients was 13 U.

The present study demonstrates that recipients who undergo OLT without transfusion of RBCs have superior patient and graft survival when compared with transfusion recipients, but other factors have a substantial effect on outcome after OLT, namely, age, male sex, and medical condition at the time of transplantation. When the effect of intraoperative blood transfusion on survival was examined as a continuous variable, an independent association with survival was noted, suggesting that blood loss should be kept to a minimum during the transplantation.

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IN OTHER AMA JOURNALS

JAMA

Acupuncture

NIN Consensus Development Panel on Acupuncture

Objective: To provide clinicians, patients, and the general public with a responsible assessment of the use and effectiveness of acupuncture to treat a variety of conditions.

Participants: A nonfederal, nonadvocate, 12-member panel representing the fields of acupuncture, pain, psychology, psychiatry, physical medicine and rehabilitation, drug abuse, family practice, internal medicine, health policy, epidemiology, statistics, physiology, biophysics, and the representatives of the public. In addition, 25 experts from these same fields presented data to the panel and a conference audience of 1200. Presentations and discussions were divided into 3 phases over 2½ days: (1) presentations by investigators working in areas relevant to the consensus questions during a 2-day public session; (2) questions and statements from conference attendees during open discussion periods that were part of the public session; and (3) closed deliberations by the panel during the remainder of the second day and morning of the third. The conference was organized and supported by the Office of Alternative Medicine and the Office of Medical Applications of Research, National Institutes of Health, Bethesda, Md.

Evidence: The literature, produced from January 1970 to October 1997, was searched through MEDLINE, Allied and Alternative Medicine, EMBASE, and MANTIS, as well as through a hand search of 9 journals that were not indexed by the National Library of Medicine. An extensive bibliography of 2302 references was provided to the panel and the conference audience. Expert speakers prepared abstracts of their own conference presentations with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience.

Consensus Process: The panel, answering predefined questions, developed their conclusions based on the scientific evidence presented in the open forum and scientific literature. The panel composed a draft statement, which was read in its entirety and circulated to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement at the end of the conference. The panel finalized the revisions within a few weeks after the conference. The draft statement was made available on the World Wide Web immediately following its release at the conference and was updated with the panel's final revisions within a few weeks of the conference. The statement is available at http://consensus.nih.gov.

Conclusions: Acupuncture as a therapeutic intervention is widely practiced in the United States. Although there have been many studies of its potential usefulness, many of these studies provide equivocal results because of design, sample size, and other factors. The issue is further complicated by inherent difficulties in the use of appropriate controls, such as placebos and sham acupuncture groups. However, promising results have emerged, for example, showing efficacy of acupuncture in adult postoperative and chemotherapy nausea and vomiting and in postoperative dental pain. There are other situations, such as addiction, stroke rehabilitation, headache, menstrual cramps, tennis elbow, fibromyalgia, myofascial pain, osteoarthritis, low back pain, carpal tunnel syndrome, and asthma, in which acupuncture may be useful as an adjunct treatment or an acceptable alternative or be included in a comprehensive management program. Further research is likely to uncover additional areas where acupuncture interventions will be useful. (*1998;280:1518-1524*)

NIH Consensus Statements, NIH Technology Assessment Statements, and related materials are available by writing to the NIH Consensus Program Information Center, PO Box 2577, Kensington, MD 20891, by calling toll free 1 (888) 644-2667, or by visiting the NIH Consensus Development Program home page at http://consensus.nih.gov.