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PROLONGATION EFFECT OF BLOOD TRANSFUSIONS ON KIDNEY GRAFT SURVIVAL[1]

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SUMMARY

Transfusion data were collected during a 3-year period on 382 hemodialysis patients with the aid of a computerized followup system. Thirty-seven per cent of the patients did not receive any blood transfusions prior to transplantation. The graft survival in nontransfused patients was statistically significantly lower than that in transfused patients. These results confirm our previous findings in an independent series of patients.

Transfusion guidelines for potential kidney transplant recipients are of growing concern to dialysis and transplant physicians. Although we have provided evidence that, contrary to expectation, pretransplant blood transfusions have a prolongation effect on the survival of kidney grafts (*8*, *10*), these data have been met with skepticism. Fear of recipient preimmunization to transplantation antigens and of hepatitis transmission has led to restriction of transfusion policies at most dialysis units in the United States, and increasing numbers of patients are now receiving transplants without having been exposed to blood transfusions.

A potential deficiency of our previous studies was that they were based on transfusion data collected retrospectively from hospital files. Because patients had often been transferred from one hospital to another, or because patient files were sometimes incomplete, it was difficult to determine the accuracy of our analyses. This is a report on the first study based on transfusion data that were collected in a systematic manner during the patient's pretransplant dialysis period. The results in this entirely new series of patients substantiate our previous findings that blood transfusions have a beneficial effect on the outcome of renal allografts.

[1] This study was supported solely by the aid of the 20 transplant and dialysis centers that contributed their data.

MATERIALS AND METHODS

Following our preliminary analysis in 1972 of the effect of blood transfusions on cadaver kidney transplants (*8*), we decided to institute a mechanism whereby transfusions into hemodialysis patients could be monitored regularly. Twenty United States transplant centers volunteered to cooperate in this effort. A computerized followup and data storage system were developed. Each center was requested to update biweekly transfusion data on all prospective transplant candidates. Date, type of blood product, and number of transfused units were recorded. Whenever possible, sera samples were obtained from patients approximately 2 weeks after each transfusion and tested for the presence of lymphocytotoxic antibodies against a panel of 90 random lymphocyte donors. Reactivity against more than 5% of the donor panel was considered to indicate presence of cytotoxic antibodies (*9*). All data were computerized and returned to the contributing centers for verification. The majority (over 90%) of nonfrozen blood transfusions were given in the form of packed cells, and the remainder as whole blood; no distinction between these two categories was made in this analysis.

It should be emphasized that this new series of patients without pretransplant transfusions did not include any transplants that had been analyzed in our previous studies. Our report published in 1974 was the result of a one-time

nationwide survey and did not include patients that were part of this continuous transfusion followup study.

All transplants analyzed in this study were done between June 1972 and June 1975. Only first transplants from cadaver donors with a clinical followup of at least 3 months were analyzed. No exclusions of technical or other nonimmunological failures were made. Graft survival rates were calculated by actuarial methods by using the BMD program series of the UCLA Health Sciences Computing Facility (2).

RESULTS

A total of 382 patients in whom transfusion data had been collected since the onset of treatment for chronic renal failure received primary transplants from cadaver donors at the 20 participating centers. Of these patients, 143 from 16 centers were transplanted without having been transfused at all, 49 patients had received exclusively frozen blood, and 190 had received packed cells or whole blood.

Patients without pretransplant transfusions had a clearly inferior graft survival rate of 31 ± 4% (mean ± standard error) at 1 year and 21 ± 4% at 2 years, compared to 124 patients with 1–5 units of blood (49 ± 5% at 1 year, $P < 0.01$; 37 ± 5% at 2 years, $P < 0.02$) or to 66 patients with more than 5 units (48 ± 6% at 1 yr, $P < 0.03$; 48 ± 6% at 2 years, $P < 0.001$) (Fig. 1). The 49 patients who had only received frozen blood had an intermediate graft survival of 42 ± 7% at 1 year. A meaningful comparison of transplant outcome in transfused and nontransfused patients at individual transplant centers could not be made because of the small numbers of patients involved.

All 143 patients without transfusions were tested for the presence of lymphocytotoxic antibodies prior to transplantation, and the serum of 10 (7%) reacted against more than 5% of the test panel. Grafts in nine of these 10 patients failed within the first year. The remaining 133 patients without evidence of preformed antibodies had a poor 1-year graft survival rate of 34 ± 4%.

In comparison, patients with pretransplant transfusions fared much better. Of 90 patients with one to five transfusions who were tested, 14 (16%) had antibodies. At 1 year, the graft survival rate in these patients (57 ± 13%) was not significantly different from the 54 ± 6% in 76 patients without antibodies. In the more than five-transfusion category, 13 patients (23%) had antibodies and their grafts survived at a rate of 37 ± 14% at 1 year, compared to 51 ± 8% in 44 patients without antibodies. The number of patients with preformed antibodies is too small to allow definite conclusions although, in general, patients with antibodies did less well than patients without. However, even if antibodies had been formed in transfused patients, their transplant survival was not inferior to that in patients who had no antibodies and had never been transfused. When only patients without preformed antibodies are compared, those who had received transfusions again had higher survival rates than those without transfusions ($P < 0.005$).

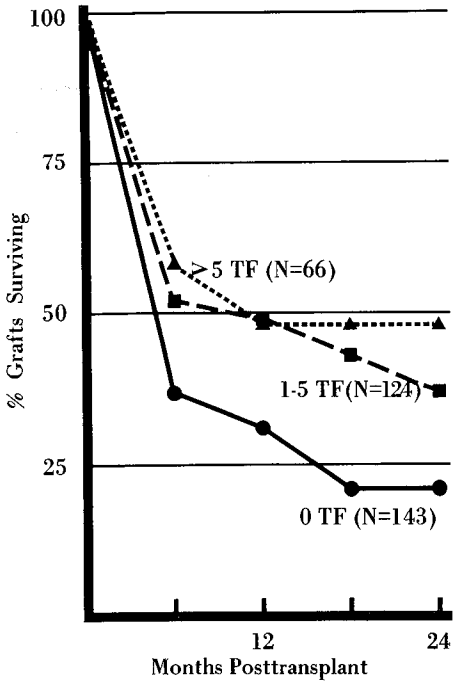

FIGURE 1. Actuarial graft survival for cadaver transplants in recipients with 0, 1–5, or more than 5 pretransplant blood transfusions. The success rate in nontransfused patients was statistically significantly lower than in transfused patients.

DISCUSSION

Although it is commonly assumed that transfusions lead to presentization or preimmuniza-

tion, there is abundant evidence in the animal model that not all injection of blood before a graft will result in immunization. In fact, in many instances prolongation and enhancement of graft survival has been found (*1*, *4*, *11*). Despite this evidence, and because of the poor transplant survival in patients with high levels of preformed cytotoxic antibodies, clinicians have equated transfusions with immunizations and have resisted the concept that transfusions could induce graft enhancement. An indication of how rapidly the immunization concept has gained momentum in recent years is shown by the fact that we had great difficulty in finding 25 patients who had been transplanted without any transfusions in 1972. By contrast, in this study there are 143 patients with no transfusions. At least in this series 37% of the patients had not received any transfusions. This proportion may be reasonably representative of the current policy among centers in the United States.

In clinical kidney transplantation, over the past few years there have been relatively few changes in immunosuppressive therapy, and this rather drastic change in transfusion policy may be one of the most significant changes in transplantation. We have thus proposed that the decreasing overall transplant survival rates may be attributable to this change in transfusion protocols (*12*).

The close correlation of the survival rates observed in our three studies is striking (Table 1). The paradoxical effect of transfusions described by us (*8–10*) has now been confirmed in series of patients from Boston (*5*), Leiden (J. Van Rood, personal communication), and London (*3*). The present study again reconfirms the beneficial effect of transfusions, and for the first time in patients whose transfusion data has been collected during the time of dialysis. Since transfusion data are notoriously inaccurate, we took pains to collect data on a biweekly basis. Interestingly, it appears from this study that the graft prolongation effect can be produced by only a few units of transfused blood. The data accumulated thus far indicate that frozen blood is an inferior "inducer" compared to packed cells or whole blood; however, the number of patients studied were small and the results were variable. Identification of the most effective method of inducing unresponsiveness should be a primary target of future investigations.

TABLE 1. Graft survival rates in three independent series of cadaver transplant recipients without pretransplant transfusions

Year of study	No. of patients	1-year graft survival rates (% ± SE)
1972 (*8*)	25	29 ± 10
1974 (*10*)	62	32 ± 7
1976	143	31 ± 4

There still may be difficulties in accepting these results at face value. For example, certain types of lower risk patients may tend to receive transfusions. Hypertensive patients on certain drug regimens may respond differently to transfusions and transplants. Possibly, a transplant center effect in which poor centers have not tended to transfuse could have an influence. Such a center was not readily apparent in this series.

Overall, the evidence does point to the conclusion that the basic success rate of cadaver donor transplants is about 30% at 1 year in untreated patients and the 50% 1-year survival rate commonly quoted is produced by the effect of transfusions. If this were true, what can now be done?

It is most urgent that a prospective transfusion history collection system be initiated at all dialysis centers. These data are needed for all patients being transplanted. At least on a retrospective basis, data such as the effect of dose, frequency, timing before transplantation, and type of blood product given can yield the necessary information. We wish to appeal to the United States and Canadian centers to incorporate the computerized transfusion update file as part of their ongoing program.

Regarding the possibility of taking a positive step, one approach is to try to maintain a dialysis patient at a higher hematocrit level. Family members with known negative hepatitis histories could be used as blood donors. This would also permit the use of limited HLA specificities as the stimulus. The extreme treatment of transfusing the patient with blood from the transplant donor has been used in several instances with remarkable success. Grafts in all four patients treated by Newton and Anderson (*6*) survived for more than a year. Two of these

patients who received unrelated living donor grafts have still functioning grafts, one of them after 4½ years in spite of a positive pretransplant crossmatch test (W. T. Newton, personal communication). The other two patients died of seemingly nonimmunological reasons. Interestingly, three of these four patients had not developed cytotoxic antibodies in spite of repeated white cell injection (*6*). A fifth patient who had been transfused with 2 units of blood from his mother has a functioning graft 1½ years post-transplant (R. N. Fine, personal communication). Results of recent experiments in dogs also support the concept of induced unresponsiveness by transfusions (*7*).

A program of indiscriminate transfusions in prospective transplant recipients can certainly not be advocated. Carefully controlled studies and scientific evaluation of the effect of all transfusions, as proposed by us, should be the logical next step. Identification of methods to accurately determine a patient's immunological responsiveness *in vitro* would greatly enhance the applicability of planned transfusion therapy. The computerized transfusion followup system advocated by us will provide the basis for these studies.

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