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Effect of Donor Pretreatment on the Graft Survival of Human Cadaver Kidneys

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The effect of donor pretreatment on perfused cadaver kidney allografts was evaluated in 40 recipients at Henry Ford Hospital over a two-year period. Of the 40, 23 received kidneys from donors pretreated with 40 mg/K each of cyclophosphamide and methylprednisolone during the first year of the study and up to 70 mg/K during the second year. Our results indicated that donor pretreatment for five to eight hours did not consistently improve survival rates in pretreated perfused cadaver kidneys following transplantation. The use of cyclophosphamide for donor pretreatment does not prevent the use of continuous perfusion to preserve human kidneys. Dosages up to 70 mg/K may be used without an apparent increase in acute tubular necrosis or significant early loss of renal function.

ALTHOUGH prolongation of renal allograft survival by donor pretreatment with immunosuppressives in animal studies has been well established,[1] these findings have not been conclusive in humans. Guttmann and co-workers[2] have reported improved graft survival following donor pretreatment with a combination of cyclophosphamide (40 mg/K) and methylprednisolone (40 mg/K) five to eight hours before harvesting. Zincke and Woods[3] have reported that cyclophosphamide (60 mg/K) six to eight hours before harvesting followed in three to five hours by the same dose of methylprednisolone was also effective. Initially, in our Michigan study pretreatment with 40 mg/K each of cyclophosphamide and methylprednisolone before harvesting showed prolonged graft survival. However, when donors were completely randomized, this augmented graft survival was no longer apparent.[4] Chatterjee used 70 mg/K of methylprednisolone alone as pretreatment in a controlled double-blind study and found it to be ineffective in prolonging graft survival.[5] Jeffery *et al* in a randomized study used cyclophosphamide (100 mg/K) and methylprednisolone (70 mg/K) four hours before nephrectomy, but found no beneficial effect on graft survival or function.[6] The purpose of this study is to evaluate the effect of donor pretreatment on perfused cadaver kidney allografts at Henry Ford Hospital.

Patients and Methods

From June 1973 to July 1975, 23 recipients received kidneys from pretreated donors and 17 from nonpretreated. During the first year, donors were selected and pretreated five to eight hours before nephrectomy with 40 mg/K each of cyclophosphamide and methylprednisolone. Afterward, donors were alternated and finally randomized between treated and control groups. First the dosage of cyclophosphamide and then of methylprednisolone was increased to 70 mg/K after the first year. These drugs were given after brain death had been declared.

Blood pressure of the donors was supported to 100 mm Hg systolic with dopamine as necessary, and urine output was maintained with adequate fluid replacement. All kidneys

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were preserved at 4°C by hypothermic pulsatile perfusion with cryoprecipitated plasma for variable periods of time (average of 14 hours). The surgical technique, immunosuppression, and postoperative treatment remained constant throughout the study. A cooling jacket during transplantation was used to reduce rewarming time.[7-8] Azathioprine 5.0 mg/K was given for one day, then 2.0 mg/K/day for 14 days, and then 1.0-2.0 mg/K/day adjusted to the level of the white blood cell count. Methylprednisolone was given at a dose of 1.2 mg/K/day on the day of surgery. Thereafter, the total dose was reduced by 2.0 mg each day to a maintenance dose of 10 to 30 mg daily. For rejection episodes, patients were treated with 1.0 gm of intravenously administered methylprednisolone for each of three consecutive days.

All patients have been at risk for at least six months. The life table method of Merrell and Shulman[9] was used to determine the graft survival.

Results

The actuarial functional survival rate of all recipients who received grafts from all pretreated donors at one, two, and three years was 48%, 35%, and 30%, respectively (Figure 1). These figures do not significantly differ from those for nonpretreated group, in which the survival rate at one, two, and three years was 47%, 41%, and 41%, respectively (Figure 1). Better survival was achieved in the first group in which donors had been selected and treated with 40 mg/K of cyclophosphamide and methylprednisolone. The actuarial graft survival rates in this group were 63%, 50%, and 38% at one, two, and three years, respectively (Figure 2).

Diabetes, the number of previous transplants, and sex did not significantly affect the survival rate of the grafts in either the pretreated or nonpretreated groups. Graft failure due to acute tubular necrosis (Figure 1) and infection occurred in both treated and control groups equally.

Discussion

Overall, donor pretreatment for five to eight hours did not consistently improve survival rates in pretreated perfused cadaver kidneys following transplantation. These results contrast with the findings of Guttmann *et al*[2] and Zincke,[3] who have had excellent results with pretreated kidneys. Three variables must be considered in comparing these clinical studies: 1) method of preservation, 2) dosage and timing of the pretreatment drugs, and 3) the degree to which the kidney donor source has been randomized.

In Guttmann's series, continuous perfusion was not used. The kidneys were cooled by flushing and by surface cooling with cold Ringer's lactate. They were then transplanted with a maximum of cold preservation time, generally two to six hours.[2] This routine is supported by studies showing that canine kidneys on perfusion or in Collins solution will not survive as viable grafts in the recipient if the donor is pretreated with cyclophosphamide. As a result of this "preservation intolerance" many programs dependent on perfusion have been discouraged from studying pretreatment. However, both Zincke's study[3] of the substantial number of human kidneys that functioned well after cyclophosphamide pretreatment (60 mg/K) and our work with good function of 24-hour perfused, pretreated dog

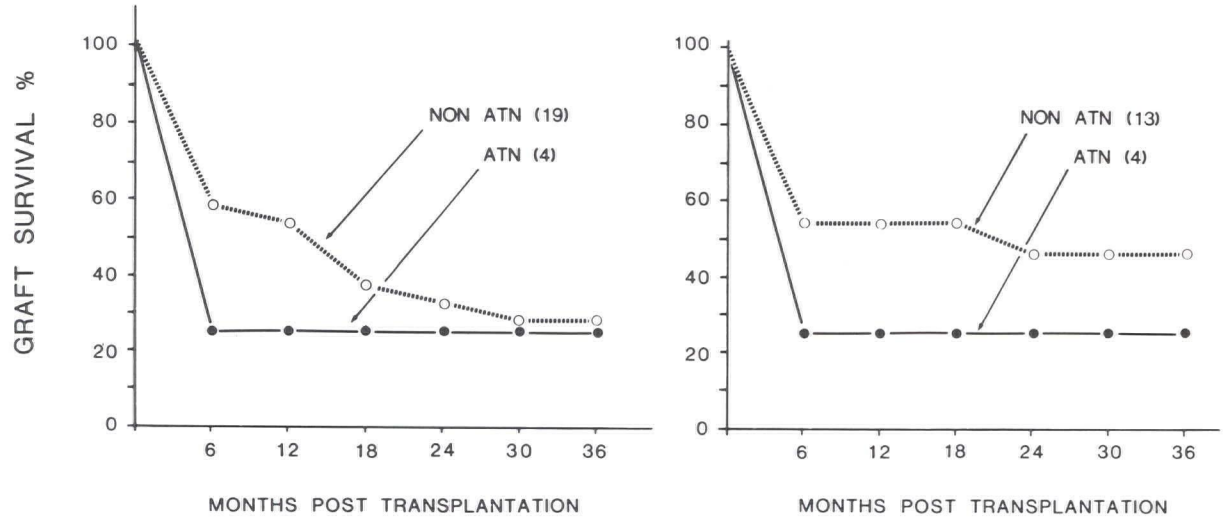

Fig. 1
Graft survival in months of kidneys with and without acute tubular necrosis (ATN) Left: pretreated kidneys. Right: nonpretreated kidneys.

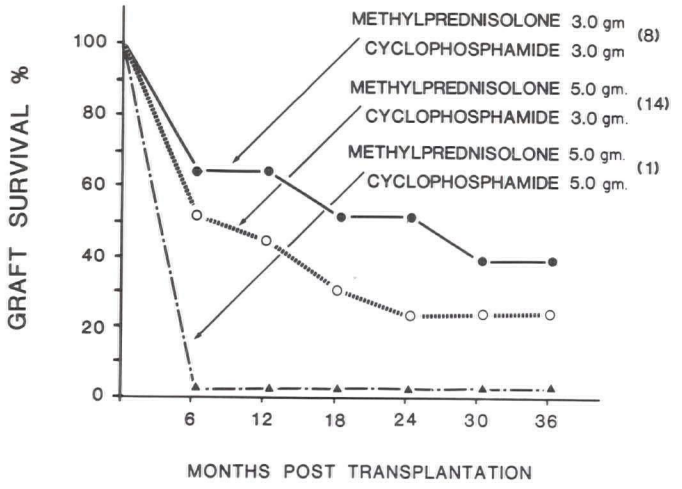

Fig. 2
Graft survival in months for three different dosage regimens: Selected (·—·—·), alternated (○ ····· ○ ····· ○), and randomized (▲·—·—▲—·).

kidneys (100 mg/K) now tend to minimize the hazard of using perfusion to preserve pretreated kidneys.

The dosage of cyclophosphamide and methylprednisolone in these clinical studies has varied from 40 to 80 mg/K. The higher dose of cyclophosphamide has not produced any appreciable loss of renal function, and the preferred dose has become 5.0 gm or 70 mg/K for an adult donor. In fact, pretreated kidneys provide the recipients with a lower mean creatinine level during the first four weeks postoperatively. The optimal dosage of methylprednisolone is more equivocal. Although dosages have been increased to as high as 70 mg/K, a fall in graft survival of pretreated kidneys was associated with dosages between 40 and 70 mg/K in both this study and in the Michigan study.[4] This may or may not be a significant variable. Observations from the use of three consecutive daily doses of methylprednisolone systemically in the dog after transplantation indicate that 70 mg/K will produce a consistent loss of function and definite glomerular and tubular lesions.[10] Therefore, 30 to 50 mg/K of methylprednisolone would seem to be the appropriate range.

The third variable in these clinical trials was the randomizing of kidneys between pretreated and control groups. In Guttmann's series, the pretreated donors came from the transplant center hospital, while the donors used for controls were harvested at other hospitals. In both groups, ice storage was the method of preservation.[3] The grafts were followed for three and a half years, and survival between pretreated and nontreated was 81% versus 60%. Similarly, in the study by Zincke at the Mayo Clinic, pretreated kidneys were harvested locally, while kidneys harvested by other teams and transported long distances were used as the control kidneys. All of the kidneys in the Zincke's study were preserved by continuous perfusion. The difference in one-year graft survival between pretreated and nontreated groups was more substantial than in Guttmann's series (82% versus 43%).

In both of these studies, it is important to question the role of donor selection on the results in the control group. Programs analyzing their kidney procurement program often report an increase in the survival of kidneys harvested locally. In the Michigan study kidneys were harvested from all over the state through its cooperative organ donor program, and an effort was made to keep the number of treated and nontreated patients equal. It is true that pretreated kidneys came from donors who were known to be stable and from institutions that would transport blood or nodes for typing before pretreatment started. However, the statistics of age and length of perfusion did not differ between the pretreated and nonpretreated groups. The most significant indications from the Michigan study were that when the assignment of donors was made nonselective as alternate cases or was completely randomized, graft survival in the control and treated groups was equalized.

The general scientific criticism of donor pretreatment as an applied clinical method for augmenting kidney graft survival is that, like other immunological methods which work well in small inbred animals, it has not been shown to be effective in an outbred species. However, Woods has shown moderate prolongation of mongrel canine kidney allografts by pretreatment of the donors with procarbazine.[11] We have recently shown in dogs that cyclophosphamide and methylprednisolone acting over 18 to 24 hours in the donor can produce very significant extension of graft survival. It remains to be determined whether a protocol with a longer donor pretreatment interval such as this is necessary for human cadaver kidney doners.

Conclusions

1) The use of continuous perfusion preservation for human kidneys does not interdict the use of cyclophosphamide for donor pretreatment.

2) Dosages of up to 70 mg/K of cyclophosphamide may be used without an apparent increase in acute tubular necrosis or significant early loss of renal function.

3) Further truly randomized clinical trials will be necessary to establish donor pretreatment as a means of reducing rejection and extending human kidney graft survival.

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