A CONTROLLED TRIAL EVALUATING INTENSIVE PLASMA EXCHANGE IN RENAL TRANSPLANT RECIPIENTS

C J Cardella, D M C Sutton, A Katz, P R Uldall, M Harding, P N Corey, G T Cook, G A Deveber

Departments of Medicine, Pathology, and Preventative Medicine and Biostatistics, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada

Summary

Sixty patients have been entered into a controlled trial evaluating the use of intensive plasma exchange (IPE) in renal transplant recipients. During the first three months post-transplant, patients receive either conventional anti-rejection therapy alone (control group) or conventional anti-rejection therapy and IPE (IPE group) for all rejection episodes. Twenty percent of the grafts in the control group versus 10% in the IPE group have been lost to rejection (p = NS). The actual three month patient and graft survival in the control group (97% and 70%), respectively, is similar to the IPE group (94% and 80%), as is the one year actuarial graft and patient survival in the two groups. No statistically significant benefit of IPE has yet been demonstrated but the trend is encouraging and the complication rate sufficiently low so as to justify continuing the study.

Introduction

Previous reports have suggested that intensive plasma exchange (IPE) may favourably modify the effect of humoral rejection in renal allografts [1—4]. Several problems, however, are raised by these observations. The lack of appropriate controls and the effect of other anti-rejection therapy put into question the effectiveness of plasma exchange therapy alone in the treatment of rejection episodes. Moreover, if there is a beneficial effect of IPE, the frequency of exchanges, the time to initiate them, and the type of rejection episodes likely to respond have not been defined by these studies. Also, it is not clear if plasma exchange should be used alone or as an adjunct to conventional anti-rejection therapy.

In order to clarify these concerns, a controlled trial of IPE in renal transplant recipients was initiated two and a half years ago. The aims of this study are to evaluate the safety and effectiveness of repeated courses of plasma exchange in transplant patients, to define the role of IPE in the therapy of acute rejection
episodes, and to establish if IPE has a beneficial effect on immediate and long term graft survival. This report summarises the preliminary results of this trial in which plasma exchange is used as an adjunct to conventional anti-rejection therapy in patients undergoing rejection episodes in the first three months post transplant.

Patients and Methods

Sixty non-diabetic first renal transplant recipients performed at the Toronto Western Hospital since November 1977 have been entered into the study thus far. At the time of transplantation, patients were stratified into three categories: firstly, those with a living related donor; secondly, those with a cadaveric donor and the kidney preserved by cold storage; and, thirdly, those with a cadaveric donor and the kidney preserved by machine perfusion. Stratification was used because the numbers in the study were not expected to be large enough to overcome the effects of these variables on graft outcome [5]. After patients were assigned to each stratum, they were then randomly allocated to the control group or to the IPE group. Both groups were operated on by the same transplant surgeon and received the same baseline immunosuppressive drug therapy (azathioprine and prednisone). Patients were entered into the study for the first three months post-transplant and during this time all rejection episodes in both groups were treated as below, providing no clinical contraindication was present.

In both groups, the first rejection episode was treated with 150 Rads of radiation daily for three days and all rejection episodes were treated for three consecutive days with bolus methylprednisolone (10mg/kg/day) and then the dose of steroid was slowly reduced to baseline. In the IPE group, a rejection episode was also treated with five consecutive days of IPE. Vascular access was obtained by the use of a pre-existing AV fistula or by the insertion of a large lumen subclavian cannula [6]. Using a Haemonetics 30 cell separator, four litres of plasma were exchanged for albumin in saline and one unit of fresh frozen plasma on each day of therapy. The first plasma exchange was instituted within 24 hours of the onset of a rejection episode. During a rejection episode in either group, if graft function did not start to improve by day three after the onset of the rejection or if the serum creatinine plateaued on day six significantly above baseline, rabbit antithymocyte serum was added to the anti-rejection therapy for six days.

When a rejection episode took place after the three month trial period, treatment was individualised according to the clinical status of the patient. Patients were monitored with daily serum creatinine and haematology in the early post-transplant period. Other biochemical and immunological data were obtained as required.

Patients underwent renal biopsy if a rejection episode did not respond to therapy or to aid in the diagnosis of a change in graft function. Each biopsy was interpreted by the same pathologist who was unaware of the patient's group allocation. On the basis of the usual histological, electron microscopic, and immunofluorescence criteria, each biopsy was evaluated regarding the presence of humoral and/or cellular rejection. Severity was graded as mild, moderate, or severe for each type of rejection process.

430
Results

Thirty patients in the control group have received conventional anti-rejection therapy only (no IPE group) and 30 have received IPE and conventional anti-rejection therapy (IPE group). There is no significant difference in the number of pre-transplant blood transfusions, number of months on dialysis, number of living related and cadaveric donors, number of HLA matches, and maximum percent pre-transplant cytotoxic antibody in the two groups. By chance alone, the average age of the patients in the IPE group (36 years) is significantly less than that in the control group (44 years) \( p = 0.02 \).

Renal biopsies were performed during 53 rejection episodes. Of the 26 biopsies in the IPE group, 17 showed moderate or severe humoral rejection and 15 of the 27 biopsies in the control group had similar changes. There was evidence of moderate or severe cellular rejection in 12 biopsies in the IPE patients and 11 in the controls.

During the first three months post transplant, 62 rejection episodes occurred in the IPE group (average 2.0 per patient), of which three (5.0%) led to graft failure, whereas 46 rejection episodes occurred in the control group (average 1.5 per patient) and six (13%) of these led to graft failure (\( p = \text{N.S.} \)). After the three month study period, six rejection episodes occurred in the IPE group and one led to graft failure, whereas two of three did so in the control group. The total number of rejection episodes observed during the entire follow-up period was 68 in the IPE group versus 49 in the control group (\( p = \text{N.S.} \)). Six patients in the control group versus one in the IPE group did not have a rejection episode. The time interval between the first and second rejection episodes in the control group (23 days) was not significantly different than in the IPE group (34 days). In patients with two or more rejection episodes (23 in the IPE group and 16 in the control group), the risk of graft loss was two times greater in the control group than in the IPE group. In the second and third months post transplant, the risk of graft loss from rejection was 2.7 times greater in the control group than in the IPE group.

Table I summarises the outcome of therapy. All patients have been followed for at least three months; 52 for at least six months, and 41 for one year or longer. Twenty percent of the grafts in the control group versus 10% in the IPE group have been lost to rejection (\( p = \text{N.S.} \)). The actual three month patient and graft survival is 97% and 70%, respectively, in the control group and 94% and

<table>
<thead>
<tr>
<th></th>
<th>IPE</th>
<th>No IPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functioning grafts</td>
<td>24 (80%)</td>
<td>20 (70%)</td>
</tr>
<tr>
<td>Technical loss</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Rejection</td>
<td>3 (10%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

431
80% in the IPE group (p = N.S.). The one year actuarial patient and graft survival in the control group is 89% and 59%, respectively, and in the IPE group is 86% and 72% (p = N.S.). Seven deaths have occurred in the 60 patients; three during the time of study (first three months) and four afterwards. Of the two deaths in the IPE group, one occurred during a rejection episode and was due to sepsis (day four post transplant), and the other occurred while the patient was receiving an IPE treatment (day 14 post transplant). A post mortem examination in the latter did not reveal a cause of death. The patient in the control group died of bowel infarction during the first week post transplant. The four other patients (two in each group) died from five to twelve months post transplant.

The complication rate was similar in both groups except for the incidence of arrhythmias and subclavian line related sepsis. Four patients had arrhythmias while undergoing a plasma exchange (one atrial fibrillation, two bradycardia and one a presumed fatal arrhythmia). Sixty-four episodes of infection occurred in the control patients and 63 in the IPE treated patients. There was a 12% incidence of line related sepsis in the IPE group.

Discussion

In our series, one year cadaveric survival has remained at approximately 60% for several years. The most important cause of graft loss during this time has been uncontrolled humoral rejection. High dose corticosteroid therapy has generally been ineffective or only temporarily effective in modifying the effect of humoral rejection on the graft. Our initial experience with the use of IPE in the treatment of resistant rejection episodes suggested it might be a useful and safe adjunct to conventional anti-rejection therapy for acute rejection episodes, particularly those with a predominantly humoral component. Since it is often difficult to identify humoral mediators in any rejection episode, the trial was designed so that all rejection episodes in the first three months post transplant were treated with either high dose prednisone therapy alone or in combination with IPE. It was postulated that IPE may exert its effect by removal of humoral mediators which could reverse some rejection episodes which would have otherwise led to graft failure, or it may reduce the amount of permanent damage to a graft undergoing several rejection episodes and thus allow time for those factors responsible for immunological unresponsiveness to develop in a better preserved graft.

In the small number of patients studied thus far, there is no statistically significant improvement in graft survival in the IPE group, but the trend is favourable with the IPE group having an approximately 10% higher actual graft survival rate, which may be due to a 10% reduction in graft loss due to rejection. If this trend continues, approximately 200 patients will be needed before statistical significance is reached. Although the IPE group is approximately eight years younger than the control group, this is an unlikely explanation for the difference in the number of rejected grafts in the two groups since the average age of the patients who lost their grafts to rejection is similar (40 years versus 41 years) in the two groups.

There is no evidence to indicate that rejection episodes have been accelerated or prolonged by the use of IPE. In those patients that have had two or more rejec-
tion episodes, the time interval between the first and second rejection episode was similar. It is possible that IPE, at a time when graft function is stable, could be harmful in terms of removing factors which are beneficial to the graft [2]. Thus, it has been our policy to avoid the use of IPE when graft function is stable or improving because of the risk of disturbing these factors.

In the IPE group, 97% (29 of 30) of the patients experienced a rejection episode, whereas only 80% (24 of 30) did in the control group. Although this difference is not statistically significant (p = 0.09), it is sufficiently large to merit some consideration. The control group, by chance alone, may be less immunologically responsive than the IPE group.

Further careful study of IPE in the treatment of rejection episodes is warranted. It may be an effective adjunct to high dose steroid therapy in the treatment of some rejection episodes, especially second or third rejection episodes which occur in the second or third month post transplant. There appears to be no advantage to the treatment of first rejection episodes with IPE. The long term benefit of IPE therapy to transplant recipients remains to be determined.

Acknowledgments

We wish to thank Ms L Cossette for her secretarial assistance and Ms A Pullar for her technical assistance.

References

1 Cardella CJ, Sutton D, Uldall PR, deVeber GA. Lancet 1977; i: 264
6 Uldall PR, Dyck RF, Woods F, Merchant N, Martin GS, Cardella CJ, Sutton D, deVeber GA. Dial & Transplant 1979; 8: 963

Open Discussion

BRIGGS (Glasgow) As you suggested, one would expect that humoral rejections would be the ones that respond best. Did you see any evidence on the biopsies which might distinguish humoral from cellular rejection and whether this is related to success or failure of plasma exchange?

CARDELLA As you know the expression of humoral rejection in the graft can involve either the large interstitial vessels or the glomeruli and we are at present analysing the types of rejection that we see and trying to correlate that with the rejection episode to see if it responded to plasma exchange or not. I do not have that information yet to present to you, but I do think that is a very worthwhile pursuit to try and define which type of process will respond.
KURUVILA (Bombay) We have been able to prevent hyperacute rejection in an admittedly limited number of patients by plasmapheresis pre-transplant. I wonder whether you have experience with this?

CARDELLA Yes, I have experience with three patients in this regard. In one patient who had virtually 100% cytotoxic antibodies prior to transplantation, we did intensively plasma exchange her to try and prepare her for transplantation in the hope that she would get a negative cross match. In fact we did deplete her antibody level by about 50 or 60%, but never sufficiently that she became negative, and I think the technology of plasma exchange has to be improved before we can totally remove an antibody from the circulation. Two other patients inadvertently were transplanted with positive cross matches and when this was realised, we plasma exchanged both those patients as soon as possible after the time of transplant and in both the levels did fall. Both patients have done very well and have functioning grafts now at 6 and 9 months.

McGEOWN (Belfast) Did you do plasma exchange by machine centrifugation or by membrane?

CARDELLA We used a Hemonetics model 30.

REES (London) In your anti-rejection regimen you used anti-thymocyte globulin for severe rejection episodes. Was the proportion of patients in whom you needed to use that different in the two groups?

CARDELLA No, it wasn’t. There were 20 patients in the control and I think 18 in the plasma exchange group that got the anti-thymocyte globulin.

THIEL (Basel) Two out of four patients treated with plasmapheresis after transplantation developed non-A-non-B hepatitis in our group. Was that just coincidence or did you see more hepatitis in your patients?

CARDELLA No, we have not seen an increase in hepatitis. I believe your experience to be unique. I do not know of any other centre that has, either.