SHORT-TERM KIDNEY PRESERVATION: TO PERFUSE OR NOT TO PERFUSE WITH THE NEW BELZER PERFUSATE

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Summary

Delayed graft function is ischaemically induced and the consequence of high energy phosphate depletion. A new perfusate, described by Belzer, has been used in 43 kidney preservations, 16 of which had prolonged cold ischaemia. The overall immediate function rate was 37 of 43 kidneys or 86 per cent. Of 18 kidneys cold-stored during the same period, only nine functioned immediately. Twenty-six of these patients received cyclosporine for immunosuppression without an increase in delayed graft function or evidence of increased nephrotoxicity because of ischaemic injury or prolonged preservation.

Introduction

In the absence of effective centralised cross-matching capability, kidney preservation time has necessarily been extended throughout the United States to fully utilise all available kidneys in an increasingly cytotoxic recipient pool. As a consequence, the incidence of delayed graft function (DGF) had approached 80 per cent [1,2] for kidneys cold-stored longer than 36 hours in Collins Solution. Stiller [2] reported primary non-function in the cyclosporine immunosuppressed patient when preservation, especially by perfusion was extended beyond 24 hours. It is apparent that traditional methods of kidney preservation may no longer be adequate.

Belzer [3] has developed a new perfusate (Table I) for machine preservation that has an albumin base, a phosphate buffer in lieu of bicarbonate and a non-permeable anion gluconate instead of chloride and adenosine substrate. The perfusate was designed to reduce ischaemically-induced cell swelling and results in ATP synthesis during machine preservation. Successful five day canine kidney preservations were reported.

We have used this new perfusate in our laboratory for the past 12 months with gratifying results.
TABLE I. Composition of Belzer II perfusate

Distilled, deionised H₂O 800ml
  Sodium gluconate 17.5g
  K₂HPO₄ 3.4g
  Glucose 1.5g
  Glutathione 0.9g
  Adenosine 1.3g
  HEPES (buffer) 4.7g
  NaOH 5 N ~ 8ml, adjust pH to 7.8 - 7.9
  Penicillin 200,000 U
  Dexamethasone 8mg
  Phenol sulphathiazole 12mg
  Insulin 40 U
  H₂O to bring volume to 850ml
  Filter sterile and store
  Before use add Albumin (sterile) 150ml
  MgSO₄ 1g (sterile)

Final values:
  Na⁺ = 133 ± 3mEq/L
  K⁺ = 24 ± 2mEq/L
  mOsm = 300 ± 5mOsm/L
  pH = 7.6 - 7.7

Materials and methods

Over a four month period starting June 15, 1983, all kidneys received in our laboratory were placed on the Waters Mox 100 Perfusion Circuit primed with Belzer II perfusate. Systolic pressure was initially set at 50mmHg at a standard pulse rate for our laboratory of 60, without further adjustment.

Thirty-one kidneys were perfused and transplanted during this period. Subsequently, 30 additional kidneys were also preserved, 12 by perfusion and 18 by cold storage in Collins C2 solution.

TABLE II. Incidence of delayed graft failure in the preserved renal allograft
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<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of kidneys</th>
<th>Mean cold storage in hours (range)</th>
<th>Mean perfusion in hours (range)</th>
<th>Immediate function (%)</th>
<th>Delayed function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I Perfusion with Belzer II</td>
<td>27</td>
<td>–</td>
<td>35.8 (21–60)</td>
<td>24 (89)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Group II C.S. + perfusion with Belzer II</td>
<td>16</td>
<td>10.5 (2–36)</td>
<td>25.0 (13–50)</td>
<td>13 (81)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Group III C.S. alone</td>
<td>18</td>
<td>37.2 (21–58)</td>
<td>–</td>
<td>9 (50)</td>
<td>9 (50)</td>
</tr>
</tbody>
</table>

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Twenty-seven kidneys (Table II, Group I) were placed on the perfusion circuit at the time of recovery without cold storage; the mean perfusion time was 35.8 hours with a range of 21–60 hours. Sixteen kidneys (Group II) were recovered from more distant centres and had a mean cold storage period of 10.5 hours with a range of 2–36 hours before a mean perfusion time of 25.0 hours (range 13–50 hours). The total preservation time in these 16 kidneys was 36.5 hours with a range of 27–68 hours. The 18 cold-stored kidneys (Group III) had a mean preservation time of 37.2 hours (range 21–58 hours).

Donors were between the ages of 10–55 (mean 31.5 years). Cerebral death was present in all. The circulation was supported by a respiratory and urinary output terminally stabilised with vasopressors, electrolyte solutions, volume expanders and diuretics as necessary.

Eighteen of the 43 recipients who received a machine preserved kidney and six who received a cold-stored kidney were immunosuppressed with cyclosporine. All recipients had a negative cross match to the donor antigen without regard to the HLA or DR match.

Post-transplant renal function was documented by a daily report on urinary output, serum BUN and creatinine determinations and the need for post-transplant haemodialysis at the recipient centre.

Results

Twenty-four of the 27 kidneys transplanted (89%) after perfusion with Belzer II solution alone (Group I) functioned immediately and the recipients did not require post-operative dialysis (see Table II).

In two of three patients with delayed graft function, there were peri-operative complications that contributed to delayed graft function. These three patients required dialysis only one to three times before life-sustaining function returned.

Of the 16 kidneys perfused with Belzer II solution after 2–36 hours of cold storage (Group II), 13 functioned immediately (81%). Of the 18 cold-stored kidneys in Group III, only nine functioned immediately; at least six life-sustaining haemodialysis treatments were required in the remaining nine. There was no correlation between the incidence of delayed graft function and the type of immunosuppression. Cyclosporine immunosuppression was well tolerated in all kidneys independent of the method or length of time of preservation. Primary non-function was not observed, even with cyclosporine immunosuppression.

Discussion

Delayed graft function is primarily due to ischaemic injury to the kidney during terminal events in the donor or to problems related to the recovery but increased by cold storage. Further damage may occur as a consequence of the management of the recipient. Delayed graft function may also result from immunological injury to an ischaemically damaged kidney in spite of a negative T and B cell cross match due to the presence of undetected endothelial antibodies. Delayed graft function is not acute tubular necrosis alone, but rather is a combination of
interstitial oedema, cell swelling in the glomerulus, and damage to both endothelial surfaces and tubular epithelium. Ischaemic damage is initiated by high energy phosphate (ATP) depletion that ultimately results in damage and cell death. With warm ischaemia, ATP is rapidly depleted and these changes become irreversible, but with hypothermia oxygen requirements are reduced by 95 per cent, thus permitting many hours of safe storage in properly designed electrolyte solutions. These changes are arrested and may even be reversed by perfusion (Figure 1) with the adenosine-phosphate buffered perfusate.

![Graph showing ATP depletion over time with perfusion](image)

**Figure 1.** Effect of perfusion with adenosine on the ATP depletion

Clearly perfusion of the cold stored kidney with Belzer II solution was beneficial to the kidney, and effectively reduced the incidence of delayed graft function to an acceptably low level. Active oxygen transport afforded by perfusion is required for this benefit, as ATP synthesis does not occur in O₂-deprived cold storage solutions. Although our numbers are small [3], and not statistically significant, we postulate that at least 12 hours of perfusion is necessary to restore ATP depleted by only a few hours of cold storage; perfusion for less than 12 hours seemed to contribute to delayed graft function. Belzer has furthermore shown that in a canine model the kidney may be safely stored in the perfusate for 24 hours while shipping from the preservation facility to the recipient centre [4,5].

Perfusion is clearly a more expensive method of preservation than cold storage and the quality is dependent upon the skills of a highly trained technician, but it is cost-effective by reducing delayed graft function and shortening the period of hospitalisation that delayed function entails. With cyclosporine
immunosuppression and a kidney that functions immediately, the compliant recipient is ready for discharge within one to two weeks after transplantation.

On the basis of one year’s experience in the preservation of human cadaver kidneys for transplantation by perfusion with Belzer II solution, we recommend widespread use of these techniques in the preservation of all kidneys in order to facilitate post-transplant management of the recipient.

Conclusion

1. Perfusion with Belzer II solution affords dependable preservation of the kidney for prolonged periods up to 72 hours, even those with prolonged pre-perfusion cold storage.

2. Cyclosporine immunosuppression does not increase incidence or severity of delayed graft function in those kidneys preserved over 24 hours with Belzer II solution.

3. Perfusion with Belzer II solution is the preservation method of choice.

References

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