PAPERS AND ORIGINALS

Results of 250 consecutive cadaver kidney transplants

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Summary

The results of 250 cadaver kidney transplants performed at this hospital between May 1968 and December 1974 were analysed. A functioning transplant was defined strictly as one that maintained the recipient in good health with a serum creatinine below $442 \mu\text{mol/l}$ (5 mg/100 ml) without any need for dialysis. The proportions of kidneys functioning after one, two, and three years were 40.4%, 33.9%, and 31.1% respectively, the corresponding survival rates of patients being 62.6%, 57.4%, and 43.8%. The primary failure rate overall was 21.6%, while the failure rates for first, second, and third transplants were 18.1%, 39.9%, and 66.7% respectively. Half of the primary failures were attributed to the use of cadaver kidneys with abnormal vasculature or long ischaemic times or originating from non-ventilated donors. Of the initially successful transplants 49% were subsequently lost due to rejection (53%) or death of the patient with a functioning transplant (46%), and of the secondary losses 58% occurred within three months of transplantation. HLA matching of donor and recipient for two or more antigens was associated with a significant increase in transplant survival—46% at three years as opposed to 9.5% at three years for kidneys with poorer matches.

Ninety-six patients died during the study period, 61.5% within three months after transplantation; 41.7% of the deaths were due to infection with bacteria that appeared to be sensitive to conventional antibiotics but failed to respond despite intensive treatment.

A "low risk" cadaver kidney is one from a ventilated donor, with single vessels, an initial warm ischaemic time of less than 20 minutes, and a cold ischaemic time of less than 450 minutes.

Introduction

Cadaver kidney transplantation is an established method of treating chronic renal failure, and the results from major centres in many countries are similar for both patient survival and kidney transplant survival. Despite advances in surgical technique and immunosuppressive treatment and the advent of tissue typing and antilymphocyte globulin the results of cadaver kidney transplantation have not greatly improved in recent years.^{1 2}

In December 1974 the 250th cadaver kidney transplant was performed at this hospital, which provided an opportunity to review the fate of the transplants and their recipients in an attempt to identify the factors of importance in the success or failure of a cadaver kidney transplant.

Patients and unit policy

Patients aged between 5 and 65 years were accepted for transplantation if there was no severe organic disease other than that associated with chronic renal failure. Between May 1968 and December 1974, 216 patients received a single transplant, 28 a second, and 6 a third. The 216 patients, 131 male and 85 female, had a mean age of $34.9 \pm \text{SD} 11.9$ years; 176 of them were maintained by haemodialysis before transplantation and could return to dialysis if the transplant failed. These patients were selected for transplantation according to the best HLA matching with the donor kidneys available, except when a patient was considered on clinical grounds, such as an advancing peripheral neuropathy or the repeated failure of shunt or fistula sites, to be in urgent need of a transplant. Owing to a shortage of dialysis facilities in the Birmingham region 28 patients were accepted for urgent transplantation with the first ABO compatible kidney available; 21 were transplanted without prior haemodialysis and seven were

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maintained for short periods before transplantation by peritoneal dialysis. In the event of transplant failure haemodialysis could be made available to only two of these patients.

During 1970 an outbreak of hepatitis-B surface antigen (HBsAg) positive hepatitis occurred, affecting 14 members of staff. This was traced to 12 patients on haemodialysis who were HBsAg-positive carriers. As facilities were not available to dialyse these patients in isolation, a policy of urgent transplantation without return to haemodialysis in the event of transplant failure was decided on.³

Methods

Altogether 130 of the cadaver kidneys were removed locally and 120 obtained through the National Organ Matching Service, Bristol, and the London Hospital Transplant Group and by direct contact with other units. The transplant operations were performed by a team of surgeons whose standard technique did not change appreciably during the period.

Immunosuppressive treatment was with hydrocortisone 200 mg intravenously and azathioprine 5 mg/kg intravenously preoperatively followed by oral prednisolone 75 mg/day and oral azathioprine 50 mg/day postoperatively until the transplants began to secrete urine. Azathioprine was then increased to the maximum dose tolerated (2-2.5 mg/kg/day) and the prednisolone reduced in 5 mg stages over six months to a maintenance dose of 5-15 mg/day. Rejection episodes were diagnosed clinically and biochemically^{4,5} and treated with prednisolone 200 mg by mouth daily for three days. After discharge from hospital the patients attended regularly for control of their immunosuppressive treatment, assessment of the function of their transplant, and observation of their general health.

Definitions—(1) A functioning transplant was defined strictly as one that maintained the recipient in good health with a serum creatinine below 442 $\mu\text{mol/l}$ (5 mg/100 ml) without any need for dialysis. (2) A primary failure was a transplant that failed to secrete urine or maintain the recipient without the need for continuing dialysis. (3) A secondary failure was a transplant that secreted urine and maintained the recipient with a serum creatinine below 442 $\mu\text{mol/l}$ but subsequently ceased to function. (4) The histological diagnosis of rejection was based on cellular intimal thickening in the arteries and arterioles with fibrin deposition in the intima or media coupled with atypical glomerular proliferation, glomerular thromboses, or generalised dilatation of glomerular capillaries. The histological features of a kidney rendered non-viable by prolonged ischaemia may resemble those of rejection, and occasionally both factors may contribute to the primary failure of the transplant. In classifying the cause of transplant failure, rejection was diagnosed only when the above histological criteria were fulfilled. Transplants that became primary failures and did not show these criteria or renal vascular thrombosis were grouped under "other causes."

Survival curves were calculated by the direct fractional method⁶ in which at any time interval the percentage survival of either patients or kidney transplants is given by (number surviving/number that could have survived) $\times 100$. When expressed by this graphic method it has the advantage over serial or truly actuarial methods in that the uncertainties imposed by small numbers are shown by irregularities in the graph, which may actually rise, as in figs 2 and 3 at 30 to 36 months after transplantation, rather than decline smoothly.

Results

Kidney survival and recipient survival—At 3, 6, 12, 24, and 36 months after transplantation 54.2%, 49.5%, 40.4%, 33.9%, and 31.1% of the kidney transplants were functioning satisfactorily, the corresponding figures for recipient survival being 73.3%, 68.8%, 62.6%, 57.4%, and 43.8% (fig 1). Fifty-four kidneys failed to function at all after transplantation (table I), giving an overall primary failure rate of 21.6%. For first transplants (216), however, the primary failure rate was 18.1%, whereas for second transplants (28) it was 39.3% ($P < 0.01$) and for third transplants (6) 66.7% ($P < 0.01$). There were no statistically significant differences in death rates after the first, second, and third transplants (table I). Of the 54 primary failures (table II) 27 were thought histologically to be due to acute rejection. In 19 kidneys thrombosis of the renal vessels, without the histological changes of acute rejection, appeared to be the primary event. The remaining eight kidneys were lost from various other causes.⁷ A further 56 transplants were lost by three months after transplantation (table II). These losses were due to rejection in 23 cases, the death of patients

FIG 1—Patient and kidney transplant survival curves ($\pm$ SE).

TABLE I—Primary failure rate of transplants and deaths after first, second, and third transplant operations

	No of Transplants	Primary failures		Deaths	
		No	%	No	%
First transplants ..	216	39	18.1*	84	38.9†
Second transplants ..	28	11	39.3*	10	35.7†
Third transplants ..	6	4	66.7*	2	33.3†
Total ..	250	54	21.6	96	44.4

* $P < 0.01$ † $P > 0.5$.

TABLE II—Causes of loss of kidney transplants and time after transplantation failure occurred

Cause of transplant loss	Primary failure (n = 54)	Secondary failure (n = 97)				Total (%)
		< 3 months	-6 months	-12 months	-36 months	
Rejection	27	23	8	10	10	51.7
Death of patient with functioning transplant		32	4	5	4	29.8
Renal vascular thrombosis	19					12.6
Other	8	1				6.0

with functioning transplants in 32 cases, and in 1 case to a urinary leak that could not be repaired. Between three and 12 months after transplantation 18 kidneys were destroyed by rejection and nine patients died with functioning transplants, and between 12 and 36 months a further 10 kidneys were rejected and four patients died with functioning transplants. Thus altogether 97 transplants that initially functioned satisfactorily were subsequently lost. The causes of the secondary failures were rejection in 51 cases, a urinary leak in one case, and the death of patients with functioning transplants in 45 cases.

HLA matching and kidney survival (all transplants)—Kidney transplants with two, three, or four antigens in common with the recipient had a significantly higher success rate than transplants with only one or no matching antigens (fig 2). Furthermore, the difference in transplant survival became more pronounced with time, so that by 36 months after transplantation 46% of the well matched kidneys (two, three, or four antigen matches) were functioning satisfactorily as opposed to only 9.5% of the poorly matched kidneys (0 or 1 antigen match) ($P < 0.001$).

Causes of death—Ninety-six patients (44.4%) died during the study period (table III). In the first three months there were 59 deaths (61.5%), which were due equally to non-infective (30) and infective (29) causes. In the first postoperative week non-infective causes, including anastomotic haemorrhage (5), hyperkalaemia (3), cerebrovascular accidents (2), and cardiovascular accidents (2), predominated. From the second week to the twelfth week, however, infections, particularly septicaemia (18) and pneumonia (11), were the commonest causes of death. Between three and six months after transplantation the number of deaths from non-infective causes (6) (cerebrovascular accident 2, coronary thrombosis 2, pulmonary embolism 1, uraemia 1)

FIG 2—Survival of 232 kidney transplants according to HLA matching (18 transplants excluded owing to lack of information). (Numbers of transplants are shown in parentheses.)

TABLE III—Time and cause of the 96 deaths after transplantation

Cause of death	Time of death after transplantation			% of total deaths
	<3 months	3-6 months	>6 months	
Non-infective	30	6	20	58.3
Infective	29	6	5	41.7
% of total deaths	61.5	12.5	26.0	

was the same as that from infective causes (6) (septicaemia 3, pneumonia 2, disseminated tuberculosis 1). After the sixth month, deaths from non-infective causes (20) outnumbered deaths from infective causes (5) by four to one. Many of the deaths, both non-infective and infective, at that stage were attributable to complications of the immunosuppressive treatment (disseminated tuberculosis 2, pneumonia 3, peptic ulcer 2, pancreatitis 2, and ischaemic colitis 2). Equally frequent causes of death, however, were uraemia (lack of dialysis facilities) (6), coronary thrombosis (3), pulmonary embolism (3), and cerebrovascular accidents (2).

Deaths due to infection—The numbers of deaths due to infection and the probable causative organisms are shown in table IV, though in many patients there was good evidence of infection by more than one organism. Of the 96 deaths 40 were caused by infection, of which 21 were septicaemias, 16 pneumonias, and 3 disseminated tuberculosis. Whereas 86% of the deaths from septicaemia and 69% of the deaths from pneumonia occurred within three months of transplantation, death from tuberculosis occurred only after at least three months had elapsed. Unusual portals of entry included ulceration of the pharynx (streptococci), oesophagus (clostridia), stomach and small and large bowel (staphylococci, clostridia, pseudomonas, and Gram-negative organisms), and vagina (Gram-negative organisms). Many bacterial infections failed to respond to large doses of bactericidal antibiotics in synergistic combinations to which the organisms had been shown to be sensitive *in vitro*. Intensive antibiotic treatment often led to the appearance of resistant organisms such as pseudomonas and opportunistic infections including candida, aspergillus, pneumocystis, and cytomegalovirus. The presence of these infections, although suspected clinically, was often confirmed only at necropsy.

TABLE IV—Deaths due to infection and probable causative organisms

	No	Time after transplantation			Probable causative organisms
		<3 months	3-6 months	>6 months	
Septicaemia	21	18	3		6 Gram negative, 5 staphylococcus aureus, 4 Pseudomonas pyocyanea, 2 Candida, 2 Clostridium welchii, 1 β-haemolytic streptococcus, 1 cytomegalovirus
Pneumonia	16	11	2	3	8 Staphylococcus aureus, 4 Gram negative, 1 Klebsiella aerogenes, 1 Candida, 1 Aspergillus, 1 Pneumocystis
Disseminated tuberculosis	3		1	2	2 Human, 1 atypical
Total	40	29	6	5	

Discussion

The kidney survival rate reported here is lower than in several other series.²⁻¹⁰ This is due to the strict definition of satisfactory transplant function as a kidney that maintained the recipient with a serum creatinine below 442 μmol/l (5 mg/100 ml) rather than the more commonly used time from transplantation to return to dialysis, retransplantation, or death from uraemia. This strict definition was chosen as patients with a serum creatinine below 442 μmol/l can lead a normal and active life.

The primary failure rate of transplants in this series was 21.6%, which, although considerably higher than the 10% reported by Hulme *et al.*¹¹ was similar to the rates reported by Festenstein *et al.*¹² and Nelson and Tovey¹³ (20.7% and 17.3% respectively). The primary failure rates of second and third transplants (39.3% and 66.7% respectively) were significantly higher than that of the first transplants (18.1%), confirming the report of Nelson and Tovey.¹³

Detailed analyses of the causes of the high primary failure rates^{4,5} showed that a cadaver kidney with an initial warm ischaemic time (IWIT) of over 20 minutes when "preserved" by surface cooling should not be subjected to a cold ischaemic time (CIT) of longer than 450 minutes. Furthermore, it was observed that the primary failure rate of kidneys from non-ventilated donors was 31.0%, confirming the report of Festenstein *et al.*¹² and that that of kidneys with vascular anomalies, anything other than a single renal artery and vein, was 38.2%, which was due mainly to a sixfold increase in the incidence of thrombosis of the renal vessels as compared with transplants with single vessels.

Thus a "low-risk" cadaver kidney may be defined as one from a ventilated donor, with single vessels, an IWIT of less than 20 minutes, and a CIT of less than 450 minutes. When the results of transplanting only the low-risk kidneys in this series were considered (fig 3) the primary failure rate was reduced to 11.4% and the two-year kidney survival increased to 50%. The primary failure rate of the high-risk kidneys was 31.8% and the two-year kidney survival 23.3%. The survival at three years of the low-risk kidneys (36.4%) appeared to be little better than that of the high-risk kidneys (27.8%) owing to the few transplants in each group at that time (eight and 10 respectively).

FIG 3—Survival of high-risk and low-risk kidneys ($\pm$ SE).

Of the 250 kidneys only 88 could be classified as low risk, whereas 107 were high risk, and in 55 cases there was inadequate information for any classification to be made. Thus less than half of the kidneys removed from cadaver donors in Britain during the study period could be considered with confidence to be suitable for transplantation. If the results of cadaver kidney transplantation are to be improved by the use of only low-risk kidneys the implications in terms of the number of kidneys required—at present estimated to be 3000 a year¹⁴—and the

waiting time for transplantation—now averaging two years^{1,2}—are self evident.

This series shows the value of HLA matching of donor and recipient for two, three, or four antigens, which was particularly important for the long-term survival of the transplants. As 77% of transplant failures after 12 months were due to rejection it appears that close HLA matching of donor and recipient confers considerable benefit in decreasing kidney loss due to late rejection. The importance of the first transplant, which had significantly the lowest primary failure rate as compared with second and third transplants, was also evident, despite the second and third transplants being performed only in the absence of recipient cytotoxic and haemagglutinating antibodies to donor tissue.

Analysis of the causes of the loss of transplants (table II) shows that rejection was responsible in 52% of cases, that the death of the patient with a functioning transplant was responsible in 30%, that renal vascular thrombosis was responsible in 12%, and that miscellaneous causes, including urinary leak and kidney necrosis due to causes other than rejection, were responsible in 6%. Transplant loss due to renal vascular thrombosis and miscellaneous causes resulted mainly from using cadaver kidneys unsuitable for transplantation. These kidneys, which originated from non-ventilated donors or had vascular anomalies or prolonged ischaemic times, constituted half of the primary failures, and elimination of these high-risk kidneys has been shown to reduce the primary failure rate from 21% overall to 11%, which was due mainly to rejection. The incidence of rejection may be reduced by close HLA matching of donor and recipient. When the donor and recipient had two or more antigens in common the three-year kidney survival rate was 46%, as opposed to 9.5% for poorer matches. Altogether 21% of the patients died with functioning transplants and 40% of the deaths appeared to be due to infections with bacteria sensitive to conventional antibiotics. Intensive antibiotic treatment sometimes failed in the immunosuppressed patient owing to the emergence of resistant bacteria, opportunistic organisms, and

infection with several different organisms. The importance of using only low-risk kidneys with the best possible HLA matching and scrupulous patient care is shown by the finding that if the patient survives one year with a functioning transplant there is a 77% chance of surviving to at least three years with satisfactory renal function.

Clearly for the results of cadaver kidney transplantation to be improved more kidneys are required from well maintained donors to enable the strict selection of only kidneys that are suitable for transplantation to be made. Then the three-year functioning kidney transplant survival rate should improve to more than 50% instead of the 31% reported at present. For this to be achieved changes will be required in both medical and public attitudes that prevail in Britain to cadaver kidney transplantation.

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Streptokinase in central retinal vein occlusion: a controlled clinical trial

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Summary

Forty patients with central retinal vein occlusion were allocated at random either to a treatment group given streptokinase followed by anticoagulants or to a control group given no specific treatment. The two groups, which were each of 20 patients, were broadly similar in respect

of clinical and laboratory values and similar in their initial visual acuity. At follow-up ("final" vision) the visual acuity in the treated group was significantly better than in the untreated group. Only one treated patient developed thrombotic glaucoma compared with four controls. Streptokinase may, however, have been responsible for vitreous haemorrhage (and permanent loss of vision) in three patients and hence probably has only a limited role in the treatment of central retinal vein occlusion.

Introduction

Several reports¹⁻⁴ have indicated that anticoagulants and fibrinolytic agents may be of benefit in retinal vein occlusion. These studies, however, were uncontrolled and patients with both central and branch vein occlusion were included. Because of the variable history of central retinal vein occlusion only randomised, controlled studies will show the efficacy of any treatment. Such a study is reported here.

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