Kidney Preservation by Surface Cooling: Analysis of 130 Transplants

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British Medical Journal, 1972, 4, 139-141

Summary

An analysis of 130 consecutive cadaveric renal transplants has shown the effectiveness of simple surface cooling of organs before transplantation. The primary graft failure rate was 10%, and kidneys could be stored for periods of up to 12 hours including warm ischaemia times of 150 minutes. Forty-eight patients received haemodialysis before transplantation and 78 patients received peritoneal dialysis. There were significant differences in the incidence of tubular necrosis in the two groups: these may have been linked to the differences in fluid and osmotic load presented to the transplants.

Introduction

Organs removed from cadavers to be used for transplantation are inevitably damaged by the ischaemia after cardiac and respiratory action has stopped. Before death the patient may also have suffered a variable period of hypotension and tissue hypoxia. Ischaemic damage to the kidney is immediate and progressive (Selkurt, 1945) although there is an initial period of reversible damage producing temporary functional impairment. The time of reversible renal damage can be prolonged by cooling the kidney to 2 to 4°C so reducing intermediary cell metabolism and oxygen requirements. Simple surface cooling has been used in dogs and the kidneys functioned adequately after 12 hours' storage (Fisher, Copeland, and Fisher, 1967). The same technique has been reported in human cadaveric renal transplantation (Mowbray *et al.*, 1965; White, Evans, and Calne, 1968).

Organs can be cooled more rapidly by intra-arterial infusions of cold solutions and dog kidneys have been preserved for 30 to 48 hours in this technique (Collins, Bravo-Shugartman, and Terasaki, 1969; Lui, Humphries, Russell, Stoddard, and Moretz, 1971), and human kidneys have functioned satisfactorily after storage of 16 hours (Brunius, Bergertz, Ekman, Gelin, and Westberg, 1968; Festenstein *et al.*, 1971). More elaborate techniques utilizing continuous perfusion with or without hyperbaric oxygen have been reported (Belzer, Ashby, Huang, and Dunphy, 1968; Ackermann, Hopkinson, and Gradman, 1969), and human kidneys have been successfully stored for up to 72 hours (Belzer, 1971).

The introduction of a United Kingdom national kidney tissue typing and distribution service increases the likelihood of prolonging the time from death to the completion of the renal transplant procedure. Furthermore the kidneys are often removed in smaller hospitals by surgeons without great experience in organ preservation and we feel the technique should be as simple as is compatible with a viable graft. Over 210 cadaveric renal transplants have been performed in this hospital since 1960, and the kidneys have been preserved by surface cooling before transplantation. We report the results of the last 130

consecutive transplants which have been undertaken by using this simple technique.

Patients and Methods

Kidney Recipients.—The analysis has been restricted to the patients who have received nonperfused cadaveric renal allografts between January 1966 and July 1971. During this period 130 such transplants were performed; 78 patients transplanted before January 1969 were maintained by regular peritoneal dialysis, and the technique used in this centre has been reported previously (Cohen and Percival, 1968). Forty-eight patients received regular haemodialysis treatment using an individual patient single pass dialysate system and either coil or Kiil dialysers. Those requiring dialysis after the transplant procedure received the same method of dialysis as preoperatively. Four patients were transplanted without an initial period of dialysis.

Organ Donors.—Over 90% of the organ donors were located up to 100 miles (161 km) from this hospital. Most patients received artificial ventilation before death, and the diagnoses were road traffic accidents with cerebral damage, intracranial haemorrhage, and primary cerebral tumours. All donors had an adequate urine output to the moment of death.

Graft Nephrectomy.—Both kidneys were removed en bloc by an anterior abdominal transperitoneal route by the technique of Ackermann and Snell (1968). The donor was routinely given 20,000 units of heparin before asystole. The kidneys with a segment of inferior vena cava and aorta were placed in two sterile plastic bags, and the necks of the bags were tied and placed in a flask surrounded by ice. The kidneys were subsequently temporarily removed from the flask dissection in the operating theatre. The organ ischaemia time was arbitrarily defined as a "warm time" which included the time between death and completion of nephrectomy together with the vascular anastomosis time; the "cold time" included the time of the organ dissection in the operating theatre.

Duration of Tubular Necrosis.—The onset of effective renal function was defined arbitrarily as when the transplant achieved an endogenous creatinine clearance greater than 20 ml/min. A proportion of the transplants had a period of oliguria with a urine output of less than 1,000 ml a day, and although the renal function subsequently improved the creatinine clearance never reached 20 ml/min.

Results

The number of kidneys transplanted each year and for the first six months of 1971 are shown in Table I together with the mean ischaemia times. The organ warm times have decreased since January 1969 and there has been a noticeable increase in the cold ischaemia times. The Table shows an increasing proportion of patients receiving haemodialysis treatment while awaiting a graft, and many lived over 50 miles (64 km) from the transplant centre. Those on peritoneal dialysis spent most of their time awaiting a transplant in the immediate vicinity of the hospital.

Thirteen transplants (10%) never functioned and the distribution was fairly uniform over the time period under study as shown in Table I. There were four cases of renal vein thrombosis, one case of renal artery thrombosis, and eight cases of

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TABLE I—Annual Review of Kidney Storage Data

Year	No. of Transplants	No. Receiving Haemodialysis	Organ Ischaemia in Minutes (Mean $\pm$ 1 S.D.)		No. of Non-functioning Grafts	Cases of Acute Tubular Necrosis
			Warm	Cold		
1966	28	0	97.4 $\pm$ 22.3	86.5 $\pm$ 33.2	2	19
1967	23	0	117.0 $\pm$ 21.7	121.6 $\pm$ 31.0	5	14
1968	26	3	112.5 $\pm$ 23.7	106.6 $\pm$ 34.7	0	19
1969	20	13	80.4 $\pm$ 24.0	129.6 $\pm$ 42.0	1	13
1970	15	15	82.4 $\pm$ 30.1	197.7 $\pm$ 69.7	3	12
1971	18	17	66.1 $\pm$ 17.0	249.5 $\pm$ 118.1	2	11

complete cortical necrosis with no large vessel occlusion. Eighty-eight transplants (68%) suffered a period of tubular necrosis before onset of effective renal function, and the proportion of cases of tubular necrosis was fairly uniform over the five and a half years.

The correlation between warm time and the onset of effective renal function for patients receiving peritoneal dialysis and haemodialysis is shown in Fig. 1. There was a noticeable difference in the duration of warm time of the kidneys which

FIG. 1—The Relation between duration of acute tubular necrosis (A.T.N.) and cadaveric kidney warm ischaemia time for patients receiving peritoneal dialysis (○), haemodialysis (●), and no dialysis (▼).

never functioned which had been transplanted into patients receiving peritoneal dialysis and of those which had been transplanted into patients receiving haemodialysis; the failed kidneys of patients on peritoneal dialysis had warm times of 85 minutes to 153 minutes while five of the seven failed kidneys in patients on haemodialysis had warm ischaemia times of less than 80 minutes. There was a direct correlation between the duration of acute tubular necrosis and the warm ischaemia times for the haemodialysis patients. Of the 18 kidneys with a warm time longer than 70 minutes 16 suffered tubular necrosis while nine of the 19 kidneys with a shorter warm time had immediate onset of effective renal function; the $\chi^2 2 \times 2$ test gave a P value of 0.02-0.01 (Table II). There was no such correlation for peritoneal dialysis; 38 transplants had a warm time longer than 95 minutes and 29 suffered acute tubular necrosis, while ischaemic damage occurred in 14 of the 34 transplants with a shorter warm time ($\chi^2 2 \times 2$ P 0.2).

The relation between cold time and the onset of effective renal function is shown in Fig. 2. Of the 73 kidneys transplanted

TABLE II—Relation between Acute Tubular Necrosis (A.T.N.) and Duration of Cold Ischaemia Time and Warm Ischaemia Time for Haemodialysis-treated Recipients (χ^2 test)

	No. with Acute Tubular Necrosis	No. without Acute Tubular Necrosis	P
Cold ischaemia time {			
<175 min	11	7	0.02-0.01
>175 min	16	3	
Warm ischaemia time {			
<70 min	10	9	0.02-0.01
>70 min	16	2

FIG. 2—Relation between duration of acute tubular necrosis (A.T.N.) and cadaveric kidney cold ischaemia time for patients receiving peritoneal dialysis (△), haemodialysis (▲), and no dialysis (■).

FIG. 3—Relation between duration of acute tubular necrosis (A.T.N.) and the endogenous creatinine clearance three months after transplantation for patients receiving peritoneal dialysis (◇), haemodialysis (◆), or no dialysis (▼).

into patients receiving peritoneal dialysis 59 had cold ischaemic times of less than 150 minutes. There was no correlation between either the duration of cold time and the incidence of transplant failure, or with the incidence of tubular necrosis. The kidneys transplanted into patients receiving haemodialysis, however, had longer periods of cold ischaemia and 26 of the 37 kidneys had cold times between 150 and 600 minutes. Statistical analysis when using the χ^2 test (Table II) showed a significant difference (P 0.01) in the incidence of tubular necrosis with cold times of less than 175 minutes when compared with longer cold times.

The effect of tubular necrosis on renal function as determined by endogenous creatinine clearance three months after transplantation is shown in Fig. 3. No kidney transplant with tubular necrosis lasting longer than 28 days ever achieved a clearance greater than 45 ml/min, while 14 of the 17 kidneys with immediate onset of renal function had creatinine clearances greater than 45 ml/min.

Discussion

The analysis of the data from 130 consecutive cadaveric renal transplant procedures has shown how simple surface cooling will allow preservation of viable kidneys with warm ischaemia times of over 150 minutes and cold ischaemia times of over 450 minutes. The definition of warm time has included the 20 to 40 minutes for completion of the vascular anastomoses, and in other reports (Brunius *et al.*, 1968; Festenstein *et al.*, 1971) this has been included in the cold time. The 10% incidence of primary non-function of the organs stored by this method is lower than the results of Brunius *et al.* (1968) and Festenstein *et al.* (1971) for perfused organs. Most donor patients, however, were maintained by artificial ventilation before death and the organs were removed by a team from the transplant unit. Higher failure rates have been associated with patients who were not maintained on ventilators (Festenstein *et al.*, 1971).

Over the period covered by this survey there was a transfer from peritoneal dialysis to haemodialysis for the patients awaiting transplantation, and the results from other transplant centres usually refer to patients receiving haemodialysis treatment. We have, however, observed significant differences in graft behaviour between recipients treated with peritoneal dialysis and those treated with haemodialysis. There was a correlation between the duration of warm ischaemia and primary graft failure in the patients receiving peritoneal dialysis in that no grafts failed if the warm time was less than 90 minutes, but there was no arbitrary time less than 150 minutes at which one could predict an unacceptably high incidence of primary graft failure. The grafts transplanted into patients receiving haemodialysis had shorter warm times, and again there was no easily defined upper limit or organ acceptance if the warm time did not exceed 150 minutes, although there was a significant incidence of tubular necrosis (16 out of 18 grafts) when the warm time exceeded 70 minutes in these patients. The patients treated with peritoneal dialysis received kidneys with longer warm times, and over half the organs had warm times longer than 95 minutes. The longer warm times, however, were not associated with a pronounced increase in the incidence of acute tubular necrosis and there are a number of possible explanations for this observation. Firstly, the patients on peritoneal dialysis may have had higher blood urea concentrations at the time of transplantation and, secondly, their extracellular fluid volume may have been

greater than that for the patients receiving haemodialysis. Both criteria would present a greater fluid and osmotic load to the transplant at the moment of revascularization and this may have provided some degree of protection against acute tubular necrosis. All recipients were given an intravenous infusion of 20 g of mannitol before release of the vascular clamps, and it may be that the extracellular fluid volume at the time of transplantation is of greater significance.

The data on the effects of organ cold ischaemia time has shown that organs will function when stored for up to 600 minutes by this technique, and there was a correlation for patients receiving haemodialysis between the duration of cold time and the incidence of acute tubular necrosis shown in Table II, while there was no such relation for patients receiving peritoneal dialysis.

The effect of acute tubular necrosis on later renal function as measured by the endogenous clearance three months after transplantation showed better renal function in the patients who did not suffer a period of acute tubular necrosis, but the picture is complicated by the effect of immunological damage to the kidney in addition to residual permanent ischaemic damage from organ preservation. Indeed Williams, White, and Hume (1967) found no correlation between the duration of tubular necrosis and eventual renal function, and it was thought that tubular necrosis may even have conferred some protection to the graft.

In conclusion, the surface cooling of renal transplants has provided a simple method of preserving organs for up to 12 hours with warm ischaemia times of up to 150 minutes and cold times of 600 minutes with a primary failure rate of 10% in a series of 130 consecutive cadaveric transplants. In the laboratory continuous perfusion with cryoprecipitated plasma (Belzer and Kountz, 1970) or similar perfusates and flush perfusion with Collins solution (Collins *et al.*, 1969) result in better preservation than can be achieved by simple surface cooling, and clinical experience with Collins C₃ solution has borne out the animal experimental work (Hartley, Collins, and Clunie, 1971; Tanaka, Stevens, and Terasaki, 1971). There is no convincing evidence, however, that flushing the kidney with chilled solutions of any other description affords better preservation than simple surface cooling.

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