PAPERS AND ORIGINALS

Survival in 200 patients treated by haemodialysis and renal transplantation

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British Medical Journal, 1977, 1, 409-412

Summary

The survival rates in 200 patients with terminal renal failure treated by maintenance haemodialysis and renal transplantation were analysed. The overall survival rate ($\pm$ SE) was $81.4 \pm 3\%$ at two years, $68.4 \pm 4\%$ at five years, and $60.8 \pm 4.8\%$ at eight years. Survival was inversely related to age: in those aged 15-34 years overall survival was $89.7 \pm 3.7\%$ at two years, $87.8 \pm 4.1\%$ at five years, and $83.9 \pm 5.5\%$ at eight years. Eighty per cent of the surviving patients were able to work full time. The survival rate in patients returned to dialysis after graft rejection was $87.5\% \pm 8.3$ at three years.

Introduction

Maintenance haemodialysis in Charing Cross Hospital was started in March 1964. The unit initially carried out only hospital dialysis, but a home dialysis programme was started in August 1967 and renal transplantation was first performed in October 1969. By December 1975 200 patients had been treated by maintenance haemodialysis or renal transplantation, or both. We describe here our methods of treatment and the results in these patients.

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Methods

DIALYSIS TECHNIQUES

Dialyses were originally carried out with modified 2-layer Kiil dialysers (surface area 1.15 m^2) using cuprophane membranes (PT 150) with a dialysate flow rate of 500 ml/min. Until January 1966 patients were dialysed for 12 hours twice a week and from then until January 1973 for 14 hours twice a week. From January 1973 all patients used Meltec Maxi multipoint dialysers (surface area 1.0 m^2) and have been dialysed for 10 hours twice weekly. Disposable Gambro or Travenol kidneys are used occasionally for technical emergencies. Long-term peritoneal dialysis has not been used.

Until mid-1965 dialyses were performed by recirculating dialysis fluid in a refrigerated tank, the blood being cooled as it passed through the dialyser and then rewarmed before being returned to the patient. Subsequently a single pass system was used with warm dialysis fluid (38°C), which made blood rewarming unnecessary. The dialysis fluid was prepared with dialysate concentrate in large tanks by the batch method until January 1967, when a central continuous automatic proportioning system (Watson-Marlow) was introduced. This system was used for all patients undergoing dialysis in hospital until 1971. Home dialysis was started in 1967 on Lucas proportioning systems. Later some home dialysis patients were established on Cambridge or Dylade proportioning machines. By 1971 all patients both in hospital and at home were using Dylade single patient proportioning systems with blood flows of at least 200 ml/min.

The dialysis fluid was initially prepared from London tap water, which contained 2.5 mmol/l (10 mg/100 ml) of calcium. This was mixed half-and-half with distilled or deionised water. In January 1967 softened water was used and the concentrate was adjusted to give a final dialysate calcium concentration of about 1.5 mmol/l (6 mg/100 ml). The concentrations of the other constituents were: sodium 130 mmol (mEq)/l , potassium 1 mmol (mEq)/l , chloride 95 mmol (mEq)/l , acetate 35 mmol (mEq)/l , magnesium 0.5 mmol/l (1.0 mEq/l), and glucose 11.1 mmol/l (200 mg/100 ml).

From January 1973 deionised water was used to prepare the dialysis fluid for the hospital patients but the home dialysis patients continued to use softened water.

SELECTION OF PATIENTS FOR DIALYSIS

In the early years some selection was necessary because of limited facilities. Most patients were then aged under 35 years when treatment was started. Patients with terminal renal failure due to primary renal

disease were accepted but those with terminal renal failure due to multisystem diseases such as systemic lupus erythematosus or diabetes were rejected. The men were skilled or semi-skilled workers, most were married, and many had family responsibilities. Most of the women were married. Recently we have been less selective. Several patients with multisystem diseases such as systemic lupus erythematosus, polyarteritis nodosa, diabetes, and amyloidosis have been treated, and the mean age on starting has been about 40 years. One patient known to be positive for hepatitis B antigen has been accepted and another was found to be positive for hepatitis B surface antigen (HBsAg) one week after starting dialysis. The commonest causes of chronic renal failure were chronic glomerulonephritis (38%), polycystic kidneys (13.5%), and nephrosclerosis secondary to hypertension (12%). Only two patients (19%) had phenacetin nephropathy.

Between March 1964 and December 1975 200 patients were accepted for haemodialysis. Their mean age was 39.2 years (range 6.7-66 years), and 131 (65%) were men. There has been an increase in the mean age of the patients placed on haemodialysis from 25.5 years in 1964 to 45.8 years in 1973. The proportion of patients aged 50 or over has increased from none in 1966 and 1967 to 44.4% in 1973.

HOME DIALYSIS

Because of the expense of establishing a patient on home dialysis, our general strategy has been to maintain patients on home dialysis for at least a year before considering them for renal transplantation. One hundred and forty-nine patients have been established on home dialysis; 11 returned to home dialysis after a failed renal transplant. Six started home dialysis for the first time after failure of a transplant.

VASCULAR ACCESS

Scribner external arteriovenous shunts were used exclusively during the early years. Cimino-Brescia fistulae were first used in 1969. Most of our established patients have been dialysed using Cimino-Brescia fistulae, although Scribner shunts have been widely used at the beginning of dialysis treatment and pending the establishment of a satisfactory internal fistula. Most patients with a fistula used two needles, but two used single needles. Most fistulae were sited in the forearm. Most of the Scribner shunts were in the lower leg or forearm. Seven patients had an upper arm Scribner shunt, and four patients had popliteal-saphenous fistulae.¹

DIET

Before starting patients on maintenance haemodialysis we have occasionally reduced their protein intake as part of conservative treatment. Our aim, however, has always been to give sufficient protein to prevent negative nitrogen balance—that is, at least 0.4-0.5 g protein/kg body weight/day²—and to change to maintenance haemodialysis treatment as soon as this dietary regimen is no longer acceptable, biochemically or symptomatically.

Once the patients started maintenance haemodialysis the protein intake was increased to 60 g/day or more, and some patients were allowed whatever protein intake they liked. Caloric intake on maintenance haemodialysis varied from 6.27 to 14.63 MJ (1500 to 3500 kcal/day) with a potassium intake of 55-80 mmol (mEq)/day and a sodium intake, adjusted according to blood pressure, of 25-200 mmol (mEq)/day. The calcium content of the 60-g protein diet was 8.75 mmol (350 mg) with a phosphate content of about 25.0 mmol (750 mg). A fluid allowance of 300 ml/day was prescribed for anephric or anuric patients. Other patients were allowed a greater fluid intake depending on their urine output.

Recently we discovered that patients tended to eat less protein than they were prescribed, or their "free" diets contained an inadequate amount of protein. We therefore advised patients to eat a specific amount of protein, usually 60-100 g/day, and closer dietetic supervision became necessary. Oral essential amino-acid supplements were given to patients who did not eat sufficient protein.

DRUGS USED

Aluminium hydroxide has been used intermittently for six weeks to lower the plasma inorganic phosphorus concentration in those whose plasma calcium $\times$ plasma phosphorus product (in mg) exceeded

70 (5.7 mmol). All patients took one Orovite tablet and 5 mg of folic acid daily. A few patients were given hydralazine and propranolol to control hypertension. An average of 2 g of intravenous iron (iron dextran) was given to each patient each year. Sometimes more was given to those with evidence of iron deficiency. Barbiturates and magnesium-containing drugs were not given.

MONITORING OF TREATMENT

The patients were initially assessed by barium meal examination, bone marrow examination, measurement of nerve conduction time, and skeletal x-ray survey. An ophthalmic and dental assessment was made. Predialysis and postdialysis concentrations of urea, electrolytes, creatinine, calcium, phosphorus, urate, albumin, liver enzymes, and haemoglobin were initially estimated at each dialysis and later once a month. Home dialysis patients had these estimations performed every two to three months in the outpatient clinic. HBsAg screening was carried out every one to two weeks in hospital patients and at every outpatient visit in those on home dialysis. Skeletal x-ray surveys and chest x-ray examinations were carried out once or twice a year.

SELECTION OF PATIENTS FOR TRANSPLANTATION

Patients were usually considered for transplantation only after they had been established on home dialysis for at least a year. Earlier transplantation was sometimes necessary because of difficulties of access to the circulation, or because of psychological or social factors. Each patient has been encouraged to decide for himself whether or not to accept a renal transplant, although this option was generally given only to those aged under 60 and fit enough to undergo major surgery. No other criteria were generally applied. Those accepted on the transplant programme underwent a pentagastrin test. If this showed hypersecretion of gastric acid transplantation was postponed until the hyperacidity had been corrected surgically by highly selective vagotomy. In the case of hyposecretion of acid, mucosal barrier medicines were given after operation.

TRANSPLANTATION METHODS

Recipient nephrectomy was not performed routinely either before or after transplantation, although nephrectomy was sometimes necessary because of hypertension, pain, infection, and haemorrhage. All potential recipients were tissue typed at least twice and underwent screening for cytotoxic antibodies every month.

Most of the cadaver kidneys were obtained through the National Organ Matching Service. A kidney was usually accepted if there was good evidence of satisfactory function up to the time of removal, a warm ischaemia time of less than 30 minutes, a cold ischaemia time of less than 10 hours, and, preferably, more than two compatible HLA antigens between donor and recipient. With a kidney from a live related donor two compatible antigens were readily accepted.

Azathioprine 2.5 mg/kg and methylprednisolone 1.5 mg/kg were each given as a bolus intravenously immediately before operation and again over the next 24 hours by continuous intravenous infusion. Subsequently the dose of azathioprine was reduced to 3 mg/kg/day given in one dose by mouth and reduced further if a falling platelet or white cell count suggested toxic bone marrow suppression. After two to three months patients were maintained on 75-150 mg daily. Oral prednisone 1.5 mg/kg was started 24 hours after operation. This was given in divided doses and the total daily dose reduced by 10 mg every 10th day until the patient was taking 40 mg/day. Thereafter the prednisone was reduced steadily over three months until a maintenance dose of 5-10 mg was achieved.

Intravenous frusemide 80 mg was given routinely just before revascularisation of the transplanted kidney. Anticoagulants were not used at operation, but warfarin was started 36 hours after operation. Graft rejection was recognised by the combination of symptoms, signs, and biochemical findings that form the basis of diagnosis in most centres.³ Radioisotope renal scanning has been particularly valuable in evaluating the "silent" kidney, but if we found no convincing explanation for loss of function our policy was to explore the kidney as soon as possible. Needle biopsy of the kidney was never used. Rejection episodes were treated with methylprednisolone 1 g/day for three days as well as intravenous heparin. If this was not effective the graft was irradiated (200 rads/day for three days). Actinomycin D (200 μ g/day for three days) was sometimes used. Since 1973 patients

were cared for after operation in a special transplant unit equipped with dialysis facilities. Prophylactic antibiotics were not used, but anti-fungal agents and vitamins were prescribed daily, being withdrawn only after four to six months. The urological surgeons were responsible for the primary care of transplanted patients.

HEPATITIS

There have been two outbreaks of HBsAg-negative hepatitis in the dialysis and transplantation units.^{4,5} One patient died in the first outbreak. After the second outbreak eight patients on maintenance haemodialysis had persistently raised serum transaminase concentrations, and liver biopsy in seven of these patients showed chronic aggressive hepatitis in three, chronic persistent hepatitis in two, and non-specific changes associated with iron overload in the remaining two.⁶ Two of the three patients with chronic aggressive hepatitis developed cirrhosis, and one later died. None of the eight patients were HBsAg-positive, but there was a higher frequency of cellular immunity to HBsAg in those patients who had had acute hepatitis.

Only three patients were HBsAg positive, two being positive before being placed on dialysis. The only patient who became positive during dialysis developed hepatitis a few months later. The other two had no biochemical or clinical evidence of hepatitis. All three were quickly established on home dialysis. The medical, nursing, and technical staff were screened at frequent intervals. None became positive to HBsAg.

Since 1967 gammaglobulin 750 mg intramuscularly was given to all patients on hospital dialysis every three months and to all home dialysis patients if they have needed temporary dialysis in hospital. Gammaglobulin was also offered to nursing staff, technicians, and doctors every three months.

REHABILITATION

In December 1975 the degree of rehabilitation of all surviving patients was assessed according to the classification of the European Dialysis and Transplant Association (EDTA, 1976).

METHOD OF ANALYSIS

The data from the 200 patients was analysed by the life-table method as applied by Merrell and Schulman,⁷ Cutler and Ederer,⁸ Lewis *et al.*,⁹ and Parsons *et al.*¹⁰ The cumulative survival rate and its standard error (SE) are expressed as percentages. As the age-related survival rate of patients on hospital dialysis was similar to that of patients on home dialysis the survival rate in both groups was combined. The period from the onset of dialysis to the date of transfer to another unit, transplantation, death, or the end of the study (31 December 1975) is the first dialysis period. The period from restarting

haemodialysis after failure of transplantation to the date of transfer to another unit, transplantation, death, or 31 December 1975 is the second dialysis period. Six patients had already been on haemodialysis before transfer to the unit. Three had had a failed transplant. Seven patients were transferred from our unit to other units after an initial period of hospital dialysis. Periods of peritoneal dialysis before the start of haemodialysis treatment are not included in the survival analysis

Results

SURVIVAL

When the results of haemodialysis and transplantation were combined the mean survival time was 3.5 years (range 1 month to 11.75 years). The cumulative survival ($\pm$ SE) was $81.4 \pm 3\%$ at two years; $68.4 \pm 4\%$ at five years; and $57.0 \pm 5.5\%$ at 10 years (fig 1; table I). The five-year survival was $75.8 \pm 6\%$ in women and $64.0 \pm 5.3\%$ in men. The mean duration of the first dialysis period was 2.7 years (1 month-11.75 years). The cumulative survival during the first dialysis period was $91.2 \pm 2.1\%$ at one year; $82.0 \pm 3.0\%$ at two years; and $71.5 \pm 4.4\%$ at five years (fig 2; table I).

When the results of haemodialysis and transplantation were combined survival was inversely related to age. Thus the five-year survival was $87.8 \pm 4.1\%$ in those aged 15-34 years and $59.2 \pm 8.7\%$ in those aged 45-54 (fig 1). This trend occurred particularly in patients

FIG 1—Age-related cumulative survival on both forms of treatment. Numbers of patients entered are shown at the end of each line, and figures in parentheses are numbers of patients alive at end of interval. Overall number of patients includes one aged over 65 years.

TABLE I—Cumulative survival in 200 patients

Intervals:	1 Month	2 Month	3 Month	6 Month	1 Year	2 Years	3 Years	4 Years	5 Years	6 Years	7 Years	8 Years	9 Years	10 Years
Overall survival (n = 200)														
No exposed to risk of dying	200.0	196.5	189.5	183.0	169.0	141.0	103.0	78.0	60.0	49.5	37.0	27.5	20.0	10.5
No of deaths (n = 53)	2	4	2	3	6	15	10	5	1	3	2	0	1	0
Cumulative survival rate ($\pm$ SE) (%)	99.0 ± 0.7	97.0 ± 1.2	96.0 ± 1.4	94.0 ± 1.6	91.0 ± 2.1	81.4 ± 3.0	74.3 ± 3.6	69.5 ± 3.9	68.4 ± 4.0	64.2 ± 4.4	60.8 ± 4.8	60.8 ± 4.8	57.7 ± 5.5	57.7 ± 5.5
1st Haemodialysis period (n = 197)														
No exposed to risk of dying	196.5	192.0	184.0	176.0	160.5	127.0	82.5	55.5	39.0	27.0	16.0	11.0	7.0	4.0
No of deaths (n = 40)	2	4	2	2	6	12	5	3	1	3	0	0	0	0
Cumulative survival rate ($\pm$ SE) (%)	99.0 ± 0.7	96.9 ± 1.2	95.9 ± 1.4	94.8 ± 1.6	91.2 ± 2.1	82.6 ± 3.0	77.6 ± 3.6	73.4 ± 4.1	71.5 ± 4.4	63.6 ± 5.9	63.6 ± 5.9	63.6 ± 5.9	63.6 ± 5.9	63.6 ± 5.9
2nd Haemodialysis period (n = 20)														
No exposed to risk of dying	20	20	20	19	18	16	10	6.5	3	1.5	0.5			
No of deaths (n = 3)	0	0	0	0	0	2	0	1	0	0	0			
Cumulative survival rate ($\pm$ SE) (%)	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0	87.5 ± 8.3	87.5 ± 8.3	74.0 ± 14.2	74.0 ± 14.2	74.0 ± 14.2	74.0 ± 14.2			
Patient survival after cadaver transplant (n = 46)														
No exposed to risk of dying	41.5	34.5	30.5	29	24	18	13	12.5	10.5	5	0.5			
No of deaths (n = 8)	2	3	0	1	2	0	0	0	0	0	0			
Cumulative survival rate ($\pm$ SE) (%)	95.2 ± 3.3	86.9 ± 5.5	86.9 ± 5.5	83.9 ± 6.1	76.9 ± 7.3	76.9 ± 7.3	76.9 ± 7.3	76.9 ± 7.3	76.9 ± 7.3	76.9 ± 7.3	76.9 ± 7.3			
Graft survival after cadaver transplant (n = 46)														
No exposed to risk of failure	46.0	35	31	29.5	25	18	15.5	12.5	10.5	5.5	0.5			
No of graft failures and deaths (n = 24)	11	4	1	2	4	0	1	0	0	1	0			
Cumulative survival rate ($\pm$ SE) (%)	76.1 ± 6.3	67.4 ± 6.9	65.2 ± 7.0	60.8 ± 7.2	51.1 ± 7.5	51.1 ± 7.5	47.8 ± 7.7	47.8 ± 7.7	47.8 ± 7.7	39.1 ± 10.1	39.1 ± 10.1			

on haemodialysis, in whom the five-year survival was $91.6 \pm 3.6\%$ among those aged 15-34 and $57.6 \pm 10.1\%$ in those aged 45-54 years (fig 2). The number of patients treated by renal transplantation in each age group was too small to justify similar calculations. The mean duration of the second dialysis period was 2.7 years (0.4-6.4 years). The cumulative survival during the period was 100% at one year and $87.5 \pm 8.3\%$ at three years (table I).

FIG 2—Age-related cumulative survival of first dialysis period. Numbers of patients entered are shown at end of each line, and figures in parentheses are numbers of patients alive at end of interval. Overall number of patients includes one aged over 65 years.

Fifty-four patients received 55 renal grafts (47 from cadavers and eight from related living donors). The mean length of dialysis before transplantation was 2.8 years (1 month-7.2 years). The mean age of the recipients was 36.6 years (7-62 years). The survival of patients receiving cadaver kidneys was $76.9 \pm 7.3\%$ at both one year and five years. Cadaver graft survival was $51.1 \pm 7.5\%$ at one year and two years and $47.8 \pm 7.7\%$ at five years (table I). At one year the survival of the eight patients who received live donor grafts was $87.5 \pm 11.7\%$ and their graft survival was $75.0 \pm 15.3\%$.

REHABILITATION

Rehabilitation was assessed in the surviving patients in December 1975 and the results are shown in table II. Altogether 93% of the

TABLE II—Degree of rehabilitation of patients in relation to treatment

	Able to work*				Unable to work	
	Full time	Part time	No work available	Earning capacity less than state pension	Able to care for most personal needs	Unable to care for self
Haemodialysis	83%	5.5%	3.5%	1%	7%	7%
Transplantation	72.0%	7%	3.5%	7%	3.5%	7%

*Work includes housework.

patients on haemodialysis could work, and 83% were doing full-time work (including full-time housework and school). The 7% who could not work were able to care for their personal needs. Of the transplanted patients 89.5% could work, and 72.0% were working full time.

CAUSES OF DEATH

The commonest causes of death in patients on haemodialysis were myocardial infarction, cerebrovascular accident, and sudden dialysis death of unknown cause. Infection was the commonest cause of death after renal transplantation.

MALIGNANT TUMOURS

A malignant tumour developed in four patients on dialysis; the tumours were in the kidney, bladder, and thyroid. One was a generalised reticulum cell sarcoma. No tumours were noted among the transplant patients.

Discussion

The survival rate of the 200 patients in the present study is very close to the overall European experience.¹¹ The one-, three-, and five-year survival rates of our patients during the first dialysis period were 91.2%, 77.6%, and 71.5% respectively, while those of EDTA home dialysis patients were 93.1%, 79.0%, and 71.0% respectively. During our 12 years' experience of haemodialysis there were no postoperative deaths in over 100 major operations, which included bilateral nephrectomy, cystectomy, hysterectomy, gastrectomy, and parathyroidectomy. Only three patients died of sepsis. Perhaps one of our most striking findings was the excellent survival rate during the second dialysis period, after graft failure. The adverse effect of increasing age on the survival rate of patients on dialysis confirms the results obtained in Europe.¹¹

After a cadaveric transplant 76.9% of patients survived for one, three, and five years, and the survival rates of the cadaveric grafts at one, three, and five years were 51.1%, 47.8%, and 47.8% respectively. The corresponding results reported by the EDTA¹¹ were 72%, 59%, and 51% for the patients and 50%, 39%, and 32% for the grafts. The reduction in our late post-transplant mortality was encouraging. Certain aspects of management may have contributed favourably to the results. Firstly, most transplant recipients were well stabilised on haemodialysis at the time of transplantation (the mean period of dialysis before transplantation was 2.8 years). They had, therefore, been thoroughly assessed and had largely recovered from the debilitating effects of chronic uraemia. They withstood major surgery well and, if the kidney failed, the return to dialysis could be accomplished. Secondly, preoperative gastric assessment minimised gastrointestinal problems after transplantation.¹² Thirdly, patients were seen every two or three weeks for the first six months after transplantation, a policy that has proved very valuable in the early detection of complications. In patients with progressive deterioration of renal function due to chronic rejection only a short course of immunosuppressive agents was given in an attempt to prolong the life of the graft. If this was not successful the patient was returned to dialysis without delay.

We thank Mr John Borland of the Charing Cross Medical School Computing Department for his help and co-operation in programming the life table analysis.

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(Accepted 30 November 1976)