Transpl Int (1997) 10: 7–12

ORIGINAL ARTICLE

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Transplantation of kidneys donated from the USA: long-term results and viability testing using ^{31}P-MRS

Received: 3 June 1996
Received after revision: 14 August 1996
Accepted: 16 September 1996

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Abstract Since June 1983, 27 kidneys have been shipped to the Kidney Center at the Tokyo Women's Medical College (TWMC) from the United States. These organs were divided into two groups, based on the years of their donation; 13 kidneys were assigned to group 1 and 14 to group 2. The differences between the two groups were as follows: donor age 19.8 ± 10.0 years vs 51.9 ± 14.5 years in group 2 ($P < 0.0001$); total ischemic time 42 h 12 min in group 1 vs 65 h 42 min in group 2 ($P = 0.0002$); and Euro-Collins preservation solution in group 1 vs University of Wisconsin (UW) solution in group 2. One hundred percent of the kidneys in group 1 and 85.7 % of those in group 2 recovered their function. The lowest serum creatinine levels averaged 96 ± 38.4 μmol/l and 185.8 ± 101.0 μmol/l, respectively ($P = 0.01$). The viability of 9 out of 14 grafts in group 2 were tested using ^{31}P magnetic resonance spectroscopy (^{31}P-MRS). The results showed that all of the grafts having a monophosphate/inorganic phosphate (MP/Pi) ratio higher than 0.3 recovered their function and those lower than 0.2 did not. The problems associated with international organ sharing are discussed, along with the difficulties encountered at TWMC.

Key words Organ sharing, Japan, USA · Japan, USA, organ sharing · ^{31}P Magnetic resonance spectroscopy, viability · Viability, ^{31}P Magnetic resonance spectroscopy

Introduction

In May 1981, Dr. Paul Terasaki initiated the sending of kidneys from the United States to Japan because he believed it was necessary to try to change the negative attitude of Japanese citizens towards the postmortem donation of their organs [9, 10]. Thanks to Dr. Terasaki's efforts, approximately 160 kidneys were sent to ten centers throughout Japan during the following 2 years. The impact of this project was sufficiently dramatic to increase the number of kidney donations within Japan.

In 1980, the year just prior to the start of the project, the number of cadaver kidneys donated in Japan was 49. Three years later it had reached 191, including those donated from the United States. After 1983, when donations from the United States abruptly decreased because of the increased domestic demand, the number of kidneys donated in Japan remained at around 160, which was approximately triple the number at the start of the project.

The shipment of kidneys to our center from the United States (hereafter called "US kidneys") started in June 1981. At that time, the immunosuppressants used were azathioprine and steroids. Since June 1983, azathioprine has been replaced by cyclosporin, and 13 recipients of US kidneys were treated with this new regimen. However, in September 1986, the shipment was temporarily stopped because of the increased demand in the United States caused by the widespread use of cyclosporin.

Table 1 Demographic data of the recipients (*TIT* total ischemic time, *Mp/Pi ratio* monophosphate esters to inorganic phosphate ratio)

	No.	Sex	Age (Years)	HLA-AB mismatch	HLA-DR mismatch	TIT	Dialysis (Days)	Creatinine (μmol/l)[a]	Mp/Pi ratio	Survival/ graft loss
Group 1	1	M	44	2	0	50· 15′	9	53.1		Alive
	2	F	41	2	2	46· 10′	21	141.6		Loss
	3	M	57	2	1	50· 43′	34	123.9		Alive
	4	M	44	3	2	48· 28′	18	106.2		Dead
	5	M	34	3	2	50· 08′	31	106.2		Alive
	6	F	41	3	1	47· 48′	0	62.0		Alive
	7	M	32	3	1	53· 00′	18	97.4		Alive
	8	M	35	3	1	37· 05′	14	9.7		Alive
	9	M	50	3	2	37· 25′	12	88.5		Alive
	10	M	23	2	1	37· 13′	13	79.7		Alive
	11	F	58	3	2	29· 47′	19	44.3		Alive
	12	F	36	3	1	33· 28′	18	79.7		Loss
	13	F	32	2	1	27· 29′	17	185.8		Dead
Total:	13	61.5 %[b]	40.5 ± 10.2			42· 12′	17.2 ± 8.7	96.0 ± 38.4		
Group 2	1	F	40	3	1	67· 34′	26	407.1		Alive
	2	M	65	4	1	66· 14′	26	318.6		Alive
	3	M	16	3	2	73· 00′	19	62.0		Alive
	4	F	51	3	2[d]	82· 00′	–	NE	0.20	Loss
	5	F	37	3	1[d]	82· 00′	–	NE	0.20	Loss
	6	F	38	3	2	69· 49′	39	159.3	0.39	Alive
	7[c]	F	38	1	1	68· 25′	0	88.5	0.70	Alive
	8	M	52	1	1	62· 00′	–	97.4		Alive
	9	M	45	1	1	61· 00′	–	194.7		Dead
	10[c]	M	52	1	1	60· 00′	10	247.8	0.64	Alive
	11	M	53	2	0	71· 32′	9	203.5	0.38	Alive
	12	M	42	2	0	72· 00′	26	203.5	0.40	Alive
	13	M	63	1	2	50· 00′	10	115.0	1.17	Alive
	14[c]	M	60	2	2	34· 00′	13	132.7	0.76	Alive
Total:	14	64.3 %[b]	46.6 ± 12.9			65· 42′	17.8 ± 11.5	185.8 ± 101.0	0.54	
		NS	NS	NS	NS	$P = 0.0002$	NS	$P = 0.01$		

[a] Lowest value post-transplantation; [b] Percentage of male;
[c] HCV-Ab-positive; [d] primary nonfunction

To stimulate donation in Japan once again, the project was resumed by Dr. Yuichi Iwaki in September 1993. In this second project, 17 kidneys were sent to our center at TWMC and 14 kidneys were transplanted. However, since May 1995, because of a change in the organization of the Japanese kidney sharing network, shipments have once again stopped.

These two projects covered a period of 14 years, when the development of transplantation technology was most marked. Because of changes in the immunosuppressive regimen, it was difficult to include all possible cases. In this report, we present an evaluation of the donated kidneys, the measures taken to judge viability, and the long-term outcomes of the recipients, with the exception of those who underwent transplantation before May 1983 and did not receive cyclosporin. We also discuss the problems associated with international donation and the difficulties we have encountered at TWMC.

Patients and methods

Recipients and donors

The recipients were divided into two groups, based on the years in which the operation was carried out. Thirteen recipients, 8 males and 5 females, who were operated on between June 1983 and September 1986, comprise the first group, and 14 recipients, 9 males and 5 females, who were operated on after September 1993 make up the second group. The average age in group 1 was 40.5 ± 10.2 years, and that in group 2 was 46.6 ± 12.9 years. There was, therefore, no significant age difference. The average age of the donor in group 1 was 19.8 ± 10.0 years, and in group 2, 51.9 ± 14.5 years. This difference is statistically significant ($P < 0.0001$). Details of the recipients in both of the groups are listed in Table 1 and those of the donors are summarized in Table 2.

Preservation and viability tests

Euro-Collins solution was used as the preservation fluid in group 1, and UW solution was utilized in group 2. In all cases, preoperative 1-h-responsive biopsies were routinely done, and the results ob-

Table 2 Demographic data of the donors

	No.	Sex	Age (Years)	Causes of death
Group 1	1	M	7	Automobile accident
	2	M	12	Intracranial bleeding
	3	F	27	Unknown
	4	F	44	Motor vehicle accident
	5	M	11	Gunshot wound
	6	M	14	Intracranial bleeding
	7	M	18	Head injury
	8	M	16	Automobile accident
	9	M	16	Intracranial bleeding
	10	F	16	Automobile accident
	11	M	30	Motorvechele accident
	12	M	28	Gunshot wound
	13	M	18	Aneurysm
Total:	13	76.9 %[a]	19.8 ± 10.0	
Group 2	1	M	34	Intracranial bleeding
	2	M	34	
	3	M	54	Intracranial bleeding
	4	M[b]	55	Head injury
	5	M[b]	55	
	6	M	68	Cardiovascular accident
	7[c]	M	40	Cardiovascular accident
	8	F	69	Cardiovascular accident
	9	F	69	
	10[c]	F	62	Cardiovascular accident
	11	M	38	Intracranial bleeding
	12	M	38	
	13	M	72	Intracranial bleeding
	14[c]	M	38	Motorcycle accident
Total:	14	78.6 %[a]	51.9 ± 14.5	
		NS	$P < 0.0001$	

[a] Percentage of male
[b] Primary nonfunction
[c] HCV-Ab-positive

tained were used to judge viability, along with the hydrostatic pressure obtained at the time of irrigation.

For the nine kidneys in group 2 that were donated to cases 4–7 and 10–14, viability was tested using ^{31}P magnetic resonance spectroscopy (^{31}P-MRS). The apparatus used was a BEM 250/80 NMR spectrometer of 2.1 Tesla (Otsuka Electronics, Shiga, Japan) with ^{31}P surface coil (2.5 cm diameter) operating at 34.45 MHz for ^{31}P-NMS. Each spectrum represents the accumulation of 300 pulses with a pulse delay of 34 μs, an acquisition time of about 2.0 s and pulse width of 0.020 ms, with the exception of cases 4 and 5 in group 2. A pulse width of 0.025 ms was used in those cases [6].

Viability was judged based on the ratio of monophosphate esters, including adenosine monophosphate and sugar monophosphates, to inorganic phosphate (MP/Pi) [3].

Immunosuppression

In both groups, cyclosporin was used in combination with a maintenance dose of steroids. Either azathioprine or mizoribine was also administered. Pulse therapy with methylprednisolone and/or OKT3 was used in cases of acute rejection, and gusperimus (15-deoxyspergualin) was injected when indicated.

Statistics

A Mann-Whitney U-test was used to analyze age, HLA-AB and HLA-DR mismatches, total ischemic time, duration of dialysis, and serum creatinine. Fisher's exact probability test was used to establish the male/female ratio.

Results

Ischemic time and kidney function

Apart from two grafts in group 2, renal function was recovered in all cases. The two unsuccessful grafts were obtained from the same donor and transplanted after 83 h of cold ischemia.

The total ischemic times in group 1 ranged from 27 h 29 min to 53 h, with an average of 42 h 12 min ± 8 h 8min. In group 2, ischemic times ranged from 34 to 73 h, with an average of 65 h 42 min ± 12 h 4 min, except in the unsuccessful cases described above. The difference is statistically significant ($P = 0.0002$).

All but one recipient had acute tubular necrosis. The duration of dialysis ranged from 9 to 34 days, with an average of 17.2 ± 8.7 days in group 1, and from 9 to 39 days with an average of 17.8 ± 11.5 days in group 2.

The longest ischemic time of a graft free of acute tubular necrosis was 68 h 25 min. The lowest postoperative serum creatinine levels of each patient in group 1 ranged from 44.3 to 185.8 μmol/l, with an average of 96 ± 38.4 μmol/l; those in group 2 ranged from 62.0 to 407.1 μmol/l with an average of 185.8 ± 101.0 μmol/l, except for the two cases of primary nonfunction described previously. The difference is statistically significant ($P = 0.01$).

^{31}P-MRS test

Results were obtained from nine patients in group 2. The MP/Pi ratio ranged from 0.20 to 1.17 with an average of 0.54. There was no correlation between the duration of acute tubular necrosis (ATN) and the values obtained.

Patient and graft survival

As shown in Fig. 1, 1-year, 5-year, and 10-year patient survival rates for the entire group of patients were 96.3 %, 89.4 %, and 82.5 %, respectively, and those for the grafts were 88.9 %, 76.6 %, and 70.2 %.

Three patients died: one at 8 years 8 months from sepsis, a second at 4 years 9 months from unknown causes, and the third from gastrointestinal bleeding followed by drug-induced hepatic failure on the 137th day

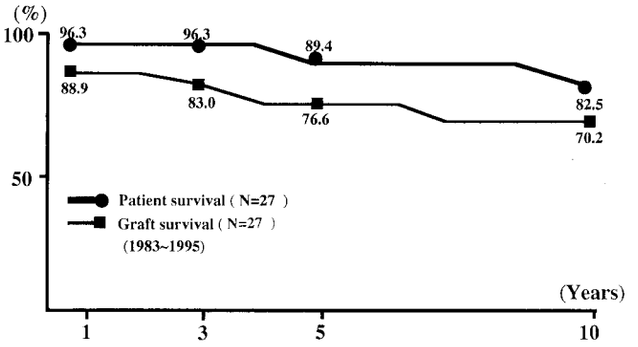

Fig. 1 Patient and graft survival rates after transplantation of U.S. kidneys

after transplantation. Malignant tumors were found in two other patients – a skin cancer and a gastric cancer – both of which were successfully resected.

Discussion

In Japan, the number of dialysis patients has increased very rapidly, with a total of 154, 413 by the end of 1995. This means that for every million people, there are approximately 1300 dialysis patients.

Despite the rapid increase in dialysis patients, the development of kidney transplantation has been very slow, and the total number of transplantations per year remains around 600, including 400 with grafts from living donors.

In 1977, Japan set up a national organ sharing network and started to register patients for kidney transplantation. Since the total number of patients on the waiting list was approximately 17000, the likelihood of transplantation was approximately 1.2 % per year. This situation forced a considerable number of Japanese patients to go abroad for transplantation.

At that time in the United States, nearly 8500 cadaver kidneys were being recovered annually, approximately 7700 of which were transplanted [12]. Since a considerable number of kidneys were being discarded for various reasons, it was reasonable to think about sending those kidneys to other countries where they were urgently needed. Among the many reasons for discarding donated kidneys are: age of the donor, length of ischemic time, a positive crossmatch, causes of death of the donor, viral and bacterial infection, and other complications. There may also be problems on the recipient side, including institutional difficulties associated with the availability of beds and/or doctors. As a result, some of the kidneys – designated as "marginal" kidneys in the United States – were sent to Japan.

After the United Network for Organ Sharing (UNOS) started to evaluate the worth of each transplant center in terms of the percentage of graft survival [5], centers in the United States worked to improve their actuarial survival rates by avoiding the use of marginal kidneys. This may be one of the reasons why the sending of kidneys to Japan resumed after September 1993.

The annual report from UNOS states that organs from HBV and/or HIV-positive donors are not usable [12]. However, there are no restrictions in connection with HCV-positive kidneys when transplanted into HCV-positive recipients.

In our series, three HCV-positive kidneys were transplanted into three HCV-positive recipients after fully informed consent had been obtained, although the HCV subclasses were not identified. Two of these three recipients had a mild elevation in serum transaminases that subsided in the course of 2 weeks. Many investigators [7, 8, 13] have reported that these results are comparable to those obtained with an HCV-negative combination. However, follow-up studies that include longterm extrahepatic complications may be necessary [2].

Other approaches to HCV, such as matching the subclass in recipient selection, treatment to minimize the presence of the virus in the graft [14], and treatment of the recipient with drugs including interferon-α [4] are additional issues that need to be addressed.

Despite the advanced age of the donor and the length of cold ischemia, 85.7 % of the kidneys in group 2 functioned with an acceptable average serum creatinine level, although it was significantly higher than that in group 1 ($P = 0.01$). Recently, the use of elderly donors has been re-evaluated worldwide in order to expand the donor pool [1]. It cannot be denied that the function of the kidney deteriorates with age and prolonged ischemia [11]; however, individual differences do exist. An effort should be made to locate kidneys from elderly donors that may be suitable for transplantation in countries where there is a great shortage of kidney grafts. One other kidney in group 2, taken from a donor addicted to oral amphetamines, was transplanted into a 38-year-old female recipient with immediate function, despite prolonged cold ischemia of 68 h 25 min.

These results indicate that, in the era since UW solution has come to be used routinely, the cold ischemic time may be prolonged and the upper age limit raised, based on survival and functional studies of the grafts. International sharing, which necessarily imposes a long ischemic time on the kidney, may be a very useful model for studying the limits of preservation.

The results of the ^{31}P-MRS test, along with the biopsy findings, proved to be very useful in judging the viability of donated kidneys. Kidneys that had a MP/Pi ratio of 0.3 or higher recovered their function, while those showing 0.2 did not. Accordingly, the ratio of 0.3 should be considered the limit with regard to viability. In spite of prolonged ischemic times, the patient and graft survival

rates were better than those obtained from Japanese cadaver kidney transplants.

Since, in Japan, kidneys are removed after cardiac arrest, the duration of warm ischemia is often a major consideration. This ranges from 15 to 60 min and often causes acute tubular necrosis. Another important factor is the early detection of acute rejection while the recipient is still anuric. The blood flow pattern obtained by Doppler ultrasonography is very useful for this purpose.

As for the average serum creatinine level, in group 2 it was approximately double that in group 1. A high serum creatinine level in the early stage of transplantation is considered an ominous sign for survival of the graft. However, in our series, elevated serum creatinine levels stabilized over a long period of time. This suggests that elevation of creatinine caused by ischemic damage behaves differently from that caused by rejection.

Social problems

Two social problems arose when transplanting grafts donated from the United States. One was related to the organ sharing network system and the other to the economy.

In April 1995, a new kidney transplant network was set up in Japan, replacing the pre-existing kidney bank system. The new network took responsibility for the sharing of kidneys, including those donated from foreign countries with legal transplant networks. It proved to be exceedingly difficult to integrate the pre-existing arrangement with the United States into the new network. Since similar problems may occur in other countries, we will now discuss the details of the difficulties we encountered, including misleading reports in the mass media and in some medical journals.

When the new network was first set up, we at the TWMC wrote a letter to the president of the network suggesting three possible options: (1) to accept the US kidneys and to share them in the same way domestic ones are shared, (2) to stop donation until the network became fully established or (3) to accept the US kidneys and to entrust the TWMC with the selection of the recipients while the network was organizing itself. Their response was "to leave the matter undecided until all preparations had been completed", since at that time they had no budget and no committee to deal with the matter.

On 17 April 1995, a kidney arrived at Narita airport, as had others from the United States in the past. This information was reported to the network; however, they refused to accept the kidney since they were not prepared to do so. It was suggested that there was no alternative but for TWMC to use it. Since the viability of the kidney was good, it was transplanted into a patient selected from the recipient pool at our center, based on HLA matching. The same process was repeated for four other kidneys that arrived from the United States shortly after the first one. Each time, information was sent to the network about the arrival of the kidneys in Japan.

On the morning of 7 June 1995, the *Yomiuri Shinbun*, a leading newspaper in Japan, reported and criticized our use of the US kidneys. However, the report contained many false statements because the source of their information was inaccurate. Due to this negative publicity, the importation of kidneys from the United States has since been stopped.

Since the network is still not prepared to receive organs of foreign origin despite the severe shortage of kidneys in Japan, an increase in domestic donation is urgently needed. The most important steps that need to be taken are to stimulate Japanese citizens to donate organs, to encourage cooperation among emergency medicine doctors and, in addition, to have legislation passed making transplantation from brain-dead donors legal.

A bill was, in fact, introduced into the House of Representatives in April of 1994; however, deliberation has come to a stop because of the current unstable political situation in Japan and the unwillingness of members of the House of Representatives to discuss this critical problem, which is a matter of human life and death.

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