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Development of a program for kidney transplants using organs donated from donors awaiting cardiac arrest (type III Maastricht)

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ABSTRACT

Introduction: The availability of organ donors is a limiting factor for kidney transplants. Donations from non-heart-beating donors (NHBD) can provide as many as one-third of all organs. Controlled patients awaiting cardiac arrest following limitation of life support techniques, or type III Maastricht donors, constitute an alternative that still has yet to be systematically developed. **Study type:** Descriptive series of 10 cases occurring between January and April 2012. **Method:** Over a period of 6 months, we designed a protocol for extracting and managing kidney transplants and providing immunosuppression therapy. Patients are evaluated in accordance with the criteria agreed by a different team responsible for transplant coordination. We established a maximum duration of time between limitation of life-sustaining therapy and death of 120 minutes and 60 minutes warm ischaemia. Two types of graft perfusion were used, one in situ through direct application to the surgical area, and another using antemortem vascular canalisation. Immunosuppression therapy included induction with thymoglobulin, steroids, and mycophenolate, with introduction of tacrolimus on the seventh day. Data are expressed as median and (range). **Results:** We included the first 10 cases of kidney transplants with organs from 5 NHBD (type III Maastricht): 4 males, mean age of 57 years (45-66 years), with limitation of life-sustaining therapy due to anoxic encephalopathy (2), intoxication (1), acute stroke (2) and terminal respiratory failure (1). The following mean time intervals were recorded: effective warm ischaemia: 20 minutes (8-23 minutes) and cold ischaemia: 7.5 hours (4-14.1 hours). Recipients had a mean age of 58 years (32-71 years), with various aetiologies (2 cases of glomerulonephritis, 1 polycystic kidney disease, 2 tubulo-interstitial nephropathy, 4 vascular, and 1 unknown), with a mean 31.7 months on haemodialysis (11-84 months); the kidney was a second transplant in two cases. No patients were hyper-immunised. Six patients required a dialysis session at some point, and four had prolonged acute tubular necrosis, over a mean hospitalisation period of 24.5 days (8-44 days). Mean creatinine (Cr) one month after transplantation was 2.1mg/dl (0.7-3.2mg/dl), and mean nadir creatinine was 1.2mg/dl (0.7-3.2mg/dl). One patient did not improve upon Cr values <3.2mg/dl, despite the absence of evidence of toxicity or rejection in a renal biopsy, and the transplant pair reached a Cr of 1.4mg/dl. Throughout the series, similar surgical complications were recorded to those observed in conventional donor situations. **Conclusions:** Despite the limitations of this preliminary study, the use of this type of transplant produces favourable short-term evolution. Expanded use of this type of donor could reduce the waiting list time for a kidney transplant.

Keywords: Non Heart-beating donor. Maastricht type III donor. Expanded criteria donor.

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Desarrollo de un programa de trasplante renal con órganos procedentes de donación tras asistolia controlada, tipo III de Maastricht

RESUMEN

Introducción: *La disponibilidad de donantes es el factor limitante para el trasplante renal. El donante en asistolia*

(DAS) no controlado proporciona hasta un tercio de los órganos. El DAS controlado tras limitación de técnicas de soporte vital (LTSV) o tipo III de Maastricht constituye una alternativa aún por desarrollar de forma sistemática. ***Tipo de estudio****: Descriptivo, serie de 10 casos realizados entre enero y abril 2012.* ***Métodos:*** *A lo largo de 6 meses se diseña el protocolo de extracción y manejo del trasplante e inmunosupresión entre los equipos implicados. Se evalúan los pacientes de acuerdo con los criterios consensuados por un equipo distinto al responsable de coordinación de trasplante. Se establece un tiempo máximo 120 min desde LTSV hasta fallecimiento y de 60 min de isquemia caliente. Se utilizan dos tipos de perfusión de injerto, uno in situ por abordaje directo en lecho quirúrgico y otro con canalización vascular antemortem. La pauta de inmunosupresión incluye inducción con timoglobulina, esteroides y micofenolato e introducción de tacrolimus al séptimo día. Se muestran datos como mediana y (rango).* ***Resultados:*** *Se incluyen los 10 primeros casos de trasplante renal con órganos procedentes de 5 DAS tipo III de Maastricht: 4 varones, edad media 57 años (45-66) con LTSV por encefalopatía anóxica (2), intoxicación (1), accidente cerebrovascular agudo (2) e insuficiencia respiratoria terminal (1). Los tiempos registrados fueron: isquemia caliente efectiva de 20 min (8-23) e isquemia fría de 7,5 horas (4-14,1). Los receptores tenían 58 años (32-71), con distintas etiologías (2 glomerulonefritis, 1 poliquistosis, 2 nefropatía tubulointersticial, 4 vasculares y 1 no filiada), llevaban en hemodiálisis 31,7 meses (11-84) y para 2 de ellos era su segundo trasplante. Ninguno era hiperinmunizado. Seis pacientes precisaron alguna sesión de diálisis y cuatro presentaron necrosis tubular aguda prolongada, durante un ingreso de 24,5 días (8-44 d). La creatinina (Cr) al mes del trasplante fue de 2,1 mg/dl (0,7-3,2) y la Cr nadir fue de 1,2 mg/dl (0,7-3,2 mg/dl). Un paciente no mejoró su Cr por debajo de 3,2 mg/dl aunque la biopsia no mostró toxicidad ni rechazo, y su pareja de trasplante alcanzó una Cr de 1,4 mg/dl. En toda la serie se constataron complicaciones quirúrgicas similares a las de nuestra serie histórica de donantes convencionales.* ***Conclusiones:*** *Con las limitaciones de un estudio preliminar, el uso de este tipo de injertos presenta una evolución favorable a corto plazo. La utilización de este tipo de donante puede ayudar a reducir el tiempo de espera para un trasplante.*

Palabras clave: *Donante en asistolia. Donante tipo III Maastricht. Donante criterios expandidos.*

INTRODUCTION

The number of donors after brain death (DBD) has been on the decrease in recent years, with progressive changes to the characteristics of these cases. Currently, DBD are most frequently males older than 65 years of age who die of cerebrovascular problems.[1] Organ transplant coordination teams have improved the rate of effective donation to the point of reaching success in 63% of all patients with brain death, but despite this progress there is a disparity between the number of available organs and the number of patients on the organ waiting list.

The strategy for increasing access to transplants includes three approaches: optimising live transplantation in all of its different modalities, considering the use of expanded-criteria donors, and developing programmes for non-heart beating donors. In one Spanish autonomous community, uncontrolled non-heart beating donation (Maastricht types I and II) constituted 37% of all donations.[2] This group includes donors who do not recover cardiac function following cardiopulmonary arrest whether inside or outside of the hospital. However, in other countries, controlled donation is much more common, stemming from situations of cardiac arrest following limitation of life sustaining treatments (LST) within the hospital (Maastricht type III).[3] This model of non-heart beating donation is respectful of the patient's family's wishes, has been approved by ethics committees, and was recognised in a recent expert consensus document published by the National Transplant Organisation (ONT).[4,5] However, the level of experience and familiarity with this very new type of transplant option is very scarce in our country, with only two cases published in 2011.[6,7]

Here we present our experience from the establishment of a programme specifically designed for this type of organ donation, covering the short-term follow-up for the first 10 such transplants performed during a 4-month period.

PATIENTS AND PROTOCOL

Ours was a descriptive case series including all controlled donations from non-heart beating donors performed between January and April 2011. During the last trimester in 2011, a protocol was established for organ donation following controlled cardiac arrest, and the kidney transplantation process in general was restructured and prioritised in order to reduce cold ischaemia time. The transplant coordination, nephrology, urology, immunology, and anaesthesiology departments all participated in this process. The protocol for organ donation from patients after controlled cardiac arrest was presented to all of the departments involved in kidney transplants and the transplant committee, and was approved by the hospital health care ethics committee, the regional office for transplant coordination, and the ONT. The priority structure for the complete kidney donation and transplantation process was also backed by the hospital administration, and was presented in a general hospital conference.

Patients with irreversible neurological damage, terminal neuromuscular diseases, upper spinal cord injuries, and terminal respiratory diseases are all candidates for this

programme for donation following limitation of LST. Once the medical team in the intensive care unit (ICU) makes the decision to remove LST based on the department's standard protocol, the family of the patient is notified. Only after the proposal for limiting LST is accepted by the patient's family does the transplant coordination team consider the possibility of organ donation. In this manner, the procedure for limiting a patient from LST is separated from the donation process, thus avoiding ethical conflicts of interest.

We used the inclusion criteria for kidney transplantation established by the British Transplantation Society: age <65 years, normal renal function or creatinine (Cr) <2mg/dl if normal renal function was evaluated prior to the event. If renal function is inconclusive, a renal biopsy is taken.[8] We use the University of Wisconsin score to estimate the expected waiting time between limitation of LST and death.[9] Following cardiac arrest, patient death was registered after 5 minutes of observation. If cardiac arrest did not occur within 120 minutes of limitation of LST, organ donation was suspended and the patient was returned to normal health care until death.

We used one of two different protocols for organ extraction. The first consisted of a rapid laparotomy with direct cannulation of the aorta and *in situ* perfusion with a storage solution together with local cooling and organ extraction. The second required *ante mortem* cannulation of the femoral vessels with double-balloon triple-lumen catheters (AJ6536 by Porgès S.A., Le Plessis-Robinson, France), leaving the balloons uninflated until patient death. After 5 minutes had passed, we perfused the patient with cold storage solution (Celsior®), thereby minimising the time of warm ischaemia (WIT). WIT should not surpass 60 minutes in order to consider the kidneys valid for transplantation. WIT was quantified as the time period between the appearance of functional hypoperfusion (MAP<60mm Hg) and the start of cold perfusion with organ storage solution.[9] We have designed a specific informed consent document for the recipient detailing the particularities of this type of donor, usage data, risks, and results published in other studies.

The immunosuppression protocol used takes into account the high risk of delayed graft function inherent to kidneys donated by non-heart beating donors. This entailed an induction phase with steroids and thymoglobulin (1mg/kg/day x 7 days); we added mycophenolate mofetil (1-2g/day) starting at day 1, and started tacrolimus (0.1mg/kg/day) on the seventh day. When no significant improvement was observed in renal function, the conversion from thymoglobulin to tacrolimus was performed earlier. We added prophylaxis against cytomegalovirus infection as per guideline recommendations.[10]

Here we present the results from 10 patients that received a kidney from one of 5 non-heart beating donors (NHBD), with a follow-up of the evolution of clinical and laboratory parameters lasting 6-24 weeks. Since this was a small sample of patients in which the numerical values did not follow a normal distribution, we expressed values as median and range. No statistical tests were performed.

RESULTS

We have included the transplant results from the first 5 non-heart beating donors (4 male and 1 female) at our hospital between January and April 2012. The median donor age was 57 years (range: 45-66 years). The reasons for limiting LST were: three cases of severe encephalopathy (two following cardiopulmonary arrest due to myocardial infarction and one due to methanol intoxication), one massive cerebral haemorrhage, and one case of terminal pulmonary fibrosis. The characteristics of the donors and extraction processes

Table 1. Baseline characteristics of organ donors

	Donor 1	Donor 2	Donor 3	Donor 4	Donor 5
Age	45	58	54	57	66
Reason for hospitalisation in ICU	AE	CVA	Pulmonary fibrosis	Methanol intoxication	AE
Days in ICU	5	7	17	3	4
Cr (mg/dl)	0.6	0.8	0.2	0.3	0.2
Biopsy	No	No	No	No	Yes
Ante mortem cannulation	No	No	Yes	Yes	Yes
Effective warm ischaemic time (min)	23	28	8	20	12

CVA: cerebrovascular accident-massive haemorrhage; Cr: creatinine; AE: anoxic encephalopathy following cardiopulmonary arrest due to myocardial infarction; ICU: intensive care unit.
Effective warm ischaemia described as the time interval between MAP<50mm Hg and perfusion.

used are summarised in Table 1. We used rapid organ extraction with perfusion in the surgical area in the first two cases, and the organs from the following three donors were extracted using *ante mortem* cannulation and cold perfusion after confirmation of donor death. All organs were certified as viable upon inspection and clinical evaluation, but we performed a renal biopsy of the kidneys from donor 3 due to the advanced donor age, which were also considered viable after the pathologist observed only one sclerosed glomerulus out of 35 evaluated.

The baseline characteristics of the transplant recipients are summarised in Table 2. The median recipient age was 58 years (range: 32-71 years), with a mean duration of time on dialysis of 31.7 months (range: 11-84 months). Two of these patients were receiving their second transplant, and none were hyper-immunised. The mean HLA compatibility score was 1.2/6, the median effective warm ischaemia time was 20 minutes (range: 8-23 minutes), and median cold ischaemia time was 7.5 hours (range: 4-14.1 hours). Six patients required dialysis or ultrafiltration following transplantation, and 4 patients developed prolonged acute tubular necrosis (ATN), with delayed graft function. The median duration of recipient hospital stay was 24.5 days (range: 8-44 days). Median Cr one month after transplantation was 2.1mg/dl (range: 0.7-3.2mg/dl) and median nadir Cr was 1.2mg/dl (range: 0.7-3.3mg/dl).

The only patient whose Cr did not decrease below 3.2mg/dl was biopsied, but only slight glomerular sclerosis was observed, with no signs of acute rejection, hyalinosis, or other types of vascular damage. We also found no signs of acute or chronic toxicity from calcineurin inhibitors, and polyomavirus tests were negative. The other kidney from the same donor reached a nadir Cr of 1.4mg/dl. During the entire study, the rate of surgical complications was very similar to that produced in our long-term registry of transplantations from conventional donors.

DISCUSSION

Here we present the first results from our new programme for non-heart beating donors following limitation of LST. In a very short follow-up period, our patients reached a median Cr of 1.2mg/dl, and only one patient had sustained high Cr levels despite this being the case with the longest follow-up period. Overall, the results are very similar to those achieved in other international studies[11] of much larger scope, and are sufficiently promising for us to continue with the programme.

The experiences communicated from other transplant centres in the country have used a less systematic approach, and do not appear to be destined towards a standardised programme

Table 2. Characteristics of the transplant recipients and the evolution of their clinical/laboratory parameters

	1	2	3	4	5	6	7	8	9	10
Donor age	45	45	58	58	54	54	57	57	66	66
Cold ischaemia (h:min)	5:00	8:00	10:00	12:30	7:00	4:00	2:00	14:00	4:50	15:00
Compatibility	A; A; DR	A;B; DR	A.B	B	A	B	No	No	DR	DR
Recipient age	32	50	54	57	71	50	59	64	69	59
CKD aetiology	IgA GN	Unknown	PKD	TIN	NAS	NAS	NAS	NAS	IgA GN	TIN
No. transplant	1st	1st	1st	1st	1st	1st	1st	1st	2nd	2nd
Months on HD	17	53	11	12	20	34	12	24	84	50
Post-transplant HD sessions	16	12	11	7	2	0	13	0	0	0
Cr on 7th day	7.7	9.3	6.1	9.1	2.0	0.9	6.2	5.7	1.0	1.3
Cr on 14th day	7.8	6.5	4.2	5.6	1.5	1.2	4.4	5.4	0.9	1.0
Cr at 1st month	2.0	2.1	2.5	3.2	1.0	1.0	2.8	2.5	0.7	0.9
Nadir Cr (mg/dl)	1.2	1.9	1.4	3.2	1.0	0.9	2.0	2.2	0.7	0.9
Duration of hospital stay (days)	44	24	20	25	10	8	34	33	25	8
Urological complications	Lymphocele							AUR	Haematoma	Seroma

PKD: polycystic kidney disease; Cr: creatinine; CKD: chronic kidney disease; GN: glomerulonephritis; HD: haemodialysis; NAS: nephroangiosclerosis; TIN: tubulo-interstitial nephropathy; AUR: acute urinary retention..

per se, but are rather reports of sporadic cases. We believe that this type of donor deserves a specific approach and the design of a standardised action plan, since this type of organ donation may come to constitute an important portion of transplant activity. In fact, our initial estimate led us to expect 3-4 appropriate donors of this type per year, and yet we have observed a higher incidence of patients that are appropriate cases for limitation of LST, with excellent responses by family members and optimal use of available organs. This low rate of negative responses coincides with the results traditionally observed for uncontrolled non-heart beating donors. Results compiled from the regional transplant office in Madrid from 2011 report a rate of negative results of 22% for DBD, and only 8% for NHBD.[12]

The meagre use of this type of donor in Spain is due to the sufficient availability of conventional donors and a certain level of reticence to this methodology among potential donors, which was expressed in a document published by the ONT in 1999. Both of these conditions have changed, which has facilitated the progression towards a new phase of organ transplantation in Spain. The document recently published by the ONT is aligned with the stipulations in consensus documents from other countries, and is of great value for those who wish to develop this type of programme for controlled non-heart beating donors.[4,5]

Organs donated from Maastricht type III donors constitute 50% of kidney transplantations in nearby countries, such as Belgium, the United Kingdom, and Holland.[3] According to data published by the United Network for Organ Sharing (UNOS), the number of transplanted kidneys provided by DBD increased by 22% between 2000 and 2005, with kidneys from non-heart beating donors increasing by 36.1% during this same time period.[2]

The development of programmes for controlled non-heart beating donors for more than 15 years has allowed us to apply the results from previous experiences into our own model.[13] Uncontrolled non-heart beating donors imply an inferior situation for the viability of the organ, since the exact conditions of the organ are unknown and the organs generally spend a greater length of time without life support after cardiopulmonary arrest. As such, as many as 35% of these organs are rejected for transplantation, and high rates of prolonged ATN are produced, increasing the amount of time needed for nadir Cr to be reached. Despite this, mid-term functioning of these kidneys is comparable to that of organs from brain dead donors.[13]

In the case of donors with controlled cardiac arrest, the scenario of available information and organ management is very different, and could produce better results. In our study, all extracted kidneys were transplanted into recipients; the evolution of renal function in these recipients was slower than in cases of kidneys from DBD in our long-term registry, but a reasonable nadir Cr was reached, which could continue to improve in the patients who have only been monitored for a short time. Another added value of the implementation of this programme is that it has contributed to the reorientation of the health care process for kidney transplantations in our hospital, reducing cold ischaemia times to half that of the previous records for organs derived from DBD.

On average, the donors in our study were somewhat younger, spent a shorter period of time in the ICU, and had lower acute comorbidity rates than is usual for donors after brain death. We did not consider it necessary to systematically take biopsies from extracted organs, and we preferred to use more restrictive clinical criteria and a macroscopic evaluation of the organ.

Some authors believe that organ donation following removal of LST anticipates the situation of brain death, which reduces the availability of other organs that would be viable in the case of a conventional donor.[1] However, the patient profiles for these two situations are quite different, requiring a precise clinical diagnosis made in the ICU. In addition, it is important to demarcate a separation between the decision to remove LST, which is a common practice in the ICU, from the donation process. In our short experience, the rate of conventional donors in the hospital has remained constant. In light of these considerations, we believe that the transplants performed under this modality would not have occurred if a specific programme for this type of donation had not been put into place.

The use of Maastricht type III donors implies a much less complex organisational paradigm than type I and II donors, and such a programme can be implemented in many hospitals with scarce need for additional resources. It is only necessary to develop a protocol within the hospital oriented to this type of transplant. In fact, the Canadian consensus recommends that centres that wish to work with non-heart beating donors should do so under controlled conditions.[4]

Obviously, ours is a preliminary short-term analysis, which presents the greatest limitation for our study. However, it is in the initial phase of implementing a new programme that the most blatant organisational issues arise, and in the first individual case that the majority of issues for the patient are brought to light, such as surgical complications and delayed graft function. Other authors have indicated that kidneys derived from this type of donor have a greater tendency for acute rejection, although mid-term graft and patient survival does not differ from that of a registry of transplants coming from donors after brain death.[12] The immunosuppression therapy used was intended to avoid added tubular damage during initial phases, but was also sufficiently effective to protect against rejection. In our short follow-up period, we did not observe any cases of acute rejection. Long-term follow-up should also compare the results between kidneys

derived from the different types of donors. To this end, we propose that registries of kidney patients include a specific variable that classifies patients by the type of kidney donated in order to compile results from the experience of multiple groups.

We believe that patients should be provided with specific information regarding the type of organ that they will receive, especially if the kidney comes from an expanded-criteria, non-heart beating donor. In these cases, the potential recipient should be informed as to the specific risks implied in order to properly evaluate this option as compared to the risks of continued dialysis treatment while waiting for a conventional donor. For this purpose we have created a specific model for organ transplants derived from controlled non-heart beating donors. In our study, only one patient refused this type of transplant in light of the information provided.

We can conclude that the implementation of a kidney transplant programme for Maastricht type III non-heart beating donors is an adequate alternative for increasing the number of kidney transplants, thus decreasing the waiting list time for potential recipients. Although ours was a small series of kidney transplants, it has allowed us to consider this option to be a valid and adequate alternative for overcoming the progressive decrease in the availability of DBD.

Conflicts of interest

The authors declare that they have no potential conflicts of interest related to the contents of this article.

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