A tale of two kidneys, and the case for machine perfusion in South Africa

N B Leech,[1] FCS (SA); **Z Keyser,**[2] FCS (SA); **D E du Plessis,**[3] MMed (Urol); **V Soyizwapi,**[1] RN; **L Bertels,**[1] FCS (SA); **T du Toit,**[1] MMed (Surg)

[1] *Division of General Surgery, Department of Surgery, Groote Schuur Hospital and Faculty of Health Sciences, University of Cape Town, South Africa*
[2] *Trauma Unit, Division of General Surgery, Tygerberg Academic Hospital and Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa*
[3] *Department of Urology, Tygerberg Academic Hospital and Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa*

Corresponding author: *N B Leech (nicholasbleech@gmail.com)*

Extended-criteria donors (ECDs) are seen as a means of addressing the shortfall in solid-organ availability for transplant. However, the use of ECD kidneys is associated with a greater risk of primary non-function compared with standard-criteria donor kidneys, and a higher discard rate has been described internationally. There seems to be a lack of consensus in the consideration of ECD kidneys for transplant, with reliance often placed on the subjective assessment of individual clinicians. The following case examines the difference in the institutional decision-making process applied to two kidneys from a single donor, and provides an argument for the use of hypothermic machine perfusion in low- to middle-income countries as an efficacious and objective means of assessing ECD kidney suitability.

S Afr Med J 2024;114(3b):e1328. https://doi.org/10.7196/SAMJ.2024.v114i3b.1328

Extended-criteria donors (ECDs) have been considered as a means of overcoming the shortfall in organ availability, specifically kidneys. ECDs are defined as brain-dead donors aged >60 years, or between the ages of 50 and 59 with at least two of the following three criteria present: terminal serum creatinine >133 µmol/L, cerebrovascular incident as cause of death, and a preceding history of hypertension.[1]

Prolonged waiting times on dialysis have been associated with considerable morbidity and mortality. Some patients with end-stage kidney disease (ESKD) may choose to be considered for an ECD graft, as it may provide a survival benefit compared with waiting for a standard-criteria donor (SCD) kidney.[2] However, the relative risk of primary non-function (PNF) is ~1.7 times greater than in kidneys from SCDs.[3]

The following case presentation describes the clinical details of an ECD and the decision-making that followed, with one kidney being discarded and the other successfully transplanted. We consider the importance of identifying ECD grafts that are destined to fail, and critically discuss the strategies that could assist us in doing so.

Case presentation

A 52-year-old man who had sustained a self-inflicted gunshot wound was referred to the transplant co-ordinator at a private-sector hospital in 2022. Collateral history from his family revealed that he suffered from depression and hypertension, but was otherwise healthy and did not smoke or drink alcohol. He was found ~2 hours after the injury, with a reported Glasgow Coma Scale score of 3/15, and he was severely hypotensive. Emergency service personnel intubated him at the scene and began resuscitation with intravenous crystalloids, followed by inotropic support. He received further critical care at a private healthcare facility ~500 km from Cape Town. On further investigation, he was found to have suffered a devastating brain injury and was certified brain dead. The terminal serum creatinine level was 623 µmol/L, the urea level was 23.9 µmol/L, and he had poor urine output of <0.5 mL/kg/h. However, a normal serum creatinine level had been recorded when he visited an outpatient department 1 month prior to this event. Consent for organ donation was acquired from his next of kin. Preoperative echocardiogram findings precluded retrieval and transplantation of the heart. The donor was classified as an ECD based on his age, history of preceding hypertension, and raised serum creatinine.

The donor underwent a standard sternolaparotomy for procurement of lungs, kidneys and liver. Prior to cross-clamping of the aorta, 30 000 IU (>300 IU/kg) of unfractionated heparin was administered. *In situ*, retrograde aortic perfusion was performed with 9 L (1 L/10 kg) of histidine-tryptophan-ketoglutarate (Custodiol HTK solution; Dr. Franz Köhler Chemie GmbH, Germany), and procurement of the organs proceeded in a standard fashion during the cold phase. The kidneys were enveloped in perinephric fat and no attempt was made to macroscopically assess them at this time. The kidneys were allocated to two referral hospitals in Cape Town, in accordance with the Western Cape Allocation System.

At back-table preparation of both kidneys, multiple and diffuse petechial haemorrhages could be seen (Fig. 1). One transplant team decided to discard the allocated kidney because of the macroscopic findings and a subjectively high resistance during flushing of the renal artery with preservation solution. The discarded kidney was sent for histological assessment and was found to have thrombotic microangiopathy with fibrin thrombi and early infarction. The other transplant team decided to proceed with transplanting their kidney, despite the visible petechiae, as the kidney could be flushed easily.

The recipient was a 44-year-old man with a body weight of 60 kg and ESKD secondary to chronic glomerulonephritis and hypertension. He was initially started on peritoneal dialysis in 2016, but owing to multiple episodes of peritonitis the modality was changed to haemodialysis in 2019 and an arteriovenous fistula was created.

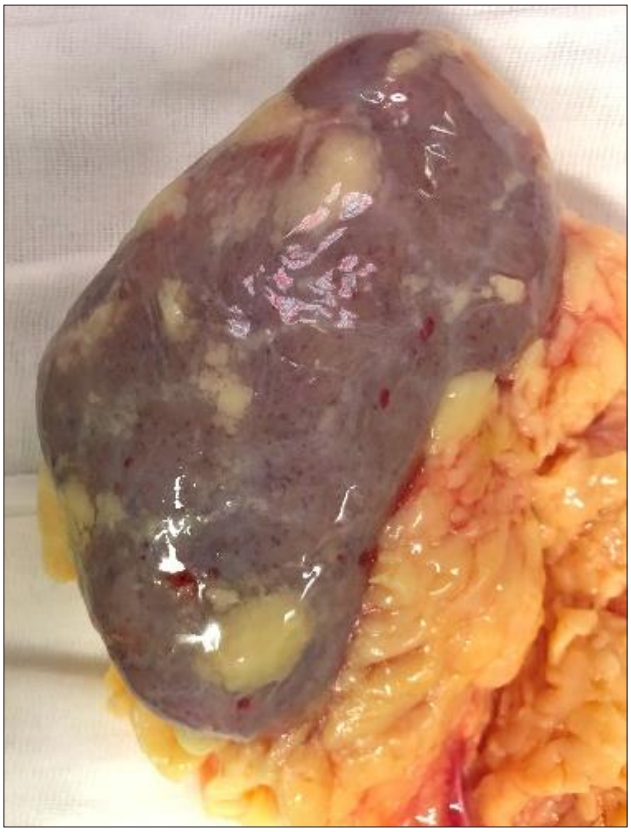

Fig. 1. Kidney with macroscopic petechiae.

Preoperatively, the recipient underwent a 3-hour session of intermittent haemodialysis and received cyclosporin A, azathioprine and methylprednisolone as part of his immunosuppressive regimen. A standard right-sided extraperitoneal exploration revealed no evidence of external iliac arterial or venous disease. Prior to vessel occlusion, 3 000 IU of unfractionated heparin was administered intravenously, and the vascular anastomoses were performed in 37 minutes, with a 7-hour cold ischaemic time (CIT). At reperfusion, excessive oozing from the kidney and surrounding tissue was noted, necessitating the use of topical haemostatic agents, reversal of heparin with protamine sulphate (15 mg), and systemic desmopressin administration. Additionally, 2 U of leucocyte-depleted packed red blood cells, 1 U of fresh-frozen plasma and 1 U of cryoprecipitate were administered intraoperatively. Haemostasis was achieved and the procedure was concluded after 2 hours and 58 minutes.

The postoperative period was complicated by delayed graft function (DGF), with the first session of haemodialysis administered on the 3rd postoperative day. An early ultrasound scan was reassuring, with normal allograft morphology, good corticomedullary differentiation, and a patent renal artery and vein with a resistive index of 0.8 in the main renal artery. Three renograms were performed within the first 2 weeks post-transplant, which showed progressive parenchymal concentration suggestive of acute tubular necrosis. A total of five sessions of haemodialysis was required, followed by an eventual recovery in urine output to 1 930 mL on the 14th postoperative day. The double-J stent was removed 6 weeks post-transplant and cyclosporin A levels remained within the therapeutic range, without the need for allograft biopsy. A satisfactory urine output (>1 mL/kg/h) was maintained, and a steady decline in the serum creatinine level was observed during the subsequent 3 months. The recipient has since returned to work, and at 1-year follow-up the serum creatinine level was reported to be 270 μmol/L.

Discussion

SA has one of the lowest deceased organ donor rates in the world (1.62 donors per million population in 2018),[4] with ~3 500 patients awaiting kidney transplantation.[5] Living-donor programmes have not been able to bridge the gap between organ supply and demand, and waiting lists continue to grow.[5] The shortage of donor organs is not unique to SA, and many institutions worldwide have implemented a more flexible approach to deceased-donor selection, including the use of ECD kidneys to improve access to transplantation.[3,6-8]

One-year survival on kidney replacement therapy in SA is 90.4%,[9] which compares favourably with 1-year mortality of 9 - 16% and 5-year mortality of 34% as reported in the international literature.[10,11] Nevertheless, patients undergoing dialysis have considerable morbidity and mortality associated with prolonged waiting times and may choose to be considered for an ECD graft, as previous reports have demonstrated a survival benefit compared with waiting on dialysis for an SCD.[2]

However, the relative risk of PNF with the use of ECD kidneys is estimated to be 1.7 times greater than with kidneys procured from SCDs.[3] A sensitising event such as PNF may present a major immunological setback for ESKD patients, which could negatively affect access to and the outcome of a subsequent transplant. It is therefore evident that the use of ECD kidneys may have both positive and negative effects, that not all ECD kidneys will be eligible for transplant, and that discarding of an ECD kidney may be required under specific circumstances.[12,13]

Discard rates of deceased-donor kidneys have increased in recent years. Reports from the UK have demonstrated an increase in discards from 5% to 12% between 2002 and 2012.[7] A similar pattern has been observed in the USA, with discard rates rising from 5.1% to 19.2% over a 20-year period.[8] Owing to multiple confounders, such as differing institutional protocols and surgeon opinions, it is difficult to accurately determine the reason for this phenomenon. Some believe that the process of expanding the donor pool would automatically result in an increase in discard rates, whereas others consider that risk-averse hospital policies or inefficient allocation systems may be to blame.[8] Approximately 75% of ECD kidneys undergo preimplantation biopsy in the USA and they are commonly discarded on the basis of unfavourable histological features, such as the extent of glomerulosclerosis (GS). Callaghan *et al.*[7] argued that kidneys routinely discarded in the USA might well have been implanted under UK surgeons, as preimplantation histology is not frequently assessed in the UK setting.

Kidney discard rates have not been reported in SA, but unpublished data from Groote Schuur Hospital in Cape Town suggest a discard rate of 1% over the past 10 years, which included a cohort of largely SCD kidneys donated after brain death. There may be an increased pressure to use ECD grafts owing to the severe donor shortage and limited dialysis capacity for public-sector patients, or one could argue that not enough high Kidney Donor Profile Index donors are being referred or actively pursued. Further studies are needed to determine the reasons for and significance of the low discard rates at Groote Schuur Hospital.

The case presentation above illustrates how subjective the decision to use or discard can be, and highlights the need for more objective strategies to determine the suitability of an ECD kidney for transplant. Numerous strategies have been investigated to reliably identify which ECD grafts are destined to fail, while minimising discard rates. For instance, preimplantation biopsy can evaluate the percentage of GS, a marker of chronic injury. Owing to the time pressure, access to haematoxylin and eosin stains is limited, and units that employ the preimplantation biopsy method usually rely on

frozen section biopsies to assist in decision-making. Although the sensitivity and specificity of frozen section biopsies is debated, there is significant interobserver and technique-related variability. This can be minimised by using specifically trained pathologists or adopting standardised reporting systems such as the Remuzzi score.[14] A previous study demonstrated that kidneys with GS >20% had odds of discard of 16.92 compared with non-biopsied kidneys.[15] Interestingly, there was no clear relationship between the degree of GS and the relative risk of PNF.[15] This finding may indicate that evaluation based solely on preimplantation biopsy may result in the unnecessary discarding of suitable ECD kidneys.

Ex vivo machine perfusion (MP) has gained popularity over recent years, and it provides an attractive, albeit more expensive, alternative to the established norm of organ preservation, static cold storage (SCS). MP allows a dynamic assessment of graft viability by assessing the resistance to perfusate flow, among other things.[16] Until recently, SCS has been preferred owing to its low cost and perceived simplicity.[17] In 2011, a study from Germany reported a significantly lower incidence of PNF in ECD kidneys that underwent MP (3%) compared with SCS (12%) (p=0.04), with a 12.1% higher 1-year graft survival in the MP group (92.3% v. 80.2%; p=0.02).[6] Other studies have corroborated the superiority of MP over SCS in selected cases, leading to policy change in some high-resourced countries.[17-19]

A cost-utility analysis of hypothermic MP (HMP) v. SCS in the Netherlands considered direct medical expenses of transplantation, the cost of dialysis after surgery, and other complications in a mixed group of ECDs and SCDs. The study found that HMP reduced the risk of PNF and was associated with cost savings of USD86 750 per life-year gained.[20]

In addition, there are only 15 centres that perform kidney transplants in SA, of which 6 are in the public sector.[21] Patients must often travel vast distances when a deceased-donor kidney is allocated to them, resulting in logistical challenges and prolonged CITs. As a result, ECD kidneys are often allocated to local recipients to limit CIT and minimise DGF rates, which may result in geographical inequities. By safely prolonging CIT, MP may have an important role to play in ameliorating geographical disparity in access to transplantation.[22]

Major obstacles have been identified with the incorporation and implementation of MP into existing transplant programmes.[23] The barriers to routine use in low-income settings are the initial financial cost, lack of trained professionals to operate the device, and the logistics involved in transportation of the device between facilities.[23] To mitigate the cost, negotiation with suppliers to acquire the device on loan could reduce the cost per perfusion to close to that of the price of the consumables. In-service training and supervision by a representative should be negotiated as part of the rental agreement during the early stages of implementation.[24]

As suppliers and distributors are looking to expand the use of MP devices beyond the USA, Europe and Australia, and the need to improve access to transplantation is becoming more apparent, the use of MP devices in SA may be more relevant and affordable now than ever before. Macroscopic assessment may be highly subjective, and as our case illustrates, may result in two different decisions being made regarding graft utilisation. Frozen section biopsy has been associated with an inappropriately high discard rate. MP provides a platform to objectively assess graft viability, safely prolongs CIT, and decreases PNF and DGF rates in ECD kidneys. Cost-utility studies are needed in the SA context, and allocation of this technology must be governed by careful donor selection and appropriate technical and theoretical knowledge.

Declaration. None.

Acknowledgements. None.

Author contributions. NBL: contributed to the conception, data acquisition, write-up and revision of the manuscript. ZK: contributed to the data acquisition, write-up and revision of the manuscript. DEdP: contributed to the write-up and revision of the manuscript. VS: contributed to the write-up and revision of the manuscript. LB: contributed to the write-up and revision of the manuscript. TdT: contributed to the conception, write-up, revision and overall supervision of the manuscript.

Funding. None.

Conflicts of interest. None.

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Accepted 29 September 2023.