JNDS Journal of the Nuffield Department of Surgical Sciences

Case Study

The use of deceased donor organs in kidney transplantation

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Keywords:
end-stage renal disease, DBD, DCD.

Key Learning Points

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Globally, over 2.5 million people are receiving renal replacement therapy, and this is estimated to double by 2030. ESRD is responsible for 2.3-7.1 million premature deaths due to lack of access to this treatment. In most high-income countries, renal replacement services include renal transplantation services, which is the most effective form of RRT and is associated with improved patient survival, reduced morbidity and improved quality of life.

To meet the growing demand for transplantation, extension of the organ donor pool to include donation after circulatory death (DCD) organs as opposed to the brain stem death donors (DBDs) that make up the majority has been embraced by many countries, including the UK. However, these DCD grafts have traditionally been associated with worse short-term outcomes (greater primary non function and delayed graft function) which as deterred some clinicians from utilising them. It has become increasingly clear that these grafts are in fact comparable to other deceased donor organs in terms of long-term patient and graft survival. Furthermore, with the advent of novel technologies such as machine perfusion (hypothermic and normothermic) as well as Normothermic Regional Perfusion (NRP) there is scope to improve the short-term outcomes as well.

This case takes us through the transplant journey of a patient that has benefited from deceased donor transplantation in the COVID era under an adapted immunosuppression protocol. The psychosocial impact of ESRD and social determinants healthcare are illuminated by this case and highlight the critical need to expand transplant services. We explore the differences between types of deceased donor organs and the mechanisms of the clinical syndromes associated with each, including delayed graft function. Finally, we explore how emerging perfusion technologies may be able to influence the rates of delayed graft function and early complications associated with deceased donor transplantation.

Introduction

Kidney transplantation is considered the optimal therapy for end-stage renal disease (ESRD). It improves quality of life and survival and is less of a financial burden in comparison to other forms of renal replacement therapy (RRT)[1]. There are over 63,000 people with ESRD in the United Kingdom (UK) and the incidence increases with age. In the UK, ESRD has a high prevalence in non-white communities, with people from Black, Asian and minority ethnic communities at a five times greater risk than their white counterparts[2]. This has several reasons, including disparities in socioeconomic status[3]. The most common causes of ESRD in the UK are diabetic nephropathy and hypertensive nephrosclerosis.

However, there is a national shortage of organ donors, which hinders the success of kidney transplantation and can result in long waiting times. In 2019-2020, the average time spent on the adult transplant waiting list was 633 days[4]. This time varies by social factors such as region, ethnicity and accessibility of services, but also by blood group and immunological risk, thus patients can die waiting for a transplant. Furthermore, the coronavirus pandemic has led to a decrease in the number of offered, retrieved and transplanted organs in 20204, with huge regional differences related to the approach taken by different transplant units[5]. Here in Oxford, transplant activity has continued despite the pandemic, and to-date 181 transplants have been performed.

The continued mismatch between donor organ supply and patient demand has led to the exploration of new avenues for increasing the donor pool. This report will describe the case of Mr A, who had a deceased donor kidney transplant in 2020. This report will review the recent literature comparing the different types of deceased donor organs available for transplant, and discuss the strategies used to increase donor organ supply.

The case of Mr A

Mr A is a 29-year-old gentleman of Pakistani descent. He was born with a congenital single kidney, which resulted in him developing ESRD and ultimately requiring RRT.

In December 2018, Mr A presented to the Eye Clinic with visual disturbances. As a result, he was diagnosed with retinal artery occlusion, hypertensive retinopathy and severe hypertension. Blood tests at the time revealed that he had established chronic kidney disease. His eGFR was 9 mL/min and native urine output was <500 ml/day. He had also suffered from gout since 2010, which was later revealed to be secondary to renal impairment.

In January 2019, he underwent an urgent start on automated peritoneal dialysis (APD). Mr A underwent APD for 8.5 hours each night for 18 months prior to transplant. Unfortunately, he had a very difficult time with APD and was struggling psychologically to cope. He was constantly lethargic and found that APD significantly impacted his sleep and social life. He reported to have been missing at least one night of dialysis per week in the months running up to the transplant.

Mr A has no known drug allergies and was on the following medications pre-operatively to manage his chronic renal failure:

1) Doxazosin (8mg 2x daily),

2) Ramipril (5mg 1x daily) and

3) Amlodipine (5mg 1x daily) for blood pressure control.

4) Furosemide (120mg 2x daily) for blood pressure control and oedema,

5) Allopurinol (100mg 1x daily) for gout.

6) Docusate (100mg 3x daily) for constipation.

Mr A has no family history of renal pathology/ ESRD, diabetes or vascular disease. With regard to his social history, Mr A lives with his wife and is independent. He worked full-time as a shop floor worker but had to stop three months into dialysis due to lethargy.

On the 25th of July 2020, Mr A underwent a deceased donor renal transplant from a donor after brainstem death (DBD). There was an HLA mismatch of 1-1-0 (A, B, DR loci) and the cold ischaemic time (CIT) was 7 hours and 17 minutes. Both the donor and recipient were cytomegalovirus (CMV) antibody negative.

The donor kidney was implanted extra-peritoneally into the right iliac fossa via a Rutherford-Morrison incision. The donor kidney's circulation was connected to Mr A's internal iliac vessels and its ureter to Mr A's bladder. Mr A received a COVID-19 adjusted protocol of immunosuppression receiving Basiliximab induction therapy immediately prior to his operation alongside methylprednisolone and subsequently received a second dose on the 4th post-operative day. Mr A recovered well and was discharged five days following transplant.

Post-transplant, Mr A was prescribed the following new medications.

- Mycophenolate mofetil (750mg 2x daily),
- Tacrolimus (4mg 2x daily) and
- Prednisolone (15mg 1x daily) for post-transplant immunosuppression.
- Co-trimoxazole (480mg 1x daily) for post-transplant prophylaxis.
- Paracetamol (1000mg 4x daily) for pain.

Post-discharge, Mr A has been doing very well and reports no fatigue or shortness of breath. He is being followed up regularly in the post-transplant clinic. He had primary graft function and continues to have excellent kidney graft function two weeks post-transplant, with a serum creatinine level of 114 µmol/L. He is hoping to restart working after his transplant.

Meeting the growing demand

Several efforts to increase the organ donor pool have been employed, such as, in May 2020, there was a change in legislature which meant that the UK organ donation system switched from opt-in to opt-out[6]. Another effort to increase the donor pool has been the extension of the donor organ acceptance criteria. This includes increasing the upper age limit of donating and accepting donors with certain co-morbidities. Another important change has been the use of organs that have been donated after cardiac death.

Currently, donor kidneys in the UK come from three sources:

1. Living donors (which can be related or non-related).
2. Donation after Brain-stem-death (DBD) donors, previously referred to as heart-beating donors.
3. Donation after circulatory death (DCD) donors.

DBD donors provide the majority of organs for transplantation, including the organ that Mr A received. However, due to changes in neurosurgical practice and improved road safety, there has been a decline in the availability of DBD donors. In order to address the rising demand for organ transplantation, there has been a trend towards increasing use of organs from DCD donors. Statistics from the NHS Blood and Transplant Activity Report show that the number of DCD donors has been increasing each year, although they still make up the smallest proportion of kidney-only transplants[4].

DBD donors

In the UK, brain death is defined in terms of permanent functional death of the brainstem[7]. This requires a set of preconditions to be satisfied (for example, the patient must have suffered major brain damage of known aetiology, be deeply unconscious and require ventilatory support), as well as a formal clinical assessment of the brainstem reflexes.

Once brainstem death has been confirmed, organ recovery can take place. After dissection of the organs to be recovered, they are perfused in situ with a chilled organ preservation solution. This produces rapid cooling of the organs and preserves their viability by reducing their metabolic activity. The time between initiation of cold perfusion to implantation and reperfusion with the recipient's blood is known as the cold ischaemic time, prolongation of CIT is associated with worse outcomes.

DCD donors

Donation after circulatory death (DCD) donors can be categorised according to the Maastricht classification[8]:

- Category 1: Dead on arrival at hospital
- Category 2: Resuscitation attempted without success
- Category 3: "Awaiting cardiac arrest" after withdrawal of support
- Category 4: Cardiac arrest while brain dead

Maastricht categories 1 and 2 are considered "uncontrolled", since death occurs suddenly and unexpectedly, whereas categories 3 and 4 are considered "controlled". In these categories, death occurs after the withdrawal of life-sustaining treatment. Most DCD donor organs used for transplant in the UK are from controlled

(category 3) donors who have died in intensive care after planned withdrawal of futile cardiorespiratory support[9].

In DCD donor organs, there is an inevitable period of warm ischaemia (warm ischaemic time; WIT) which occurs between the diagnosis or death (i.e. cardiorespiratory arrest) and cold perfusion of the organs. Due to the ischaemic injury that takes place, previous studies have shown that WIT is associated with adverse long-term patient and graft survival after kidney transplantation. For example, a multicentre cohort study in the United States of America, which followed up 130,000 kidney transplants over 13 years, found that progressively longer WIT times were associated with an increased risk of graft failure and death. This was evident even after multivariable adjustment for donor and recipient factors[10].

In the case of DCD donors, the aim of organ recovery is to minimise the WIT. After cardiorespiratory arrest, there is an obligatory 'hands off' period which varies between different countries from five (UK) to twenty (Italy) minutes before death is certified and organ recovery can begin[11]. This no-touch period is given both out of respect to the donor and to ensure cessation of neurological activity. The length of the period depends on national transplant law. Longer durations are controversial, as they are associated with increased rates of primary non-function and delayed graft function.

Post-transplant outcomes

In some organs such as heart, lung or liver, it is critical that the transplanted organ functions immediately. However, for kidneys, immediate graft function is desirable, but not vital for patient survival.

Kidney graft function in the early postoperative period can be categorised as such:

- Immediate function
- Delayed graft function
- Primary non-function

Simply put, a graft is defined as having immediate function if the patient does not require dialysis after transplantation.

Delayed graft function (DGF) is notoriously difficult to define. It is often conceptualised as a form of acute kidney injury in the setting of transplantation, but the exact definition in the literature varies based on a range of clinical criteria dependent on individual transplant centres and country of origin[12]. This can cause an issue when comparing rates of DGF in different studies. However, most studies define DGF as the need for temporary dialysis in the post-transplant period. The timeframe in which this occurs is variable, but a time period of within one week after transplantation is commonly given.

Primary non-function occurs if there is a permanent absence of graft function, inevitably resulting in the return to RRT awaiting re-listing for transplantation is appropriate.

Concerns regarding DCD organs

The expansion of organ donation criteria to use DCD kidneys has led to shorter waiting times, higher transplant rates and lower waiting list deaths[13]. However, the main resistance to the use of DCD kidneys stems from concerns regarding ischaemic injury and delayed graft function, and the potential that these have on long-term kidney function[14].

Kidneys obtained from DCD donors inevitably suffer more ischaemic injury than DBD kidneys, due to the WIT. Hence, DGF is more common in DCD kidneys. Despite these concerns, several centres worldwide have been carrying out DCD transplants for the last few decades, making it possible to carry out high-powered studies and assess the long-term outcomes of DCD transplants, including how they fare in comparison to DBD transplants. However, one must be cautious when comparing cohorts, as international differences in donor acceptance criteria, definitions of post-transplant function and transplant policy may affect outcome measures. The debate is whether the benefits of expanding the donor organ pool and reducing waiting list time outweigh the potential risks associated with DCD kidneys.

Despite the potential concerns regarding cross-cohort data analysis, there is a general consensus in the literature that DCD kidneys have a greater rate of DGF and primary nonfunction compared to DBD kidneys[15]. Snoeijs et al.[16] found in a 25-year follow-up study that DCD transplants were associated with a 7.5 (95% CI, 4.0-14.1; P<0.001) and 10.3 (95% CI, 6.7-15.9; P<0.001) times greater risk of primary nonfunction and DGF respectively, when compared to DBD kidneys.

Another factor associated with increased rates of DGF in DCD kidneys is donor age[17,18]. In one retrospective cohort analysis of over 6000 DCD transplants, donor age above 50 was shown to be one of the strongest predictors of DGF[17]. Currently, the UK national allocation scheme aims to promote transplant effectiveness by reducing the donor-recipient age difference where possible[19].

Long-term equivalence in survival of DCD and DBD kidneys

Despite the increased incidence of short-term complications in DCD kidneys, several studies have showed no difference in long-term survival between DBD and DCD kidneys. For example, Schaapherder et al.[20] conducted a long-term follow-up study of over 6000 kidney transplants carried out in the Netherlands. In this study, they found no difference in long-term graft and recipient survival of DCD kidneys compared to DBD kidneys, after a 10-year follow-up period. Long-term equivalence in survival occurred despite the fact that DCD kidneys had an increased risk of DGF and primary non-function, and that DGF itself was correlated with an increased risk of graft loss in both types of kidneys.

This corresponds with UK data published by Summers et al.[18], who found that in over 7500 transplantations, there was an equivalence in graft survival between DCD and DBD kidneys. One potential criticism of the UK data is that less than 10% of the transplants carried out were from DCD kidneys, raising issues regarding generalisability of this data. However, 43% of the cases in the Netherlands cohort were DCD kidneys, making this less of an issue in that study[20].

In DBD transplants, DGF is considered a major predictor of acute rejection and long-term graft loss[21]. The fact that DCD and DBD kidneys demonstrate no difference in survival in the long-term, despite DCD kidneys having higher rates of DGF, suggests that DGF impacts DBD and DCD kidneys differently[22]. It is possible that the mechanism of DGF itself is different between the two kidney types[23]. For example, ischaemic injury due to the inevitable WIT may be a major cause of DGF in DCD kidneys[24], whereas neurogenic inflammation due to brainstem death may be the cause in DBD kidneys[16].

Brainstem death is an unphysiological state that is associated with systemic pro-inflammatory changes, including leucocyte accumulation in the graft organ[25]. De Vries et al.[23] showed that donor brainstem death

predisposes the kidney graft to a pro-inflammatory reaction (including T cell and macrophage infiltration and cytokine release) upon reperfusion. This pro-inflammatory state is specific for brainstem death and not cardiac death, as DCD kidney grafts do not demonstrate the same response[23]. The cytokines released upon reperfusion may attract the recipient's own leucocytes to the kidney graft and therefore increase the risk of acute rejection[26]. These findings suggest that DBD kidneys may require targeted donor pre-treatment to prevent this inflammatory response, in order to reduce rates of DGF and increase graft survival[23].

It is also possible that DGF in DBD kidneys represents poorer graft quality, whereas DGF in DCD kidneys may relate to shorter or less deleterious ischaemic injury, rather than giving an indication of underlying graft quality[22].

Measures to improve short-term outcomes in DCD kidneys

In the short term, DCD kidneys are associated with increased rates DGF, meaning patients may have to go back on dialysis. As DGF is a major limitation to the widespread use of DCD kidneys, there has been a search for methods to reduce its likelihood. Interventions targeted at reducing the WIT may reduce the incidence of DGF, since WIT is an important factor in DGF.

There have been attempts to reduce ischaemic injury in deceased donor kidneys by using pulsatile machine perfusion and extracorporeal membrane oxygenation to maintain adequate organ perfusion. Machine perfusion pumps preservation solution through the graft and can be started at the time of organ recovery and continued until implantation. This may decrease rates of DGF compared to standard static cold storage (SCS), where they kidney is stored in an ice box after removal from the donor until implantation.

Hypothermic machine perfusion (HMP) is one such technique that is used as an alternative to the standard static cold storage. On analysis of all the 11,400 deceased kidney transplants carried out in the Netherlands from 1998-2018, De Kok et al.[27] found that there were major improvements in outcomes of transplanted DCD kidneys over time. The authors suggested that this improvement may be due the change from standard static cold storage to HMP. However, in this cohort, this change was implemented in 2016, meaning that the use it may have a limited impact on overall outcome data. The improvement is likely to be multifactorial, including HMP as well as other factors, such as optimised surgical procedures and immunosuppressive regimens. Nevertheless, a meta-analysis conducted by Tingle et al.[28] found that the use of HMP does reduce the risk of DGF in kidneys from DCD donors.

Conclusion

The case of Mr A and others highlight the importance of donor organ procurement in the UK. There is a great mismatch between supply and demand of kidneys available for transplant, which has only been worsened in recent months as a result of the coronavirus pandemic.

DCD kidneys represent an important fraction of the donor pool, and evidence suggests that although DCD kidneys have increased rates of primary non-function and delayed graft function, they have similar long-term patient and graft survival rates when compared to DBD kidneys. Therefore, it is important to consider DCD kidneys as a viable option for transplant. Analysis of cost-effectiveness also supports the inclusion of DCD kidneys alongside DBD kidneys in the donor pool, due to resulting reduction in waiting list times[29]. Furthermore, the cost associated with increased rates of delayed graft function are outweighed by the cost of keeping patients on dialysis waiting for a transplant.

The initial reservations surrounding the use of DCD kidneys regarding delayed graft function have been dispelled by the recent literature, however some other concerns do remain. There is a general consensus that live donor kidneys have better overall outcomes than deceased donor kidneys[30]. Therefore, some physicians suggest that strategies aimed at increasing the living donor pool are more warranted. It is interesting to note that Mr A did not receive a living donor kidney. There could be several reasons for this, such as lack of availability of a living donor, as well as certain immunological, chronological and anatomical factors that may have influenced the decision in graft choice[31]. However, given the number of people waiting for a transplant, DCD kidneys represent a valuable source of donor organs. Further research is required to understand the mechanisms of short-term graft complications in DBD and DCD kidneys, with the aim to create interventions to reduce these.

Conflicts of interest

None.

Funding

None.

Consent

The patient has consented to the publication of this case study.

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