Outcome of Kidney Transplantation in Israel Following Uncontrolled Donation after Cardiocirculatory Determination of Death

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ABSTRACT **Background:** A limited program for kidney donation from uncontrolled donation after cardiocirculatory determination of death (uDCDD) was implemented at four hospitals in Israel in close cooperation with Magen David Adom (MDA), the national emergency medical service.

Objectives: To assess the outcome of transplantations performed between January 2017 and June 2022.

Methods: Donor data included age, sex, and cause of death. Recipient data included age, sex, and yearly serum creatinine levels. A retrospective study of out-of-hospital cardiac arrest cases treated by MDA during 2021 were analyzed to assess their compatibility as potential uDCDD donors.

Results: In total, 49 potential donors were referred to hospitals by MDA. Consent was obtained in 40 cases (83%), organ retrieval was performed in 28 cases, and 40 kidneys were transplanted from 21 donors (75% retrieval rate). At 1-year follow-up, 36 recipients had a functioning graft (4 returned to dialysis) and mean serum creatinine 1.59 ± 0.92 mg% (90% graft survival). Outcome after transplantation showed serum creatinine levels (mg%) at 2 years 1.41 ± 0.83, n=26; 3 years 1.48 ± 0.99, n=16; 4 years 1.07 ± 1.06, n=7; and 5 years 1.12 ± 0.31, n=5. One patient died of multiple myeloma at 3 years. The MDA audit revealed an unutilized pool of 125 potential cases, 90 of whom were transported to hospitals and 35 were declared dead at the scene.

Conclusions: Transplant outcomes were encouraging, suggesting that more intensive implementation of the program may increase the number of kidneys transplanted, thus shortening recipient waiting lists.

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KEY WORDS: kidney transplantation, Magen David Adom (MDA), out-of-hospital cardiac arrest (OHCA), uncontrolled donation after cardiocirculatory determination of death (uDCDD)

Kidney transplantation remains the optimal therapy for patients with end-stage renal failure. However, the gap between those needing a transplant and available donors has resulted in many patients dying each year while waiting for an appropriate donor. For this reason, donation after circulatory determination of death (DCDD) is increasingly seen as an important additional source of organs for transplantation. DCDD is classified according to the modified European Maastricht categories [1]. This classification defines DCDD as uncontrolled donation after cardiocirculatory determination of death (uDCDD), which follows an unexpected and sudden death from cardiac arrest, either in or out of the hospital, and controlled (cDCDD). This condition follows an expected cardiac arrest after withdrawal of life-sustaining therapy. The latter is the most implemented world-wide and has been developed and implemented in 17 countries [2]. However, at the present time this category is not practiced in Israel since the law does not permit withdrawal of continuous therapy, in this case, mechanical ventilation.

A limited uDCDD program, exclusively for kidney transplantation, was implemented in Israel in 2015 at four tertiary-care hospitals, and the first cases were performed in 2017 [3]. A successful program depends on three essential elements: clearly defined protocols, consideration of logistical aspects, and a system to detect potential donors. Regarding the former, a protocol was formulated incorporating medical aspects (a clinical pathway), social and ethical aspects (presentation of the protocol at a public gathering), and legal aspects (requirement for consent). Regarding logistical aspects, a pilot study confined to four medical centers was successfully implemented after the relevant medical teams underwent extensive training both in Israel and in France. Last, the detection and evacuation of potential donors to hospital depends on close cooperation with Magen David Adom (MDA), Israel's national emergency medical service (EMS). This condition required MDA to introduce changes to existing protocols regarding the transport of patients receiving cardiopulmonary resuscitation (CPR) during their evacu-

ation to hospital. Continued support for the program depends on the outcome of organ transplantation from these donors and evidence for a significant donor pool.

In this study, we describe the changes made to MDA protocols and the results of kidney transplantation from uDCDD donors.

PATIENTS AND METHODS

THE UDCDD PROTOCOL

The program, which included only type IIb Maastricht patients following an out-of-hospital cardiac arrest (OHCA), was initially active at four hospitals in Israel: Rabin Medical Center (Beilinson Campus), Petah Tikva; Hadassah Medical Center, Ein Kerem, Jerusalem; Rambam Health Care Campus, Haifa; and Soroka University Medical Center, Faculty of Health Sciences, Beer Sheva. Since 2018, the program has continued at Rabin Medical Center and Hadassah Medical Center while an additional program was implemented at Tel Aviv Sourasky Medical Center, Tel Aviv, in 2019. The technique applied for the uDCDD process has previously been fully described [3]. Organ preservation techniques included normothermic regional perfusion (at Rabin Medical Center), regional intraperitoneal cooling (Rambam Health Care Campus and Soroka University Medical Center), and rapid organ removal without preservation (Hadassah Medical Center).

MDA PROTOCOL FOR OUT-OF-HOSPITAL CARDIAC ARREST

In 2015 the MDA medical division introduced a new protocol defining criteria and interventions required for OHCA patients receiving CPR during evacuation to a hospital. These criteria included that the patient could be safely transported from the scene to the ambulance without interrupting CPR attempts, that the team was equipped with a mechanical CPR device, that there were no apparent contraindications to organ donation (e.g., positive for human immunodeficiency virus, known malignant disease, or the presence of significant intra-abdominal trauma), that the estimated call to hospital time was < 60 minutes, and that the receiving hospital had the capacity to treat reversible causes of OHCA and/or had an extracorporeal cardiopulmonary resuscitation protocol (ECPR) according to the cause of the arrest.

PATIENTS

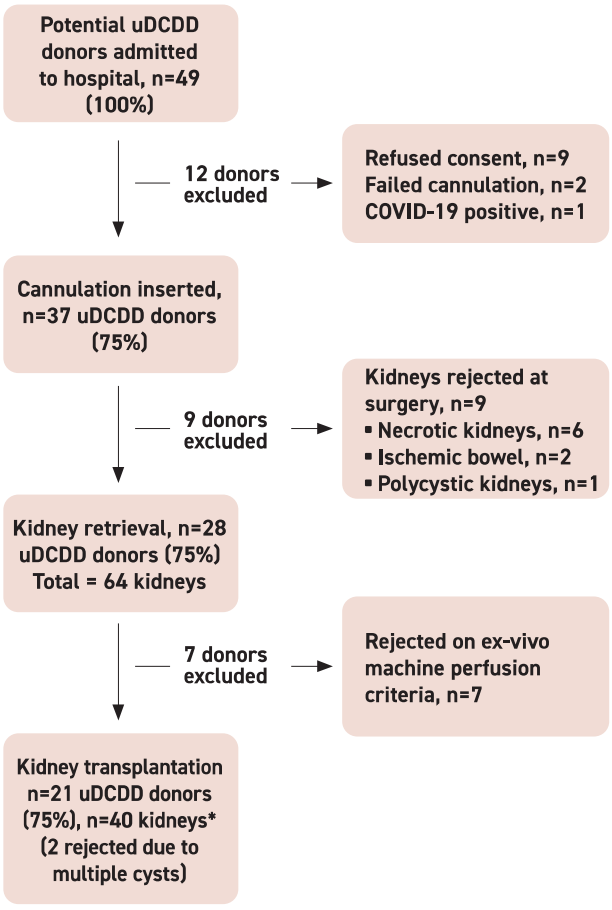
We included all potential uDCDD kidney donors admitted to a participating hospital and their recipients from 2017 to June 2022. The following data were collected from the donor: age, sex, and cause of cardiac arrest. From the recipient the data included: age, sex, and serum creatinine at yearly intervals following transplantation. Results are expressed as the mean ± standard deviation.

RESULTS

From the introduction of the program until June 2022, 49 uDCDD donors were admitted to the hospital. Their mean age was 49 ± 7.9 years. The cause of death was sudden cardiac arrest in all and 81% were male. The study profile of the donors is shown in Figure 1. Consent for kidney donation was obtained in 40 cases, representing a consent rate of 83%. Three donors were rejected prior to organ retrieval due to failure of cannulation in two cases and a positive coronavirus disease 2019 (COVID-19) test in one. Nine donors were rejected due to findings at surgery, namely, necrotic kidneys in six, ischemic bowel in two, and polycystic kidneys in one. The kidneys of a further seven donors were rejected after retrieval because of high levels of resistance on ex-vivo machine perfusion. In total, 40 kidneys were retrieved and transplanted from the remaining 21 donors, 2 kidneys (from 2 separate donors) being rejected due to the presence of significant atrophy at

Figure 1. Study profile of uDCDD donors

*1 kidney each from 2 separate donors rejected due to presence of cortical atrophy



surgery. The mean age of the recipients was 47 ± 6.4 years and 79% were males. Outcome data are shown in Table 2. At 1-year follow-up, 36 recipients had functioning grafts. Of the remaining four, three had returned to dialysis and one underwent donor nephrectomy in the week following transplantation [Table 1]. The mean serum creatinine of the 36 recipients was 1.59 ± 0.92 mg%. Thus, graft survival at 1 year was 90%. During the remaining 5-year study period, time elapsed since the transplant included 26 recipients after 2 years, 16 after 3 years, 7 after 4 years, and 5 after 5 years. The serum creatinine of these recipients was 1.41 ± 0.83, 1.48 ± 0.99, 1.07 ± 1.06, and 1.12 ± 0.31 mg%, respectively. Over the same period, one recipient returned to dialysis at 2 years while a further recipient died of multiple myeloma at 3 years. No patients were lost to follow-up.

DISCUSSION

This study revealed the ongoing successful implementation of the uDCCD program, although in a limited manner, following changes made by MDA to their evacuation protocol. Since its introduction, the consent rate for donation has been consistently high (83%), and 40 kidneys from 21 donors have been successfully retrieved and transplanted with very encouraging results.

uDCDD programs are presently active in a limited number of countries, almost exclusively in Europe [4]. However, even in those participating centers, the number of these donors and transplant procedures has been steadily decreasing. This situation has occurred despite the European Resuscitation Guidelines advocating the consideration of uDCDD after failed CPR [5]. In the United States, a uDCDD protocol for Maastricht category II cases was derived in 2010 [6]. However, the program was not continued following a prospective study that revealed many protocol violations and no organ procurement [7]. Suggested reasons for this underutilization included logistical problems related to the complexity of the process and its resource- and staff-intensive nature, concerns about the quality of organs retrieved, and concerns regarding the acceptability of the process by the public [8,9].

These obstacles appear to have been successfully overcome in the limited program in Israel. Thus, apart from two cases of failed cannulation at the start of the program, no other significant technical problems related to the process were noted. In this regard, the transplantation rate; that is, the number of kidneys transplanted/number of kidneys retrieved, was 71%. While this rate is lower than the > 95% reported from long-standing programs such as in Spain, this compares very favorably with the initial results achieved following the introduction of a similar program in France, namely 57.4% [10,11]. Although our numbers are small and the time since transplantation was only 5 years, the results of kidney transplantation were very encouraging and graft survival at 1 year of 90% is comparable with those from other centers. Importantly, it has been shown that the outcome following uDCCD kidney transplantation compares very favorably with rates following transplantation after neurologically determined death (NDD). A study from Spain reported outcomes from uDCCD donors with 10-year death censored graft survival of 82.1% and recipient survival of 86.2%, results that compared very well with those from standard criteria donors (SCD) after NDD ($P = 0.45$) [12]. A study from France showed that patient and graft survival outcomes were similar between uDCDD and extended criteria donors (ECD); however, they were lower than that of SCD donors ($P < 0.01$) [13]. Last, the consent rate in our program was 83%, suggesting general acceptance of the process. This rate is significantly higher than the consent rate for donation after NDD in Israel, which is 60%.

Possible explanations for this discrepancy might be that uDCDD donors clearly appear to be dead (no chest movement, flat ECG on monitor) compared to donors after NDD (chest movement due to mechanical ventilation and normal ECG patterns on monitor). In this regard, it is significant to note that all 10 uDCDD cases at the Hadassah Medical Center involved ultra-orthodox families who typically do not consent to donation after NDD as for this group, only cardiocirculatory determined death (cardiac death),

Table 1. Outcome of kidney transplantation (n=40) at 1-year follow-up

Time elapsed since transplantation	1 year (n = 40)
Serum creatinine, mg%, mean ± SD	1.59 ± 0.92
Number requiring dialysis or nephrectomy	4
Number of deaths	0
Number with functioning graft	36
Graft survival	90%

SD = standard deviation

Table 2. Kidney outcome from 2 to 5 years following transplantation

Time elapsed since transplantation	2 years (n=26)	3 years (n=16)	4 years (n=7)	5 years (n=5)
Serum creatinine, mg%, mean	1.41 ± 0.83	1.48 ± 0.99	1.07 ± 1.06	1.12 ± 0.31
Number requiring dialysis	1			
Number of deaths		1		
Number with functioning graft according to time elapsed since transplantation	25	15	7	5

but not NDD, is accepted as the true manifestation of death. Interestingly, none of the uDCDD donors had signed a donor card.

Until 2012, only physicians in Israel were permitted to declare the death of a human being. In 2012 a new regulation issued by the Israel Ministry of Health granted paramedics in Israel the authority to declare the death of a person in out-of-hospital settings in conjunction with confirmation by an online medical physician. Over time, there has been conflicting evidence regarding the practice of transporting a patient undergoing CPR to hospital. For some EMS organizations, transporting such patients is a routine practice, mainly because paramedics in these countries lack the authority to declare death in the absence of a physician on site [14]. Other EMS organizations have adopted guidelines that allow the paramedic, in certain situations, to declare the death of the patient at the scene [14]. The changes made to local protocols have allowed for the evacuation of patients following unsuccessful CPR while continuing to receive full resuscitative measures to a hospital participating in the uDCCD program, but with the additional potential for ECPR in the event of the return of spontaneous circulation.

Last, a recent MDA audit retrospectively examined all cases following an OHCA treated by MDA during 2021 and who fulfilled criteria as potential uDCCD donors (unpublished) and who were in proximity to hospitals with uDCCD programs that were either active or in the process of implementation. The audit revealed a potential pool of 125 unutilized donors for the year 2021. Reasons for non-utilization included transport to a non-participating hospital, failure of the admitting hospital to recognize a potential donor, and death being declared at the scene without evacuation to a hospital being considered. Similar results of underutilization have been reported from other countries. Thus, 9828 compatible potential uDCDD cases were identified in a study from the United State, while a similar study from Spain identified 571 potential cases [8,15]. While these figures, including ours, may be an overestimation as they may not capture all donors with contraindications, they nevertheless speak to a significant additional source of potential donors. The results of the audit have informed ongoing instructional interventions for relevant MDA teams together with representatives of Israel Transplant.

CONCLUSIONS

The initial results of the uDCDD program are very encouraging. There appears to be a significant potential of underutilized donors and a more intensive application of the program has the potential to increase the number of kidneys transplanted and thus shorten recipient waiting times.

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Those who dream by day are cognizant of many things which escape those who dream only by night.
Edgar Allan Poe (1809–1849), American writer, poet, editor, and literary critic

In the small matters trust the mind, in the large ones the heart.
Sigmund Freud (1856–1939), neurologist, founder of psychoanalysis