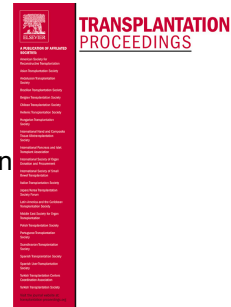


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Static cold storage vs. ex vivo machine perfusion: results from a comparative study on renal transplant outcome in a controlled donation after circulatory death program.

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Abbreviations: (in alphabetical order)

brain death donors (DBD)

donation after circulatory death (cDCD).

delayed graft function (DGF)

primary non-function (PNF)

withdrawal of life sustaining therapy (WLST)

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Static cold storage vs. *ex vivo* machine perfusion: results from a comparative study on renal transplant outcome in a controlled donation after circulatory death program.

Abstract

Introduction: We aimed to evaluate if *ex vivo* machine perfusion could minimize the negative impact of cold ischemia on those renal grafts obtained from controlled donation after circulatory death (cDCD).

Material and methods: Prospective observational paired study of kidney transplants from cDCD performed in our center.

The kidney from each pair which preserved on ice was transplanted first within the next few hours following procurement while the contralateral kidney being machine perfused (LifePort®; Organ Recovery System, Brussels, Belgium) got transplanted during the next day.

Results: A total of 12 cDCD's were included. No differences were observed in delayed graft dysfunction or graft survival between both groups.

Conclusion: The use of these *ex vivo* perfusion devices is simple and do not require any large infrastructural or high economic investments, considering the facts that it allows a better selection of recipients and no longer discard viable organs for prolonged warm ischemia times.

Key words: *ex vivo* machine perfusion, static cold storage, renal transplant, controlled donation after circulatory death

Static cold storage vs. ex vivo machine perfusion: results from a comparative study on renal transplant outcome in a controlled donation after circulatory death program.

Introduction:

Further widespread expansion of all type of organ transplants has been limited by the persistent mismatch between supply and demand of organs for transplantation. In an attempt to expand the donor pool and to make more grafts eligible for transplantation; several strategies have been proposed like further improving donor management of brain death donors (1) as well as the introduction of a donation after circulatory death program (2;3). However, the unpredictable consequences of warm ischemia which characterizes controlled donation after circulatory death (cDCD); together with impaired organ perfusion during the agonal phase, result in reluctance for accepting grafts from these donors, leading to fewer eligible donors being converted to actual donors as seen in brain death donors (DBD) (4,5).

In cDCD, the effects of warm ischemia, resulting from the hypotensive phase after withdrawal of life sustaining therapy (WLST) as well as following circulatory arrest are further exacerbated during the later period of cold ischemia. In kidney transplantation these phenomena have been identified as major risk factors for a higher incidence of primary non-function (PNF) and delayed graft function (DGF) (6).

Despite these problems, several studies in kidney transplantation have shown that the long-term results in terms of survival and functionality are comparable to those seen in kidneys from brain death donors (7,8).

Despite these higher risks at short-term, nowadays it seems evident that the survival benefit from receiving a DCD renal graft outweighs the risks from remaining on dialysis while waiting for a DBD graft (9).

Several groups have studied the impact of ex vivo renal perfusion devices as an alternative method for the preservation of kidneys compared to the traditional method of static conservation

on ice with encouraging results in favor of perfusion for reducing rates of delayed graft dysfunction in children and cDCD's. (10,11). Since the results were not yet fully conclusive; we designed a paired study for kidneys obtained from cDCD's in order to evaluate whether or not ex vivo machine perfusion could minimize the negative impact of cold ischemia on those renal grafts.

Material and methods:

Prospective observational paired study of kidney transplants from donors after controlled cardiac arrest performed at the University Hospital "Marqués de Valdecilla" in the period from September 2014 to December 2017.

One kidney from each pair was preserved on ice and transplanted first within the next few hours following procurement (Group A) while the contralateral kidney of the same pair was machine perfused (LifePort®; Organ Recovery System, Brussels, Belgium) and transplanted in the next day after retrieval (Group B).

All kidneys were removed from cDCD donors after a period of regional normothermic abdominal perfusion and after controlled cardiac arrest occurred.

Recipient characteristic such as mean age, gender distribution, number of retransplants and number of HLA incompatibilities were compared between groups.

The primary endpoints for the analysis of our study were incidence of delayed graft function (defined as the need for dialysis during the first week after transplantation) and overall graft survival. The secondary endpoints were renal function (creatinine at 1, 3, 6 and 12 months) and in case DGF occurred, the number of dialysis sessions required.

Data were analyzed using the T-student test for quantitative variables and the Mc Nemar test for categorical variables. Kidneys from donors with prolonged functional warm ischemia time (greater than 1 hour) were excluded from the study.

Results:

During the study period, a total of 12 cDCD's were identified and resulted in 24 renal grafts procured from those donors and transplanted at our center. Cold ischemia time was 6h on average in Group A and 19,9h on average in Group B.

Main characteristics of donors are detailed in Table 1. Twenty five percent of donors fulfilled the criteria for expanded criteria donors.

Both groups were comparable with respect to recipients' characteristics. Cold ischemia time was significantly longer in Group B.

No significant differences were observed between groups with respect to incidence of DGF, number of dialysis sessions and renal function during the first postransplant year. Table 2.

In terms of graft survival, one kidney in the machine group presented an early vascular thrombosis at 72 hours.

Discussion:

Every year the proportion of cDCD's gains more weight, which contributes to increasing the number of organs eligible for transplantation. Several series have shown that the main disadvantage for using renal graft from such cDCD donors as compared to DBD donors is the higher rate of delayed graft function, with advanced donor age and prolonged cold ischemia time being identified as extra major risk factors (12).

Ex vivo perfusion machine might offer a solution to this problem since it might allow safe prolongation of the time window between procurement and transplantation. Although our series of cases is small, the fact that we have used a pair design for our study implies that both kidneys received identical pre-extraction care; in combination with the observation that recipients in both arms had similar characteristics in terms of age and comorbidities, allowed us to demonstrate that by using these perfusion devices we could safely increase cold ischemia

time without jeopardizing renal outcome in terms of survival and functionality. Other studies carried out in the United Kingdom in recent years (13, 14) have demonstrated similar results in terms of safe mild prolongation of cold ischemic time. In contrast to the UK studies in which most of the kidneys were first cold stored prior to being machine perfused upon arrival at the transplant hospital, the kidneys in our study were machine perfused as from procurement until transplant. Palayo et al have shown that in DCD kidneys, prolonged use of cold storage preceding machine perfusion was associated with worse results (15).

In clinical practice, the use of ex vivo perfusion devices might enable longer transportation time between centers which could facilitate organ exchange between centers located remotely from each other. This somewhat wider time window could allow more optimal selection of recipients; hereby increasing the possibility for getting a transplant for hyperimmunized patients.

Using these perfusion devices for donors with prolonged warm ischemia times also generates additional viability assessment information: Poor machine perfusion parameters like renal resistance and flow have been associated with higher incidence of DGF and graft loss. This additional viability information might prevent us from discarding perfectly viable organs on the one hand while on the other hand, it might avoid transplanting kidneys with poor function post-operatively.

So, in conclusion, the use of ex vivo perfusion devices might allow to significantly prolong the cold ischemia time compared to cold storage maintaining similar results with respect to DGF and mid-term graft function. This longer period might allow a more accurate selection of recipients.

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TABLES.

Table 1. Donor characteristics

Donor Characteristics	N: 12
Age (years)	51.4 (SD 11.9)
Sex (male)	10 (83.3%)
Cause of death:	CVA 1 (8.3%) Anoxia 6 (50%) TBI 1 (8.3%) Other 4 (33.3%)
Diabetes mellitus	2 (16.7%)
Hypertension	2 (16.7%)

Expanded-criteria donor.	3 (25%)
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TBI: traumatic brain injury. CVA: cerebrovascular accident;

Table 2. Kidney transplants and recipients' characteristics

Recipients	Cold stored kidney (n: 12)	Machine perfused kidney (n: 12)	p
Gender (male)	10 (83.3%)	7 (58.3%)	0.375
Age (years)	52.6 (SD 14.8)	51 (SD 10,1)	0.983
Retransplanted	0	3 (25%)	---
HLA Incompatibility > 3	9 (75%)	9 (75%)	1.000
HLA A Incompatibility			
0	1 (8.3%)	2 (16.7%)	0.549
1	6 (50%)	7 (58.3%)	
2	5 (41.7%)	3 (25%)	
HLA B Incompatibility			
1	6 (50%)	5 (41.7%)	1,000
2	6 (50%)	7 (58.3%)	
HLA DR Incompatibility			
0	1 (8.3%)	1 (8,3%)	0.392
1	4 (33.3%)	7 (58.3%)	
2	7 (58.3%)	4 (33.3%)	
Cold Ischemia (min)	365.3 (SD 81.3)	1203.7 (SD 371)	0.0001
Creat 10 days (mg/dl)	3.2 (SD 2)	2.9 (SD 2.2)	0.367
Creat 1 month (mg/dl)	1.3 (SD 0.5)	1.5 (SD 0,7)	0.190
Creat 90 days (mg/dl)	1.3 (SD 0.4)	1.4 (SD 0.6)	0.09

Creat 180 days (mg/dl)	1.3 (SD 0.4)	1.5 (SD 0.7)	0.121
Creat 1 year (mg/dl)	1.3 (SD 0.4)	1.5 (SD 0.7)	0.521
DGF	3 (25%)	4 (33.3%)	1.000
Dialysis sessions 1 or 2	2 (16.7%)	2 (16.7%)	1.000
Dialysis sessions > 3	1 (8.3%)	2 (16.7%)	1.000

Creat., serum creatinine. DGF, delayed graft function.

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Highlights

- *ex vivo* machine perfusion could attenuate the negative impact of cold ischemia.
- minimizing the effect of cold ischemia.
- outcomes of kidney obtained from controlled donation after circulatory death donors.

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