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Cold Storage for Renal Graft Preservation at the Start of Machine Perfusion Era. Retrospective Analysis in Our Series

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Abstract

Introduction: Due to the increase in the demand of renal grafts, the criteria for organ acceptance have been widened. It has been accepted the definition of expanded criteria donor (ECD) and it has been developed new extraction techniques such as organ donation after circulatory death (DCD). In order to better preserve the renal grafts and optimize their function, graft perfusion techniques have been developed through different a system, which allows an increase in the hours of cold ischemia.

Material and Methods: Data base is created with the inclusion criteria where both donor kidneys were transplanted in different receptors, preserving one kidney in cold storage (CS) and the other using a continuous pulse machine perfusion device. Lifeport Kidney Transporter device is used in this study. T student for independent means analysis is carried out with the objective to find statistically significant differences in the analytical and functional parameters.

Results: There were no differences on receptors characteristics. It was found statistically significant difference in time of cold ischemia between cold storage and machine perfusion (p= 0.00). It is remarkable that diuresis, creatinine and urea seems to be better on MP group even when p value is not significant. Postsurgical complications, blood transfusions and hospitalization days are also less on MP group.

Conclusion: The preservation of the renal graft by MP achieves similar short-term results compared to cold storage irrespective of the greater time of cold ischemia.

Keywords: Renal graft; Kidney; Transplant; Diuresis

Abbreviations: ECD: Expanded Criteria Donor; DCD: Donation after Circulatory Death; CS: Cold Storage.

Introduction

Population ageing and the stabilization of the donation of corpses increase waiting lists for kidney transplants over the years. In order to solve this problem the accepted criteria for the organs becomes wider, creating the term of donation with expanded criteria. It was observed that these sub-optimal donors, although demonstrating worse long-term graft survival [1] and an increase in early renal dysfunction [2], when compared to the overall survival of the patient, mortality was lower when the groups of patients on the waiting list were taken into consideration [3]. At present, with the generalization of the extraction technique in asystole, new candidates for donation are appearing in view of the decrease in deaths from natural causes and accidents, which has meant an increase in donation in general terms and in the number of transplants [4]. Recent years have also seen an increase in early kidney transplants as a method of replacement therapy, rising from 1.4% of transplants in 2006

to 4.8% in 2016.

Thanks to all these efforts in donation, coordination between different services and the implementation of donation in asystole, since 2014 there has been an increase in the number of kidney transplants per million inhabitants, which had remained stable since 2000 [5]. The risk posed by the increase in the number of transplants is the lengthening of the cold ischemic period. For this reason, different techniques have been developed for renal conservation that make it possible to maintain renal flow with cold serum. Several studies have been carried out to check the effect of these machines on renal conservation. Already in 2009, a randomised study showed improved survival and graft function [6] although it was initially developed with the idea of being able to extend cold ischemic times. Several subsequent studies have given consistency to these findings in both asystole donors [7] and cadaver donors. In fact, in the case of the cadaver donor, substantial improvements in long-term renal function have been found by reducing the evolution to dialysis [8].

Due to the importance of correct renal preservation in post-transplant function, percentage of initial delay of organ function, acute tubular necrosis and graft survival, the debate about the use or not using perfusion machines is relevant for the usual medical practice, even more considering the contradictory results of some studies such as the one by Watson et al. [9], which was suspended because no difference was found between types of preservation (futility stop).

The absence of clear differences has made the use of perfusion machines open to debate [10], although there is an increasing evidence in favour of the use of machine perfusion devices [11-15], in that it helps to reduce delayed graft function and improves graft survival during the first year. However, its advantage in decreasing primary graft failure is not clear [11].

Material and Methods

In order to observe the effect of the LifePort Kidney Transporter kidney perfusion machine, a database was created incorporating the transplants performed from 2016 to May 2020. The main inclusion criteria was the acceptance of both donor kidneys, being implanted in different recipients and keeping one kidney cold with Celsior preservation fluid and another with a LifePort Kidney Transporter pulsed chase machine with KPS solution. Although most studies use the Wisconsin storage medium, there are no significant differences with Celsior [16] and its use is therefore considered valid.

Kidney transplants were carried out sequentially due to logistic reasons. The first transplanted organ was the one preserved in CS, followed by the second transplant using the kidney from MP. By obtaining two organs from each donor, it is estimated that selection bias has been avoided because the transplanted organs have the same characteristics, so that the overall result only depends on variables of the recipient and on the type of organ conservation. The Student t of independent measures is used to perform a mean difference analysis in the values between both groups in order to observe significant differences in the early function of the graft and creatinine levels evolution.

Results

In a preliminary analysis of the demographic data, there were no statistically significant differences between the two groups (Table 1).

Item	Lifeport	N	Media	Standard deviation	Media error	P value
Age	Yes	21	58,29	10,978	2,396	0.94
	No	21	58,62	17,405	3,798	
MBI	Yes	21	25,850	3,7958	,8283	0.6
	No	21	26,503	4,1179	,8986	
Dialisis time	Yes	21	621,78	346,332	81,631	0.33
	No	21	775,11	570,070	130,783	
Residual urine output	Yes	21	982,50	547,248	122,368	0.38
	No	21	811,90	643,021	140,319	
Previous creatinine	Yes	21	6,2333	2,56755	,56029	0.81
	No	21	6,4238	2,38849	,52121	

Table 1: Receptors data.

There are no statistically significant differences in organ laterality between the two groups, which mostly have been placed on the right side. Three patients underwent a second transplant. The kidneys preserved by the LifePort Kidney Transporter System were monitored for improved resistivity and flow between the implant and the machine and the time prior to removal of the organ from the machine. Average initial resistance values of 0.52 and flow rates of 70.71ml/min and final resistance values of 0.22 and 129ml/min were observed at a maximum pressure of 30/20mmHg. The kidneys were perfused for an average time of 1055 minutes.

On Table 2 are shown storage and suture data. There were no differences in the vascular suture times of the graft and the arterial clamping time of the recipient. There were statistically significant differences in the cold ischemia time of the organ, with an average difference of six and a half hours between both groups.

Item	Lifeport	N	Media	Standard deviation	Media error	P value
Cold ischemic time	Yes	21	1227.38	213.37	46.56	0.00
	No	21	834.81	189.45	41.34	
Suture time	Yes	21	57.48	12.18	2.66	0.87
	No	21	56.76	15.09	3.29	
Arterial suture	Yes	21	25.13	8.89	2.22	0.75
	No	21	24.29	8.89	2.16	

Table 2: Storage and vascular data.

Item	Lifeport	N	Media	Standard deviation	Media error	P value
Creatinine 24h	Yes	21	5.07	2.81	0.61	0.88
	No	21	5.2	2.66	0.58	
Creatinine at discharge	Yes	21	2.35	1.46	0.32	0.76
	No	21	2.50	1.64	0.36	
Diuresis 24h	Yes	21	5737.14	2663.65	581.256	0.84
	No	21	5992.1	5185.22	1131.51	
Diuresis at discharge	Yes	21	2350.00	781.19	170.47	0.32
	No	21	2126.19	654.34	142.79	
Urea 24h	Yes	21	110.38	41.51	9.06	0.40
	No	21	90.29	34.16	7.46	
Urea at discharge	Yes	21	104.71	56.23	12.27	0.73
	No	21	110.62	54.97	11.99	
Presurgical haemoglobin	Yes	21	11.83	1.34	0.29	0.62
	No	21	11.62	1.32	0.29	
Postsurgical haemoglobin	Yes	21	9.65	2.68	0.58	0.75
	No	21	9.87	1.60	0.35	
Transfusion needed	Yes	21	0.76	1.45	0.32	0.23
	No	21	1.33	1.56	0.34	
Clavien-Dindo media	Yes	21	1.14	1.15	0.25	0.27
	No	21	1.62	1.57	0.34	
Hospitalization days	Yes	21	9.67	4.49	0.98	0.50
	No	21	10.57	4.15	0.91	

Table 3: Post surgical data.

This difference is explained on the operation room availability, performing one transplant after the other. Kidneys preserved in using MP were performed secondly. When analytical items are analyzed, there were no significant differences between both groups. When Analytical and post surgical data were analyzed (Table 3), creatinine is lower on Lifeport group, which is consistent with the urea values. We have observed that the Lifeport group had better diuresis at discharge, less post surgical complications, less need for a blood transfusion and fewer days of hospitalization.

Despite the numbers are not statistically significant, it is important to notice the improvement that the use of a perfusion device can provide, even when this group has more than 5 hours of ischemic time above cold storage. When creatinine, urea and diuresis were measured at discharge, it is important to notice that all functional values are better on Lifeport group. Surgical measurements were better to, with less requirements of blood transfusions, less complications and less hospitalization days.

Discussion

The need to increase the donor pool because of the demand for organs is not a problem that affects us in isolation. With the increase in half-life and chronic pathologies, the costs associated with long-term dialysis represent a significant economic burden in our environment, so methods that allow optimization of grafts that can be considered transplantable are a relevant issue [17]. In this study almost all of the transplanted kidneys corresponded to donors considered to have expanded criteria, defined as donors aged 60 or over or aged 50 or over with two associated risk factors (serum creatinine greater than 1.5mg/dl, high blood pressure or cause of death by stroke).

In the study by Wight et al. [18] the economic benefit of the use of the perfusion machine compared to cold storage was observed in donors with circulatory death or asystole. In other studies, advantages have been observed in donors with expanded criteria, above all due to the reduced need for dialysis during the immediate post-operative period and hospital admission [19]. In the analysis by Bond et al. [20], no differences were found between the different perfusion devices, and more data is needed in the future to know which system is better. In this study, the decrease in days of admission and complications in the graft perfusion group is constantly observed, which supports the theory of lower costs despite the use of these devices.

Many studies have tried to explain why these results are obtained with a perfusion machine. In the study by Yland et al. [21], better renal conservation was observed in relation to TPA levels and homeostasis. There is also evidence suggesting a reduction in apoptosis and tissue inflammation by observing reduced expression of endothelin-1 and increased nitric acid [22] and reduced oxidative stress and inflammation of the grafts [23]. Other works observe a reduction in endothelial damage, observing better reperfusion by measuring cortical microcirculation and tubular damage markers [24, 25]. It has also been studied that cessation of renal flow is associated with increased endothelial dysfunction of the renal graft when comparing graft perfusion with cold storage [26].

In this sense, the review carried out by Hameed et al. [14] is very revealing by including animal trials in their systematic review, concluding the improvement that perfusion brings in the short term after kidney transplantation. Although with a more doubtful effect in the long term, it may be more beneficial in terms of survival than remaining on dialysis, even with suboptimal kidneys [3].

A hypothesis that can justify these results of early recovery of renal graft function and less ischemic damage is the shorter ischemia-reperfusion time, as capillaries and small vessels are open. For this reason, it is possible that lower results could be obtained in our study, using maximum perfusion pressures of 30mmHg, in contrast to the average of the studies analyzed, which reported 50mmHg. There is evidence of improvement in renal function and delayed graft function with expanded criteria donors [27-29], so that the improvement in early function of transplants is justified in our work, although it does not reach significance.

Conclusion

Renal graft preservation by means of perfusion machines achieves short-term results comparable to cold preservation regardless of the longer cold ischemic time. The decrease in days of admission and complications in transplant patients after optimizing the graft with a renal MP, although not significant, may be relevant from an economic point of view as observed in the analyzed studies. The improvement on creatinine levels, urea and diuresis at discharge on MP group can be explained by the optimization of the transplanted graft. The sample needs to be enlarged so that the p value can reach the signification, but these results are promising for future measurements.

References

1. Pascual J, Zamora J, Pirsch JD (2008) A systematic review of kidney transplantation from expanded criteria donors. Am J Kidney Dis 52(3): 553-586.

2. Port FK, Bragg-Gresham JL, Metzger RA, Dykstra DM, Gillespie BW, et al. (2002) Donor characteristics associated with reduced graft survival: an approach to

expanding the pool of kidney donors. Transplantation 74(9): 1281-1286.

3. Ojo AO, Hanson JA, Meier-Kriesche H, Okechukwu CN, Wolfe RA, et al. (2001) Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. J Am Soc Nephrol 12(3): 589-597.

4. Organización Nacional de Trasplante 2017. Memoria de actividad.

5. Balance de actividad de la Organización Nacional de Trasplantes en 2017.

6. Moers C, Smits JM, Maathuis MH, Treckmann J, Gelder FV, et al. (2009) Machine perfusión or cold storage in deceased-donor kidney transplantation. N Engl J Med 360(1): 7-19.

7. Jochmans I, Moers C, Smits JM, Leuvenink HG, Treckmann J, et al. (2010) Machine perfusion versus cold storage for the preservation of kidneys donated after cardiac death: a multicenter, randomized, controlled trial. Ann Surg 252(5): 756-764.

8. Kwiatkowski A, Wszoła M, Kosieradzki M, Danielewicz R, Ostrowski K, et al. (2009) The early and long term function and survival of kidney allografts stored before transplantation by hypothermic pulsatile perfusion. A prospective randomized study. Ann Transplant 14(1): 14-17.

9. Watson CJ, Wells AC, Roberts RJ, Akoh JA, Friend PJ, et al. (2010) Cold machine perfusion versus static cold storage of kidneys donated after cardiac death: a UK multicenter randomized controlled trial. Am J Transplant 10(9): 1991-1999.

10. Irish W D, Katz E (2010) Cold Machine Perfusion or Static Cold Storage of Kidneys: Why the Debate Continues. Am J Transplant 10(9): 1955-1956.

11. Domínguez JI, Amesti M, Majerson (2018) Hypothermic machine perfusion versus static cold preservation in kidney transplantation. Medwave 18(7): e7360.

12. O'Callaghan JM, Morgan RD, Knight SR, Morris PJ (2013) Systematic review and meta-analysis of hypothermic machine perfusion versus static cold storage of kidney allografts on transplant outcomes. Br J Surg 100(8): 991-1001.

13. Jiao B, Liu S, Liu H, Cheng D, Cheng Y, et al. (2013) Hypothermic machine perfusion reduces delayed graft function and improves one-year graft survival of kidneys from expanded criteria donors: a meta-analysis. PLoS One 8(12): e81826.

14. Hameed AM, Pleass HC, Wong G, Hawthorne WJ (2016) Maximizing kidneys for transplantation using machine perfusion: from the past to the future: A comprehensive systematic review and meta-analysis. Medicine (Baltimore) 95(40): e5083.

15. Hu XY, Wang YF, Ye QF, Chen ZQ, Fan XL, et al. (2015) Effects of hypothermic machine perfusion versus static cold storage of kidney allografts on transplant outcomes: A Meta-analysis. Chinese Journal of Tissue Engineering Research 19(42): 6882-6888.

16. Sanz PP, Revilla FJB, Letosa RM, Santos JP, Rivas JLM, et al. (2004) Preservación con Celsior en trasplante renal: Nuestra experiencia. Actas Urol Esp 28(1): 49-53.

17. Garcia GG, Harden P, Chapman J (2012) The global role of kidney transplantation. The Lancet 379(9820): E36-E38.

18. Wight J, Chilcott J, Holmes M, Brewer N (2003) The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors. Health Technol Assess 7(25): 1-94.

19. Groen H, Moers C, Smits JM, Treckmann J, Monbailu D, et al. (2012) Cost-effectiveness of hypothermic machine preservation versus static cold storage in renal transplantation. Am J Transplant 12(7): 1824-1830.

20. Bond M, Pitt M, Akoh J, Moxham T, Hoyle M, et al. (2009) The effectiveness and cost-effectiveness of methods of storing donated kidneys from deceased donors: a systematic review and economic evaluation. Health Technol Assess 13(38): 1-156.

21. Yland MJ, Todo S, Zhu Y, Suzuki T, Hamada N, et al. (1996) An automated and portable low-flow pulsatile perfusion system for organ preservation. Transpl Int 9(6): 535-540.

22. Gallinat A, Fox M, Luer B, Efferz P, Paul A, et al. (2013) Role of pulsatility in hypothermic reconditioning of porcine kidney grafts by machine perfusion after cold storage. Transplantation 96(6): 538-542.

23. Salahudeen AK (2004) Cold ischemic injury of transplanted kidneys: new insights from experimental studies. Am J Physiol Renal Physiol 287(2): F181–187.

24. Minor T, Sitzia M, Dombrowski F (2005) Kidney transplantation from non-heart-beating donors after oxygenated low-flow machine perfusion preservation with histidine-tryptophan-ketoglutarate solution. Transpl Int 17(11): 707-712.

25. Maathuis MH, Manekeller S, van der Plaats A, Leuvenink HGD, Hart NA, et al. (2017) Improved kidney graft function after preservation using a novel hypothermic machine perfusion device. Ann Surg 246(6): 982-988.

26. Gracia-Sancho J, Villarreal G Jr, Zhang Y, Yu JX, Liu Y, et al. (2010) Flow cessation triggers endothelial dysfunction during organ cold storage conditions: strategies for pharmacologic intervention. Transplantation 90(2): 142-149.

27. Lam VW, Laurence JM, Richardson AJ, Pleass HCC, Allen R DM (2013) Hypothermic machine perfusion in deceased donor kidney transplantation: a systematic review. J Surg Res 180(1): 176-182.

28. Wight JP, Chilcott JB, Holmes MW, Brewer N (2003) Pulsatile machine perfusion vs. cold storage of kidneys for transplantation: a rapid and systematic review. Clin Transplant 17(4): 293-307.

29. Matsuoka L, Shah T, Aswad S, Bunnapradist S, Cho Y, et al. (2006) Pulsatile perfusion reduces the incidence of delayed graft function in expanded criteria donor kidney transplantation. Am J Transplant 6(6): 1473-1478.