Transplant International

LETTER TO THE EDITORS

Machine perfusion in clinical trials: the preservation solution bias

doi:10.1111/j.1432-2277.2011.01300.x

Dear Sirs,

Clinical studies have yielded conflicting results about the benefits of kidney preservation by machine perfusion (MP) in comparison to static cold storage (CS) [1–3]. A turning point in favor of MP has been the publication by Moers *et al.* of results of the largest multicentric clinical trial reporting a decrease in delayed graft function associated with MP preservation of kidneys obtained from all donor types [4]. These benefits have recently been confirmed by Treckmann *et al.* in a subgroup analysis limited to extended criteria donors (ECD) [5].

In their discussion Treckmann *et al.* state 'we focused on the effect of MP in kidneys from ECDs…'. One has to bear in mind that in experiments designed to compare two conditions, only one parameter must change between the two assessed conditions. However, this is not the case in all the clinical trials to date as both the preservation modes and the solutions used were different in the two arms of the studies: the University of Wisconsin, Viaspan® (UW) or histidine-tryptophane-ketoglutarate (HTK) solutions were used for CS whereas the kidney preservation solution-1 (KPS-1®) was used for MP. These solutions have very distinct ionic compositions (low K^+ and low Na^+ for HTK; high K^+ and low Na^+ for UW; low K^+ and high Na^+ for KPS-1®) and colloid contents [6].

However, the intrinsic MP effect is strongly dependent on the composition of the solution. In a preclinical study using a porcine model of kidney autotransplantation partially mimicking deceased after cardiac arrest donation with a drastic 60-min period of warm ischemia before preservation [7], we compared the effects of MP versus CS using the same solutions in both preservation modes. With UW, MP greatly improved preservation as no grafted animals survived past 7 days in the CS group whereas 75.0% survived in the MP group (Table 1). With KPS-1, the MP-mediated improvement in survival was not as obvious (KPS-1-CS: 57.2%; KPS-1-MP: 71.4%) (Table 1). Chronic follow-up revealed a clear superiority of MP over CS in terms of function and outcome, independently of the solution used, as well as a superiority of KPS-1 for CS in comparison to UW. Extrapolating these results to the Treckman *et al.* study, we can expect that the UW solution (with a high potassium content deleterious for kidney preservation [8,9]) in the CS arm pulls down the survival curve in this donor population which is probably more elevated with the HTK solution, a solution with a potassium content closer to KPS-1®.

Table 1. Survival of animals transplanted with kidneys subjected to 60 min of warm ischemia prior to preservation by machine perfusion or cold storage with either the UW or KPS-1 preservation solutions.

Group	Survivors/operated animals	%
UW-CS	0/6	0.0
UW-MP	6/8	75.0
KPS-1-CS	4/7	57.2
KPS-1-MP	5/7	71.4

CS, cold storage; KPS-1, kidney preservation solution-1; MP, machine perfusion; UW, University of Wisconsin.

These experimental observations raise the question whether the 'MP effect' in the Treckmann *et al.* study would have been as clear if KPS-1 had been used in the CS arm instead of UW or HTK. Clinical comparisons of static CS and MP cannot be done without considering the 'solution effect'. Therefore, conclusions about the MP benefits should be drawn with care from the current clinical studies as we cannot exclude the hypothesis that third generation CS solutions could give results equivalent (or better) than any other solution used with MP.

N. Chatauret,[1,2] R. Thuillier,[1,2] B. Barrou,[1,3] T. Hauet[1,2] and M. Eugene[1,4]
1 INSERM U927, Poitiers, France
2 CHU de Poitiers, Pole UBM, Service de Biochimie, Poitiers, France
3 Hôpital Pitié Salpétrière, Groupe Hospitalier Universitaire Est, Service d'Urologie et Transplantation, Paris
4 CHU de Poitiers, Direction de la Recherche, Poitiers, France

References

1. Jochmans I, Moers C, Smits JM, *et al.* Machine perfusion versus cold storage for the preservation of kidneys donated after cardiac death: a multicenter, randomized, controlled trial. *Ann Surg* 2011; **252**: 756.
2. Watson CJ, Wells AC, Roberts RJ, *et al.* Cold machine perfusion versus static cold storage of kidneys donated after cardiac death: a UK multicenter randomized controlled trial. *Am J Transplant* 2010; **10**: 1991.
3. van der Vliet JA, Kievit JK, Hene RJ, Hilbrands LB, Kootstra G. Preservation of non-heart-beating donor kidneys: a clinical prospective randomised case-control study of machine perfusion versus cold storage. *Transpl Proc* 2001; **33**: 847.
4. Moers C, Smits JM, Maathuis MH, *et al.* Machine perfusion or cold storage in deceased-donor kidney transplantation. *N Eng J Med* 2009; **360**: 7.
5. Treckmann J, Moers C, Smits JM, *et al.* Machine perfusion versus cold storage for preservation of kidneys from expanded criteria donors after brain death. *Transpl Int* 2011; **24**: 548.
6. Yuan X, Theruvath AJ, Ge X, *et al.* Machine perfusion or cold storage in organ transplantation: indication, mechanisms, and future perspectives. *Transpl Int* 2010; **23**: 561.
7. Vaziri N, Thuillier R, Favreau FD, *et al.* Analysis of machine perfusion benefits in kidney grafts: a preclinical study. *J Transl Med* 2011; **9**: 15.
8. Hauet T, Han Z, Doucet C, *et al.* A modified University of Wisconsin preservation solution with high-NA+ low-K+ content reduces reperfusion injury of the pig kidney graft. *Transplantation* 2003; **76**: 18.
9. Ramella SG, Hadj-Aissa A, Barbieux A, *et al.* Evaluation of a high sodium-low potassium cold-storage solution by the isolated perfused rat kidney technique. *Nephrol Dial Transplant* 1995; **10**: 842.