Choosing the Right Preservation Solution

a report by
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The value of organ preservation has been made evident to the field of organ donation and transplantation over the past 40 years. Through positive transplant patient outcomes and the increased number of organs available for transplant, organ preservation has proven itself an integral part of transplantation.

Organ transplantation was first made possible in the 1960s/1970s using organs procured through non-heart beating donation, and machine-perfused kidneys. Then came short-term, cold-storage solutions in the 1970s/1980s with EuroCollins (EC) and Marshall solutions. Soon after this, two other solutions were developed as cardioplegia solutions and for use in heart preservation – HTK-Custodiol (histidine-tryptophan-ketoglutarate) and Celsior. Both of these solutions have since been tested for short-term preservation of the intra-abdominal organs. However, the field of transplantation needed a solution for long-term preservation and, by 1987, UW (University of Wisconsin, ViaSpan) solution was introduced – its studies supported safe organ preservation for 48 to 72 hours.[1] This intracellular solution became the clinical standard for cold-preservation throughout the world, demonstrating its superiority in comparison to the aforementioned preservation solutions.

The goal of cold storage organ preservation is to induce hypothermia in order to suppress the rate of cell deterioration in the organs, to counteract the degenerative affects of hypothermia (cell-swelling and enzyme leakage) and minimise organ damage. The optimal preservation solution should contain impermeants to reduce cell-swelling, buffers to maintain pH balance, antioxidants to scavenge oxygen-free radicals and adenosine triphosphate (ATP) precursors to provide energy upon reperfusion, all of which is contained in UW.

Although EC is a good intracellular buffer solution, it lacks the ability to ensure the quality of organs beyond short preservation times. In addition, the high content of glucose in EC can be detrimental to the liver where it is more readily permeable than in the kidney. Thus, glucose is not a good impermeant in the liver. In a prospective, randomised trial of 695 cadaveric renal transplants comparing kidneys preserved in UW and EC, the incidence of delayed graft function was significantly less in transplant recipients receiving UW-preserved kidneys than those receiving EC-preserved kidneys (23% versus 33% respectively; ρ=.003).[2] Distribution of EC ceased in the US in 2002 but continues to be used in Europe.

HTK-Custodiol was originally developed as a cardioplegia solution by Dr Bretschneider in Germany. This extracellular solution consists of histidine as the buffer, tryptophan as a membrane stabiliser and ketoglutarate as the energy substrate. It was approved in the US for kidney preservation in 2001 and liver preservation in 2002. To date, HTK has still not received US Food and Drug Administration (FDA) approval for pancreas preservation.

While there are studies claiming equivalence of UW and HTK solutions at eight to 12 hours of preservation, there are vast differences in the efficacy of the two solutions when the preservation times exceed 24 hours. The advantage of UW usage for long-term preservation is demonstrated in several clinical studies.

In a retrospective analysis of 323 cadaveric kidney transplants, there was no significant difference in delayed graft function in those kidneys preserved for less than 24 hours. However, when cold ischaemic time (CIT) exceeded 24 hours, the delayed graft function rates for UW-preserved kidneys were 23.9% versus 50% with HTK-preserved kidneys (ρ=.006). Furthermore, graft survival at one year was 91% in those patients receiving UW preserved kidneys compared with 77.4% for HTK (ρ=.059).[3]

In a study of 12 non-heart-beating canine kidneys, after two weeks four of the six UW-preserved kidney

1. *Southard J H and Belzer F O, "Organ preservation",* Annual Review of Medicine *(1995), 46: pp. 235–247.*
2. *Ploeg R J, van Bockel J H and Langendijk P T, et al., "Effect of preservation solution on results of cadaveric kidney transplantation", The European Multicentre Study Group*, Lancet *(1992), 340 (8812): pp. 129–137.*

recipients survived and only one of six in the HTK group survived. This study also examined Total Adenine Nucleotide (TAN) levels, showing that higher TAN levels indicate better preservation of energy metabolism, enhanced protection against the deleterious effects of warm ischaemia and more cellular viability. In this study, one hour after reperfusion TAN levels were significantly higher in the UW group ($\rho < .05$). There was no recovery of TAN levels observed within one hour of reperfusion in the HTK group. The results of this study demonstrate that UW solution is superior to HTK for cold storage preservation of ischaemically damaged kidneys.[4]

Endothelial cells are the first targets of deterioration during cold ischaemia and endothelial damage has been shown to cause liver failure. In a study to test the viability of endothelial cells stored in UW, HTK and EC, the UW-preserved cells maintained 99% cell viability after 24 and 48 hours of cold storage and 86.7% cell viability after 72 hours. However, preservation with HTK and EC allowed cell-survival for only 24 hours with no viable cells seen after 48 hours.[5]

Lastly, in a study examining cell death in 69 rat livers using ViaSpan, HTK and Celsior, bile secretion was best preserved in UW. Leakage of hepatocellular enzymes, i.e. serum glutamic-oxaloacetic transaminase (SGOT) and lactate dehydrogenase (LDH), was lower in UW than HTK at all time points and lower than Celsior after 16 hours. In this study, rat livers were best preserved in UW for long-term storage (16 to 24 hours) and the data suggest that even for short-term cold storage of liver grafts (eight hours), HTK is less effective than UW.[6]

ViaSpan demonstrates superior long-term, intra-abdominal preservation when compared with HTK, Celsior and EC. Although the costs of UW and HTK are comparable, the results may not be. There may be overall healthcare cost reductions with UW-preserved organs due to a lessened need for dialysis and fewer hospitalisation days. If a single organ suffers because of inadequate organ preservation, the patient-outcome and cost-savings become void. For instance, it costs approximately US$200,000 for a liver transplant. If a liver is damaged and a re-transplant is needed, the cost is increased by US$200,000. If one patient's kidney fails and he/she needs dialysis because of a poor flush-out/longer exposure to a different solution, the cost savings are negated.

HTK purports greater cost savings than UW. The average wholesale price (AWP) for UW solution is US$282 per litre and the AWP for HTK is US$211 per litre. However, since HTK is less viscous than UW solution, HTK requires more volume than UW in order to completely flush the extracellular space and maintain equilibration of the preservation solution throughout the organ, thereby minimising any savings. The product labelling for HTK indicates that, as a general rule, eight to 12 litres of HTK at 2°C to 4°C should be perfused (about 300ml per kg of body weight) versus the product labelling for UW, which indicates using four to six litres for the same procedure.[8,9]

In a randomised study of 711 kidney donors, the recommended volume for the *in situ* flush-out was 5,000ml to 6,000ml for HTK, 4,000ml for EC and 1,000ml to 2,000ml for UW.[7] In another study of 60 human liver transplants comparing preservation with UW and HTK, the preservation solution costs were equivalent due to the increased volume requirements for HTK.[10]

UW solution has become the clinical standard for cold-preservation of organs throughout the world, demonstrating its superiority in comparison to the aforementioned preservation solutions.

3. *Roels L, Coosemans W and Donck J, et al., "Inferior outcome of cadaveric kidneys preserved for more than 24 hr in histidine-tryptophan-ketoglutarate solution", Leuven Collaborative Group for Transplantation,* Transplantation, *(1998) 66(12): pp. 1,660–1,664.*
4. *Booster M H, van der Vusse G J, Wijnen R M, Yin M, Stubenitsky B M and Kootstra G, "University of Wisconsin solution is superior to histidine tryptophan ketoglutarate for preservation of ischemically damaged kidneys",* Transplantation, *(1994), 58(9): pp. 979–984.*
5. *Eberl T, Schmid T and Hengster P, et al., "Protective effects of various preservation solutions on cultured endothelial cells",* Annals of Thoracic Surgery *(1994), 58(2): pp. 489–495.*
6. *Straatsburg I H, Abrahamse S L, Song S W, Hartman R J and Van Gulik T M, "Evaluation of rat liver apoptotic and necrotic cell death after cold storage using UW, HTK, and Celsior",* Transplantation *(2002), 74(4): pp. 458–464.*
7. *de Boer J, De Meester J and Smits J M, et al., "Eurotransplant randomized multicenter kidney graft preservation study comparing HTK with UW and Euro-Collins",* Transplant International *(1999), 12(6): pp. 447–453.*
8. *"Custodiol HTK Solution for Kidney/Liver Preservation",* Prescribing information *(2003).*
9. *"ViaSpan (Belzer UW) Cold Storage Solution",* Prescribing information *(2002).*
10. *Erhard J, Lange R and Scherer R, et al., "Comparison of histidine-tryptophan-ketoglutarate (HTK) solution versus University of Wisconsin (UW) solution for organ preservation in human liver transplantation. A prospective, randomized study",* Transplant International *(1994), 7(3): pp. 177–181.*

The composition of UW solution culminates to optimise the outcomes of cold-preservation. UW solution has consistently proven superior protection to organs against hypothermia-induced ischaemia, preservation of organ function and viability when compared to other cold-storage solutions. For short-term ischaemia, all organ preservation solutions can be effective. However, due to logistics with organ allocation, donor procedures and organ transport, short-term preservation cannot be guaranteed. Therefore, it is essential for organs to be preserved with UW solution (ViaSpan), the most effective solution with proven results for long-term organ preservation. ■