

The Right Solution for Organ Preservation

a report by

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Organ transplantation is very successful, due in part to the availability of cadaveric organs that can be preserved for 24 hours or more and safely shipped between the donor and recipient hospitals. The quality of preservation and the length of safe storage are dependent upon the type of preservation solution and method of preservation. The preferred method of organ preservation is simple cold storage (CS), which involves flushing the organ with the preservative and storing at 0°C to 4°C prior to transplantation. The preferred organ preservation solution varies between transplant centers.

In the 1970s, Collins developed a preservation solution later modified in Europe (EuroCollins solution, (EC)), which became the standard for CS of kidneys.¹ This solution was a phosphate-buffered saccharide solution and the high concentration of glucose-suppressed hypothermic-induced cell swelling, which made these solutions suitable for 24 to 30-hour preservation of kidneys. For the liver and pancreas, the safe preservation time was less (four to eight hours). Distribution of EC ceased in the US in 2002 but continues to be used in Europe.

During the same decade, a hypertonic solution was developed by Marshall that contained citrate as an agent to suppress hypothermic-induced cell swelling.² This solution was also successful in kidney preservation for approximately 30 hours and in liver preservation for up to approximately eight hours. The short period of safe preservation for the kidney (24 to 30 hours) was not a large detriment to sharing cadaveric kidneys,

which could be shared nationally or internationally within the safe preservation time of 30 hours; however, the short-safe preservation period for the liver (four to eight hours) inhibited widespread use of this solution for liver transplantation.

The author's group developed University of Wisconsin (UW) solution (ViaSpan) for cold storage of the pancreas, liver, and kidney in the late 1980s.¹ This solution was shown to be equally effective for relatively long-term preservation of all three organs with safe preservation in dogs for 48 to 72 hours. This solution became the clinical standard throughout the world with excellent results.

In a prospective, randomized trial of 695 cadaveric renal transplants comparing kidneys preserved in UW with EC, the incidence of delayed graft function was significantly less in transplant recipients receiving UW-preserved kidneys than those receiving EC-preserved kidneys (23% compared with 33%, respectively; $p=0.003$).³ Another study conducted at the University of Pittsburgh demonstrated UW to safely increase preservation time for livers to more than 15 hours (maximum of 37 hours) compared with EC.⁴

Currently, UW solution continues to be the gold standard for organ preservation; however, two other solutions, Celsior and histidine-tryptophan-ketoglutarate (HTK), claim equivalency based upon laboratory and clinical studies.^{5,6} Celsior is a modified UW solution that takes advantage of the primary

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agent in UW that makes it a superior preservation solution – lactobionic acid.^{1,7} It is therefore not surprising that Celsior should provide similar preservation efficacy to UW solution; however, Celsior has not been tested for long-term (48 to 72 hour) preservation in renal, pancreas, or liver transplant models. Celsior is suggested to be superior to UW because it has a lower concentration of potassium (replaced with sodium) and a decrease in viscosity due to the elimination of hydroxyethyl starch. There is no definitive evidence that either lowering the potassium concentration or omitting the colloid affects preservation efficacy.

Furthermore, in a study examining cell death in 69 rat livers preserved with UW, HTK and Celsior after 24-hour storage, bile secretion was best preserved in UW.⁷ 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.

HTK solution, originally developed as a cardioplegia solution, is being touted as a solution of equal efficacy to UW solution.⁸⁻¹⁰ Some centers are now comparing the solutions clinically. The claimed advantages of HTK solution to ViaSpan include lower cost per liter, lower viscosity resulting in easier diffusion into the organ, faster cooling rates, and low potassium so that HTK can be allowed direct release into the patients circulation. These claims are unsupported as important in organ preservation.

The role of viscosity and the rate of cooling in preservation efficacy are not clear. Release of a high concentration of potassium from residual preservative in a large organ such as the liver can lead to cardiac arrhythmias. This is not a problem with smaller organs like the kidney because of the smaller vascular and extracellular space. The organ is therefore flushed with a solution containing a low concentration of potassium prior to transplantation (i.e., lactated ringers). Instead of this pre-transplant vascular flush being perceived as an

extra task, this step may be highly beneficial to the organ since it washes out the potentially harmful cellular metabolites that can accumulate during the period of cold ischemia. Some of these are powerful vasoconstrictors (chemokines and cytokines) and can exacerbate reperfusion injury in the organ. Furthermore, various intracellular, catabolic enzymes are released from cells during cold storage and removal of these enzymes with a pre-transplant vascular flush should be performed regardless of the potassium content.

The best method for comparing various solutions exists in a laboratory or clinical trial where the only variable is the composition of the preservation solution. This is difficult in clinical studies because it is not possible to control for the many variables including donor characteristics (i.e., age, pre-existing health condition, intensive care unit (ICU) treatment, and cause of death), skill of the organ procurement team and surgical staff, method of preservation solution application or health of the recipient. Furthermore, in clinical organ transplantation, there is an immunological factor that can have a dramatic effect on both short- and long-term organ function.

The best method for comparing solutions therefore occurs in an experimental setting where most transplant variables can be controlled. For kidney studies, performing auto-transplants can eliminate the immunological complications. In a study conducted in the University of Wisconsin laboratory, UW was compared with phosphate-buffered sucrose (PBS) and HTK in three-day preservation of dog kidneys. In those dogs receiving UW-preserved kidneys there was 100% survival (six dogs) and a rapid return of kidney function to normal after three-day preservation, with PBS survival was only 17% (one in six) and HTK survival was 83% (five in six). In all cases, there was delayed graft function with serum creatinines elevated to an average of 8mg/dl on day three and it remained high out to 10 days (4mg/dl compared with 2mg/dl for UW).

A comparative study with dog livers also showed that HTK was not efficacious. No dogs survived after liver transplantation with a 48-hour preservation time with HTK. All dogs receiving a liver preserved with UW for 48 hours survived.

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Three studies further support the superiority of UW in comparison with HTK when the cold ischemic time (CIT) exceeds 24 hours.^{11–13} In a retrospective analysis of 323 cadaveric kidney transplantation, there was no significant difference in delayed graft function in those kidneys preserved for less than 24 hours;¹² however, when CIT exceeded 24 hours, the delayed graft function rates for UW-preserved kidneys were 23.9% compared with 50% with HTK-preserved kidneys ($p=0.006$). Furthermore, graft survival at one year was 91% in those patients receiving UW-preserved kidneys compared with 77.4% for HTK ($p=0.059$).

In a small study of 12 non-heart-beating canine kidneys, after two weeks four of the six UW preserved kidney recipients survived and only one of six in the HTK group survived.¹¹ 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 ischemia and more cellular viability. In this study, one hour after reperfusion, TAN levels were significantly higher in the UW group ($p<0.05$). 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 ischemically damaged kidneys.

Lastly, another study tested the viability of endothelial cells stored in UW, HTK, and EC.¹³ Endothelial cells are the first targets of deterioration during cold ischemia. Endothelial damage has been shown to cause liver failure. In this trial, 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.

Experimentally, no other preservation solution has been shown to consistently preserve kidneys and livers for as long as UW. The solution is safe for long-term preservation of livers, kidneys, and pancreas and is ideally suited as a universal intra-aortic flush and CS solution.^{4,12,14–19} Preservation times in the clinical setting are usually shorter than the maximum allowed by UW due to the differences in the initial quality of the organs. In the laboratory, the organs are ideal; they come from healthy donors and are transplanted into healthy recipients.

These conditions do not exist clinically, so safe preservation times are considered to be less than 24 hours. Since short preservation times are typical in the clinical setting, many preservation solutions may yield similar results. For instance, in comparing UW with HTK and Celsior clinically, equivalency is claimed because preservation times are short. If the goal is shortened preservation time, then EC, Marshall's solution and PBS may also be suitable. Only UW has been shown to give effective, safe, long-term kidney and liver preservation.

Some clinical studies have questioned the efficacy of HTK solution for use in the ideally harvested and non-ideally harvested kidney.^{11,12} The extra margin of safety given by long-term organ preservation with UW should provide surgeons with a degree of assurance that if organs could not be transplanted within a short preservation time, the longer times would be well tolerated in most cases. Furthermore, the quality of organs preserved with UW continues to be excellent.

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Lastly, HTK purports greater cost savings than UW. The average wholesale price (AWP) for UW solution is US\$282 per liter and the AWP for HTK is US\$211 per liter. 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 minimizing any savings.

In a study of 60 human liver transplants comparing preservation with UW and HTK, the preservation costs were equivalent due to the increased volume requirements for HTK.²⁰ In a randomized 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.⁸ In addition, the product labeling for HTK indicates that, as a general rule, eight to 12 liters of HTK at 2°C to 4°C should be perfused (about 300ml per kg of body weight) compared with the product labeling for UW, which indicates using four to six liters for the same procedure.^{21,22}

The question of which solution to use is a controversial question for some transplant centers. For short-term preservation and with a highly skilled team for organ procurement and surgery, many solutions will give similar results; however, UW continues to be the state-of-the-art preservation solution, continues to be widely used in the US, and produces outstanding results. ■

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21. "Custodiol HTK Solution for Kidney/Liver Preservation", Prescribing information (2003).

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