

ORGAN PRESERVATION SOLUTION IN KIDNEY TRANSPLANT





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Background and Objective of the Survey



Organ preservation solutions play a crucial role in kidney transplantation by providing an optimal environment for organ preservation during the transplant process. These solutions are designed to minimize ischemic injury, maintain cellular integrity, and prolong organ viability from the time of procurement to transplantation.

One of the most commonly used organ preservation solutions in kidney transplantation is University of Wisconsin (UW) solution. UW solution is a cold storage solution that contains a balanced electrolyte composition, impermeant osmolytes, and antioxidants to protect the kidney from ischemic damage during the period of cold ischemia. Its low potassium concentration and high magnesium content help maintain cellular membrane integrity and prevent cellular swelling, while its high viscosity aids in preserving microcirculation.

Another widely used preservation solution is histidine-tryptophan-ketoglutarate (HTK) solution. HTK solution is also a cold storage solution that contains histidine, tryptophan, ketoglutarate, and mannitol. It provides effective intracellular buffering and scavenging of free radicals, thereby reducing oxidative stress and preserving cellular function during cold ischemia. HTK solution has the advantage of a lower viscosity compared to UW solution, allowing for easier perfusion and distribution within the kidney.

In addition to UW and HTK solutions, other preservation solutions such as Celsior solution and Euro-Collins solution may also be used in kidney transplantation, although less commonly. These solutions have similar goals of minimizing ischemic injury and preserving organ viability during cold storage.

The objective of the survey is:

To understand the role of organ preservation solution in kidney transplant



Methodology of the Survey



A survey was conducted to understand the role of organ preservation solution in kidney transplant. A total of 50 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- History
- Commonly used solutions for kidney preservation
- Recent Advances in Kidney Preservation Solutions
- Colloids
- Gases
- Amino Acids, Peptides and Proteins
- Other Pharmacological Additives
- Mechanisms of Preservation Solutions Against Ischemic/Hypoxic Renal Injury
- ATP Depletion and Loss of Electrolytes Homeostasis

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.



Literature Review



Introduction

The 20th century had witnessed great advances in organ transplantation since the first human kidney transplant was attempted by Yuriy Voroniy in 1933. Kidney transplantation offers the opportunity to replace failed kidneys that are unable to perform their normal physiological functions. It is vital to preserve kidneys in optimal condition before transplantation takes place. The majority of kidney donations are now from non-heart-beating donors (NHBD), and it often takes hours, or even days under some circumstances, to transport organs between medical centers, with high risk of ischemic/hypoxic damage.

Numerous preservation solutions have been developed for organ storage to prevent ischemic/hypoxic injury, improve histocompatibility matches, and ensure immediate and normal organ function after implantation. Previous studies and clinical applications have demonstrated that the choices of different preservation solutions may affect both short-term and long-term transplant outcomes. To minimize ischemic damage, preservation solutions have been designed to specifically target against the biological changes that may occur during the ischemic/hypoxic process. Pharmacological, biochemical, hormonal, and immunological approaches have been applied in the development of preservation solutions (see previous reviews¹⁻³).

Based on our research experience, we will discuss in this review the history of several “gold-standard” preservation solutions, recent advances, and future developments in kidney preservation solutions. We highlight the underlying molecular mechanisms of commonly used preservation solutions against ischemic/hypoxic injury at present. Literature searches were conducted of online databases, including PubMed and MEDLINE, using kidney transplantation, preservation solutions, additives, ischemia, and hypoxia as keywords to capture all relevant publications. The final date for literature searches was July 15, 2019.



History

The importance of ensuring the preservation of kidneys in optimal condition between retrieval and implantation has been long recognized. Cold storage, in which a preservation solution is infused into the organ and the organ is stored at hypothermic conditions, is a process used to reduce the metabolic requirements of organs and attenuate ischemic/hypoxic injury. It has been successfully applied in kidney transplantation for more than 50 years, and for decades has been the most widely used organ preservation method due to its simplicity and low cost. Cold storage preservation solutions have continued to evolve since their early development. In the late 19th century, the concept of continuous perfusion and simple cooling with cold solutions was developed for organ preservation. In the 1930s, it was believed that continuous hypothermic perfusion could help eliminate toxic metabolic products and provide nutrients to preserved organs. In 1968, Belzer et al. performed a successful kidney perfusion preservation. A year later, Geoffrey Collins developed the first cold storage preservation solution, named Collins Solution, which increased kidney preservation time up to 24 h. Collins Solution was further modified by the Eurotransplant Foundation in 1980 into the Euro-Collins Solution (EC), which was commonly used in Europe for about 15 years. In the late 1970s, Ross et al. developed hyperosmolar citrate (HOC) solution (also known as Marshall's solution), which is effective for 72 h of kidney preservation and is still in clinical use today. In 1986, Belzer et al. reported a newly developed University of Wisconsin (UW) solution containing lactobionate and raffinose. Another popular preservation solution in the 1980s was histidine–tryptophan–ketoglutarate (HTK) solution. UW and HTK solutions were regarded as the “gold-standard” and accounted for the majority of preservation solutions used in the clinic. Celsior is an extracellular type preservation solution for cold storage preservation developed in 1994, and has also been widely used in kidney transplantation.

Commonly used solutions for kidney preservation

Collins Solution

Collins Solution preserved kidneys successfully with simple ice storage before transplantation. It was realized that kidneys can absorb water and sodium and lose potassium when deprived of oxygen or nutrients under hypothermic conditions. Therefore, Collins Solution was designed to have high potassium, high magnesium, and low sodium concentrations to mimic the composition of intracellular fluid. It is a phosphate-based solution with high glucose



concentration that balances the osmolarity. Later, several modifications were made based on the Collins Solution, which became known as EC Solution. EC was commonly used clinically for the next 15 years, until the “gold-standard” UW solution was introduced.

Table 1. Composition of Common Kidney Preservation Solutions.

		EC	UW	HTK	Celsior	IGL-1	HC-A
Colloids (g/L)	Hydroxyethyl starch	—	50	—	—	—	—
	PEG-35	—	—	—	—	1	—
Impermeants (mM)	Glucose	198	—	—	—	—	—
	Lactobionate	—	100	—	80	100	—
	Mannitol	—	—	30	60	—	166
	Raffinose	—	30	—	—	30	—
Electrolytes (mM)	Na ⁺	10	30	15	100	120	80
	K ⁺	115	125	9	15	30	80
	Mg ²⁺	—	5	4	13	5	41
	Ca ²⁺	—	—	0.0015	0.26	0.5	—
	Cl ⁻	15	—	50	41.5	20	—
	SO ₄ ²⁻	—	5	—	—	5	41
	PO ₄ ³⁻	100	25	—	—	25	—
	HCO ₃ ⁻	10	—	—	—	—	—
	Citrate	—	—	—	—	—	55



		EC	UW	HTK	Celsior	IGL-1	HC-A
Anti-oxidants (mM)	Allopurinol	–	1	–	–	1	–
	Glutathione	–	3	–	3	3	–
Nutrients (mM)	Tryptophan	–	–	2	–	–	–
	Adenosine	–	5	–	–	5	–
	Adenine	–	–	–	–	–	0.38
	Glutamic acid	–	–	–	20	–	–
	Histidine	–	–	198	30	–	–
	Ketoglutarate	–	–	1	–	–	–
Additives	Insulin (U/L)	–	40	–	–	–	–
	Penicillin G (U/L)	–	200,000	–	–	–	–
	Dexamethasone (mg/L)	–	16	–	–	–	–
Osmolality (mOsm/L)		406	320	310	360	320	380
pH		7.0	7.4	7.2	7.3	7.4	7.0
Cost (US\$/Liter)		275	282	181	228	184	153

University of Wisconsin Solution

UW solution is the most common cold storage solution in organ preservation. It was initially developed as a preservation solution for pancreas transplantation, but has been widely used in preserving different kinds of organs, including the kidney, liver, and small bowel, since the late 1980s[–].



Like EC solution, UW is an intracellular preservation solution with low sodium and high potassium concentrations to mimic an intracellular environments. There are several advantages of UW compared with EC: a) hydroxyethyl starch (HES) serves as the colloid carrier to minimize interstitial edema during perfusion; b) metabolic substrates such as lactobionate and raffinose were introduced to replace glucose to prevent cell swelling; c) allopurinol and glutathione were added as oxygen radical scavengers to reduce oxidative stress; d) adenosine is used as an adenosine triphosphate (ATP) precursor.

UW solution has proven superior to EC solution in both animal experiments and clinical trials¹. For example, in the dog kidney autotransplant model, all kidneys were viable when stored for 72 h in UW solution, while none were viable when stored for 72 h in EC solution, suggesting that UW solution effectively preserves kidneys for 72 h. The European Multicenter Trial in the 1990s demonstrated better kidney preservation outcomes using UW solution compared with EC solution, with fewer incidences of delayed graft function (DGF, 35.8% vs. 52.2%) and better 1-year graft survival (92% vs. 86%).

Despite its popularity, recent studies have suggested potential disadvantages of UW solution, including a) high viscosity generated by HES, which complicates tissue wash-out and saturation with preservation solution; b) addition of penicillin G, dexamethasone, and insulin before use; and c) the current cost per liter of UW solution is \$282, and the total cost of UW solution per liter is over \$300 when additives are included. Therefore, further modifications have been made to create more effective or economical solutions, such as RPS-96 (UW lacking HES), dextran 40-based UW (replacing HES with dextran 40 in UW), perfluorocarbons (PFC)-based UW, hyperbranched polyglycerol (HPG) solution (replacing HES with HPG in UW), and sodium lactobionate sucrose (SLS) solution (replacing raffinose with sucrose in UW).

Histidin-Tryptophan-Ketoglutarat Solution

HTK solution was originally developed and introduced by Bretschneider as a cardioplegia solution for open heart surgery in the 1970s. Subsequently, it proved to be effective in preserving liver, kidney, and pancreas. Unlike UW solution, HTK solution is an extracellular preservation solution with high sodium and low potassium concentrations. Histidine, tryptophan, and ketoglutarate are the three key components in HTK solution. Histidine serves as a buffer and retards the tissue pH decline during cold ischemic/hypoxic conditions. Tryptophan acts as a free radical scavenger and membrane stabilizer. Another amino acid,



ketoglutarate, serves as an energy substrate. HTK solution has a viscosity similar to that of water. This lower viscosity provides a shorter cooling time to reach hypothermic conditions compared with UW solution, and also eliminates the need for pressurized perfusion.

The effectiveness of HTK solution was confirmed in clinical trials in the early 1990s. Eurotransplant conducted a randomized multicenter study comparing kidney graft preservation with HTK, UW, and EC solutions. The results showed the equivalence of HTK compared with UW in preservative ability, with an equal incidence of initial non-function and similar 3-year kidney graft survival. A minimal DGF rate was also observed in HTK as compare with EC solution (0 vs. 33.3%).

However, Stewart et al. reported that if there are additional graft factors such as donation after cardiac death, HTK preservation was associated with an increased risk of graft loss with cold ischemia time over 8 h. Another potential disadvantage of HTK solution is the higher perfusion volume caused by its low viscosity. However, even with the greater volume of HTK needed, the overall cost is decreased compared with UW solution (\$181/L vs. \$282/L,). Despite single critical papers, HTK solution is still one of the most popular kidney preservation solutions in use today.

Celsior Solution

Celsior is an extracellular type of preservation solution developed by Menasché et al. in 1994 for cold storage preservation of cardiac grafts. Currently, it has been applied successfully to heart, lung, liver, pancreas, kidney, and small bowel preservation. Celsior is a high-sodium, low-potassium solution. It adopts the key effective components of both UW and HTK solution. Lactobionate and mannitol were used as impermeants to limit cellular edema. Reduced glutathione was added to Celsior solution as a free-radical scavenger. Celsior solution has greater buffering capacity against acidosis and less viscosity than UW due to the absence of colloids .

A multicenter randomized study of 187 renal transplants showed that the kidney preservation by Celsior solution was equivalent to that of UW solution in DGF rate (31.3% vs. 33.9%) and 2-year graft survival (84% vs. 75%). The incidence of acute tubular necrosis was much lower in the Celsior group than in the UW group (23% vs. 36%) after transplantation. These results



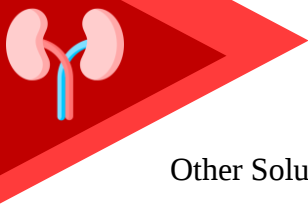
indicated equivalence, and even some advantages, of Celsior solution when compared with the traditional UW solution.

Hypertonic Citrate Adenine Solution

Hypertonic citrate adenine (HC-A) is the most widely used preservation solution for kidney transplantation in China. It was first developed in the late 1970s by Shanghai Changzheng Hospital and the Shanghai Blood Center. Since then, HC-A solution has been extensively applied in China for over three decades. HC-A is a hyperosmolar citrate-based solution with additive adenine as nutrient to improve kidney function after circulation. HC-A solution has a high mannitol concentration to act as an impermeant to limit cellular edema and oxidative stress.

Twenty years after the application of HC-A solution, HC-A II solution was developed (based on the formula of HC-A) by Shanghai Changzheng Hospital. HC-A II has a double-buffer system of citrate and phosphate to achieve enhanced buffer capacity. The concentration of magnesium was significantly reduced, and concentration of adenosine was increased compared with the HC-A solution. New ingredients of arginine, tryptophan, and ligustrazine were also added to stabilize cell membranes and protect mitochondrial function. In a multi-center randomized controlled trial conducted from 2008 to 2012 in China, HC-A II solution showed similar efficacy and safety in kidney preservation compared with HTK solution, suggesting that HC-A II solution is a promising option for clinical application.

Application of HC-A solution accounts for approximately 50% of total kidney transplantation in China nowadays due to its efficacy and low cost, although few specific studies on HC-A have been reported in the English literature. Indeed, the efficacy and safety of HC-A solution seem reasonably sound since it has been used for more than 100,000 grafts in clinical settings in China. However, more studies are needed due to lack of detailed data from basic and clinical research.



Other Solutions

Apart from the above mentioned solutions, several other solutions are also utilized for cold storage preservation of kidneys, including phosphate buffered sucrose (PBS) 140, HP16, HBS, B2, Lifor, Ecosol, Biolasol, renal preservation solution 2 (RPS-2), F-M, AQIXRS-I, WMO-II, CZ-1 solutions, etc. Each solution may vary in composition; however, the key strategy with each solution is similar: use colloids, impermeants, electrolytes, antioxidants, and nutrients to minimize ischemic/hypoxic injury and maximize kidney function after reperfusion.

Recent Advances in Kidney Preservation Solutions

Due to a deeper understanding of the process of ischemic/hypoxic injury and components of commonly used preservation solutions, efforts have been made to develop new preservation solutions. Particular components are now added to standard solutions to further prevent organs from ischemic/hypoxic injury. In the present review, we attempt to provide a summary of the effective additives available, with experimental evidence of animal models.

Table 2. Recent Advances in Kidney Preservation Solutions.

Effective additives	Solutions	Species	Target pathway(s)
PEG	IGL-1, polysol, SCOT, PBSc+PEG, SBS+PEG, EC+PEG, UW+PEG	rat, pig, rabbit	intravascular oncotic pressure
dextran	HTK-N+dextran, dextran-based UW	pig, human	intravascular oncotic pressure
H ₂ S	UW+H ₂ S	rat	necrosis, apoptosis, inflammation, mitochondrial function



Effective additives	Solutions	Species	Target pathway(s)
H ₂	UW+H ₂	rat	oxidative stress, apoptosis, fibrosis
CO	UW+CO, UW+CORM-3	rat, pig	oxidative stress, vasoconstriction, inflammation, apoptosis
O ₂ carrier	UW+M101, HTK+M101	pig	inflammation, fibrosis
Ar	CS+Ar	pig	inflammation, necrosis, fibrosis, apoptosis
endothelial receptor antagonist	UW+ET _A /ET _B receptor antagonists, EC+ET _A /ET _B receptor antagonists	rat	vasoconstriction
rho-kinase inhibitor HA1077	HTK+HA1077	pig	vasoconstriction
melagatran	UW+melagatran	pig	inflammation, fibrosis
trophic factors	UW+[BNP-1, SP, NGF-β, IGF-1, EGF], EC+HGF, EC+IGF-1	pig, dog	inflammation, fibrosis, apoptosis
rh BMP-7	saline+rh BMP-7	rat	oxidative stress
TNF-RFP	HTK+ TNF-RFP	pig	inflammation
cyclic helix B peptide	HOC+cyclic helix B peptide	pig	apoptosis, inflammation



Effective additives	Solutions	Species	Target pathway(s)
L-arginine	HTK+L-arginine	dog	oxidative stress
caspase-3 siRNA	HOC+caspase-3 siRNA	pig	apoptosis, acidosis
MMP-2 siRNA	KPS-1+MMP-2 siRNA	rat	fibrosis
ICAM-1 antisense oligodeoxynucleotide IP-9125	EC+IP-9125	rat	inflammation
taurine	UW+taurine	pig	Ca ²⁺ homeostasis
ranolazine	PBS140+ranolazine	pig	Ca ²⁺ homeostasis
verapamil	EC+verapamil	rat	Ca ²⁺ homeostasis
TMZ	EC+TMZ, UW+TMZ	pig	inflammation, mitochondrial function, oxidative stress
trolox, deferoxamine, ascorbate	UW+trolox, UW+deferoxamine, UW+ascorbate	rabbit	oxidative stress
lec-SOD	HOC+lec-SOD	rat	oxidative stress, apoptosis, inflammation
edaravone	HTK+edaravone	dog	oxidative stress
MitoQ	UW+MitoQ	pig, rat	mitochondrial function, oxidative stress



Effective additives	Solutions	Species	Target pathway(s)
quinacrine	UW+quinacrine	rabbit	mitochondrial function
N-acetylcysteine, sodium nitroprusside, phosphoramidon	N-acetylcysteine+sodium nitroprusside+phosphoramidon	rat	oxidative stress
selenium	HTK+selenium	pig	oxidative stress
nicaraven	UW+ nicaraven, EC+ nicaraven	rat, dog	oxidative stress
propofol	HTK+propofol	pig	oxidative stress
prostaglandin E1	UW+prostaglandin E1	human	oxidative stress
tanshinone IIA	CS+tanshinone IIA	rat	oxidative stress, apoptosis

PEG, polyethylene glycol; CORM, carbon monoxide releasing molecules; BNP-1, bovine neutrophil peptide-1; SP, substance P; NGF, nerve growth factor; IGF-1, insulin-like growth factor-1; EGF, epidermal growth factor; HGF, hepatocyte growth factor; rh BMP-7, recombinant human bone morphogenetic protein-7; TNF-RFP, TNF-receptor fusion protein; MMP, matrix metalloproteinase; ICAM, intercellular adhesion molecule; TMZ, trimetazidine; lec-SOD, lecithinized superoxide dismutase; MitoQ, mitoquinone; IGL-1, Institute Georges Lopez-1 solution; SCOT, Solution de Conservation des Organes et des Tissus; PBSc, Phosphate-buffered sucrose solution; SBS, sucrose-based solution; EC, Euro-Collins solution; UW, University of Wisconsin solution; HTK, Histidin-Tryptophan-Ketoglutarat solution; CS, Celsior solution; HOC, hyperosmolar citrate solution; KPS-1, kidney perfusion solution-1.



Colloids

Several high molecular weight colloids have been applied in preservation solutions to sustain the intravascular oncotic pressure and prevent interstitial edema. UW solution uses HES (50 kDa), which is a stable non-toxic oncotic agent, as the colloids. Moreover, other colloids were also utilized to substitute HES to make solutions more cost-effective.

Dextran (40 kDa) is one of the most widely investigated replacements of HES. It is a safe replacement of HES in UW solution for the purpose of clinical kidney preservation. Dextran 40 may be beneficial during the graft reperfusion phase due to reduced vascular resistance and anti-thrombogenesis function.

Poly-ethylene glycol (PEG), a neutral water soluble nontoxic polymer, has been used to substitute HES in the several newly developed preservation solutions including Institute Georges Lopez-1 (IGL-1), Polysol, and “Solution de Conservation des Organes et des Tissus” (SCOT) solution. IGL-1 is a PEG 35 kD-based preservation solution with inverted Na^+/K^+ concentration compared with that of UW solution. Encouraging results of IGL in kidney transplantation have been demonstrated in both rat and pig transplantation studies. In a multi-center study conducted in 2009, IGL-1 solution-preserved kidneys showed outcomes similar to those preserved in the UW solution in terms of DGF, rejection rates, and patient and graft survival. Polysol is another PEG 35 kD-based preservation solution that contains antioxidants, amino acids, energy substrates, and vitamins. In pig kidney transplant studies, Polysol displayed improved microcirculation and structural integrity following prolonged ischemia compared with UW and HTK solutions⁷. Nonetheless, a pilot clinical study failed to demonstrate the advantage of Polysol in living kidney transplantation, with higher acute rejection rates observed in recipients compared with UW solution controls. Therefore, the use of Polysol solution in the clinic is questionable. SCOT is another PEG-based preservation solution, which contains PEG 20kD as a colloid. The effectiveness of SCOT in kidney transplantation was displayed in a preliminary clinical study, with comparable or better outcomes versus commonly used UW or EC solutions.

PEG could spontaneously bind to cell surfaces to stabilize membrane lipids and may further enhance immunoprotective properties. It has vasodilatory, anti-fibrosis, and antioxidant effects in addition to the colloid properties. Thus, PEG-based preservation solutions are considered promising alternatives for commonly used solutions in clinical applications.



Gases

The use of therapeutic gases as effective additives in the context of preservation solutions has become popular in recent years. Several gases have been used to reduce ischemic/hypoxic injury in kidney transplantation, including oxygen (O_2), hydrogen (H_2), carbon monoxide (CO), nitric oxide (NO), hydrogen sulfide (H_2S) and argon (Ar).

The retrograde venous application of humidified pure O_2 during cold storage was developed by Isselhard et al. in 1972. The effect was further confirmed by a small pilot clinical study. In a large animal preclinical model, addition of M101 (an O_2 carrier with high-oxygen affinity) into UW and HTK solutions provided significant benefits to grafts, both in early function recovery and long-term outcomes.

H_2 is a highly diffusible antioxidant gas, which can easily enter the cell. H_2 could preserve mitochondrial function by attenuating reactive oxygen species (ROS) production, thus preventing apoptotic cell death. A rat study has demonstrated the beneficial effect of H_2 -rich UW solution during kidney transplantation. H_2 -rich UW solution showed decreased oxidative stress, tubular apoptosis, interstitial fibrosis, improved renal function and survival rate compared with UW simple cold storage.

CO, NO, and H_2S are considered to be endogenous gas transmitters. CO has been implicated to have cytoprotective effects by attenuating proinflammatory cytokines, lipid peroxidation, and improving mitochondrial function. Supplementation of UW solution with CO or CO-releasing molecules provided significant protection against renal ischemic/hypoxic injury in both rat and porcine transplantation studies⁷. NO is mainly generated from the endogenous metabolism of L-arginine to citrulline by NO synthase. The therapeutic application of NO has been implicated in attenuating ischemia-reperfusion injury. Therapeutic effects of H_2S have also been demonstrated in animal models of ischemia and reperfusion. H_2S treatment improved early allograft function and survival by attenuating the necrosis and apoptosis of glomerular and tubular cells.

In addition, argon saturated Celsior solution (Ar-Celsior) decreased inflammation, interstitial fibrosis, tubular necrosis, and apoptosis in a porcine kidney transplantation model, resulting in improved early functional recovery, graft quality, and survival. Therefore, adding gas at an appropriate level and composition into current preservation solutions is a promising approach to improve kidney preservation.

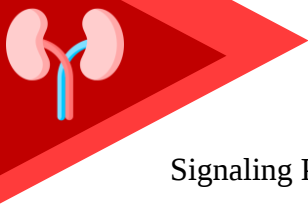


Amino Acids, Peptides and Proteins

Amino acids appear to be quite effective in providing nutrients or acting as metabolic substrates. The commonly used preservation solutions utilize amino acids, such as tryptophan in HTK solution, glutamic acid in Celsior solution, and histidine in both HTK and Celsior solution, as energy substrates. Amino acids with antioxidant effects were also introduced into newly developed preservation solutions as additives. l-arginine is the endogenous substrate for NO synthase. In an animal model of canine kidney transplantation, l-arginine-enriched preservation solution presented a beneficial and protective effect on long-term (72 h) hypothermic ischemic damage, with reduced lipid peroxidation. In a rat model, pre-administration of N-acetylcysteine attenuates renal ischemia-reperfusion injury by protecting cells against free radical damage. Oral administration of d-cysteine attenuates renal ischemia-reperfusion injury by producing H₂S. Addition of Cyclic Helix B peptide into preservation solutions ameliorated renal injury after porcine kidney transplantation, which may be associated with decreased apoptosis and inflammation.

Recent studies have focused on trophic factors as additives to improve storage efficiency of preservation solutions. With the addition of a combination of bovine neutrophil peptide-1 (BNP-1), substance P (SP), nerve growth factor- β (NGF- β), insulin-like growth factor-1 (IGF-1), and epidermal-like growth factor (EGF) to the UW solution, McAnulty et al. successfully achieved 6-day kidney preservation in a canine model. Moreover, addition of hepatocyte growth factor (HGF) to EC solution accelerated both renal blood flow recovery and glomerular filtration rate in dog kidney during cold ischemia. Experimental evidence has suggested that trophic factors protect cells against inflammation, fibrosis and apoptosis, and improve mitochondrial function as well.

Recombinant human bone morphogenetic protein-7 (rh BMP-7) perfused rat kidneys had elevated superoxide dismutase (SOD) activity and decreased lipid peroxidation level versus the UW-treated group. The same effect was also achieved by direct introduction of lecithinized superoxide dismutase (lec-SOD) into the preservation solution. TNF-receptor fusion protein (TNF-RFP) was able to suppress inflammation and promote organ survival in xenoperfused porcine kidneys.



Signaling Pathway Blockers

The use of siRNAs, oligonucleotides, specific inhibitors or antagonists represented effective approaches to specifically target signaling pathways involved in ischemic/hypoxic injury. Exogenous administration of naked siRNAs via preservation solutions have been successfully tested in animal studies. Introducing naked caspase-3 siRNA in preservation solution resulted in reduced caspase-3 expression levels, cell apoptosis, and better acid-base homeostasis in a porcine kidney transplantation model. Similarly, supplementation of preservation solution with matrix metalloproteinase (MMP)-2 siRNA protected transplant rat kidneys from preservation injury by inhibiting MMP-2 expression and tissue fibrosis.

The adhesion of immune competent cells to the endothelial wall represents an important aspect of ischemic/hypoxic injury. Thus, phosphorothioate intercellular adhesion molecule (ICAM)-1 antisense oligodeoxynucleotide was added to EC solution to reduce ICAM-1-related inflammation response. There was also experimental evidence of the benefit of blocking the vasoconstrictor mediators in improving kidney function. Studies in rats have shown that endothelial receptor antagonists could ameliorate renal ischemic/hypoxic injury after transplantation⁷. Supplementation of Rho-kinase inhibitor HA1077 could improve renal function by antagonizing vasoconstriction. Supplementing UW solution with a thrombin inhibitor melagatran in a porcine kidney transplantation model resulted in strong protection against both acute renal injury and chronic lesions, including interstitial fibrosis, apoptosis, and inflammation. Calcium channel blocker verapamil⁸ and platelet-activating factor (PAF) receptor antagonist were also candidate additives in preservation solutions, the effect of which were confirmed in animal models. The postulated benefits include reduction of calcium overload, increase in tissue ATP concentration, and sodium re-absorption. Application of proteasome inhibitor is a potential strategy to reduce ischemic/hypoxic injury in both liver and heart transplantation, which lead to the up-regulation of AMPK activity, down-regulation of mTOR signaling, and influence autophagy. Thus, supplying proteasome inhibitors into common preservation solutions can become a strategy to decrease renal ischemic/hypoxic injury as well. In conclusion, pathway-specific blockers that are based on well-defined ischemic/hypoxic mechanisms offer good opportunities to improve commonly used preservation solutions.



Other Pharmacological Additives

Apart from above-mentioned supplements, other pharmacological additives including radical scavengers, mitochondrial protectors and drugs have also been added to preservation solutions. The addition of radical scavengers (nicaraven, trolox, edaravone) could trap free radicals and protect cells against oxidative stress directly, contributing to reduced lipid peroxidation and higher survival rate of the preserved kidneys. In addition, exogenous administration of selenium, propofol (a widely used anesthetic), and tanshinone IIA (an effective component of the traditional Chinese medicine Danshen) in preservation solutions tended to have antioxidant effects to attenuate malondialdehyde concentration, followed by the improvement in long-term renal function after transplantation.

Mitoquinone (MitoQ) and quinacrine act as mitochondrial targeted antioxidant compounds to reduce the damage of mitochondrial electron transport chain and improve renal cell viability in rat and porcine studies. Trimetazidine (TMZ) is another drug with mitochondrial-protective functions. Supplementation of TMZ in UW solution was beneficial in porcine models, with improved functional recovery of preserved kidneys, higher survival rate, as well as reduced cellular and mitochondrial swelling, immune cell invasion, and interstitial fibrosis.

Other pharmacological additives that were beneficial in animal studies including prostaglandin E1, taurine, ranolazine, etc.. They also have the potential to be used in clinical transplantation. However, the underlying mechanisms and the specific signaling pathways involved are not well understood yet. Thus, more experimental studies and further clinical trials are still needed.

Mechanisms of Preservation Solutions Against Ischemic/Hypoxic Renal Injury

Ischemia and hypoxia are inevitable events during cold preservation of kidney transplantation. Ischemic/hypoxic renal injury is caused by a sudden cessation of blood flow along with the immediate oxygen deprivation to the kidneys. Tissues are starved of oxygen and nutrients, leading to the accumulation of metabolic waste products. The imbalance in metabolic supply and demand within the ischemic organ results in profound tissue hypoxia and dysfunction. Subsequent reperfusion further enhances the activation of immune responses and cell death programs. A wide range of pathophysiological processes have been identified to be related to ischemic/hypoxic renal injury during cold storage, including ATP depletion, calcium overload,



acidosis, mitochondrial dysfunction, oxidative stress, inflammatory response, and eventual cell death programs.

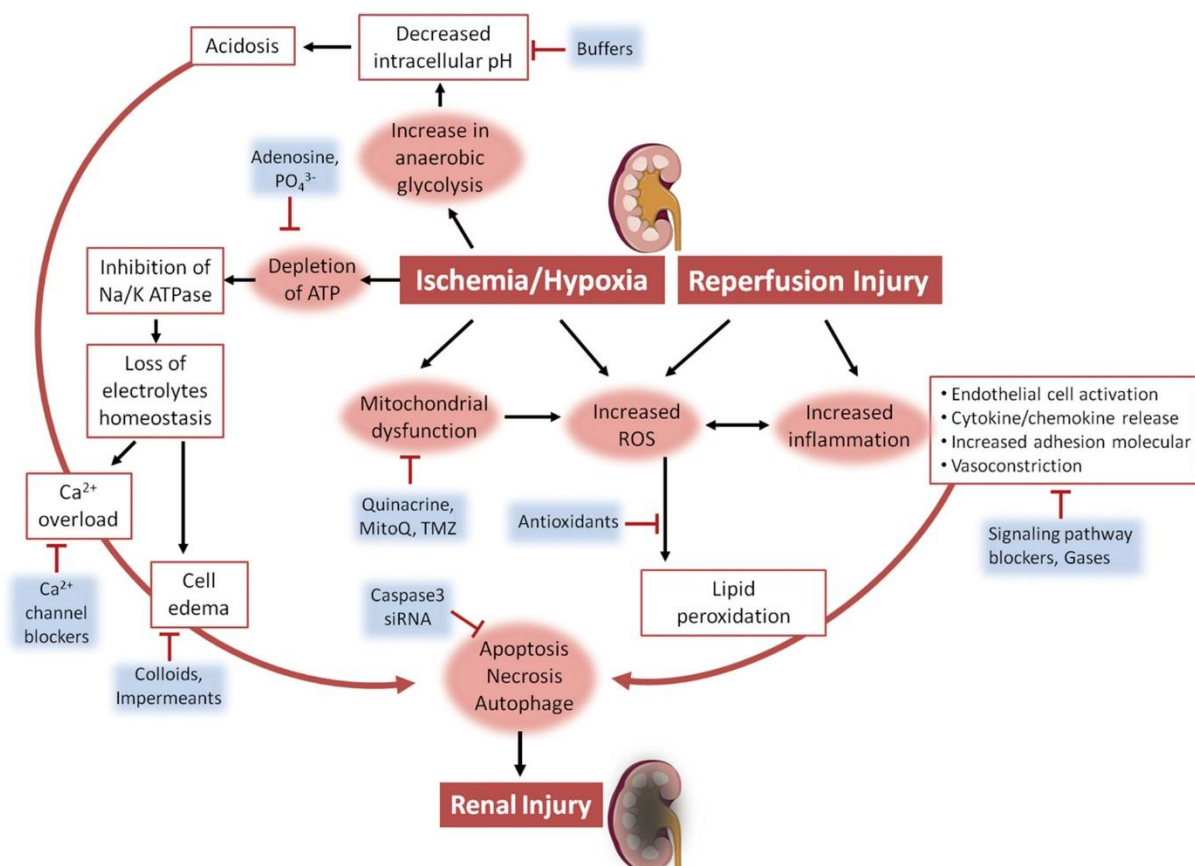


Fig 1. Schematic representation of effective supplementations in preservation solutions against ischemic/hypoxic renal injury.

ATP Depletion and Loss of Electrolytes Homeostasis

Nearly 95% of cellular ATP is depleted within 4 h as a consequence of organ cold storage during transplantation. On the one hand, ATP deficits lead to a reduced activity of Na^+/K^+ ATPase, thereby contributing to increased intracellular sodium concentration. Large amounts of water enter the cytoplasm due to the hyperosmolar intracellular environment, resulting in cell edema. On the other hand, $\text{Na}^+/\text{Ca}^{2+}$ exchangers begin to work in the reverse direction and stop pumping calcium out of the cell, leading to calcium accumulation in cells. Increased intracellular calcium levels can activate calcium-dependent phospholipase and proteases, promoting cell apoptosis.

To combat the above-mentioned ischemic/hypoxic renal injury during cold storage, a number of approaches have been used in preservation solutions. Energy substrates such as adenosine



were often provided in solutions to allow for rapid ATP regeneration during preservation. The calcium channel blocker verapamil⁻ and other pharmacological reagents, which can be beneficial to Ca²⁺ homeostasis⁻, are added into preservation solutions to prevent calcium overload. H₂S could inhibit Na⁺/H⁺ exchanger activity via the PI3K/Akt/PKG-dependent pathway, hence reducing Ca²⁺ overload. Impermeants and colloids are added to preservation solutions to prevent cell swelling. The effectiveness of impermeants in preventing cell swelling is determined by their molecular weight (MW), with larger molecules being more effective. The monosaccharide glucose (MW 180) was applied in EC solution in the early stages but was soon abolished because it could pass through the cell membrane and become a source of lactate under hypoxic conditions. The slightly larger monosaccharide mannitol (MW 182), which also has antioxidant potential, was used to replace glucose in HTK, Celsior, and HA-C solutions. Sucrose (MW 342) is a disaccharide and was used in phosphate-buffered sucrose (PBS) solution. Raffinose (MW 504) was added to UW solution, along with lactobionate. Colloids such as HES, PEG, and dextran were also common components in preservation solutions, with convincing evidence of anti-edema function (see section *Colloids* for details).

Acidosis

Under ischemic/hypoxic conditions, energy metabolism in cells switches from fatty acid oxidation to more oxidation-efficient anaerobic glycolysis, allowing organs to sustain cellular viability. Decreased intracellular pH and acidosis are the immediate results of anaerobic glycolysis, and are often observed in ischemic tissues. Mild acidosis has been suggested to favor cell survival by inhibiting activated proteases and phospholipases via the rate-limiting step in glycolysis. However, strong activation of proteases and phospholipases by severe acidosis could lead to protein and lipid breakdown, lysosomal damage, and eventual cell death. Therefore, adequate control of cellular pH has become an important function of preservation solutions. To achieve this goal, different buffering systems were applied. EC and UW solutions used phosphate as a buffer, while HTK and Celsior solutions used histidine. Among these commonly used preservation solutions, HTK has the highest buffering capacity due to a high concentration of histidine. The pH of common preservation solutions is between 7.0 and 7.4.



Mitochondrial Dysfunction

Mitochondrial dysfunction has been regarded as a critical event during ischemia. Under ischemic/hypoxic conditions, oxidative phosphorylation in the mitochondria is suppressed by a lack of oxygen, leading to impaired ATP synthesis and further severe ATP depletion. There is experimental evidence that mitochondrial Ca^{2+} uptake was dramatically increased during cold ischemia, especially when it is challenged by high extra-mitochondrial Ca^{2+} concentrations, resulting in impaired mitochondrial structure and function. Mitochondrial dysfunction may influence energy regeneration at the re-oxygenation stage. Mitochondria are the major source of intracellular ROS production. The uncoupling of the mitochondrial respiratory chain induces the formation of ROS, a process which is enhanced during the reperfusion stage. This could contribute to the denaturation of proteins, nucleic acids, and lipids, which induce cell apoptosis or necrosis.

It is thus clear that maintaining mitochondrial integrity and protecting mitochondria function are key principles in developing preservation solutions. The supplementation of preservation solutions with mitochondrial-protective reagents H_2S , MitoQ, quinacrine, and TMZ^- has proven to be effective. AP39, a novel mitochondria-targeted H_2S donor, can also stimulate cellular bioenergetics, and protect against the loss of mitochondrial DNA integrity.

Oxidative Stress

The reperfusion stage, which occurs hours or days after the initial ischemic/hypoxic insult, is regarded as the final stage of ischemic injury. It has a profound influence not only on the short-term but also the long-term recovery outcome of a transplanted kidney. During this stage, blood flow and oxygen are re-introduced into organs, leading to a burst of ROS. Hydrogen peroxide (H_2O_2) and the superoxide anion (O_2^-) are mainly generated by xanthine oxidase, and further lead to hydroxyl radical (OH^-) formation. Meanwhile, cold storage itself has been suggested to promote ROS production via mitochondrial dysfunction. ROS react rapidly with other molecules, leading to lipid peroxidation and oxidative damage of nucleic acids and proteins, and eventually contribute to cell apoptosis.

Thus, inhibiting ROS production, especially at times of reperfusion, has become a key strategy to protect organs during transplantation. The beneficial effects of antioxidants and radical scavengers against ischemic/hypoxic injury have been confirmed by numerous studies. In UW



solution, allopurinol (a xanthine oxidase inhibitor) and reduced glutathione (a thiol containing amino acid) were included to reduce ROS formation. Similarly, HTK solution contains tryptophan and histidine as ROS-scavenging amino acids. Experimental additions of antioxidant agents into common preservation solutions have proven to be effective. Direct introduction of lecithinized superoxide dismutase (lec-SOD), a catalyzer of ROS degradation, into preservation solution demonstrated a long-term benefit of reducing oxidant stress. H₂S has also been studied for its anti-oxidative properties. The benefits were possibly related to lowering the generation of free radicals, inducing antioxidant gene expression and anti-apoptotic functions. N-acetylcysteine contains a thiol group, which is readily accessible to the then intracellular compartment and could scavenge free radicals. As a widely used anesthetic, propofol displays its antioxidant activity through reduced lipid peroxidation and increased SOD levels. Moreover, several other compounds have also been added to preservation solutions, and were described to protect grafted kidneys against ischemic/hypoxic injury through direct or indirect anti-oxidative stress properties, including TMZ, rh-BMP-7, l-arginine, trolox, edaravone, selenium, nicaraven, prostaglandin E1, and tanshinone IIA. Taken together, these findings support the idea that interrupting the ROS generation pathway and scavenging existing ROS could be effective strategies in preventing ischemic/hypoxic injury during kidney preservation.

Inflammation Process

The inflammatory response is another profound consequence of blood flow restoration and re-oxygenation in the reperfusion stage. ROS generation and lipid peroxidation process seem to be major factors in the activation of innate immunity. Inflammatory cells express NADPH oxidase, which in turn leads to the formation of additional ROS, further potentiating renal damage.

During reperfusion, activation of endothelial cells trigger the downstream signaling pathways, including mitogen-activated protein kinase (MAPK) and NF- κ B, leading to the release of pro-inflammatory cytokines (e.g. IL-6 and TNF- α) and chemokines. Chemokines are regarded as major mediators of inflammation that regulate adhesion molecules expression as well as leukocyte infiltration and activation. Increased expression of adhesion molecules and Class II MHC proteins result in vasoconstriction, exacerbating tissue damage. Increased platelet



activation and adhesion to the injured vascular endothelium also reduces blood flow and exacerbates ischemia.

Multiple inflammatory pathways and factors take part in this process. Therefore, specific antibodies or pathway inhibitors have been applied in preservation solutions to modulate the inflammatory responses and attenuate post-ischemic injury. Direct inhibition of endothelial cell activation and vasoconstriction can be achieved by using endothelial receptor antagonists in preservation solutions⁻. The pro-inflammatory effects of TNF- α were effectively blocked by application of TNF-receptor fusion protein (TNF-RFP). Administration of ICM-1 antisense deoxynucleotides ameliorated inflammatory injury. Supplementation of UW solution with FR167653, a specific p38MAPK inhibitor, showed important benefits to graft function by reducing inflammation. Administration of exogenous CO or CO-releasing molecules has cytoprotective effects involving anti-inflammatory response and hypoxia-inducible factor (HIF)-1 α stabilization. In addition, agents like H₂S, O₂, Ar, melagatran, cyclic helix B peptide, TMZ⁻, and lec-SOD have also been implicated in preventing tissue inflammation during ischemia and reperfusion in various experimental models (and).

Cell Apoptosis, Necrosis and Autophagy

Ischemic/hypoxic and subsequent reperfusion injury leads to the activation of cell death programs, which can be categorized as apoptosis, necrosis, and autophagy-associated cell death. Apoptosis is a process of programmed cell death that is characterized by blebbing, cell shrinkage, loss of mitochondrial integrity, and nuclear fragmentation. Cell apoptosis may be induced by mitochondrial dysfunction. Cytochrome *c* was released into the cytosol from damaged mitochondria to induce the formation of apoptosomes. Subsequent apoptotic nuclear DNA damage was induced by the release of apoptosis-inducing factor (AIF) and endonuclease G. Ischemic/hypoxic mechanisms such as oxidative stress and inflammatory signaling may contribute to apoptosis as well. Thus, blocking these pathways to inhibit apoptosis may have promises as therapeutic strategies for ischemic/hypoxic renal injury during cold storage. In addition, apoptosis can be blocked by direct target apoptosis effectors. The glucocorticoid, dexamethasone, has an inhibitory effect against apoptosis by upregulating Bcl-XL, inhibiting Bax production, and activating caspases-3/9 in renal ischemia-reperfusion injury rodent models. Administration of naked caspase-3 siRNA in a preservation solution resulted in



reduced caspase-3 expression level and cell apoptosis, elucidating the protective effect in isolated ischemic porcine kidneys.

Necrosis, characterized by progressive cell swelling, plasma membrane rupture, and leakage of proteases and lysosomes into the extracellular compartment, is a frequent outcome of ischemic/hypoxic renal injury during cold storage. Strong innate inflammatory signaling leads to cell necrosis, while necrosis in turn promotes inflammation through leakage of cellular contents, inflammatory cell infiltration, and cytokine production.

Unlike necrosis, autophagy is a regulated, programmed process that disassembles unnecessary or dysfunctional components of the cell. Autophagy-associated cell death is also a common outcome after renal cells are exposed to ischemic/hypoxic conditions. However, whether renal cells undergo necrosis or programmed cell death appears to be ATP-concentration dependent. Studies have shown that ATP is required for programmed cell death, whereas complete ATP depletion would lead to necrosis. Experimentally, the effectiveness of pharmacological additives that may reduce cell swelling or ATP depletion on preventing necrosis have been recently illustrated. AMP-activated protein kinase (AMPK) is an energy sensor that regulates cellular metabolism and homeostasis. Renal ischemia was reported to induce AMPK phosphorylation, and sequentially promotes autophagy through phosphorylation of downstream effectors. Treatment of rat or mouse models with AMPK activator attenuates renal ischemia/reperfusion injury, with decreased tubular necrosis and expression of apoptosis-related proteins, improved glomerular filtration rate, and increased expression of autophagy-related proteins.



Survey Form



1) Which organ preservation solution/s do you use in your practice?

- A. Histidine-Tryptophan-Ketoglutarate (HTK) solution
- B. University of Wisconsin (UW) solution
- C. Ringer's Lactate solution

2) Which one of the following is your most preferred solution in Living Donor Kidney Transplant?

- A. Histidine-Tryptophan-Ketoglutarate (HTK) solution
- B. University of Wisconsin (UW) solution
- C. Ringer's Lactate solution

3) Which one of the following is your most preferred solution in Deceased Donor Kidney Transplant?

- A. Histidine-Tryptophan-Ketoglutarate (HTK) solution
- B. University of Wisconsin (UW) solution
- C. Ringer's Lactate solution

4) Before using as a perfusion solution, do you add any specific ingredients to UW solution?

- A. Yes
- B. No

5) Before using as a perfusion solution, do you add any specific ingredients in HTK solution?

- A. Yes
- B. No



6) Before using as a perfusion solution, do you add any specific ingredients in Ringer's Lactate solution?

- A. Yes
- B. No

7) How much total volume (in litres) of HTK solution (including back table flush and organ storage) is used at your centre for Living donor Kidney transplantation?

- A. < 500 ml
- B. 500 ml - 1 L
- C. 1.1- 2 L
- D. 2.1 – 3 L
- E. 3.1- 4 L
- F. > 4 L

8) How much total volume (in litres) of HTK solution (including back table flush and organ storage) is used at your centre for deceased donor kidney transplantation?

- A. 1- 2 L
- B. 2.1 to 5 L
- C. 3.1 L to 4 L
- D. 4.1 L to 5 L
- E. 5 – 6 L
- F. > 6 L

9) How much total volume (in litres) of Ringer's lactate (including back table flush and organ storage) is used at your centre for Living donor Kidney transplantation –

- A. < 500 ml
- B. 500 ml - 1 L
- C. 1.1- 2 L
- D. 2.1 – 3 L
- E. 3.1- 4 L
- F. >4 L



10) How much total volume (in litres) of UW solution (including back table flush and organ storage) is used at your centre for Living donor Kidney

transplantation –

- A. < 500 ml
- B. 500 ml - 1 L
- C. 1.1- 2 L
- D. 2.1 – 3 L
- E. 3.1- 4 L
- F. >4 L

11) How much total volume (in litres) of UW solution (including back table flush and organ storage) is used at your centre for deceased donor kidney

transplantation–

- A. 1- 2 L
- B. 2.1 to 5 L
- C. 3.1 L to 4 L
- D. 4.1 L to 5 L
- E. 5 – 6 L
- F. > 6 L

12) Which of the following is the most important parameter that you consider while choosing the organ perfusion/preservation solution?

- A. Cold Ischemia Time
- B. Viscosity of solution
- C. Type of donor (Live/deceased)
- D. Volume required
- E. Cost

13) What are the key post-transplant parameters that you assess to know the graft function?

- A. Serum Creatinine
- B. Blood urea nitrogen (BUN)
- C. Cystatin C
- D. Glomerular Filtration Rate/GFR



14) How long do you assess lab parameters after transplant?

- A. At least for a week
- B. For a month
- C. For 3 months
- D. For 6 months
- E. For 1 year

15) In the past, have you used GraftSol (HTK) solution in your practice?

- A. Yes
- B. No

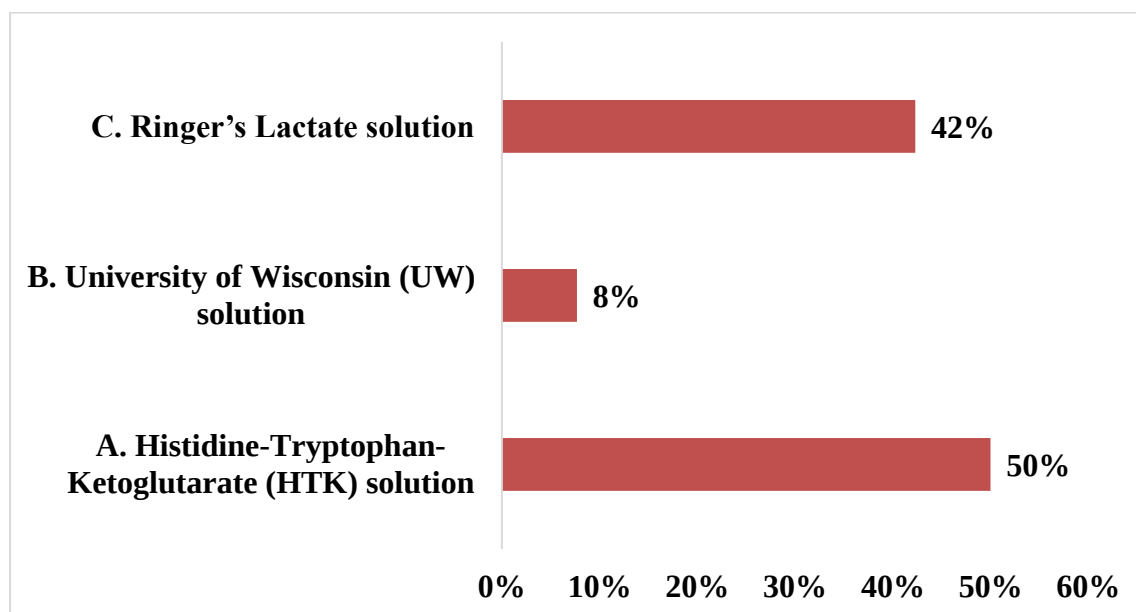


Survey Findings



1) Which organ preservation solution/s do you use in your practice?

- A. Histidine-Tryptophan-Ketoglutarate (HTK) solution
- B. University of Wisconsin (UW) solution
- C. Ringer's Lactate solution

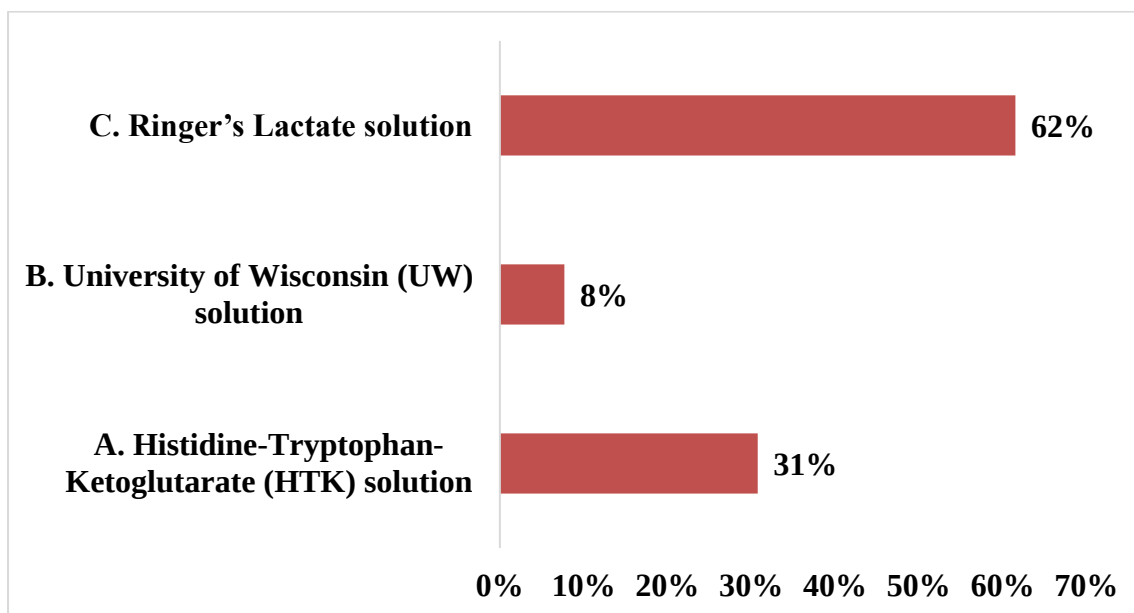


According to 50% of doctors, they use histidine-tryptophan-ketoglutarate (htk) solution in their practice.



2) Which one of the following is your most preferred solution in Living Donor Kidney Transplant?

- A. Histidine-Tryptophan-Ketoglutarate (HTK) solution
- B. University of Wisconsin (UW) solution
- C. Ringer's Lactate solution

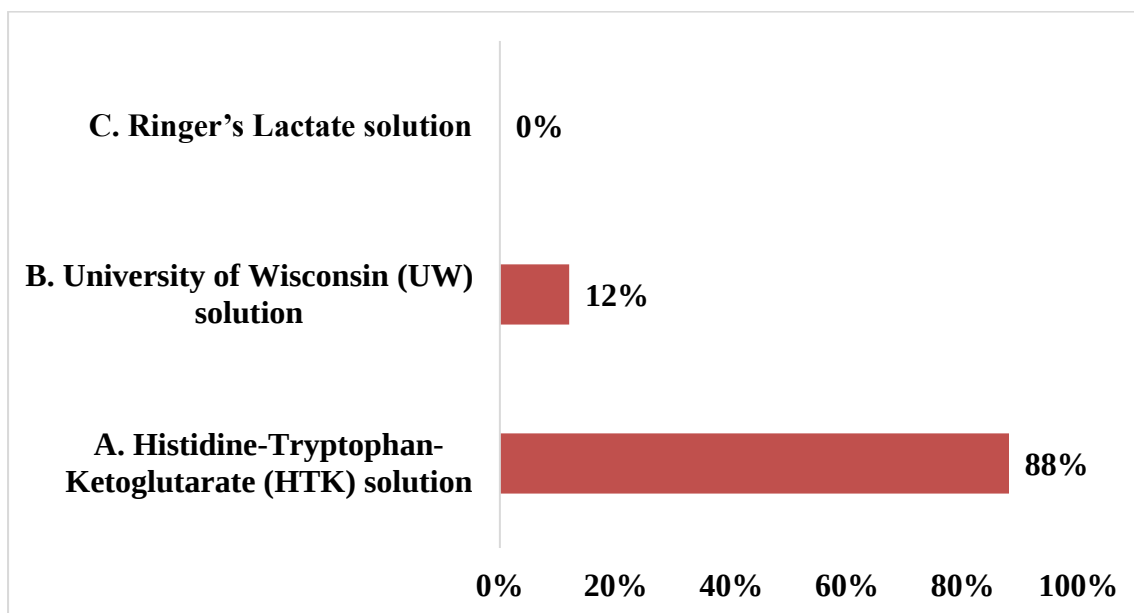


As per majority of doctors, 62%, ringer's lactate solution is the most preferred solution in living donor kidney transplant.



3) Which one of the following is your most preferred solution in Deceased Donor Kidney Transplant?

- A. Histidine-Tryptophan-Ketoglutarate (HTK) solution
- B. University of Wisconsin (UW) solution
- C. Ringer's Lactate solution

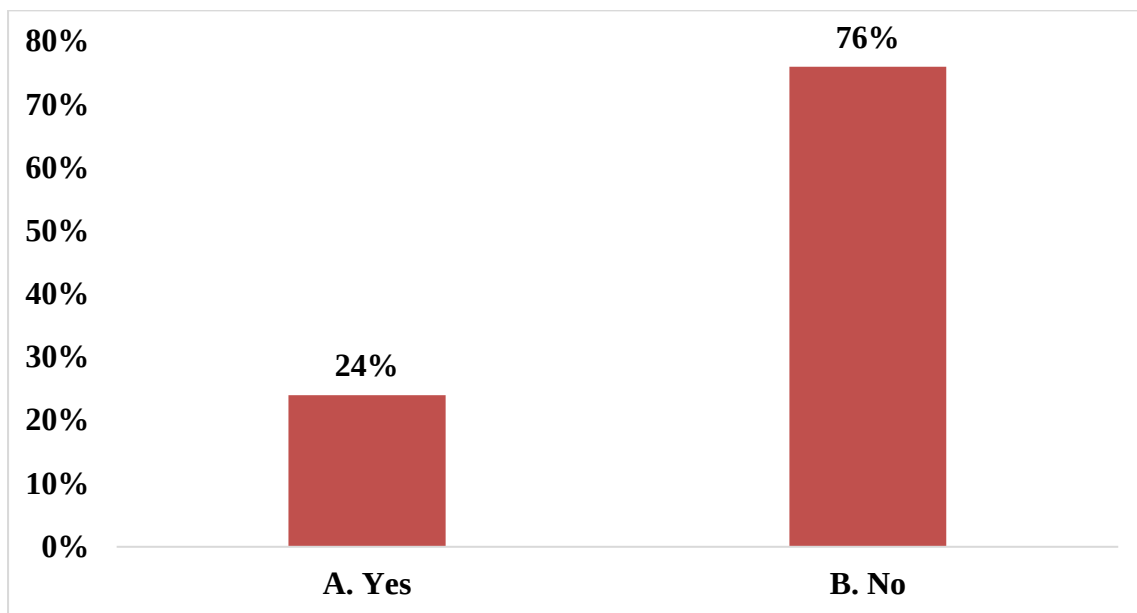


According to majority of doctors, 88%, histidine-tryptophan-ketoglutarate (htk) solution is the most preferred solution in deceased donor kidney transplant.



4) Before using as a perfusion solution, do you add any specific ingredients to UW solution?

- A. Yes
- B. No

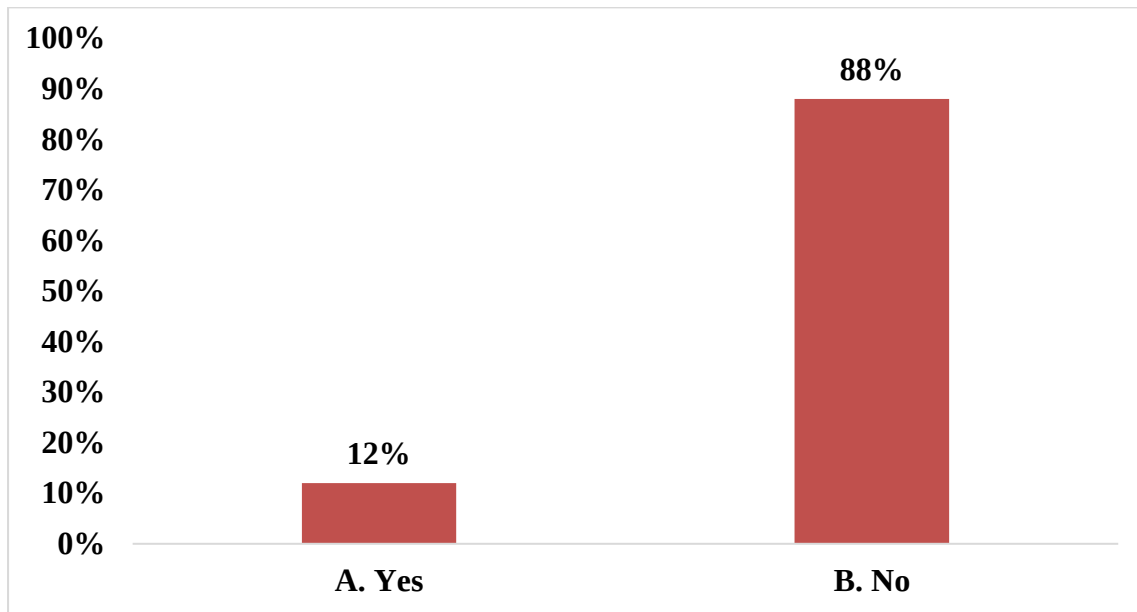


As per majority of doctors, 76%, they don't add any specific ingredients to uw solution before using as a perfusion solution.



5) Before using as a perfusion solution, do you add any specific ingredients in HTK solution?

- A. Yes
- B. No

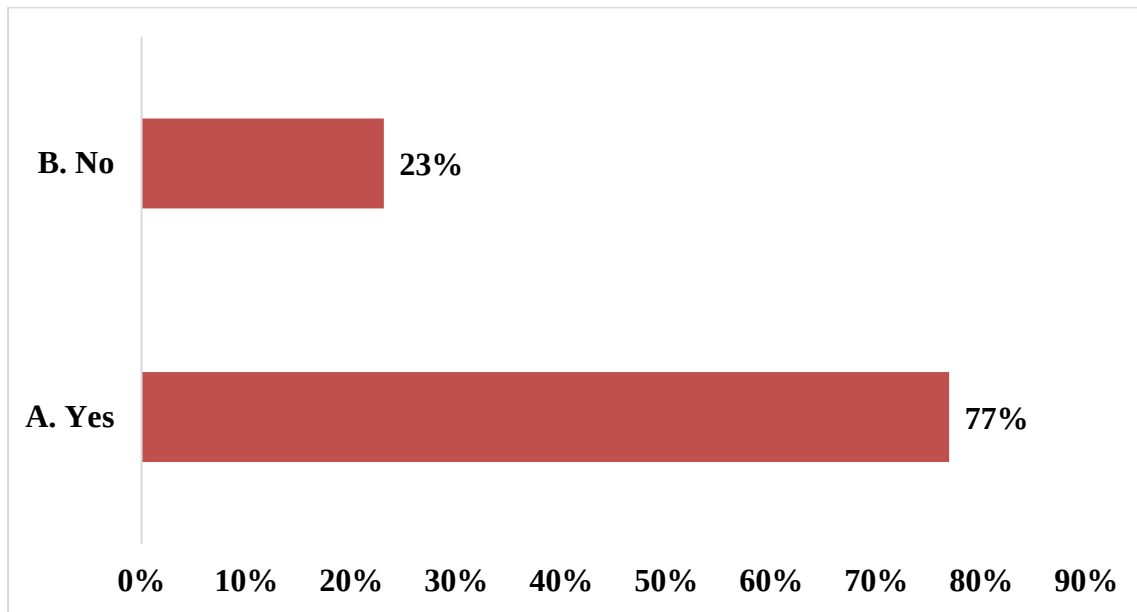


According to majority of doctors, 88%, they don't add any specific ingredients in htk solution before using as a perfusion solution.



6) Before using as a perfusion solution, do you add any specific ingredients in Ringer's Lactate solution?

- A. Yes
- B. No

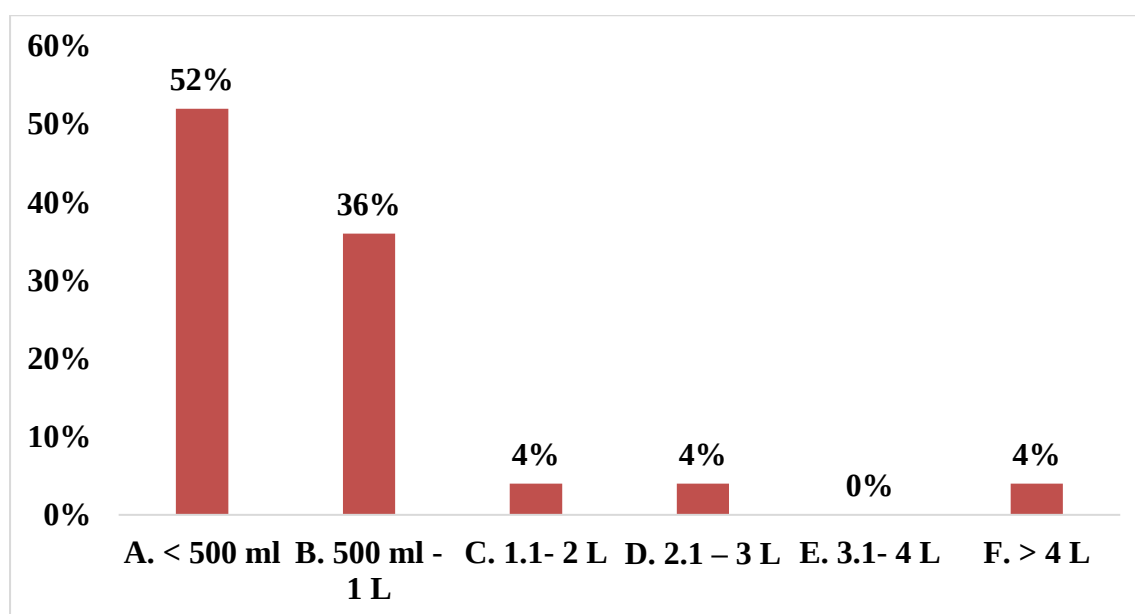


According to majority of doctors, 77%, they add any specific ingredients in ringer's lactate solution before using as a perfusion solution.



7) How much total volume (in litres) of HTK solution (including back table flush and organ storage) is used at your centre for Living donor Kidney transplantation?

- A. < 500 ml
- B. 500 ml - 1 L
- C. 1.1- 2 L
- D. 2.1 – 3 L
- E. 3.1- 4 L
- F. > 4 L

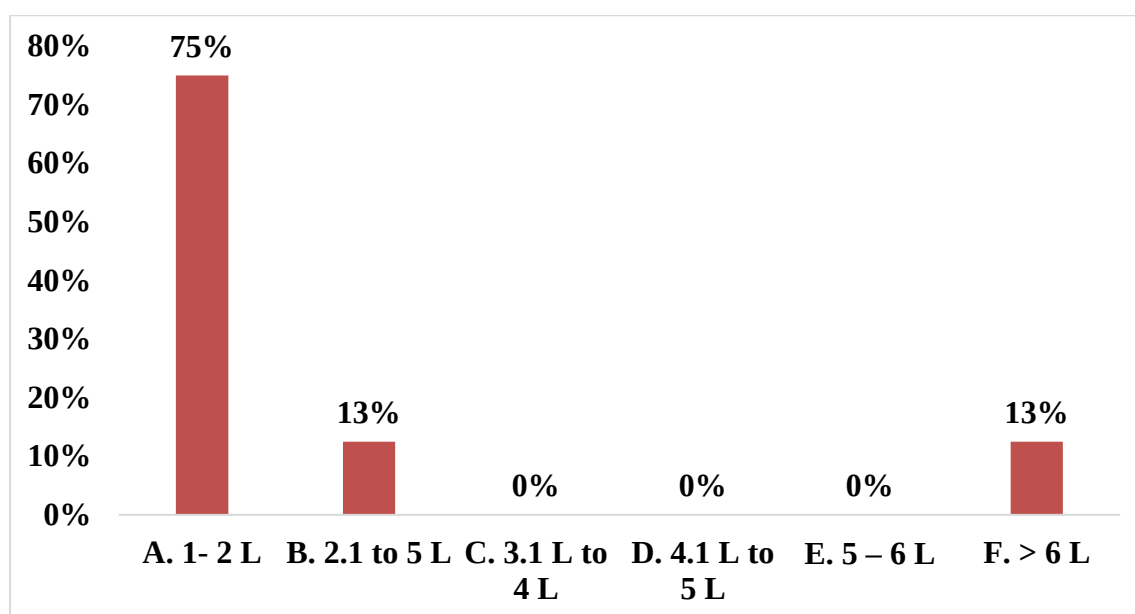


According to 52% of doctors, <500 ml of HTK solution (including back table flush and organ storage) is used at their centre for living donor kidney transplantation.



8) How much total volume (in litres) of HTK solution (including back table flush and organ storage) is used at your centre for deceased donor kidney transplantation?

- A. 1- 2 L
- B. 2.1 to 5 L
- C. 3.1 L to 4 L
- D. 4.1 L to 5 L
- E. 5 – 6 L
- F. > 6 L

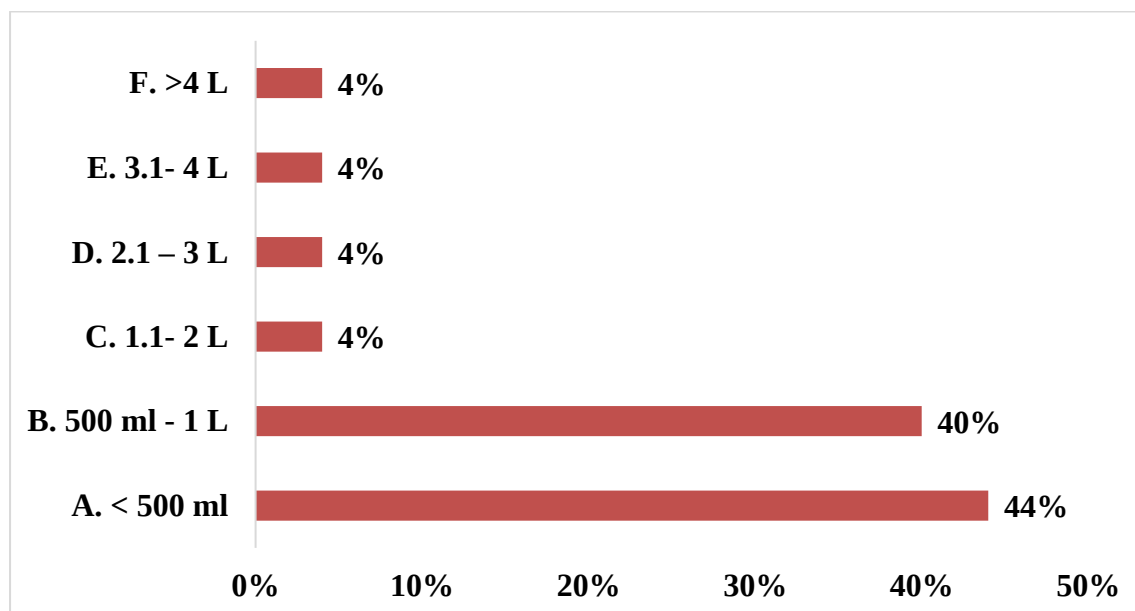


According to majority of doctors, 75%, 1- 2 L of HTK solution (including back table flush and organ storage) is used at their centre for deceased donor kidney.



9) How much total volume (in litres) of Ringer's lactate (including back table flush and organ storage) is used at your centre for Living donor Kidney transplantation-

- A. < 500 ml
- B. 500 ml - 1 L
- C. 1.1- 2 L
- D. 2.1 – 3 L
- E. 3.1- 4 L
- F. >4 L

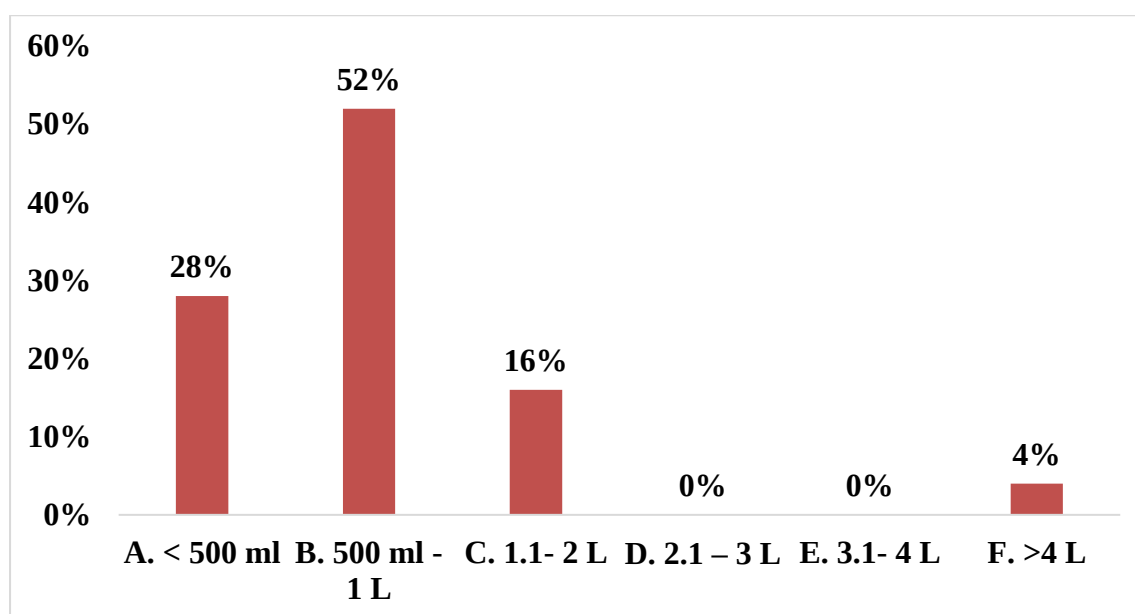


As per 44% of doctors, <500 ml of ringer's lactate (including back table flush and organ storage) is used at their centre for living donor kidney transplantation.



10) How much total volume (in litres) of UW solution (including back table flush and organ storage) is used at your centre for Living donor Kidney transplantation –

- A. < 500 ml
- B. 500 ml - 1 L
- C. 1.1- 2 L
- D. 2.1 – 3 L
- E. 3.1- 4 L
- F. >4 L

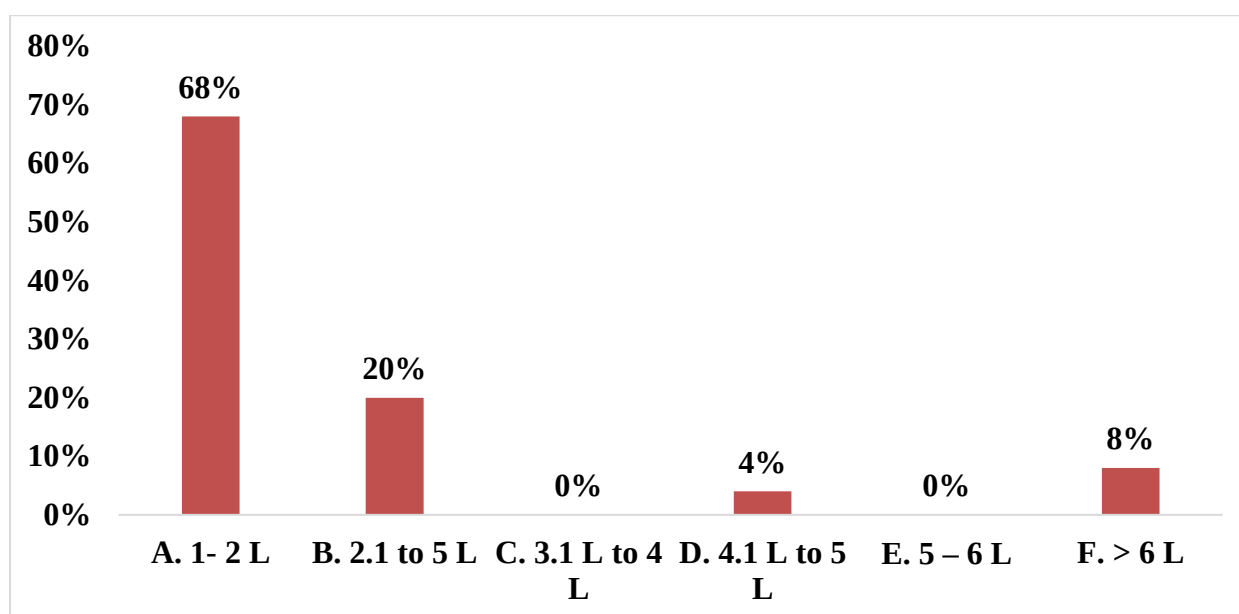


According to 52% of doctors, 500 ml - 1 L of UW solution (including back table flush and organ storage) is used at their centre for Living donor Kidney transplantation.



11) How much total volume (in litres) of UW solution (including back table flush and organ storage) is used at your centre for deceased donor kidney transplantation–

- A. 1- 2 L
- B. 2.1 to 5 L
- C. 3.1 L to 4 L
- D. 4.1 L to 5 L
- E. 5 – 6 L
- F. > 6 L

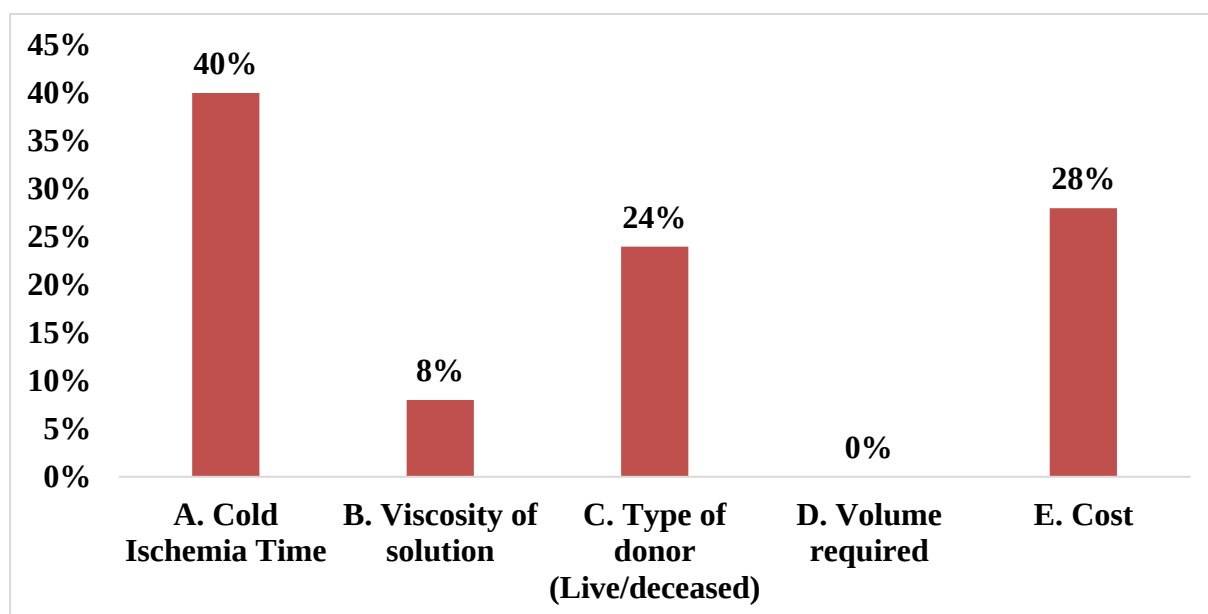


According to majority of doctors, 68%, 1- 2 L of UW solution (including back table flush and organ storage) is used at their centre for deceased donor kidney transplantation.



12) Which of the following is the most important parameter that you consider while choosing the organ perfusion/preservation solution?

- A. Cold Ischemia Time
- B. Viscosity of solution
- C. Type of donor (Live/deceased)
- D. Volume required
- E. Cost

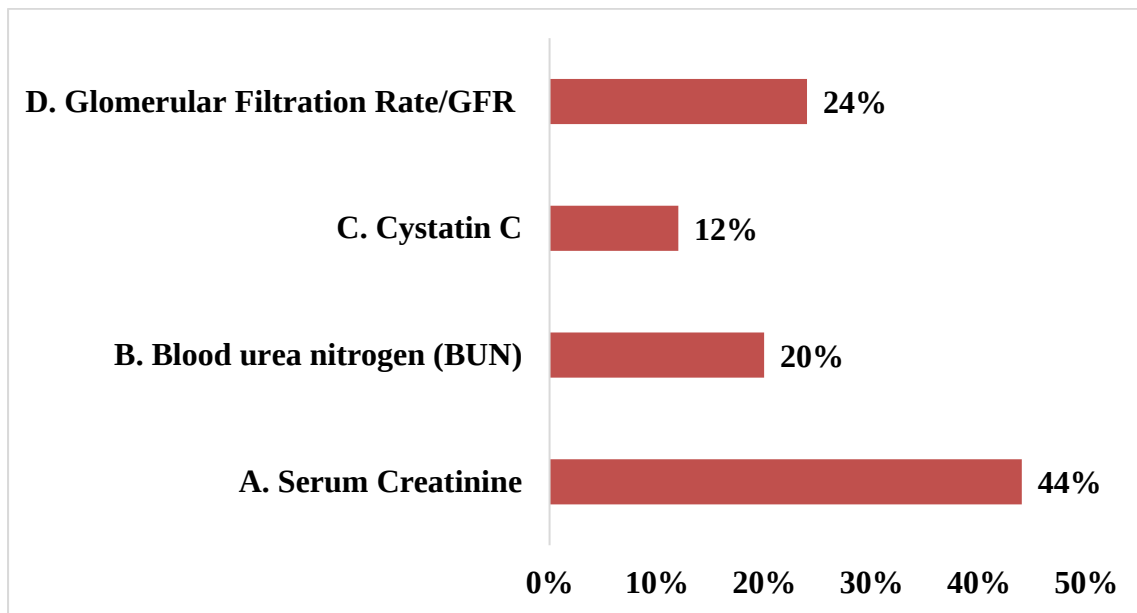


As per 40% of doctors, cold ischemia time is the most important parameter that they consider while choosing the organ perfusion/preservation solution.



13) What are the key post-transplant parameters that you assess to know the graft function?

- A. Serum Creatinine
- B. Blood urea nitrogen (BUN)
- C. Cystatin C
- D. Glomerular Filtration Rate/GFR

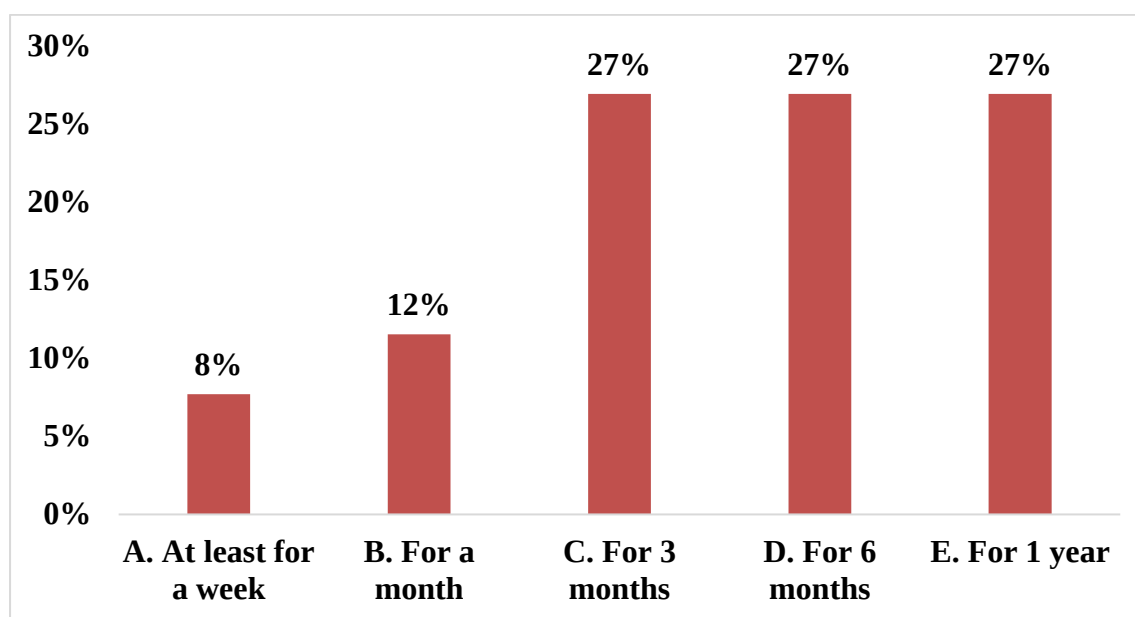


According to 44% of doctors, serum creatinine is the key post-transplant parameter that they assess to know the graft function.



14) How long do you assess lab parameters after transplant?

- A. At least for a week
- B. For a month
- C. For 3 months
- D. For 6 months
- E. For 1 year



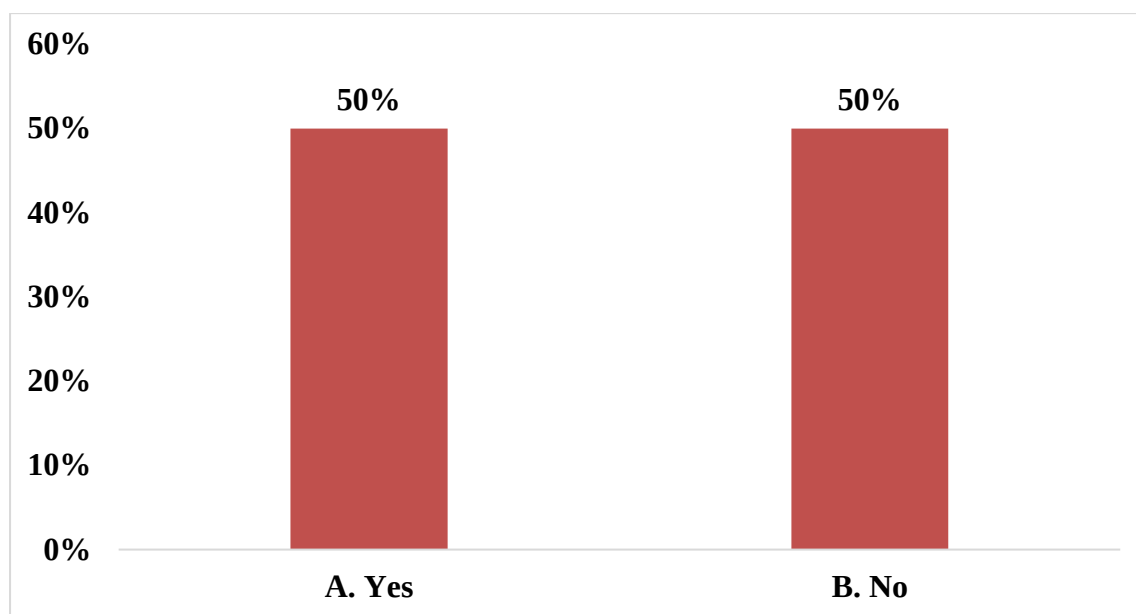
As per survey, 27% of doctors assess lab parameters after transplant for 3 months and other 54% of doctors says they assess lab parameters after transplant for 6 months and 1 year.



15) In the past, have you used GraftSol (HTK) solution in your practice?

A. Yes

B. No



As per survey, 50% of doctors have used graftsol (HTK) solution in their practice and other 50% of doctors have not used graftsol (HTK) solution in their practice.



Summary



- According to 50% of doctors, they use histidine-tryptophan-ketoglutarate (htk) solution in their practice.
- As per majority of doctors, 62%, ringer's lactate solution is the most preferred solution in living donor kidney transplant.
- According to majority of doctors, 88%, histidine-tryptophan-ketoglutarate (htk) solution is the most preferred solution in deceased donor kidney transplant.
- As per majority of doctors, 76%, they don't add any specific ingredients to uw solution before using as a perfusion solution.
- According to majority of doctors, 88%, they don't add any specific ingredients in htk solution before using as a perfusion solution.
- According to majority of doctors, 77%, they add any specific ingredients in ringer's lactate solution before using as a perfusion solution.
- According to 52% of doctors, <500 ml of HTK solution (including back table flush and organ storage) is used at their centre for living donor kidney transplantation.
- According to majority of doctors, 75%, 1- 2 L of HTK solution (including back table flush and organ storage) is used at their centre for deceased donor kidney.
- As per 44% of doctors, <500 ml of ringer's lactate (including back table flush and organ storage) is used at their centre for living donor kidney transplantation.
- According to 52% of doctors, 500 ml - 1 L of UW solution (including back table flush and organ storage) is used at their centre for Living donor Kidney transplantation.
- According to majority of doctors, 68%, 1- 2 L of UW solution (including back table flush and organ storage) is used at their centre for deceased donor kidney transplantation.
- As per 40% of doctors, cold ischemia time is the most important parameter that they consider while choosing the organ perfusion/preservation solution.
- According to 44% of doctors, serum creatinine is the key post-transplant parameter that they assess to know the graft function.
- As per survey, 27% of doctors assess lab parameters after transplant for 3 months and other 54% of doctors says they assess lab parameters after transplant for 6 months and 1 year.
- As per survey, 50% of doctors have used graftsol (HTK) solution in their practice and other 50% of doctors have not used graftsol (HTK) solution in their practice.



Consultant Opinion



Market Opportunities:

There is a market opportunity for pharmaceutical companies to develop improved formulations of kidney perfusion and preservation solutions that address the specific needs of transplant centers and healthcare professionals. Solutions tailored to different transplant scenarios, such as living donor or deceased donor kidney transplantation, could provide significant value to transplant teams.

Value for Healthcare Professionals:

Healthcare professionals should receive education and training on the optimal use of kidney perfusion and preservation solutions in different transplant settings. Continuing medical education programs can help ensure that healthcare professionals are knowledgeable about the benefits, dosing, and administration of these solutions, ultimately improving patient outcomes.

Adverse Effect Management:

Transplant teams should closely monitor patients for potential adverse effects associated with different perfusion and preservation solutions. Regular monitoring and vigilance can help mitigate the risk of complications and ensure the safety of transplant recipients.

Withdrawal Management:

Clear guidelines should be established for the selection and administration of kidney perfusion and preservation solutions based on individual patient factors, organ quality, and transplant scenarios. Healthcare professionals should have access to evidence-based protocols and algorithms to guide decision-making and optimize patient care.

Market Positioning:

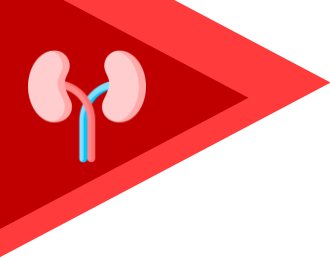
Pharmaceutical companies can differentiate their kidney perfusion and preservation solutions by highlighting their efficacy, safety profile, and ease of use. Marketing strategies should emphasize the unique features and benefits of each solution, positioning them as preferred choices for specific transplant scenarios.

**Personalized Treatment Decisions:**

Transplant teams should consider individual patient factors, organ quality, and ischemia times when selecting the appropriate perfusion and preservation solution for kidney transplantation. Personalized treatment decisions can optimize graft outcomes and improve transplant success rates.

Improving Patient Outcomes:

Regular monitoring of post-transplant parameters, such as serum creatinine levels and laboratory parameters, is essential for assessing graft function and ensuring long-term success. Transplant teams should implement standardized protocols for post-transplant monitoring and follow-up care to optimize patient outcomes and minimize complications.



NOTES

[illegible]

Developed by:



Weston Medical Education Foundation of India

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