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Review

Tips for optimizing organ preservation solutions

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Organ injury during ischemia is one of the clinical problems of today's transplantation. It occurs during warm ischemia time (WIT) when the blood flow is cut off and during cold ischemia when a graft is chilled in situ until the circulation is restored to the recipient organism. Fast cooling of the organ slows down metabolism and activates intracellular enzymes, which minimizes the effects of warm ischemia. Unfortunately, hypothermia also results in inhibition of ATP synthesis, cell swelling and intracellular acidity. That is why research is continually being conducted to develop new fluids for rinsing and storing organs, as well as to optimize the composition of those that are already in use, which will allow for longer and more effective graft storage and restoration of their optimal functions after transplantation. This article provides current information on rinsing and storage fluids available on the global market. It also discusses tips for the fluid modifications with hormones and micronutrients.

Key words: organ transplantation, preservation solution, hormones, micronutrients

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Abbreviations: ACP, acyl carrier protein; AKT, serine/threonine kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; alfa-GST,_alpha-glutathione s-transferase; ATP, adenosine-5′-triphosphate; db-cAMP, dibutyryl cyclic adenosine monophosphate; EGF, epidermal growth factor; eNOS, endothelial nitric oxide synthase; EPO, erythropoietin; ERK, extracellular signal regulated kinase; GPx, glutathione peroxidase; HEPES, (N-(2-hydroxyethyl)piperazine-N′-ethanesulfonic acid) buffer; HES, hydroxyethyl starch; HSP 70, heat shock protein 70; IGF-1, insulin-like growth factor 1; IL-10, cytokine synthesis inhibitory factor; iNOS, inducible nitric oxide synthase; LPD, low potassium dextran; MEK, MAPK/ERK kinase; mTORC1, mammalian target of rapamycin complex 1; NAC, N-acetyl cysteine; NF-κBp65, nuclear transcription factor subunit p65; PEG, polyethylene glycol; PRL, prolactin; rhEPO, recombinant human erythropoietin; rhPRL, recombinant human prolactin; SOD, superoxide dismutase; T3, triiodothyronine; T4,_thyroxine; TNF-α, proinflammatory cytokines; UCP2, mitochondrial uncoupling protein 2; WIT, warm ischemia time

INTRODUCTION

In recent years, organ transplantation has become a life-saving routine. In 2016 in Poland, there were a total of 1469 transplants from deceased donors (978 kidneys, 38 kidneys and pancreases, 317 livers, 101 hearts, 35 lungs) and 78 transplants from living donors (50 kidneys, 28 liver fragments). However, the number of people waiting for transplants is constantly increasing. In order to increase the effectiveness of transplants, intensive research is undertaken to ensure a sufficient number of grafts for transplantation, improve organ procurement and storage techniques, and reduce toxicity of the immunosuppressive treatment.

Fluids for organ rinsing and storage are an important factor affecting the success of transplantation. They are a transient environment in which the organ is stored between its removal from the donor organism and implantation into the recipient one. There are many fluids registered in the world (including one developed in Poland) dedicated to the preservation of specific organs. They differ in terms of composition, but all are intended to minimize the risk of cell damage, so as to restore proper functions of the organ after reperfusion. Ischemic damage occurs during warm ischemic time (WIT) when the blood flow is cut off and during cold ischemia when a graft is chilled *in situ* until the circulation is restored to the recipient organism. Fast cooling of the organ slows down metabolism and activates intracellular enzymes, which minimizes the effects of warm ischemia. Unfortunately, hypothermia also leads to inhibition of ATP synthesis, cell swelling and intracellular acidity. That is why research is continually being conducted to develop new organ preservation fluids, as well as to optimize the composition of those that are already in use, which will allow for longer and more effective graft storage and restoration of its optimal functions after transplantation (Birks *et al.* 2001; Rao *et al.*, 2001). The optimal time of storing kidneys in preservative fluids is about 24 hours, liver – up to 15 hours, heart and lung – less than 6 hours, pancreas – up to 24 hours, and intestines – up to 8 hours. Longer storage results in disturbances of cellular respiration, oxidative shock and induction of inflammation (Forsythe 2001; Rowiński *et al.* 2004).

FLUIDS FOR RINSING AND STORING ORGANS

Viaspan® (UW solution, University of Wisconsin solution) is a fluid used for perfusion and preservation of organs within the abdominal cavity. Its composition was developed in the 1980s by the Belzer and Southard's team at the University of Wisconsin, hence its name. The complex formula of the solution was repeatedly analysed in terms of the efficacy of individual components. The significance of some of them was not confirmed. Viaspan is an intracellular solution with high potassium (125 mmol/l) and low sodium (29 mmol/l) levels. The significant concentration of potassium is expected to counteract the escape of K^+ ions from the inside of the cell, but there is a risk of vasoconstriction. Hydroxyethylated starch (HES) retains the fluid in the endovascular space and prevents swelling of the extracellular space. It has been found that the addition of HES at 5% triples the viscosity of the fluid at 4°C relative to crystalloids, which in turn reduces the perfusion efficiency (Tullius *et al.*, 2002), and causes aggregation of erythrocytes (Mo-

rariu *et al.,* 2003; Plaats *et al.*, 2004). The use of HES in fluid therapy causes renal damage and an increased risk of bleeding, and consequently requires implementation of renal replacement therapy and transfusion of blood preparations (Golisz, 2013). The absence of HES in Viaspan does not impair organ functions after transplantation (Guibert *et al.*, 2011). Potassium lactate and raffinose present in this fluid counteract cell swelling. Glutathione neutralizes free oxygen radicals and maintains the integrity of the cell membrane. Adenosine stimulates ATP resynthesis, while allopurinol is a xanthine oxidase inhibitor and has a protective effect in ischemia. Recent studies suggest that the absence of adenosine, allopurinol, raffinose, phosphate buffer and insulin in the Viaspan composition does not significantly affect its efficacy (Ben Abdennebi *et al.*, 2002). A number of generic fluids of Viaspan have been developed: Cold Storage Solution, CoStorSol, SPS-1, KPS.

Biolasol® is the first Polish fluid registered for rinsing and storing "*ex vivo*" of the heart, liver, pancreas and kidney under hypothermic conditions using the static method. It allows for 24-hour storage of organs from the moment they are extracted from the donor, through transport and storage, to the final transplantation. The developed fluid formulation minimizes ischemia/reperfusion injury of the graft and preserves the structural and functional integrity of the organ. Biolasol is an extracellular fluid (total concentration of sodium is 105 mmol/l, potassium – 10 mmol/l) with pH 7.4 and osmolarity of 330 mOsm/l. It contains electrolytes, osmotically and oncotically active substances, buffering systems, substances that prevent cellular acidosis, which constitute energy sources, and antioxidants. The fluid was subjected to a pre-clinical study to assess its effectiveness and safety profile with the use of Polish large white pigs (Budziński *et al.*, 2014a; Budziński *et al.*, 2014b; Caban *et al.*, 2014). The impact of the fluid on organ swelling and selected biochemical indicators during perfusion, after 24 hours of storage and reperfusion, was studied on 40 kidneys, 10 livers and 10 pancreases, divided into 2 groups. The control group was the organs stored in the HTK/Viaspan fluid. There was a statistically significant decrease in concentration of enzyme markers and K^+, Na^+ ions during rinsing and preservation procedures. Histopathological examination revealed no damage to graft structures. It has been found that the degree of ischemia injury is not only influenced by the type of preservative fluid, but also the duration of its use. The sooner the organ is rinsed with the fluid, the smaller the organ swelling (Cierpka *et al.*, 2014; Dolińska *et al.*, 2012; Ostróżka-Cieślik *et al.*, 2008; Ryszka *et al.*, 2010).There was "no worse" clinical efficacy with respect to the commonly used Viaspan. Analysis of changes in the concentration of interleukin-6 in livers obtained from transgenic pigs, depending on the type of transgenesis and the type of applied preservative solution, showed potential hepatoprotective properties of Biolasol. There was a decrease in IL-6 concentration in homogenates of livers stored in Biolasol for 24 hours when compared to the control group (Budziński *et al.*, 2014a). In another study, human kidneys were stored by simple hypothermia. Half of the kidneys were washed with Biolasol and the other half with Viaspan. Delayed transplantation was observed in both groups (38% *vs.* 33% of cases, respectively, p=ns). After transplantation, an average of 2.25 patients whose kidneys were rinsed with Biolasol and 1.86 patients whose graft was washed with Viaspan were subjected to haemodialysis. Patients after transplantation also had serum creatinine concentrations tested and it was found that after 7, 30 and 60 days, the values were 4.64 mg/dl, 1.75 mg/dl, 1.7 mg/dl (Biolasol group) and 3.2 mg/dl, 1.53 mg/dl, 1.62 mg/dl (Vispan group). The results obtained after using the Biolasol and Viaspan solutions were comparable (Jóźwik *et al.*, 2016).

IGL-1® liquid is based on Viaspan, where the concentration of K^+ (25 mmol/l) and Na^+ (120 mmol/l) ions was reversed, thereby minimizing the risk of cardiovascular complications. Hydroxyethyl starch (HES) is replaced in some countries with 35 kDa polyethylene glycol (PEG-35), which stabilizes the lipid layer of the cell membrane (Dutheil *et al.*, 2009; Badet *et al.*, 2005; Codas *et al.*, 2009; Dondero *et al.*, 2010). In the USA, in accordance with the decision of FDA (Food and Drug Administration), HES is still present in the composition of IGL-1. The osmolarity of the solution is 290 mOsm/l, pH 7.4. The fluid is intended for the preservation of kidneys, livers and pancreases under hypothermic conditions. Experimental and clinical studies confirmed the superior efficacy of IGL-1 in liver and kidney transplants as compared to Viaspan. Renal studies demonstrated decreased levels of apoptotic markers and lower creatinine parameters 15 days after transplantation, whereas based on the liver transplant model, improvement of biochemical and histological parameters of the organ and improvement of microcirculation after reperfusion were observed (Franco-Gou *et al.*, 2007; Maathuis *et al.*, 2008; Mosbah *et al.*, 2012; Zaouali *et al.*, 2011).

HTK® is a cardioplegic fluid initially developed for open heart surgery. Later, its effectiveness in the storage of livers, kidneys, pancreases and lungs was confirmed. The name of the solution is derived from its three main components: histidine, tryptophan and α-ketoglutaric acid. It is an extracellular fluid (potassium and sodium concentrations are 9 mmol/l and 15 mmol/l respectively) and has a high buffer capacity (acidic – 97 mmol/l at T=5°C). Tryptophan stabilizes cell membranes and removes oxygen free radicals, whereas α-ketoglutarate is the substrate for anaerobic metabolism during organ storage. The fluid is characterized by low viscosity so it easily penetrates the microcirculation and can be used for *in situ* perfusion. It shows comparable efficacy in liver storage to IGL-1 (Meine *et al.,* 2015). It was found that porcine pancreatic islets stored in HTK showed higher survival rates under *in vitro* conditions than those preserved in Viaspan (Steffen *et al.*, 2017). For liver rinsing, IGL-1 is more cost-efficient than HTK. Although the prices of both fluids are comparable, IGL-1 consumption (4 litres) is lower than that of HTK (6–10 litres) (Meine *et al.*, 2015).

Celsior® is an extracellular (potassium and sodium concentrations are 15 mmol/l and 100 mmol/l, respectively), hypertonic (320–360 mOsm/l) solution intended for the storage of thoracic organs – hearts, lungs, and organs of the abdominal cavity – kidneys, livers and pancreases, under hypothermic conditions. The acidic buffer capacity of the fluid is about 11 mmol, alkaline – approx. 7 mmol, viscosity: 1.15 mm^2/s. The fluid contains antiedematous substances (lactobionate and mannitol), oxygen free radical scavengers (histidine and glutathione), and a high energy substrate (glutamate). Glutamate also prevents the increase of calcium concentration in the cell, and histidine prevents acidosis thanks to its buffering properties. It was found that heart storage in HTK and Celsior under hypothermic conditions using the static method had a comparable effect (Li *et al.*, 2016). Randomized, multicentre studies demonstrated high efficacy of this fluid in the recovery of bile duct functions af-

ter liver transplantation (Pedotti *et al*., 2004) and in lung preservation in the animal model (Wittwer *et al*., 1999).

Plegisol® is a crystalline cardioplegic solution for cardiac perfusion after stopping coronary circulation and preservation of this organ prior to transplantation. It is an extracellular fluid (K^+ – 16 mmol/l, Na^+ – 110 mmol/l) with osmolarity of 328 mOsm/l and pH=7.8. It also contains Ca^{2+} (2.4 mmol/l), Mg^{2+}(32 mmol/l), Cl^- (160 mmol/l) and HCO_3^- (10 mmol/l) ions (Cannata *et al*., 2012). Calcium ions stabilize cell membranes, counteract sarcolemma cracking and loss of Ca^{2+} transport capacity. Phosphate buffer counteracts the effects of metabolic acidosis. Magnesium is involved in myocardial stabilization by inhibition of myosin chain phosphorylation. Plegisol has a protective effect on the heart, comparable to HTK and Celsior in the early post-transplant period. The incidence of graft injury during storage and the occurrence of post-transplant failure were not significantly different in the analysed groups (Aldemir *et al*., 2014; Latchana *et al*., 2014).

Perfadex® is an extracellular fluid (osmolarity of 292 mOsm/l, pH=7.4) mainly intended for lung transplants under hypothermic conditions. It is often called "low-potassium dextran" (LPD) due to the K^+ concentration (6 mmol/l) and the presence of dextran 40 (50 g/l), which allows the fluid to be maintained in the endovascular space. The phosphate buffer in the fluid prevents metabolic acidosis, whereas glucose is a source of energy for ATP resynthesis (Ferng *et al*., 2017; Ohsumi *et al*., 2017). Comparative studies of the efficacy of Celsior and Perfadex in lung preservation were conducted. Menezes and coworkers reported similar effectiveness of both fluids using an animal model. Gas exchange parameters and results of histopathological analyses were comparable in both groups. There were no statistically significant differences in pulmonary arterial pressure after 6 and 12 hours of storage. The extent of pulmonary oedema was comparable for both ischemic times. No differences were observed in type II pneumocytes. Few cells have been observed to have chromatin condensation, which may suggest an early stage of apoptosis. The basement membrane thickness was comparable in both groups (Menezes *et al*., 2012). However, clinical studies by Gohrbandt et al. demonstrated that Celsior protected lungs during transplantation better than Perfadex. Three-year survival of the graft after transplantation was significantly higher in the group of patients where Celsior was used (Gohrbandt *et al*., 2015).

Polysol (PS) is a solution intended for organ storage and perfusion under hypothermic conditions. It is an extracellular fluid (total concentration of sodium is 120 mmol/l, potassium – 15 mmol/l) with pH=7.4 and osmolarity of 320 mOsm/l. It contains about 60 substances, including: electrolytes, colloid (PEG, 35kDa), buffering systems (phosphate, histidine, HEPES (buffer of N-(2-hydroxyethyl) piperazine-N-2-ethanesulfonic acid), a precursor for ATP production (adenosine), antioxidants (glutathione, α-tocopherol, ascorbic acid), raffinose, trehalose, vitamins B1, B2, B3, B4, B5, B6, B7, B8, B9, B12, C, A, D2, E, K3, and 21 amino acids (including alanine, arginine, asparagine, cysteine, glutamine, glycine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine) (Schreinemachers *et al*., 2009a). The effectiveness of individual fluid components and the potential for interaction between them have not been investigated. Due to the multi-component nature of the Polysol solution, it is important to carry out research on the proper application of all ingredients. In addition, the presence of various organic and inorganic compounds entails the risk of interaction (Schreinemachers, 2010). The solution is characterized by low viscosity (1.8 cP), high buffer capacity and high oncotic pressure. This is mainly due to the presence of polyethylene glycol in the fluid, which stabilizes the lipid membrane structure and reduces the permeability of the vascular membranes (Hauet *et al*., 2001; Schreinemachers *et al*., 2009a). Preclinical studies demonstrated high effectiveness of Polysol compared to other fluids typically used for rinsing organs. Bessems et al. found that the application of continuous perfusion under hypothermic conditions for storing rat liver using Polysol was more beneficial compared to Viaspan and HTK. The number of released ALT, AST, LDH and alpha-GST was significantly lower (Bessems *et al*., 2005a; Bessems *et al*., 2005b). Rinsing of the rat liver in Polysol using the cold hypothermia method also caused smaller mitochondrial changes in this organ compared to HTK (Hata *et al*., 2007). The use of Polysol solution for storage of porcine kidneys improved their functions and structural integrity compared to HTK (Schreinemachers *et al*., 2009b). Polysol also proved to be superior to Viaspan fluid in storing the rat large intestine (Wei *et al*., 2007). Schreinemachers et al. conducted a clinical pilot study in nine human recipients of kidneys that were stored in Viaspan and Polysol. A higher percentage of rejection was observed in patients whose kidneys were rinsed with Polysol (Schreinemachers *et al*., 2013).

ET-Kyoto is an extracellular fluid with sodium concentration of 107 mmol/l and potassium concentration of 42 mmol/l. The solution osmolarity is 366 mOsm/l. Trehalose, which has a cytoprotective effect, is not included in any other fluid. Gluconate and HES counteract cell swelling. Phosphate buffer prevents metabolic acidosis. Db-cAMP (cyclic adenosine monophosphate dibutyltin) and nitroglycerine protect the vascular endothelium. NAC (N-acetylcysteine/antioxidant) acts as a free radical scavenger (Bando *et al*., 1998; Chen *et al*., 2004; Wada *et al*., 1996). This fluid was originally developed for lung storage, but it also proved to be effective in preserving kidneys, livers, pancreases and tracheae (Chen *et al*., 2004). It is suggested that ET-Kyoto has comparable efficacy in storing kidneys and livers to Viaspan (Yoshida *et al*., 2002; Zhao *et al*., 2008).

HORMONES AFFECTING THE EFFICIENCY OF RINSING FLUIDS

An increasing attention is paid to hormones as substances that can significantly reduce the effects of organ ischemia during their storage. **Prolactin** (PRL) has a broad spectrum of therapeutic effects and is involved in more than 300 processes occurring in living organisms. It affects the regulation of calcium homeostasis by stimulating active transport in the duodenum (Charoenphandhu & Krishnamra 2007; Charoenphandhu 2001; Dolińska *et al*., 2012a). It participates in angiogenesis processes, stimulates immune cell proliferation and differentiation, inhibits apoptotic and inflammatory processes. It induces T and B cell multiplication and secretion of immunoglobulins and cytokines (Parada-Turska *et al*., 2006; Vera-Lastra *et al*., 2002). Prolactin acts on specific membrane receptors located at different sites, including liver and kidney cells, and hence it can affect their tissues. It stimulates the process of anaerobic glycolysis under hypoxic conditions, increasing the survival of organs (Parada-Turska *et al*., 2006; Ryszka *et al*., 2011). PRL has a positive effect on the regeneration of rat liv-

er after partial hepatectomy, increasing cell proliferation and differentiation (Olazabal *et al*., 2009). When added to preservative solutions, it slows down the release of transaminases, which might suggest hepatoprotective properties of this hormone. A study on an isolated rabbit liver showed that the addition of PRL to Ringer's fluid significantly reduced the amount of released ALT and AST. ALT and AST release into the intercellular space proves that structural integrity of the cell membrane is affected. Their level of activity correlates with the degree of cell damage (Ryszka *et al*., 2002; Szulc-Musioł *et al*., 2004). Inclusion of PRL in HTK positively influenced 24-hour storage of an isolated porcine liver (Ryszka *et al*., 2011). Addition of PRL to Viaspan demonstrated its significant effect on the speed and dynamics of the changes in calcium and magnesium ion concentration in the preservative solution. This hormone probably blocks access of Ca^{2+} to hepatocytes (Ryszka *et al*., 2006). Addition of recombinant human prolactin (rhPRL) to Biolasol reduced the transaminase activity during reperfusion of porcine kidneys (Ryszka *et al*., 2016). It has been also found that rhPRL can protect the islets of Langerhans during pancreas storage prior to transplantation (Yamamoto *et al*., 2010).

Melatonin is a hormone secreted by the pineal gland, and, to a lesser extent, by the retina, enterochromatophilic gastrointestinal cells and blood cells (Carrillo-Vico *et al*., 2005). It exhibits strong antioxidant properties and is one of the most effective free radical scavengers. It has been demonstrated that it is five times more effective in eliminating hydroxyl radicals than glutathione (present in the composition of Celsior, Viaspan, IGL-1) and vitamins C and E (Beyer *et al*., 1998; Popławski & Derlacz 2003; Zań *et al*., 2011). In addition, it increases the activity of antioxidant enzymes: superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (Reiter *et al*., 2000). It stimulates the production of thermal shock proteins, reduces neutrophil inflows, modulates cytokine production (IL-10 growth and TNF-α decrease), and reduces apoptosis and necrosis of damaged tissues. Strong antioxidant and immunostimulatory properties indicate its cytoprotective effect during ischemia and reperfusion of organs (Jaworek *et al*., 2007; López-Burillo *et al*., 2003). Aslaner et al. showed that 30 mg/l of melatonin added to Viaspan effectively protected kidneys during cold ischemia within up to 48 hours. Histological examination showed less damage when compared to kidneys stored in melatonin-free fluid, and significantly lower LDH release (Aslaner *et al*., 2013). Li and coworkers found that melatonin reduced damage to kidneys stored in HTK. It induces superoxide dismutase (SOD) activity and reduces the activity of lipohydroperoxides (LPO). Its overactivation may contribute to the reduction in oxidative stress indicators: expression of NF-kBp65, inducible nitric oxide synthesis (iNOS), and caspase-3 (Li *et al*., 2009). Gunal et al. studied the effect of Viaspan modified with 30 mg/l of melatonin on ischemic hepatic injury in Wistar rats. They found that, compared to the control group, melatonin had a protective effect on the Kupffer cells. The amount of released LDH, AST and ACP enzymes was significantly lower, and there was increased expression of HSP 70 thermal shock proteins and decreased lipid peroxidation (Gunal *et al*., 2010).

The effects of thyroid hormones: **thyroxine** (T4) and **triiodothyronine** (T3), on graft damage during storage have also been studied. Imberti et al. suggest that administration of thyroxine to rats increases ischemia-reperfusion injury of a liver stored in the Euro-Collins fluid (Imberti *et al*., 1998). Yang and coworkers have shown that administration of triiodothyronine to mice has protective effects on the liver under conditions of ischemia and reperfusion. T3 activated autophagy mediated by MEK (MAP-ERK kinases)/ERK (extracellular signal regulated kinase)/mTORC1 (mTORC1 kinase) (Yang *et al*., 2015). Triidothyronine induces hepatocyte proliferation in rat livers (Malik *et al*., 2003), stimulates liver regeneration after partial hepatectomy (Cervinková *et al*., 1998), and reduces apoptosis (Sukocheva & Carpenter 2006).

Insulin is a component of Viaspan. It transports glucose, which is the substrate for anaerobic glycolysis and the main source of energy in ischemia, into cells. **Dexamethasone** (synthetic hormone of the adrenal cortex), also present in Viaspan, has long-lasting, potent anti-inflammatory and immunosuppressive effects (Saruç *et al*., 2009).

Insulin-like growth factor-1 (IGF-1) belongs to insulin-like polypeptide hormones. It influences the growth processes of the body and normal cell homeostasis (Filus & Zdrojewicz 2014). Zaouali and coworkers (2010b) added 10 μg/L IGF-1 to IGL-1 and found improvement in liver function parameters after 24-hour storage. They observed an increase in the activity of AKT (serine-threonine kinase) and eNOS (endothelial nitric oxide synthase) and inhibition of TNF-α pro-inflammatory cytokine release. IGL-1 was also enriched with the *epidermal growth factor* (EGF - 10 μg/l). They found that it slowed down the release of transaminases, increased the content of adenosine triphosphate (ATP) and minimized mitochondrial damage (Zaouali *et al*., 2010a).

Erythropoietin (EPO) is a glycoprotein peptide hormone that is involved in the development of erythroblasts and promotes the release of reticulocytes from the erythroblast islets. It has been found to have anti-inflammatory, antioxidant, angiogenic and cytoprotective properties. Progressive renal and cardiac failure leads to a decrease in EPO (Jackevicius, 2014; Kopeć-Szlęzak, 2009; Saganowska, 2008). Schmeding et al. administered 8.4 μg of rhEPO to rats and observed smaller ischemia-reperfusion liver injury after orthotopic transplantation when compared to the control group (Schmeding *et al*., 2009). Eipel et al. demonstrated that HTK supplemented with α rhEPO at a dose of 0.084 was beneficial for rinsing isolated, fatty mouse livers and storing them under hypothermic conditions. The modified fluid improves the function of endothelial cells, blood vessel lining, reduces expression of UCP2 (uncoupling protein 2) and phosphorylation of ERK (extracellular regulated kinases) (Eipel *et al*., 2012). Addition of erythropoietin (0.042 mg/l) to Celsior has a cardioprotective effect on isolated rat hearts (Kumarasinghe *et al*., 2016; Watson *et al*., 2013).

MODIFICATION OF FLUID COMPOSITION WITH MICRONUTRIENTS

The addition of **micronutrients** in order to modify the composition of preservative solutions is an innovation. It has been found that the inclusion of selenium in HTK significantly affects normal functioning of kidneys after transplantation. It lowers the concentration of malonyldialdehyde, which increases under conditions of increased generation of free oxygen radicals (Treska *et al*., 2003). As a component of Euro-Collins fluid, selenium protects lungs during ischemia and reperfusion (Soncul *et al*., 1994). Zinc added to St. Thomas' Hospital No.2 fluid (Plegisol) has a beneficial effect on maintaining

normal cardiac functions and can be used in cardioplegic fluids (Bessems *et al*., 2005b). Micronutrients can also significantly affect the durability of organ rinse solutions. It has been shown that the addition of zinc to Biolasol decreases its durability by 30.5%, while the addition of selenium increases its durability by 8.21%. This indicates the synergism of antioxidant effect of vitamin C and Se^{4+} in the fluid (Ostróżka-Cieślik *et al*., 2015).

SUMMARY

The development of transplantology is conditioned by the achievements of many areas of science. Genetic discovery and improvement of genetic engineering techniques may help to develop methods for obtaining fragments or whole organs using the genetic material of the recipient. Advances in biotechnology and pharmaceutical science will enable the development of an optimal fluid for organ storage that will effectively and safely prevent the consequences of ischemia-reperfusion injury and the effects of hypothermia. The next step in fluid development will be their modification with the addition of proper hormones and bio-nutrients.

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