TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Graft rinse prior to reperfusion in liver transplantation: literature review and online survey within the Eurotransplant community

Philipp Houben,[1] Giulia Manzini,[2] Michael Kremer,[2] Joerg Arend,[3] Gabriela A. Berlakovich,[4] Ernst Klar,[5] Jürgen Klempnauer,[6] Jan Lerut,[7] Gerd Otto,[8] Jacques Pirenne,[9] Xavier Rogiers,[10] Daniel Seehofer,[11] Dirk L. Stippel[12] and Peter Schemmer[1]

1 Department of General and Transplant Surgery, University of Heidelberg, Heidelberg, Germany
2 Department of General and Visceral Surgery, University of Ulm, Ulm, Germany
3 Department of General, Visceral and Vascular Surgery, Otto-von-Guericke University, Magdeburg, Germany
4 Division of Transplantation, Department of Surgery, University of Vienna, Vienna, Austria
5 Department of General, Thoracic, Vascular and Transplantation Surgery, University of Rostock, Rostock, Germany
6 Department of General, Visceral and Transplant Surgery, Klinikum der Medizinischen Hochschule, Hannover, Germany
7 Department of Liver Transplant Surgery, University Clinic Saint-Luc, Bruxelles, Belgium
8 Department of Transplant and Hepato-Biliary-Pancreatic Surgery, Johannes-Gutenberg-University, Mainz, Germany
9 Department of Abdominal Transplant Surgery, University of Leuven, Leuven, Belgium
10 Department of Transplant Surgery, University of Gent, Gent, Belgium
11 Department of General, Visceral and Transplantation Surgery, University of Berlin, Berlin, Germany
12 Department of General, Visceral and Cancer Surgery, University of Cologne, Köln, Germany

Keywords
eurotransplant survey, graft rinse, liver transplantation.

Correspondence
Prof. Dr. med. Peter Schemmer, Department of General and Transplant Surgery, University Hospital of Heidelberg, INF 110, 69120 Heidelberg, Germany.
Tel.: 49 6221 566204;
fax: 49 6221 564215;
e-mail: Peter.Schemmer@med.uni-heidelberg.de

Equal contribution: Philipp Houben, Giulia Manzini.

Conflicts of interest
The authors of this manuscript have no conflicts of interest to disclose.

Received: 16 November 2014
Revision requested: 30 December 2014
Accepted: 22 June 2015
Published online: 22 Jul 2015

doi:10.1111/tri.12631

Summary

Graft rinse prior reperfusion in liver transplantation (LT) is believed to reduce the incidence of postreperfusion syndrome and improve clinical outcome. A MEDLINE search was performed to obtain a comprehensive review of the published literature dealing with graft rinse in LT. Moreover, all thirty-four LT centers in the Eurotransplant (ET) region were invited to participate in an online survey to whether or not graft rinse is performed and whether further research in the field is needed. Seventeen reports have been found to investigate graft rinse protocols in 1894 LT recipients. Eighteen of the thirty centers that participated in the online survey performed graft rinse prior reperfusion in LT. The most commonly used rinse solution was albumin. Nineteen centers stated interest in participating in a multicenter RCT in the field. The published literature does not provide concluding appraisal of the benefit of graft rinse in LT. Graft rinse protocols are not standardized and are based on personal experience. Appropriately designed clinical trials addressing the topic are demanded. The online survey appears to be a helpful tool for the evaluation of clinical practice and future research topics in the transplant community.

Introduction

In liver transplantation (LT), graft rinse and reperfusion methods are still a subject of controversy. Although new concepts of transplant organ procurement, such as machine perfusion or normothermic perfusion, are evolving, cold storage can be currently considered as part of the clinical routine in LT [1,2]. Application of hypothermia and graft

perfusion with organ preservation solutions has rendered LT a routine procedure for the treatment of liver failure due to numerous underlying diseases. Nonetheless, organ procurement applying cold storage implies certain limitations. Even though the possible duration of cold storage is still a matter of debate, most centers try to limit cold ischemia to a minimum [3].

Disagreement remains regarding the optimal preservation solution. After lactated Ringer's solution was initially used by Starzl to flush the graft, the University of Wisconsin (UW) solution gained striking popularity among transplant surgeons since 1988 [4,5]. In 1990, Bretschneider HTK (histidine–tryptophan–ketoglutarate) solution was shown to have comparable liver graft preservation capabilities at lower costs [6,7]. Furthermore, HTK has putative clinical advantages over UW.

The first is the viscosity of the HTK. Given that the blood supply of the biliary tract is exclusively dependent on arterial perfusion, the lower viscosity of HTK is assumed to enable better perfusion of small vessels. This in turn is believed to prevent biliary complications due to inefficient perfusion of small arterioles with subsequent microthrombosis during organ retrieval and procurement. Remarkably, this potential advantage of HTK over UW has not yet been shown in a randomized controlled trial (RCT) [8].

The second possible advantage of HTK lies in the solution′s low potassium concentration, which precipitated HTK′s widespread use and popularity [9]. The postreperfusion syndrome (PRS) in LT with intense hemodynamic instability is partially attributed to the large amount of potassium that can be effused into the systemic circulation during graft reperfusion. The type of preservation solution was shown to potentially affect the incidence of PRS in LT [10]. PRS was reported to significantly affect postoperative outcome, resulting in a higher rate of renal failure and inferior short-term survival [11].

The need for graft rinse in HTK preserved livers remains uncertain, even though it is widely applied. Several concepts of graft rinse, differing in terms of the rinse volume and the rinse solution itself, are described in the literature. Usually the Ringer's lactate, preservation solution, or albumin used for graft rinse are applied by gravity or pressure. While most transplant surgeons perform antegrade flushing of the graft, some authors promote retrograde flushing of the liver via the superior caval vein [12]. RCTs sufficiently addressing the topic and indicating which graft rinse concept offers best graft protection and limitation of ischemia reperfusion damage are missing. With the aim of summarizing the published data from clinical trials dealing with graft rinse in LT, this group has performed a comprehensive review of the literature. Additionally, an online survey was designed and sent to all liver transplant centers within the Eurotransplant (ET) region in order to evaluate current clinical practices. Moreover, an aim of the project was to reveal issues related to graft rinse that could be primarily relevant in future multicenter clinical trials.

Methods

Review of literature on graft rinse in liver transplantation

A search of the literature in MEDLINE was performed using the following search terms: liver transplantation, human, clinical trial and flush/rinse/irrigation, respectively. All abstracts were checked for relevance and full texts of those papers that appeared to be pertinent to the matter were obtained. Citations in all full texts were scanned for references to other relevant papers. Patient cohorts that were reported twice were only considered once [12,13]. Baseline data, results, and conclusions of all papers were filled in a standard data extraction sheet for comparison and interpretation of data. Focus was put on trials examining different techniques of graft flushing immediately before reperfusion of the graft during the second warm ischemic period. Trials that applied perfusion of grafts before or during cold ischemia (e.g. back table procedures) with certain solutions or drugs were not considered relevant for this review.

Online survey

An online survey was programmed by an experienced information scientist utilizing the open source software LimeSurvey® (www.limesurvey.org). The heads of all thirty-four liver transplant centers within the ET region were invited to participate by an email containing a personalized link to the survey. Modes of graft rinse were queried using click boxes according to the data displayed in the results section. The subject here was also the graft rinse immediately before reperfusion (during the second warm ischemia period). Backtable procedures were not considered. The single subjects queried were as follows: the technical aspects of graft rinse, the solution that is used, the force which the rinse is applied by, the volume and temperature of the rinse medium and whether the practice of graft rinse is standardized. Moreover, the need for clinical trials and the attendance to participate were subjects of the survey. When applicable, the opportunity was given to insert free-text statements. The entire, originally structured online survey is available as a supplement. The analysis of the data was carried out in a descriptive fashion. The online survey on graft rinse protocols was carried out in addition to a survey about the sequence of reperfusion in LT, the results of which have been previously reported [14].

Results

Literature review

According to the search strategy, seventeen reports were identified as being relevant. In these reports, graft rinse prior reperfusion was done in 1894 LT recipients. The basic characteristics of these trials, all of them published in English, are summarized in Table 1.

Online survey

Thirty of thirty-four centers answered the online survey. Twelve of these centers do not perform graft rinse before reperfusion as part of their clinical routine. Among the remaining eighteen centers, arterial graft rinse is only performed in one clinic. The majority of the participating centers use albumin as the rinse solution of choice (Fig. 1). Pressurized rinse is only performed by three centers. A cooled rinse solution is used in ten of the eighteen centers, mostly when albumin rinse is performed. Crystalloid rinse solution is commonly applied at room temperature. Fourteen of the eighteen participants in the survey stated that their practice is based on personal or institutional experience, the option "based on literature" was not chosen. Nineteen centers stated that they would participate in a multicenter RCT in the field.

Discussion

Graft rinse protocols and solutions can potentially influence the outcome of LT via the limitation of ischemia reperfusion injury and ultimate prevention of reperfusion syndrome. In experimental LT, the use of a glycine-based rinse solution has been studied extensively with promising results. The Carolina rinse solution (CRS) reduced the damage from ischemia reperfusion injury and improved post-transplant survival in the experimental setting and has shown promising results in clinical pilot trials [15–18]. Despite these findings, CRS is not used in clinical routine.

Only a few clinical trials addressing graft rinse were found in the systematic search of the published literature. A retrospective evaluation of two or more different types of graft rinse protocols was carried out in the majority of the identified trials. UW was used for cold preservation in eleven of the seventeen trials. In three cases, different solutions were used during the trial and HTK was used in only one study from Austria [19]. Two reports have not stated which preservation solution was used for cold storage. The average duration of cold ischemia has only been reported to differ significantly between treatment groups by one author. Ghafaripour *et al.* [20] found a significantly lower mean total ischemia time (5.8 and 6.3 vs. 9.5 h) for their flushed and nonflushed HTK group compared to UW preserved grafts. An explanation for this finding has not been given by the authors. The varying protocols and the chosen endpoints used to determine the effect of graft rinse were too inhomogeneous to pool the results for a meta-analysis. The endpoints evaluated in most reports could be summarized in three main categories. In the first category, laboratory parameters were tested, in which case transaminases and bilirubin were usually used to determine differences in graft damage and function [18,19,21–25]. According to the potential benefit of various graft rinse protocols in preventing PRS, hemodynamic parameters were classified as the second common category [11,24–29], and the third category focused on graft function and survival data [16,19–21,25,27,30,31]. Given the rather low evidence levels and the absence of appropriately designed RCT on the topic, the findings of the literature review failed to indicate which graft rinse protocol provides the best graft quality. The situation is exasperated by the inhomogeneity of the study populations and differing baseline characteristics of the reviewed trials.

It is worth to mention that the measurement of certain parameters in the effluent can possibly be used for prediction of the graft function. In this context, the proteolytic activity in the effluent was shown to indicate Kupffer cell activation and predict graft survival in experimental LT [32]. Nonetheless, this has not yet been introduced to clinical routine and was not in the focus of the literature review or the online survey.

Despite this, three different graft rinse principles or reperfusion without previous flushing were commonly compared:

Portal blood rinse – The use of portal blood to rinse the graft with subsequent disposal of a certain amount of the effluent blood before completion of the caval anastomosis and unclamping the recipient's caval vein.

Drug rinse – The addition of specific pharmaceutical agents to the rinse solution to improve reperfusion quality and to limit ischemic reperfusion injury.

Retrograde flushing – A retrograde, low pressure, low oxygen blood rinse via recipient IVC is done in an attempt to reduce the production of oxygen free radicals.

Given below is an overview of the reports categorized according to the three mentioned groups:

Portal blood rinse

Eight of the sixteen trials focused on the use of portal blood for graft rinse. In a retrospective trial published by J.J. Brems in 1993, fourteen grafts were flushed with portal blood prior to reperfusion in comparison with fourteen grafts that were reperfused primarily via the portal vein without any flushing [26]. Flushing of the graft with portal blood was found to significantly decrease the incidence of hemodynamic instability following reperfusion. Menegaux

Table 1. Characteristics of the identified trials on graft rinse in LT.

First Author	Type of trial	Year	*n*	Preservation solution	Treatment	Endpoints	Conclusion
Menegaux [21]	Retrospective	1993	155	UW/SLS	UW Ringer versus UW colloid versus UW blood versus SLS Ringer versus SLS colloid versus SLS blood	Transfusion requirements, operative time, TA, bilirubin, INR	Portal blood beneficial (transfusion requirements in UW/UW + SLS)
Brems [26]	Retrospective	1993	28	Not stated	Crystalloid flush followed by portal blood reperfusion versus portal blood flush	PRS, MAP, SVR, K+	Portal flush effective to prevent PRS
Emre [22]	Retrospective	1994	412	UW	Low-flow Ringer versus low-flow Ringer + portal blood versus High-flow Ringer + portal blood versus Portal blood	TA, PT, PNF	Portal blood alone best
Fukuzawa [27]	Retrospective	1994	83	UW	Ringer versus Ringer + portal blood	K+, hemodynamics, graft + patient survival	Ringer + portal blood significantly better
Post [17]	Retrospective	1995	60	UW	Ringer's solution, modified Carolina rinse, and autologous blood	Graft function	No difference
Mirza [23]	Prospective, not randomized	1996	209	UW	500 ml portal blood versus 0,5% dextrose	TA, function, survival	Lower TA in blood group, function and survival equal
Millis [28]	RCT	1997	100	UW	Portal vein flush, no vena cava venting; hepatic arterial flush, no vena cava venting; portal vein flush with vena cava venting; hepatic artery flush with vena cava venting	Hemodynamics	Insignificant regarding Hemodynamics (30 min) and graft survival
Bachmann [18]	Prospective randomized pilot trial	1997	30	UW	Simultaneous arterial + portal flush with CRS, human albumin, blood	TA, cholestasis parameters, bile production	CRS performing best (not significant)
Fisher [33]	RCT	1999	43	UW	Normosol + adenosine versus Normosol	Bile production, factor 7	Insignificant regarding graft survival, bile production enhanced
St Peter [24]	RCT	2003	20	UW	Tacrolimus versus placebo	TA, function	Beneficial effect
Kniepeiss [12]	Retrospective	2004	53	HTK / UW	Retrograde venous blood flush via IVC	Incidence of PRS	Technique applicable
Gruttadauria [29]	Retrospective	2006	50	UW	Ringer flush no caval vent versus portal blood + caval vent	Hemodynamics, graft function	Portal vein flush favorable
Homvises [30]	Retrospective	2008	11	UW	Albumin 5% flush	Effluent K+, hemodynamics	Minimal flush volume 500 ml
Ghafaripour [20]	RCT	2010	89	HTK / UW	UW cold storage versus (HTK cold storage versus HTK + flush)	Hemodynamics	Flushing HTK beneficial
Busuttil [25]	RCT	2011	47	not stated	rPSGL-Ig versus placebo	TA, Bilirubin, IL 10, IP10	Beneficial effect
Kristo [19]	RCT	2011	26	HTK	1.5 l 5% albumin + tacrolimus versus 1.5 l 5% albumin + placebo	TA	Equal outcome
Fukazawa [31]	Retrospective	2013	478	UW	Crystalloid flush + backward unclamping versus portal blood flush + forward unclamping	Clinical outcome	Crystalloid flush preferable

UW, University of Wisconsin solution; SLS, sodium lactobionate sucrose; TA, transaminases; INR, international normalized ratio; K+, potassium; PRS, postreperfusion syndrome; CRS, Carolina rinse solution; MAP, mean arterial pressure; SVR, systemic vascular resistance; PT, prothrombin time; PNF, primary non-function; RCT, randomized controlled trial; IVC, inferior vena cava; HTK, histidine–tryptophan–ketoglutarate; rPSGL-Ig, recombinant P-selectin glycoprotein ligand IgG; IL-10, interleukin-10; IP 10, interferon-gamma-induced protein 10 kD.

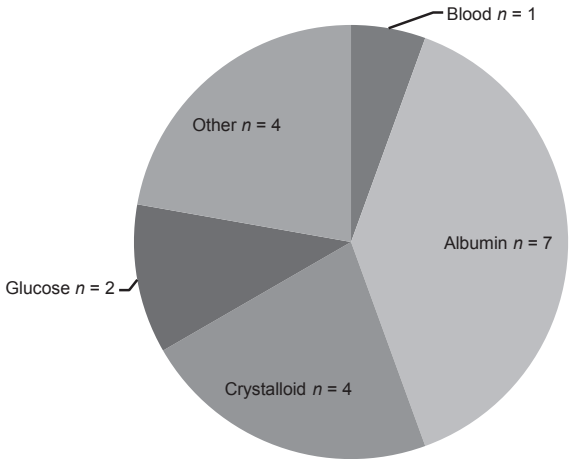

Figure 1 Rinse solutions applied by centers according to online survey (total $n = 18$).

also favored portal blood as the rinse medium of choice, retrospectively, analyzing six different graft rinse protocols in one hundred and fifty-five patients with the focus on transfusion requirements [21].

In 1994, K. Fukuzawa reported on the beneficial effects of rinsing with 500 ml of portal blood in addition to a graft rinse with 500 ml of lactated Ringer's solution [27]. This protocol improved hemodynamic stability, graft function, and graft and patient survival. However, the retrospective analysis of eighty-three consecutive transplants reveals substantial methodical shortcomings. In 2013, the author reported a second set of 313 patients that underwent crystalloid flush and backward unclamping compared to 165 patients with portal blood flush and forward unclamping. The retrospective analysis favored the use of crystalloid graft rinse for lower incidences of intra-operative cardiac arrest and primary graft nonfunction [31].

In 1994, Emre postulated an advantage of portal blood rinse over graft rinse with lactated Ringer's solution with regard to the incidence of poor early graft function [22]. In this retrospective work, four modes of graft rinse with lactated Ringer's solution and/or portal blood were studied. In 1995, Post′s retrospective analysis of sixty transplants found no difference in the subsequent graft function when the graft rinse was performed with portal blood versus Ringer's solution and a modified Carolina rinse [17]. Mirza′s 1996 study stated that rinsing the graft with 500 ml of portal blood significantly reduced peak AST levels in ninety-five transplants in comparison with graft rinses with one liter of 0.5% dextrose solution in 114 transplant cases [23]. The authors interpreted the lower AST peak values as an indication of a reduction of hepatocellular damage in the portal blood rinse group, but failed to show any beneficial clinical outcome. Portal blood rinse was also studied in a prospective trial by Millis *et al.* [28.]. One hundred patients were randomized into four groups: one set received portal vein flush without vena cava venting, another received portal vein flush with vena cava venting, and the last two groups had hepatic arterial flush with or without vena cava venting. The studied endpoint was the incidence of PRS. Biochemical changes, such as serum potassium load, following reperfusion and postoperative graft function were evaluated. The authors favored portal vein flush without caval vein venting due to earlier achievement of hemodynamic stability, but stated that the differences between all groups equalized after 30 min postreperfusion with comparable graft function results.

A more recent report by Gruttadauria from 2006 stated that a favorable outcome was achieved with a portal vein flush with lactated Ringer's solution without caval vein venting than in caval vein venting without portal vein flush [29]. The endpoints in this retrospective analysis for the twenty-five patients in each group were hemodynamic stability and graft function.

Drug rinse

Adding specific pharmacologic agents to the rinse solution was studied by four authors. In a prospective pilot trial, published in 1997, Bachmann and colleagues studied the simultaneous portal and arterial rinse with different solutions [18]. CRS showed the best results compared to human albumin and blood, but the groups were small with ten patients each and due to the pilot character of the trial, statistical tests for significance have not been performed. In their report from 1999, Fisher *et al.* prospectively randomized forty-three transplants into two groups: in one group, Normosol solution flush was performed, and in the other, adenosine was added to the Normosol solution [33]. Although the adenosine flushed livers showed significantly better function in terms of bile production, a significant impact on graft function or patient survival was not found. St. Peter *et al.* studied the influence of tacrolimus added to plasmalyte-A in a relatively small randomized controlled trial of twenty patients [24]. Rinsing the graft with tacrolimus resulted in significantly improved laboratory parameters representing hepatocellular damage and graft function as reported in 2003. A similar trial by Kristo *et al.* [19] in 2011 also evaluated the use of tacrolimus added to the portal flush solution in a randomized blinded fashion in twenty-six recipients. No significant differences in transaminase levels, liver synthesis, or cholestasis parameters were found within the first week after transplantation.

Retrograde flushing

In 2004, the concept of retrograde flushing of the graft was studied by Kniepeiss *et al.* The authors reported fifty-three

transplantations that were carried out with retrograde reperfusion via the caval vein after completion of the piggyback anastomosis [13]. Antegrade reperfusion was established via the portal vein once the anastomosis was completed. With good short- and midterm outcomes, the authors showed that retrograde flushing via the caval vein with low oxygenated blood was feasible.

Other

Two reports focused on other aspects of graft rinse in LT. In 2008, Homvises reported on a trial to determine the minimum flush volume of albumin to prevent PRS due to hyperkalemia [30]. Their measurements in eleven patients revealed that portal vein flush with 500 milliliters of 5% albumin solution washed out more than 90% of the potassium load in the graft. A study published by Ghafaripour in 2010 evaluated the incidence of postreperfusion syndrome after cold storage with HTK versus UW solution, whereas half of the grafts in the HTK group were flushed before reperfusion [20]. The authors concluded that flushing the graft can improve the outcome if cold storage with HTK is applied.

The authors of most of the analyzed reports assumed that graft rinse was commonly performed in LT. Nevertheless, almost half (12/30) of the participants in the online survey stated that graft rinse prior to reperfusion is not performed generally at their respective centers. This could indirectly indicate that LT can be performed safely without flushing of the graft. According to actual numbers provided by ET, approximately seven percent of the livers that are transplanted in the ET region are donated after cardiac death. As in other marginal grafts, rinsing before reperfusion could have more relevance in these cases; however, this could not be evaluated using the data presented here. As thirty of thirty-four LT centers in the ET area participated in the survey, these findings most likely reflect common practice in the vast majority of LT cases within ET. The online survey revealed that graft rinse protocols differ significantly among centers in the ET region. According to the current standard procedure of the German Organ Procurement Organization (Deutsche Stiftung Organtransplantation – DSO), all German deceased donor organs are preserved with HTK. As mentioned before, the HTK solution has a relatively low potassium concentration that potentially enables reperfusion without flushing of the graft. This is in accordance with the fact that the vast majority of graft rinse trials applied cold preservation with UW.

The shortcomings of this report are obviously based on the inhomogeneity of the reviewed literature, preventing final conclusions on the optimal rinse protocol to be drawn from pooled data. Furthermore, it has to be stated that the online survey presented here was neither designed to give a final appraisal of the ideal graft rinse technique nor have outcome parameters been queried. It was designed to illustrate the current practice of graft rinse among ET LT centers, additionally aiming to gauge the need and attendance of a clinical trial on the subject. Interestingly, fourteen of the eighteen centers that perform graft rinse stated that rinse protocols are based on personal or institutional experience. The available literature does not provide a final appraisal of the benefit of graft rinse in LT, especially in HTK preserved grafts. Nineteen ET centers showed continued interest in participating in a multicenter RCT on the topic. A possible clinical trial could therefore test rinse versus no rinse in LT grafts immediately prior to reperfusion. Stratifying for the use of UW and HTK, this clinical trial could answer whether the graft rinse has any effect and whether there is a difference between the cold preservation solutions. In such a design, a neutral, low viscosity rinse solution such as glucose 5% might be chosen. Rare clinical endpoints like PRS or initial graft nonfunction demand relatively large groups to reveal significant group differences. This problem can be counteracted by the use of composite clinical endpoints like the early allograft dysfunction score (EAD) [34]. Alternatively, indicators of an inflammatory response in both the graft and recipient side could be used as endpoints to ensure the feasibility of such a trial. Finally, the online survey appears to be a very helpful, virtually cost-free and effective tool to identify relevant topics for cooperative clinical research in the international transplant community.

Authorship

PH: participated in research design, conducted the research, performed data analysis, and wrote the manuscript. GM: participated in research design, conducted the research. MK: conducted the research. JA, GAB, EK, JK, JL, GO, JP, XR, DS, and DLS: participated in the performance of the research, performed critical review, and wrote the manuscript; PS: participated in research design, wrote the manuscript, conducted the research, and data analysis.

Funding

The authors have declared no funding.

Acknowledgements

The following institutions have participated in the online survey without qualifying for co-authorship of the manuscript:

Department of General and Vascular Surgery, Johann Wolfgang Goethe University, Frankfurt am Main,

Germany; Department of General and Thoracic Surgery Christian-Albrechts-University Kiel, Germany; Department of General Surgery, Klinikum Rechts der Isar, Technical University of Munich, Germany; Department of General Surgery, Campus Grosshadern, University of Munich, Germany; Department of General Surgery, University of Erlangen, Germany; Department of Surgery, Erasmus MC, University Medical Center Rotterdam, Netherlands; Department of Visceral, Transplant, Thoracic and Vascular Surgery, University of Leipzig, Germany; Department of General Surgery, University of Bonn, Germany; Department of General and Visceral Surgery, University of Göttingen, Germany; Department of General, Visceral and Transplant Surgery, Eberhard-Karls University, Tübingen, Germany; Department of Hepatobiliary and Transplant Surgery, University of Hamburg-Eppendorf, Germany; Department of General, Visceral and Transplant Surgery, University of Essen, Germany; Department of Visceral, Transplant and Thoracic Surgery, University of Innsbruck, Austria; Department of Transplant Surgery, University of Leiden, Netherlands; Department of General, Visceral, Vascular and Paediatric Surgery, University of Saarland, Homburg/Saar, Germany; Department of General and Visceral Surgery, University of Münster, Germany; Department of General, Visceral and Vascular Surgery, Friedrich Schiller University, Jena, Germany; Department of General Surgery, University of Graz, Austria; Department of Hepatobiliary, Transplant and Endocrine Surgery, University Hospital of Antwerpen, Edegem, Belgium

Heidrun Binder programmed the online survey and helped to collect the data. The authors thank Nadya-Kaye Phillips-Houben for language review of the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Online survey on graft rinse in liver transplantation.

References

1. Guarrera JV, Karim NA. Liver preservation: is there anything new yet? *Curr Opin Organ Transplant* 2008 Apr; **13**: 148.
2. Monbaliu D, Brassil J. Machine perfusion of the liver: past, present and future. *Curr Opin Organ Transplant* 2010 Apr; **15**: 160.
3. Stratta RJ, Wood RP, Langnas AN, *et al.* The impact of extended preservation on clinical liver transplantation. *Transplantation* 1990; **50**: 438.
4. Kalayoglu M, Sollinger HW, Stratta RJ, *et al.* Extended preservation of the liver for clinical transplantation. *Lancet* 1988; **1**: 617.
5. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. Homotransplantation of the liver in humans. *Surg Gynecol Obstet* 1963; **117**: 659.
6. Gubernatis G, Pichlmayr R, Lamesch P, *et al.* HTK-solution (Bretschneider) for human liver transplantation. First clinical experiences. *Langenbecks Arch Chir* 1990; **375**: 66.
7. Moray G, Sevmis S, Karakayali FY, Gorur SK, Haberal M. Comparison of histidine-tryptophan-ketoglutarate and University of Wisconsin in living-donor liver transplantation. *Transplant Proc* 2006 Dec; **38**: 3572.
8. Gurusamy KS, Gonzalez HD, Davidson BR. Current protective strategies in liver surgery. *World J Gastroenterol* 2010 Dec 28; **16**: 6098.
9. Ringe B, Braun F, Moritz M, Zeldin G, Soriano H, Meyers W. Safety and efficacy of living donor liver preservation with HTK solution. *Transplant Proc* 2005 Jan; **37**: 316.
10. Garcia-Gil FA, Serrano MT, Fuentes-Broto L, *et al.* Celsior versus University of Wisconsin preserving solutions for liver transplantation: postreperfusion syndrome and outcome of a 5-year prospective randomized controlled study. *World J Surg* 2011 Jul; **35**: 1598.
11. Paugam-Burtz C, Kavafyan J, Merckx P, *et al.* Postreperfusion syndrome during liver transplantation for cirrhosis: outcome and predictors. *Liver Transpl* 2009 May; **15**: 522.
12. Kniepeiss D, Iberer F, Grasser B, Schaffellner S, Stadlbauer V, Tscheliessnigg KH. A single-center experience with retrograde reperfusion in liver transplantation. *Transpl Int* 2003 Oct; **16**: 730.
13. Daniela K, Michael Z, Florian I, *et al.* Influence of retrograde flushing via the caval vein on the post-reperfusion syndrome in liver transplantation. *Clin Transplant* 2004 Dec; **18**: 638.
14. Manzini G, Kremer M, Houben P, *et al.* Reperfusion of liver graft during transplantation: techniques used in transplant centres within eurotransplant and meta-analysis of the literature. *Transpl Int* 2013 May; **26**: 508.
15. Gao WS, Takei Y, Marzi I, *et al.* Carolina rinse solution–a new strategy to increase survival time after orthotopic liver transplantation in the rat. *Transplantation* 1991 Sep; **52**: 417.
16. Thurman RG, Schemmer P, Zhong Z, Bunzendahl H, von Frankenberg M, Lemasters JJ. Kupffer cell-dependent reperfusion injury in liver transplantation: new clinically relevant use of glycine. *Langenbecks Arch Chir Suppl Kongressbd* 1998; **115**: 185.
17. Post S, Bleyl J, Golling M, Herfarth C, Otto G. Modes of reperfusion in clinical liver transplantation. *Langenbecks Arch Chir* 1995; **380**: 53.
18. Bachmann S, Bechstein WO, Keck H, *et al.* Pilot study: Carolina rinse solution improves graft function after orthotopic liver transplantation in humans. *Transplant Proc* 1997 Feb; **29**: 390.
19. Kristo I, Wilflingseder J, Kainz A, *et al.* Effect of intraportal infusion of tacrolimus on ischaemic reperfusion injury in

orthotopic liver transplantation: a randomized controlled trial. *Transpl Int* 2011; **24**: 912.
20. Ghafaripour S, Sahmeddini MA, Lahsaee SM, *et al.* Hypotension after reperfusion in liver transplantation: histidine-tryptophan-ketoglutarate versus University of Wisconsin solution. *Prog Transplant* 2010; **20**: 256.
21. Menegaux F, Egawa H, Keeffe EB, *et al.* Comparative effects of blood, colloid, and Ringer's lactate terminal allograft rinse on the results of orthotopic liver transplantation. *Transplant Proc* 1993 Dec; **25**: 3196.
22. Emre S, Schwartz ME, Mor E, *et al.* Obviation of prereperfusion rinsing and decrease in preservation/reperfusion injury in liver transplantation by portal blood flushing. *Transplantation* 1994 Mar 27; **57**: 799.
23. Mirza DF, Gunson BK, Khalaf H, *et al.* Effect of pre-reperfusion portal venous blood flush on early liver transplant function. *Transpl Int* 1996; **9** (Suppl. 1): S188.
24. St Peter SD, Post DJ, Rodriguez-Davalos MI, Douglas DD, Moss AA, Mulligan DC. Tacrolimus as a liver flush solution to ameliorate the effects of ischemia/reperfusion injury following liver transplantation. *Liver Transpl* 2003; **9**: 144.
25. Busuttil RW, Lipshutz GS, Kupiec-Weglinski JW, *et al.* rPSGL-Ig for improvement of early liver allograft function: a double-blind, placebo-controlled, single-center phase II study. *Am J Transplant* 2011 Apr; **11**: 786.
26. Brems JJ, Takiff H, McHutchison J, Collins D, Biermann LA, Pockros P. Systemic versus nonsystemic reperfusion of the transplanted liver. *Transplantation* 1993 Mar; **55**: 527.
27. Fukuzawa K, Schwartz ME, Acarli K, *et al.* Flushing with autologous blood improves intraoperative hemodynamic stability and early graft function in clinical hepatic transplantation. *J Am Coll Surg* 1994 Jun; **178**: 541.
28. Millis JM, Melinek J, Csete M, *et al.* Randomized controlled trial to evaluate flush and reperfusion techniques in liver transplantation. *Transplantation* 1997 Feb 15; **63**: 397.
29. Gruttadauria S, Cintorino D, Musumeci A, *et al.* Comparison of two different techniques of reperfusion in adult orthotopic liver transplantation. *Clin Transplant* 2006 Mar; **20**: 159.
30. Homvises B, Sirivatanauksorn Y, Limsrichamrern S, Pongraweewan O, Sujirattanawimol K, Raksakietisak M. The minimal flush volume for washout of preservation fluid in liver transplantation. *Transplant Proc* 2008; **40**: 2123.
31. Fukazawa K, Nishida S, Hibi T, Pretto EA Jr. Crystalloid flush with backward unclamping may decrease post-reperfusion cardiac arrest and improve short-term graft function when compared to portal blood flush with forward unclamping during liver transplantation. *Clin Transplant* 2013 Aug; **27**: 492.
32. Schemmer P, Bunzendahl H, Herfarth C, Klar E, Thurman RG. Arginine-specific proteolytic activity predicts graft survival. *Transplant Proc* 2001 Mar; **33**: 833.
33. Fisher RA, Posner MP, Shiffman ML, *et al.* Adenosine rinse in human orthotopic liver transplantation: results of a randomized, double-blind trial. *Int J Surg Investig* 1999; **1**: 55.
34. Olthoff KM, Kulik L, Samstein B, *et al.* Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. *Liver Transpl* 2010 Aug; **16**: 943.