



Sebészeti Műtéttani Intézet

Igazgató: Dr. Boros Mihály
tanszékvezető egyetemi tanár
6720 Szeged, Szőkefalvi-Nagy Béla u. 6.
Levélcím: 6701 Szeged, Pf. 427
Tel: +36 (62) 545103 Fax: +36 (62)
545743

Institute of Surgical Research

Director: Prof. Mihály Boros M.D., Ph.D., D.Sc.
Szőkefalvi-Nagy B. u. 6., H-6720 Szeged, Hungary
Postal address: P.O. Box 427
H-6701 Szeged, Hungary
E-mail: office.expsur@med.u-szeged.hu



Ze-Mao Gong
Science Editor
World Journal of Gastroenterology
2018

April 02,

Re: Ms. entitled “**Compared efficacy of preservation solutions on the outcome of the liver transplantation. Meta-analysis**” by Szilágyi A.L. et al. (Manuscript N° 37970)

Dear Professor Gong,

Thank you very much for your letter of 27th February 2018 and for the constructive criticism of our paper. We thank you and the Reviewers for the valuable comments, which gave us the opportunity to clarify the novel aspects of our review and to improve the manuscript.

We have revised the Introduction, Discussion and the References have been updated. Highlights and the contribution of the authors' is listed and added to the manuscript. Other corrections of the text and figures were made in an effort to make our study more consistent. We do hope that we have sufficiently addressed all your concerns and also hope that the comments below adequately answer your questions.

Reviewers 00053888 and 02860897

Thank you for the overall positive criticism of our paper.

Reviewer 01221925

1) “Wich solution would they recommend and why? Should cost be an issue?”

We appreciate the comment of the Reviewer. We compared data of RCTs of the present meta-analysis. Accordingly, costs of preservation solutions ranged from 45-268 EUR. The average price/liter of solutions increased in the following order: HTK (82 EUR)< IGL-1 (165 EUR)< CS (170 EUR)< UW (225 EUR). However, if the price is adjusted to the volume necessary for flushing the graft, the order changed and the average total cost was: HTK (676 EUR) < UW (887 EUR)< CS (942 EUR) < IGL-1 (990 EUR). These differences in the price of preservative solutions did not significantly affect the high overall clinical costs of transplantation. Therefore, the answer is in brief: cost should not be an issue.

2) Can the authors add a paragraph in the discussion regarding the role of these solutions in more complex donors, ie non-heart beating donors or living donors or extended criteria donors?

We thank the Reviewer for pointing out this highly important aspect. We added the following paragraph to Discussion:

“In recent times, the crisis in organ supply has made it necessary to extend the scope of potential donors by using extended criteria donors (ECD). Although there is no precise definition of ECD, frequently cited characteristics are donor age, steatosis, donation after

cardiac death (DCD), donors with increased risk of disease transmission and transplantation after prolonged CIT, as well as the use of partial grafts (split grafts and living donor liver transplantation).^[41] Unfortunately, higher rates of graft failure were documented in this class of extended allograft; in addition, very little data is available on the influence of preservation solutions on their post-transplant outcomes.^[42] A single-center study by Mangus et al. failed to find statistically significant differences in overall graft survival when they compared UW to HTK in ECD transplantations.^[30] However, they suggested that HTK may be protective against biliary complications. In contrast, in 2009, the UNOS database analysis reported that HTK was associated with an increased risk of graft loss and early graft loss.^[18] More recently, Adam et al. compared the four most frequently used preservation solutions and concluded that HTK is an independent risk factor for graft loss after ECD liver transplantations.^[10] The remaining three solutions, UW, CE and IGL-1, provided similar results in post-transplant outcomes after ECD transplantations. In the special condition of using a partially deceased donor liver graft, IGL-1 offered the best graft outcome.^[10] In another study, it was suggested that IGL-1 was superior to other solutions for preserving fatty livers by protecting against PNF and early allograft dysfunction.^[43] However, a prospective randomized study could not show any significant improvement in the subgroup of patients receiving IGL-1-preserved grafts.^[36] In living donor liver transplantations, risk-adjusted analyses of single- and double-center studies consistently reported that UW and HTK were equally effective and safe for cold preservation.^[44-47] There is currently no evidence-based recommendation on the optimal preservation solution in ECD liver transplantations because the number and quality of RCTs are not sufficient. However, based on the above data, differences in the indications of various preservation solutions are expected.”

Reviewer 00051373

1) “The author would like to looking forward the points to interpretation the primary non-function and graft survival for 1 year on the difference preservation solutions, but it is closely related to the intrinsic factors such as the ischemic time and a normal functional graft coming from the donor.”

We appreciate this remark of the Reviewer and agree with the notion that primary and secondary outcomes of this meta-analysis i.e.: the primary non-function (PNF) and the one-year post-transplant survival of the graft (OGS-1) are related to other factors rather than differences among the preservation solutions. In order to identify potential sources of heterogeneity in characteristics of donors and recipients, we defined a priori subgroup analyses by the cold ischemia time (CIT) and the model of end-stage liver disease (MELD) score. According to the statistical analysis, donors and recipients were homogenous in all trials. The results of the subgroup analysis and the demographic and clinical characteristics of donors and recipients are demonstrated in supplementary figures and tables (Figure S1A, Figure S1B, Table S1, Table S2, Table S3).

2) “The author needs to deeply interpretation the different content with the high sodium in the IGL-1 and CS, and what about the low sodium content in UW and HTK.”

Thank you for pointing out this clinical issue. Preservation solutions can be divided into two main groups according to their composition: extracellular or intracellular-type solutions. In the revised version of the paper, we mention the potential mechanism of action in two paragraphs of the Introduction: (page 6 para 1)” UW is an intracellular colloid solution with high potassium and low sodium concentration that inhibits activity of Na-K-adenosine triphosphatase and the resultant depletion of adenosine triphosphate stores. However, its low sodium content promotes the accumulation of calcium during ischemia, resulting in calcium-dependent endothelial dysfunction in renal glomeruli and in bile ducts during reperfusion.^[4,5]

Additionally, the high potassium increases the risk for hyperkalemia-induced cardiac arrest, requiring liver flushing before reperfusion.” and in page 9 para 2: “CS and HTK belong to the extracellular type of preservation fluids, however, their buffering systems and substrates to provide high energy phosphates are different. CS with its high sodium (above 70 mmol/L) and low potassium content is specifically designed to limit calcium overload.”

Reviewer 00842923

1) Studies reported by Adam in AJT et al should be commented in detail.

Thank you for this comment. We added the following sentences to the Introduction:

“In 2015, Adam et al. analyzed the efficacy of the four most commonly used preservation solutions based on the European Liver Transplant Registry (ELTR) database.^[10] The largest and most comprehensive study in recent times was performed by analyzing outcomes of 42,869 (first) liver transplantations, including living and deceased donors, as well as partial liver graft transplantations. Although the study population in this registry data analysis was relatively large, non-selective groups of donors were included.^[10,18,20]”

We also added a new paragraph to the Discussion, and we comment the results of Adam et al. in detail. See response 2 to Reviewer 01221925.

“More recently, Adam et al. compared the four most frequently used preservation solutions and concluded that HTK is an independent risk factor for graft loss after ECD liver transplantations.^[10] The remaining three solutions, UW, CE and IGL-1, provided similar results in post-transplant outcomes after ECD transplantations. In the special condition of using a partially deceased donor liver graft, IGL-1 offered the best graft outcome.^[10]”

Finally, we would like to thank the Reviewers for their conscientious and constructive work, and we hope that the revised paper is now acceptable for publication in World Journal of Gastroenterology.

Sincerely yours,

Dr. Petra Hartmann
(on behalf of all authors)