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Review

Systematic review of preservation solutions for allografts for liver transplantation based on a network meta-analysis

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ABSTRACT

Aims: The aim of this work was to determine the best preservation solutions for allografts for liver transplantation by quantitative network meta-analysis.

Methods: Global electronic databases including PubMed, EMBASE, and Cochrane Library were searched for relevant randomized controlled trials. Seven pieces of parametric data were extracted from included studies for pooled estimation. A consistency model was used for direct and indirect comparisons. The cumulative probability *P* value was utilized to rank the solutions. A node-splitting model was utilized for testing the consistency of final data. Quality of evidence was assessed using the GRADE (Grades of Recommendations Assessment, Development and Evaluation) system.

Results: Eleven 2-arm trials including 1319 patients and 5 different solutions were finally included. HTK (Histidine-tryptophan-ketoglutarate) solution exhibited the best efficacy for decreasing the primary dysfunction rate, biliary complications and ICU-stay time (probability $P = 0.43$, 0.45 and 0.58, respectively). Celsior solution significantly decreased the rate of rejection and early retransplantation (probability $P = 0.73$ and 0.38, respectively), and enhanced patient and graft survival (probability $P = 0.90$ and 0.98, respectively) more than did other solutions. Overall, the quality of evidence was rated high or moderate.

Conclusions: We suggested that HTK solution may offer the best safety during the perioperative period. However, Celsior solution led to better graft tolerance and exhibited greater benefit for long-term outcomes. And our conclusions still need to be further validated.

1. Introduction

Hepatocellular carcinoma and hepatic failure are the end-stage outcomes of many liver diseases [1]. The final remedies may be artificial liver or liver transplantation. Liver transplantation currently appears to be the better way to prolong patient survival [2,3]. For liver transplantation, the implications for the recipient of a poorly functioning graft or early graft loss are catastrophic, thus, adequate preservation of liver grafts during retrieval and storage are of critical importance. Used since the late 1980s, UW (University of Wisconsin) preservation solution led to significant progress in terms of quality and duration of cold ischaemia tolerance of abdominal organs used for transplantation [4–6]. However, other solutions, including Celsior preservation solution [7] and HTK (histidine-tryptophan-ketoglutarate) solution [8,9], were later used for liver preservation, showing clinical efficiency. Currently, donor liver preservation still relies on various graft preservation solutions. Areas, national economies, medical background and other factors led to generation of various allograft preservation principles [10–12]. Therefore, currently, various preservation solutions are used in various medical centres without a global unified standard [10,13]. In other words, the best preservation solution for hepatic transplantation remains undetermined.

To understand and address the best preservation solution for hepatic grafts for transplantation, a systematic review and quantitative comparison were necessary. A previous mini-review was not able to determine the best solution due to lack of a quantitative comparison [14]. Another authoritative meta-analysis claimed that UW and Celsior solutions appeared to be superior to others [15]. However, this meta-

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analysis had deficiencies in terms of literature retrieval and did not include a direct comprehensive comparison. These defects may render their conclusions unreliable.

Therefore, in this study, we aimed to determine the best preservation solution for hepatic graft for transplantation to systematically appraise the evidence in RCTs (randomized controlled trials) using quantitative network meta-analysis based on the Bayesian theorem. We expect that our conclusion may objectively bring appropriate evidence for clinical decision-making.

2. Methods

This study was conducted in accordance with the Preferred Reporting Items in Systematic Reviews and Meta-Analysis (PRISMA) statement [16]. The review was registered with the Research Registry Online system.

2.1. Literature search and retrieval

To avoid local publication bias and to ensure the authority of our results, we only conducted our retrieval in 3 global electronic databases: PubMed, EMBASE, and Cochrane Library. Searches were conducted using MeSH and relative keywords, combined with free-text search terms for liver transplantation and various preservation solutions (the search strategy is presented in Supplementary Table S1). In addition, to maintain the currency of our conclusions, we only included papers published in the last 2 decades. English abstracts were addressed, although we did not apply any language restriction. The publication dates were set as 1999 to 2018. All relevant papers were selected for next full-text review.

2.2. Parametric data selection

Considering representativeness and reporting frequency, we chose 7 parameters to represent the clinical efficacy and long-term outcomes: PDF (primary dysfunction), time of ICU-stay, BC (biliary complications), ERT (early retransplantation), PS (patient survival) and GS (graft survival). All relative data regarding respective parameters was pooled and estimated for comprehensive assessment.

2.3. Eligibility criteria

Inclusion criteria were as follows: 1) relative RCTs (randomized controlled trials) in humans comparing various allograft preservation solutions for liver transplantation; 2) English-language titles or abstracts must be located in abovementioned databases; and 3) each study must provide at least 3 pieces of relative parametric data.

The exclusion criteria were as follows: 1) non-RCT; 2) incomplete raw data; 3) experiments on cells or animals; 4) reviews, study protocols, comments, or case reports; and 5) studies out of time range.

2.4. Data extraction and quality assessment

Available data and general information (such as authors' names and publication year) were extracted into a pre-designed Microsoft Excel spreadsheet. Comparative parametric data were pooled, extracted and inputted into meta-analysis software for analysis. Any discrepancies in the extraction of comparative data were resolved by group discussion.

The risk of bias was assessed using the Cochrane collaboration tool. Studies were evaluated as to whether they met all of the following criteria: 1) free of selection bias, 2) free of performance bias, 3) free of detection bias, 4) free of attrition bias, 5) free of reporting bias, and 6) free of other bias. The controversial items were discussed by the group until final decisions were made.

To determine the quality of our results, we chose the Grades of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the methodological quality of evidence [17]. Five factors that may reduce the quality of evidence were considered, including research limitations, inconsistent findings, uncertain direct evidence, inaccuracy or wide confidence intervals, and publication bias. Additionally, three factors that could enhance the quality of evidence were also reviewed, which were effect size, possible confounding factors, and dose-effect relationship. Each direct comparison between 2 different solutions were considered in detail and were rated based on these factors. A comprehensive description of the evidence quality for each parametric data was presented.

2.5. Statistical analysis

We made a comprehensive network comparison according to the Bayesian theorem. Therefore, multiple comparisons of various solutions based on indirect quantitative calculation were performed [18,19]. For quantitative analysis, probability P values were calculated for the best solutions regarding respective parametric data. Meanwhile, node-splitting analysis was also conducted to show the statistical inconsistency at $P < 0.05$. If all the P values > 0.05, a consistency model was used to draw conclusions to determine the best solution based on the ranks of probability P values. Furthermore, Potential Scale Reduction Factor (PSRF) values were limited to 1 to complete the calculation. For the record, for continuous variables, data were presented in terms of medians and ranges in some studies; in such cases, the Hozo formula was used for data estimation and conversion [20]. Finally, pair-wise comparisons between each 2 solutions were also performed to determine the direct quality of evidence regarding the GRADE system.

The automated ADDIS (Aggregate Data Drug Information System, version 1.16) software package was used for the network pooled estimation and node-splitting analysis. A Summary of Findings table of the GRADE system was made by the GRADEprofiler (version 3.6) software.

3. Results

We initially identified 4295 studies across all databases, and 11 RCTs [21–31] including 1319 patients were finally included in our study (Fig. 1). Then, we addressed the 5 allograft preservation solutions for final comparisons: UW (University of Wisconsin) solution, Celsior solution, IGL-1 (Institut Georges Lopez-1) solution, HTK (Histidine-Tryptophan-Ketoglutarate) solution and Belzer solution (Table 1). The relationships and network connections for all included studies are presented in Fig. 2. Most of these 11 RCTs were performed without blinding methods, yet selective reporting bias was not apparent (Supplementary Fig. S1).

3.1. Primary dysfunction

In included studies, primary dysfunction was used to describe the abnormal biochemical indices during the perioperative period, according to blood tests. There were 10 trials including all 5 solutions reporting parametric data for primary dysfunction rates (Table 1). After quantitative network meta-analysis, we concluded that HTK solution appeared to be best to decrease the primary dysfunction rate after liver transplantation (probability $P = 0.43$) (Fig. 3 and Supplementary Table S2).

3.2. ICU-stay

To a certain extent, number of postoperative days in ICU reflects the recovery of liver function. Seven included studies covering all 5 solutions were pooled to estimate the shortest ICU-stay period (Table 1). After pooled estimation based on the Bayesian theorem, HTK solution gave the shortest postoperative ICU-stay time (probability $P = 0.45$) (Fig. 3 and Supplementary Table S2).