INPLASY PROTOCOL

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Review Stage at time of this submission: **Data analysis.**

Conflicts of interest:
The authors declare that they have no competing interests.

Normothermic machine perfusion versus static cold storage for liver graft preservation: a systematic review and meta-analysis

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Review question / Objective: **A debate exists over whether normothermic machine perfusion (NMP) is better than static cold storage (SCS) for liver preservation in transplant. We conducted this meta-analysis of all available studies to systematically evaluate the influence of both preservation methods on patients' post-surgery outcomes.**
Condition being studied: **There is no doubt that the gap between limited graft pool and high demand for liver transplantation (LT) is widening. Due to the shortage of liver resources, a good preservation method becomes particularly important in LT. Static cold storage (SCS) has been the standard method for organ preservation for the past 5 decades owing to its simplicity, cost-efficiency and efficacy, particularly for ideal or low-risk organs. But the insufficient oxygen supply and limited substrate can only preserve the organ for a short time. With the extension of preservation, hypoxia in tissues tends to promote the generation of oxygen free radicals, increasing the probability of ischemia/reperfusion injury (IRI). Cell damage caused by IRI cannot be easily repaired which further results in intrahepatic inflammation and subsequent liver injury. Clinicians and scientists have been trying to develop new methods for liver preservation in recent years. Among which, normothermic machine perfusion (NMP) showed great potential. NMP was first validated successful in kidney transplantation and since then its application has been expanded to other organs. However, a debate exists over whether NMP is better than traditional SCS in LT.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 June 2020 and was last updated on 11 June 2020 (registration number INPLASY202060038).

INTRODUCTION

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both preservation methods on patients' post-surgery outcomes.

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METHODS

Search strategy: Databases including PubMed, Embase, Cochrane library and Science Citation Index Expanded were searched to collect all available studies about NMP prior to LT. The primary search strategy was based on medical subject headings terms (MeSH), combined with free text words. The following key words were used as MeSH: "liver transplantation", "transplantation", "normothermic", "machine perfusion" "preservation", "NMP". The searching cutoff date was 15 February 2020. We also checked the reference lists of all identified studies for additional eligible data.

Participant or population: Patients who underwent liver transplant and liver grafts preserved by normothermic machine perfusion (NMP).

Intervention: liver grafts preserved by normothermic machine perfusion.

Comparator: Patients who underwent liver transplant and liver grafts preserved by static cold storage.

Study designs to be included: Controlled studies(Randomly controlled trials, observational studies).

Eligibility criteria: (1)Patients: who underwent liver transplant; (2) Inventions: liver grafts preserved by normothermic machine perfusion (NMP) versus Static cold storage(SCS); (3) Comparison: controlled studies with clear experimental (NMP) group versus control group (SCS); (4) Outcomes: the reported outcomes contain at least one item of preservation details (cold ischemia time, CIT; warm ischemia time, WIT, total preservation time), laboratory test after LT (peak AST, one week bilirubin, one week INR), perioperative safety (PNF, PRS, EAD, major complications, hospital and ICU stay) and survival data.

Information sources: Databases including PubMed, Embase, Cochrane library and Science Citation Index Expanded were searched to collect all available studies about NMP prior to LT We also checked the reference lists of all identified studies for additional eligible data.

Main outcome(s): Perioperative safety (PNF, EAD, major complications).

Additional outcome(s): Preservation details (cold ischemia time, CIT; warm ischemia time, WIT, total preservation time), laboratory test after LT (peak AST, one week bilirubin, one week INR), Hospital and ICU stay time, graft survival data(30d-6 month).

Data management: Patients' basic characteristics, graft preservation details,

results of laboratory tests after LT, postoperative complications, and 30-day to 6-month graft survival information were exacted from each study using a pre-designed data extraction form. The evaluation of postoperative complications was performed by the instruction of Clavien-Dindo Classification. For the missing information, we tried to contact the authors of original articles.

Quality assessment / Risk of bias analysis: The Cochrane Risk of bias graph and summary were performed to evaluate the study quality. During the process of study assessment, any disagreement was resolved by discussion or with a third reviewer if necessary.

Strategy of data synthesis: Review Manager (version 5.3, The Cochrane Collaboration, Copenhagen) recommended by Cochrane Collaboration was used to perform the meta-analysis. Dichotomous variables were tested by Risk Ratio (RR) with a 95% confidence interval (CI), and continuous variables were tested by the standardized mean difference (SMD) with a 95%CI. Data presented as Median (interquartile range, IQR), the value conversion was conducted using Wang X et al's method. Random effect model was used for all calculations. Heterogeneity between studies was tested by chi-squared test (with significance set at $p>0.1$) and I-squared test. Funnel plots were also used to investigate the publication bias if sufficient studies existed. A value of $p<0.05$ was considered statistically significant.

Subgroup analysis: Subgroup analysis was performed according to the length of perfusion time.

Sensibility analysis: Sensitivity analysis was performed to identify the source of heterogeneity when appropriate.

Language: The language of published literatures is limited to English only.

Country(ies) involved: Authors were from China and England.

Keywords: Normothermic machine perfusion, cold storage, preservation, meta-analysis.

Contributions of each author:

Author 1 - Tengfei SI - Study Design, Data collection and analysis, Result discussion, Manuscript writing, Proof reading and editing.

Author 2 - Zhenlin Huang - Study Design, Data collection and analysis, Result discussion, Proof reading and editing.

Author 3 - Salma Mujib - Result discussion, Manuscript writing, Proof reading and editing.

Author 4 - Yun Ma - Result discussion, Proof reading and editing.