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Efficacy and safety of plasmapheresis for hyperlipidemic pancreatitis: A systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - The authors declare that there are no financial conflicts of interest during the study or in the writing of the paper that could affect the objectivity and impartiality of the results of the study. At the same time, the authors found no other factors that might constitute a conflict of interest.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 May 2024 and was last updated on 13 May 2024.

INTRODUCTION

Review question / Objective Our research will aim to answer the following questions:
(1) Validity problem: How effective is plasmapheresis in hyperlipidemic acute pancreatitis (HLAP)? Is plasmapheresis more effective in reducing lipid levels, reducing pancreatic inflammation, and improving clinical symptoms and outcomes than conventional treatments? By combining the results of multiple studies, is plasmapheresis generally beneficial for patients with HLAP?
(2) Security issues: How safe is plasmapheresis in patients with HLAP? Does this approach increase the incidence of complications or cause other adverse events? Is plasmapheresis less risky or manageable than conventional treatments?
(3) Heterogeneity and robustness: Is there heterogeneity among studies in the results regarding the efficacy and safety of plasmapheresis for HLAP? If there is heterogeneity, what causes it? Do these reasons influence the conclusions of the meta-analysis? Are the conclusions of the meta-analysis robust, i.e. can they withstand further research and validation?
(4) Strength of evidence: What is the current strength of the evidence on plasmapheresis for HLAP? Is the evidence sufficient to support widespread use of plasma exchange for HLAP in the clinic? What further research is needed to strengthen or refine the existing evidence?

Rationale The basic principles of the research mainly involve the following key aspects: The basic principle of the research mainly involves the following key aspects: I. Overview of meta-analysis Meta-analysis is a statistical method that aggregates and analyzes the results of multiple

independent studies to provide a comprehensive assessment of a particular research question. In the medical field, meta-analysis is often used to evaluate the effectiveness and safety of different treatment schemes, so as to provide more reliable evidence support for clinical practice. Second, the research question is clear One of the basic principles of this meta-analysis was to clarify the research question, namely, the efficacy and safety of plasmapheresis in the treatment of hyperlipidemic acute pancreatitis. This question is proposed based on the needs of clinical practice and the shortcomings of existing studies, aiming to provide a more comprehensive and accurate evaluation of plasmapheresis in the treatment of hyperlipidemic acute pancreatitis through a comprehensive analysis of existing evidence. 3. Literature search and screening. The basic principle of meta-analysis also includes extensive search and rigorous screening of relevant literature. Through a systematic search of major medical databases, we collected several original studies on plasmapheresis in the treatment of hyperlipidemic acute pancreatitis. These studies were then screened according to strict inclusion and exclusion criteria to ensure that the studies included in the meta-analysis were of sufficient quality and relevance. 4. Data extraction and integration. Data extraction and integration is one of the core steps of meta-analysis. We extracted key data from the included studies, including measures of treatment effectiveness (e.g., response rate, mortality, etc.) and safety measures (e.g., incidence of adverse reactions). These data are then integrated using appropriate statistical methods to derive the combined effect size and its confidence interval. V. Interpretation and discussion of results. In meta-analysis, interpretation of results is as important as discussion. We conducted a comprehensive evaluation of the efficacy and safety of plasmapheresis in the treatment of hyperlipidemic acute pancreatitis based on the pooled data. At the same time, combined with the existing literature and clinical practice, the results were discussed and interpreted in depth to put forward meaningful conclusions and recommendations.

Condition being studied Hyperlipidemic acute pancreatitis (HLAP) is a severe acute pancreatic disease characterized by inflammation of the pancreas in the context of hyperlipidemia. In recent years, with the change of lifestyle and the adjustment of diet structure, the incidence of hyperlipidemia has gradually increased, which has also led to an increase in the incidence of HLAP. The condition of HLAP patients is usually severe, with obvious pancreatic damage and often accompanied by a significant increase in blood lipid levels, which poses a great challenge for treatment.

In the treatment of HLAP, traditional treatment methods mainly include fasting, gastrointestinal decompression, fluid resuscitation, anti-infection and inhibition of pancreatic secretion. However, these methods have limited effectiveness in controlling blood lipid levels and reducing pancreatic inflammation. In recent years, blood purification therapy, as a new treatment method, has gradually attracted attention in the treatment of HLAP. Plasma exchange can reduce the inflammatory response of the pancreas and improve the condition of patients by removing excess blood lipids and inflammatory mediators from the body.

However, the efficacy and safety of plasmapheresis in HLAP remains controversial. Different studies have reported different treatment effects and complication rates, which has made clinicians skeptical about the use of plasma exchange to treat HLAP. Therefore, meta-analysis, combining the results of multiple studies, is of great significance for evaluating the effectiveness and safety of plasmapheresis in the treatment of HLAP.

In summary, the current treatment of hyperlipidemic acute pancreatitis (HLAP) still faces many challenges. Plasma exchange therapy, as a potential and effective treatment, has a broad application prospect but needs further verification. Through meta-analysis, we can more comprehensively understand the efficacy and safety of plasmapheresis in HLAP, and provide more reliable decision-making basis for clinical practice.

METHODS

Search strategy We searched the relevant literature of PubMed, Cochrane Library, Web of Science from the establishment of the database until May 10, 2024, without language restrictions. Identify relevant randomized controlled trials or observational studies.

Important terms with MeSH terms include pancreatitis, plasma exchange and Double Filtration Plasmapheresis.

To make our search more comprehensive, we also manually reviewed the list of references for included studies, previous review articles, and published guides on AP.

Participant or population 1.The patient was diagnosed as hyperlipidemic acute pancreatitis.Two of the following three characteristics should be met: (1) In patients with

confirmed AP, abdominal pain consistent with AP (acute onset of persistent, severe upper abdominal pain, often radiating to the back);(2) Serum lipase activity (or amylase activity) is at least 3 times higher than the upper limit of normal;(3) Characteristic imaging manifestations of AP.
Information such as disease severity, course of disease, concomitant disease or related complications.
The time interval between the onset of abdominal pain and admission to hospital was no more than 72 h.
2.HTG patients with serum TG levels ≥1000 mg/dL (11.30 mmol/L) or chylomicrons visible in the blood and serum TG levels between 500 and 1000 mg/dL (5.65 and 11.30 mmol/L).
3.Patients without other causes of AP, including biliary tract disease, alcohol, drug use, trauma, or cancer, or those receiving other treatments at the same time.

Intervention Interventions should be plasmapheresis, including but not limited to therapeutic plasmapheresis, double hemofiltration, etc. The specific method of blood purification (such as frequency, duration, purification techniques, etc.) and whether it is combined with other treatments need to be described in detail.

Comparator The control group can be standard treatment (such as fasting, gastrointestinal decompression, fluid resuscitation, etc.), or the standard treatment can be supplemented with lipid-lowering drugs, insulin, heparin, etc., or the advantages and advantages of plasma exchange compared with other treatments.

Study designs to be included Randomized controlled trials or high quality observational studies should be included as a priority. However, the quantity and quality of these RCTS may not be sufficient to support a comprehensive meta-analysis, and there may also be some inter-study heterogeneity that requires in-depth comparison and comprehensive analysis. Our preliminary search found no RCT studies in this field. This field mainly includes observational studies, case-control studies, cohort studies and case series reports. Although these studies do not provide the same high level of evidence as RCTS, they can still provide.

Eligibility criteria Inclusion criteria: Type of study: The included studies were non-randomised controlled trials that provided direct evidence of plasmapheresis in the treatment of hyperlipidemic acute pancreatitis.
Subjects: The study should explicitly target patients with hyperlipidemic acute pancreatitis and describe in detail the diagnostic criteria and inclusion criteria for patients.
Interventions: Studies should clearly describe the type of plasmapheresis (e.g., therapeutic plasmapheresis, double plasmapheresis, etc.) and the treatment regimen (e.g., frequency, duration, etc.).
Outcome measures: Studies should report clear measures of treatment efficacy (e.g. relief of pancreatitis symptoms, improvement of biochemical markers, etc.) and safety (e.g. adverse reactions, complications, etc.).
Data integrity: Studies should provide sufficient data to support meta-analysis, including sufficient sample size and complete outcome indicators.
Language and quality: It is not limited to any language and has been peer reviewed to ensure its quality and reliability.
Exclusion criteria:
Type of study: Exclude non-controlled studies, case reports, animal experiments, etc. These types of studies cannot provide direct evidence about the effectiveness of the treatment.
Study subjects: Studies without a clear diagnosis of hyperlipidemic acute pancreatitis were excluded, or studies with unclear description of subjects' characteristics were excluded.
Interventions: Studies that did not describe plasmapheresis in detail or that used other non-standard treatments were excluded.
Duplicate publication: Excluded studies that were published twice, or whose data had already been included in other studies.

Information sources The accuracy and breadth of the information sources is essential to ensure the reliability and comprehensiveness of the analysis results. Here is a detailed description of the source of the information:
1. Electronic database search
This study mainly obtains relevant research literature through electronic database search. We used authoritative databases in the medical field such as PubMed, Cochrane Library, Web of Science, etc. These databases contain a large number of medical research results from around the world, including clinical trials, observational studies, case reports, etc. By setting appropriate search terms and search strategies, we were able to find published literature relevant to this study in these databases.
2. Contact with the author
During the search, we may find some unpublished research or ongoing research. In order to obtain detailed information about these studies, we tried to contact the authors. Through email or academic

conferences and other channels, we request the author to provide research data or obtain more detailed information about the research. This approach helps us to get a more complete picture of the progress of research in the field, and may uncover some research that has not yet been published but is of great value.
3. Test registration platform
In order to obtain information about ongoing or completed clinical trials that have not yet been published, we consult clinical trial registration platforms such as ClinicalTrials.gov. These platforms provide detailed information about clinical trials, including study purposes, methods, results, and more. By consulting these platforms, we were able to ensure that our meta-analysis covered all relevant clinical trials, thus improving the accuracy and comprehensiveness of the analysis.
4. Grey literature retrieval
Grey literature refers to those documents that have not been formally published but have some academic value, such as conference papers, research reports, dissertations, etc. In order to collect relevant information as comprehensively as possible, we also conducted a search of grey literature. By consulting the proceedings of academic conferences in related fields, research reports of research institutions, etc., we can obtain some valuable research information that has not been published in formal journals.
In summary, we obtained information on the efficacy and safety of plasmapheresis in the treatment of hyperlipidemic acute pancreatitis through a variety of approaches. The accuracy and universality of these information provided a solid foundation for our meta-analysis, which ensured the reliability and validity of the analysis results. In the paper, we will describe these sources of information in detail so that readers can understand our data collection process and assess its reliability.

Main outcome(s) Main outcome one: Effectiveness
1. Improvement of biochemical indexes: reduction of serum triglyceride level
Time: Evaluation is usually performed 24 hours, 48 hours, 72 hours after treatment and upon discharge. The improvement of biochemical indicators was assessed by comparing the numerical changes before and after treatment.
2. Incidence of mortality during hospitalization
Main outcome two: Safety
1. Incidence of adverse reactions
The type, occurrence time, severity and treatment of adverse reactions were recorded. The safety of plasmapheresis was evaluated by calculating the incidence of adverse reactions.
2. Complication rate
Pay attention to possible complications during treatment and follow-up. The types, incidence and severity of complications were recorded. The safety of blood purification therapy was evaluated by comparing the complication rates of different treatments.
Other details
Duration of follow-up: To ensure the long-term reliability of the results, a certain period of follow-up (such as 3 months, 6 months, or 1 year) should be conducted to observe recurrence, that is, to observe the continuity and safety of the treatment effect.
Subgroup analysis: 1. Subgroup analysis was performed according to different characteristics of patients (such as age, gender, severity of disease, etc.) to explore the differences in effectiveness and safety of plasma exchange therapy in different populations. 2. Subgroup analysis was performed according to different modalities of plasma exchange to explore differences in the effectiveness and safety of different modalities for acute pancreatitis. Through the detailed description and measurement of these major outcomes, we were able to comprehensively evaluate the efficacy and safety of plasmapheresis in the treatment of hyperlipidemic acute pancreatitis, providing strong evidence support for clinical practice. 3. Subgroup analysis was conducted according to whether lipid-lowering drugs, insulin, and heparin were added to conventional treatment.

Additional outcome(s) 1. Mortality rate
Description: Records the deaths of patients undergoing plasmapheresis during a specific time period (e.g., during hospitalization, 30 days, 90 days, etc.).
Significance: Mortality is an important index to measure the effect of treatment, which can reflect the direct impact of treatment on the survival of patients.
2. Length of stay and ICU stay
Description: Patient's length of stay and ICU stay were recorded.
Significance: These two measures can reflect the impact of treatment on the speed of recovery and severity of the patient's disease, and shorter hospital stays and ICU stays generally indicate better treatment outcomes.
3. Recurrence
Description: Patients were recorded for recurrence of hyperlipidemic acute pancreatitis during follow-up.

Significance: The recurrence situation is an important indicator to evaluate the long-term effect of treatment, which can reflect the effect of treatment on the prevention of disease recurrence.

Data management 1. Data collection and arrangement
Source screening: Relevant research data are collected from electronic databases (such as PubMed, Cochrane Library, Web of Science, etc.), clinical trial registries, conference proceedings, and direct contact with researchers.
Data extraction: Detailed data extraction tables were developed to extract key information from each included study, including study characteristics, patient characteristics, interventions, outcome measures, etc. Ensure the accuracy and completeness of data extraction.
Data screening: Cleaning and organizing data, including removing duplicate data, processing missing values, converting data formats, etc., to ensure data availability and consistency.
Data analysis: We used Review Manager Version 5.4 for data analysis.
2. Database establishment and management
Database selection: Excel and SPSS software are used to store and manage data. Ensure that the database software can meet the needs of data analysis, and has data backup and recovery functions.
Data entry: Enter the cleaned data into the database to ensure the accuracy and integrity of the data. In the process of data entry, double entry or check mechanism is used to reduce input errors.
Data verification: Periodic verification of data, including checking for completeness, consistency, and logic. For the problems found, timely correction and supplement.
3. Data security and confidentiality
Access rights: Set strict access rights to ensure that only authorized personnel can access the database. Sensitive data is protected by encryption.
Data backup: The database is backed up regularly to prevent data loss or corruption. Backup data is stored in a safe place and is regularly tested for recovery.
Data use: When using data for analysis, comply with research ethics and legal requirements to ensure the legality and compliance of data.
Through the above data management mechanism, we can ensure that the accuracy, reliability and safety of the data are guaranteed when conducting the meta-analysis of blood purification for hyperlipidemic acute pancreatitis. This helps to improve the quality of research and provide reliable evidence support for clinical practice. In this paper, we will describe in detail the methods and processes of these data management so that readers can understand our data management strategy and assess its reliability.

Quality assessment / Risk of bias analysis 1. Quality evaluation
1. Research design evaluation
Observational studies: Evaluate whether there are clear observational measures, sufficient observation time, and appropriate control groups.
2. Quality of data collection and reporting
Check that the data is complete and accurate, and evaluate whether there is missing data and how it is handled.
Assess whether studies have followed standard reporting guidelines, such as CONSORT (Uniform standards for clinical trial reporting).
3. Control of bias and confounding factors
Evaluate whether the study took into account potential confounding factors such as patient age, gender, and severity of the condition, and make appropriate adjustments. Analyze whether there is selection bias, information bias, or execution bias, and assess their impact on the study results.
2. Bias risk analysis
1. Publication bias
Funnel plot analysis was used to assess the presence of publication bias, that is, whether the results of the study tended to publish positive or significant results.
Consider using data from unpublished studies or conducting sensitivity analyses to reduce the impact of publication bias.
2. Selective reporting bias
Check that the study report fully reports all relevant outcome measures, especially those that may be detrimental to the study hypothesis.
Compare research protocols, methods and results to ensure that there is no selective reporting.
3. Other potential bias
Analyze other possible sources of bias in the study, such as conflicts of interest, funding sources, etc., and assess their impact on the findings.
Iii. Quality assessment tools and methods
For observational studies, the Newcastle-Ottawa Scale, an existing quality assessment tool, was used to score the quality of primary studies. Studies were graded according to quality scores, and different weights were given in the meta-analysis to improve the reliability of the results.

Strategy of data synthesis 1. Data integration and standardization
First of all, the collected research data will be organized in accordance with a unified format and standards. This includes ensuring that the units, measurement methods, time nodes, etc. of the

indicators are consistent for subsequent comparison and analysis. For data that cannot be directly compared, appropriate conversion methods, such as logarithmic conversion or standardized processing, are used to ensure data comparability.

2. Selection and calculation of effect size

According to the purpose of the study and the nature of the data, the appropriate effect size was selected for calculation. For binary variables (such as mortality, adverse event incidence, etc.), the adoption rate or ratio is usually used as the effect size. For continuous variables (such as biochemical indicators, length of stay, etc.), the mean difference, median difference, or standardized mean difference were used as the effect size. When calculating the effect size, attention should be paid to the size and variation of the sample size to ensure the stability and reliability of the results.

3. Heterogeneity test and treatment

Heterogeneity among different studies is an important issue when conducting meta-analysis. Therefore, it is necessary to test the heterogeneity of the included studies, such as using chi-square test or I^2 statistics. If there is significant heterogeneity, the reasons should be further explored, such as differences in study methods, patient characteristics, and interventions. For unexplained heterogeneity, a random effects model was used for meta-analysis. If the heterogeneity is small or explainable, the fixed effect model is used.

4. Sensitivity analysis

In order to evaluate the stability and reliability of the meta-analysis results, it is necessary to conduct sensitivity analysis. Changes in the results were observed by excluding some studies one by one or by changing some analysis parameters (such as choice of effect size, treatment of heterogeneity, etc.). If there are significant changes in the results after excluding some studies, it indicates that these studies have a greater impact on the overall results, and the reasons need to be further explored.

5. Subgroup analysis and discussion

Depending on the purpose of the study and the characteristics of the data, subgroup analysis can be performed to explore the efficacy and safety of blood purification therapy in different subgroups of people. For example, patients can be grouped according to characteristics such as age, sex, and severity of disease, and differences in treatment outcomes between different subgroups can be compared. This helps to gain a more complete understanding of the applicability of blood purification therapy in different populations.

6. Result presentation and interpretation

Finally, the results of the meta-analysis are presented and explained in the form of charts and texts. The graphs visually show the effect sizes and confidence intervals for each indicator, while the text section explains and discusses the results in detail. At the same time, combined with the results of sensitivity analysis and subgroup analysis, the overall conclusion is further discussed and elaborated.

Subgroup analysis I. Basis for subgroup division

Subgroups are divided based on clinical features, disease status and treatment options. In this meta-analysis, we plan to divide subgroups according to the following factors:

(1) Patient characteristics: such as age, gender, body mass index (BMI), etc., these factors may affect the patient's response to treatment and the progression of the disease.

(2) Severity of disease: Patients were classified into mild, moderate, and severe subgroups according to the severity score of acute pancreatitis, such as the Ranson score or the APACHE II score.

(3) Treatment plan: including the type of blood purification (such as continuous veno-venous hemofiltration, plasma exchange, etc.), treatment timing, treatment dose and duration.

(4) Whether the control group was given lipid-lowering drugs, insulin, heparin, etc.

2. Subgroup analysis method

Data extraction and sorting: Data related to subgroup classification were extracted from the included primary studies and sorted according to subgroup classification.

Effect-size calculation: The effect-size and its confidence interval for the efficacy measures (such as remission rate, mortality rate, etc.) of blood purification treatment were calculated within each subgroup.

Heterogeneity tests: Heterogeneity tests were performed within each subgroup to assess whether there were significant differences in results between different studies.

Results Comparison and interpretation: The effect size and direction of different subgroups were compared to explore the influence of each factor on the therapeutic effect of blood purification. At the same time, combined with clinical practice and literature reports, the results were rationally explained and discussed.

3. Expected results and significance

Through subgroup analysis, we expected to find the following meaningful results:

Patients of different ages, genders, or BMI may respond differently to plasmapheresis therapy.

The severity of the disease may affect the efficacy and safety of plasmapheresis.

Different treatment options (such as plasmapheresis type, timing of treatment, etc.) may lead to different therapeutic effects.
The addition of lipid-lowering drugs, insulin, or heparin may vary in the efficacy of plasmapheresis.

Sensitivity analysis One by one exclusion method: Individual studies were excluded one by one, and the changes in meta-analysis results after exclusion were observed. If the results change significantly after excluding a study, it indicates that the study has a large impact on the overall results, which may be a potential source of heterogeneity or bias.
Change the effect size type: Try to use different effect size types (such as rate ratio, difference, etc.) for calculation to compare the consistency of the results under different effect size types.
Change the statistical model: Compare the difference between the results under the fixed effects model and the random effects model. If the results of the two models are consistent, the results are robust. If the difference is significant, the reasons need to be further explored.
Consider the quality of the study: The studies were weighted according to the quality of the study (such as JADAD score, methodological quality, etc.) and the changes in the results before and after the weighting were observed. If the weighted results are more reasonable or stable, it indicates that the quality of the study has an important impact on the results.

Language restriction Due to linguistic diversity, not all research will be published in English or other international languages. This may cause us to miss some studies that are not in English.

Country(ies) involved China.

Other relevant information None

Keywords Plasmapheresis; Double filtered plasmapheresis; Hypertriglyceridemia; Acute pancreatitis; Triglycerides; Meta-analysis; Efficacy; Safety.

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