INPLASY PROTOCOL

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Review Stage at time of this submission: Preliminary searches.

Conflicts of interest: None declared.

A network meta-analysis on roles of different traditional Chinese medicine injections in improving the efficacy and adequacy of dialysis

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Review question / Objective: Patients undergoing hemodialysis or peritoneal dialysis, without limitations in age, race, gender, and disease types.InterventionsThe control group was given conventional treatment (anticoagulation, correction of anemia, blood pressure control, blood lipid control, etc.). On this basis, the experimental group was injected with Shenkang injection, Shenqiong glucose injection, Huangqi injection, Shenfu injection, Shenmai injection, Danshen injection, Xuebijing injection, Xingding injection, or any two or more of the above injections for comparison. Outcome indexes①Total effective rate ②serum creatinine (Scr) ③urea nitrogen (Bun) ④serum albumin (Alb) ⑤urea clearance index (Kt/v).Exclusion Criteria①Non-RCT, such as reviews, animal experiments, theoretical guidance, guidelines, etc. ②Data cannot be extracted (including those with dialysis but having no renal function index or nutritional index or dialysis index), literature is incomplete or seriously wrong ③The route of administration for intervention measures is unknown. ④ The control measures include studies on non-western medicine conventional treatments, such as acupuncture, massage, and traditional Chinese medicine preparations.Research types:Randomized controlled trial (RCT), including Chinese and English.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 April 2022 and was last updated on 06 April 2022 (registration number INPLASY202240030).

INTRODUCTION

Review question / Objective: Conventional treatments for dialysis patients include anticoagulation, correction of anemia, and control of blood pressure, but the efficiency and adequacy of dialysis vary from person to person. In recent years, the efficacy of

traditional Chinese medicine has gradually been recognized by the public, and there are accumulating evidence-based evidences of traditional Chinese medicine injection combined with hemodialysis and peritoneal dialysis. In this study, the application of 8 traditional Chinese medicine injections commonly used in dialysis in recent years was retrieved, including Shenkang injection, Shenqiong glucose injection, Huangqi injection, Shenfu injection, Shenmai injection, Danshen injection, Xuebijing injection and Xingding injection. Nonetheless, there are few studies about direct comparison between injections, and doctors cannot prioritize drugs. Traditional meta-analysis does not support comparison of multiple interventions. In this study, network meta-analysis [4], which can better fit the research content, was taken for indirect comparison of multiple interventions. Analysis and evaluation were made on the changes of the above-mentioned injections in terms of intervention efficiency, urea clearance index (Kt/v), serum creatinine (Scr), urea nitrogen (BUN), and serum albumin (Alb) to provide evidence-based medical evidence.Research objects Patients undergoing hemodialysis or peritoneal dialysis, without limitations in age, race, gender, and disease types. Interventions The control group was given conventional treatment (anticoagulation, correction of anemia, blood pressure control, blood lipid control, etc.). On this basis, the experimental group was injected with Shenkang injection, Shenqiong glucose injection, Huangqi injection, Shenfu injection, Shenmai injection, Danshen injection, Xuebijing injection, Xingding injection, or any two or more of the above injections for comparison. Outcome indexes①Total effective rate ②serum creatinine (Scr) ③urea nitrogen (Bun) ④serum albumin (Alb) ⑤urea clearance index (Kt/v).Exclusion Criteria①Non-RCT, such as reviews, animal experiments, theoretical guidance, guidelines, etc. ②Data cannot be extracted (including those with dialysis but having no renal function index or nutritional index or

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Condition being studied: Conventional treatments for dialysis patients include anticoagulation, correction of anemia, and control of blood pressure, but the efficiency and adequacy of dialysis vary from person to person. In recent years, the efficacy of traditional Chinese medicine has gradually been recognized by the public, and there are accumulating evidence-based evidences of traditional Chinese medicine injection combined with hemodialysis and peritoneal dialysis. In this study, the application of 8 traditional Chinese medicine injections commonly used in dialysis in recent years was retrieved, including Shenkang injection, Shenqiong glucose injection, Huangqi injection, Shenfu injection, Shenmai injection, Danshen injection, Xuebijing injection and Xingding injection. Nonetheless, there are few studies about direct comparison between injections, and doctors cannot prioritize drugs. Traditional meta-analysis does not support comparison of multiple interventions. In this study, network meta-analysis [4], which can better fit the research content, was taken for indirect comparison of multiple interventions. Analysis and evaluation were made on the changes of the above-mentioned injections in terms of intervention efficiency, urea clearance index (Kt/v), serum creatinine (Scr), urea nitrogen (BUN), and serum albumin (Alb) to provide evidence-based medical evidence.

METHODS

Search strategy: Through computer retrieval of databases such as CNKI, Wanfang, VIP, CBM, Pubmed, Cochrane Library, Web of Science, etc., we collected

papers (including unpublished data such as master's and doctoral theses) from the establishment of the database to March 2021. If the full text was unaccessible, the relevant literature was collected by manual retrieval. The retrieval strategy was formulated according to different databases, and retrieval was carried out within the scope of subject, abstract and keyword. The Chinese retrieval terms include "extract", "traditional Chinese medicine", "Chinese patent medicine", "dialysis", "maintenance hemodialysis", "peritoneal dialysis" " Randomized Controlled Trials" "Clinical Studies". The English retrieval strategy takes Pubmed as an example as follows:#1(((injection[Title/Abstract]))OR(extractive[Title/Abstract]))OR(TraditionalChineseMedicine[Title/Abstract]))OR(Chinesepatentmedicine[Title/Abstract]#2(((dialysis[Title/Abstract]))OR(Hemodialysis[Title/Abstract]))OR(Maintenancehemodialysis[Title/Abstract]))OR(peritonealdialysis[Title/Abstract]#3((randomizedcontrolledtrial[Title/Abstract]))OR(clinicalresearch[Title/Abstract]))OR(clinicalobservation[Title/Abstract]), #1 AND #2 AND #3.

Participant or population: Patients undergoing hemodialysis or peritoneal dialysis, without limitations in age, race, gender, and disease types.

Intervention: The control group was given conventional treatment (anticoagulation, correction of anemia, blood pressure control, blood lipid control, etc.).

Comparator: The control group was given conventional treatment (anticoagulation, correction of anemia, blood pressure control, blood lipid control, etc.). On this basis, the experimental group was injected with Shenkang injection, Shenqiong glucose injection, Huangqi injection, Shenfu injection, Shenmai injection, Danshen injection, Xuebijing injection, Xingding injection, or any two or more of the above injections for comparison.

Study designs to be included: Randomized controlled trial (RCT).

Eligibility criteria: Outcome ①Total effective rate ②serum creatinine (Scr) ③urea nitrogen (Bun) ④serum albumin (Alb) ⑤urea clearance index (Kt/v)Exclusion Criteria①Non-RCT, such as reviews, animal experiments, theoretical guidance, guidelines, etc. ②Data cannot be extracted (including those with dialysis but having no renal function index or nutritional index or dialysis index), literature is incomplete or seriously wrong ③The route of administration for intervention measures is unknown. ④ The control measures include studies on non-western medicine conventional treatments, such as acupuncture, massage, and traditional Chinese medicine preparations.

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Main outcome(s): Two researchers independently screened literature according to pre-determined criteria, extracted and cross-checked data. In case of disagreement, it can be negotiated by a third party. After the imported literature bibliography undergoes duplicate checking by Endnote literature management software, the title is read for preliminary screening. After the preliminary screening, the full text is further read. The literature disobeying the inclusion criteria will be excluded. The extracted contents include: ①Basic information of the included studies: Title, author, date of publication, etc.

②Basic information of patients: gender, age, disease course, etc. ③Sample size, intervention and control measures, drug dose, observation course, etc., ④Outcome indexes.

Quality assessment / Risk of bias analysis:
Two researchers conducted independent assessment using RCT bias risk assessment tool recommended by the Cochrane Handbook, assessed the literature quality and cross-checked the results. The assessment covers random sequence generation, random concealment, blinding, data integrity, and withdrawal. In case of any disagreement, it will be discussed or negotiated by the third researcher.

Strategy of data synthesis:
RevMan 5.3, GEMTC software and R software were used for analysis. Firstly, RevMan 5.3 was used to perform traditional Meta-analysis on the efficacy of 8 injections for direct comparison. Then, GEMTC software and R software were used to make network Meta-analysis on the efficacy and outcome indexes of 8 injections for indirect comparison. Where, if the "95% CI" of binary variables does not contain 1, and the "95% CI" of continuous variables does not contain 0, it indicates statistically significant difference. According to clinical heterogeneity, subgroup analysis was carried out on the basis of intervention measures. Q test and I2 index were used to analyze statistical heterogeneity. In case of small heterogeneity (P≥0.1 and I2≤50%), use the fixed effect model, in case of big heterogeneity (P50%), use a random effect model.First, split all the trials into possible combinations of two-arm trials, use R software to call gemtc software package, establish a Bayesian model for network meta-analysis. The model is fitted with 4 Markov chains, with initial value 2.5. Set the number of iterations to 20,000, and calculate the potential scale reduction factor (PSRF) to quantitatively analyze and diagnose the model convergence. If it approaches 1.00, the convergence degree is satisfactory. Otherwise, continue to iterate 50,000 times until model convergence. If there is a closed loop, use nodal analysis to detect inconsistencies between direct and indirect evidence. Calculate the difference and draw a Rank chart. The greater the Rank value (probability) of the Rank chart, the greater the probability that the intervention effect (in distinguishing favorable factors or unfavorable factors) is at this rank.

Subgroup analysis:
The total effective rate of Shenkang injection group, Shenfu injection group, Shenmai injection group and Huangqi injection group was higher than that of conventional basic treatment group. I2 of Shenfu group and Shenkang group in the heterogeneity test was greater than 50%. The heterogeneity of Shenfu group was mainly studied by Zou Dongmei [5], and that of Shenfu group was mainly studied by Liu Limin [43]. It was considered that inconsistency of the disease severity, drug dosage and treatment practice among the study subjects caused the heterogeneity. As a result, after excluding the above two literatures, the original ending direction has not changed. The [95% CI] of the Shenfu group and the Xuebijing group exceeded 1, which was not statistically significant and was possibly due to the small sample size. The random effect model was not used for the time being. Overall, the total effective rate of Shenkang injection, Shenmai injection and Huangqi injection is superior to that of conventional basic treatment, and the total effective rate of Shenkang injection may be superior to that of Xuebijing injection.

Sensitivity analysis:
This study includes a total of 9 treatment measures (conventional basic western medicine and 8 traditional Chinese medicine injections). In theory, pairwise comparisons can form 36 combinations. However, due to the insufficient number of related RCTs, most of them have no basis for direct comparison. Network Meta-analysis is used for indirect comparison of the differences in efficacy. Figure 4 shows the network diagram of the effective rate, serum creatinine (Scr), urea nitrogen (Bun), serum albumin (Alb), and urea clearance index (Kt/v) in each study. The lines in the

figure mean there is direct comparison of these two drugs. The thickness of the line represents the number of RCTs, and the absence of a line means there are no RCTs for research of this index.

Country(ies) involved: China.

Keywords: meta-analysis; traditional Chinese medicine injections; dialysis.

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