INTRODUCTION

Review question / Objective: 1. For BPT patients, is NM more effective in extending filter lifespan than conventional anticoagulant therapy? 2. For BPT patients, does administration of NM result in a lower risk of bleeding complications than administration of conventional anticoagulant therapy? 3. For BPT patients, does NM provide better survival outcomes than conventional anticoagulant therapy?

Condition being studied: Acute kidney injury is a common, serious complication of severe coronavirus disease 2019 (COVID-19) necessitating hemoperfusion therapy. Anticoagulant use might cause increased coagulation and hemorrhage risks. We evaluated the safety and effectiveness of nafamostat mesilate (NM) as a novel anticoagulant for blood purification therapy (BPT).

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 August 2021 and was last updated on 31 August 2021 (registration number INPLASY202180118).
does NM provide better survival outcomes than conventional anticoagulant therapy?

**Condition being studied:** Acute kidney injury is a common, serious complication of severe coronavirus disease 2019 (COVID-19) necessitating hemopurification therapy. Anticoagulant use might cause increased coagulation and hemorrhage risks. We evaluated the safety and effectiveness of nafamostat mesilate (NM) as a novel anticoagulant for blood purification therapy (BPT).

**METHODS**

**Search strategy:** #1 "Renal Replacement Therapy"[Mesh] OR “blood purification therapy” OR “Hemopurification” OR “hemodialysis” OR “hemofiltration” OR "renal replacement" OR “hemoperfusion” OR “hemodialysis” OR “plasmapheresis” OR “plasma exchange” The second Boolean search combined keywords/Mesh headings: #2 "Nafamostat " OR " Nafamostat mediate " OR " Nafamostat Dimethanesulfonate " OR "Futhan" OR " FUT-175" #3 #1 AND #2.

**Participant or population:** Patients with various levels of organ dysfunction and all patients underwent hemopurification therapy (BPT).

**Intervention:** Traditional anticoagulation strategies such as UFH, LMWH, citrate (SC) and anticoagulant-free (NA) treatment.

**Comparator:** Nafamostat mesilate anticoagulation strategy.

**Study designs to be included:** Observational cohort and/or randomized/quasi-randomized clinical trial (RCT) design.

**Eligibility criteria:** 1) observational cohort and/or randomized/quasi-randomized clinical trial (RCT) design; 2) patients with various levels of organ dysfunction; and 3) all patients underwent BPT, and the NM anticoagulation strategy was compared with CT.

**Information sources:** A comprehensive literature search of the Cochrane Library, Web of Science and MEDLINE databases (via the PubMed search engine) was performed to identify studies meeting the inclusion criteria. In addition, the reference lists of retrieved studies and review articles were further manually searched for additional publications. No language restriction was used.

**Main outcome(s):** Bleeding complication, Mortality.

**Additional outcome(s):** Hemofilter lifespan.

**Quality assessment / Risk of bias analysis:** Randomized studies were appraised using the Cochrane Collaboration Risk of Bias Tool. The following characteristics will be evaluated: 1) sequence generation; 2) allocation concealment; 3) blinding; 4) incomplete outcome data; 5) selective outcome reporting; and 6) other potential threats to validity. In addition, observational studies (prospective and retrospective cohorts) were evaluated by using a modified version of the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies published by the National Institutes of Health. Criteria items were evaluated for each study as follows: 1) research question; 2) study population; 3) uniform eligibility criteria; 4) sample size justification; 5) timing of exposure assessment; 6) sufficient time frame to see an effect; 7) different levels of the exposure of interest; 8) exposure assessed prior to outcome measurement; 9) outcome measures; 10) blinding; and 11) statistical analyses. Quality assessments were undertaken independently by Lin Yao and Yi-Ming Shao, and any disagreements were resolved by consensus with a third reviewer (Yu-Chun Liu).

**Strategy of data synthesis:** The data were extracted and assessed by using Review Manager software (version 5.3, The Nordic Cochrane Center, Cochrane Collaboration) and STATA statistical software (version 12.0) to make the outcome assessment more comprehensive. Estimated effects were reported as RRs with 95% CIs for...
dichotomous outcomes and mean differences (MDs) with 95% CIs for continuous outcomes. Heterogeneity was assessed for each pooled summary estimate using Cochran’s Q statistic and the I2 statistic, and the thresholds for high, moderate and low heterogeneity were set at >75%, 25–75% and <25%, respectively. A random-effect model was applied to pool the results across the studies for which there was formal evidence of statistical heterogeneity (i.e., the chi-square test P<0.05). For studies with lower levels of statistical heterogeneity, both a fixed-effect and random-effect model were employed to pool the outcomes and detect discrepancies between different models. P <0.05 was used to indicate statistical significance.

Subgroup analysis: A subgroup analysis was conducted on the basis of the different anticoagulants in the conventional treatment group.

Sensitivity analysis: We will conduct sensitivity analysis when it is necessary.

Language: No language restriction was used.

Country(ies) involved: China.

Keywords: Nafamostat mesilate, blood purification therapy, anticoagulation.

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