INPLASY PROTOCOL

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None declared.

Safety and efficacy of different anticoagulant doses for patients with COVID-19 in the ICU: a systematic review and meta-analysis

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Review question / Objective: **Critically ill COVID-19 patients have a high incidence of thromboembolic events, which significantly influence the risk of mortality. Anticoagulant therapy is generally recommended to these patients but the optimal dosing regimens require further investigations. We sought to conduct a systematic review and meta-analysis to assess the efficacy and safety of prophylactic, intermediate and therapeutic dose anticoagulation in COVID-19 patients admitted to the intensive care units (ICU).**
Condition being studied: **Short-term mortality, deep-vein thrombosis, pulmonary embolism, arterial thrombosis, major bleeding, and minor bleeding in COVID-19 patients admitted to the ICU.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 February 2023 and was last updated on 07 February 2023 (registration number INPLASY202320033).

INTRODUCTION

Review question / Objective: **Critically ill COVID-19 patients have a high incidence of thromboembolic events, which significantly influence the risk of mortality. Anticoagulant therapy is generally recommended to these patients but the optimal dosing regimens require further investigations. We sought to conduct a systematic review and meta-analysis to assess the efficacy and safety of prophylactic, intermediate and therapeutic dose anticoagulation in COVID-19 patients admitted to the intensive care units (ICU).**

Rationale: **SARS-CoV-2 causes cardiovascular injuries and hypercoagulation in a large number of patients commonly manifesting with venous thromboembolism. As prophylactic doses of anticoagulants may not be**

effective for the prevention of thromboembolic events, intermittent to therapeutic doses are increasingly prescribed to COVID-19 patients admitted to the ICU despite higher risk of bleeding complications and possible lack of influence on in-hospital mortality. Given that the new prospective trials addressing the issue of thromboprophylaxis in ICU COVID-19 subjects become available, we seek to reassess the whole range of collected data regarding the thromboprophylaxis in this subset of patients.

Condition being studied: Short-term mortality, deep-vein thrombosis, pulmonary embolism, arterial thrombosis, major bleeding, and minor bleeding in COVID-19 patients admitted to the ICU.

METHODS

Search strategy: A systematic search for eligible trials was performed in online databases including PubMed, EMBASE, Web of Science, Cochrane Library Database, Clinicaltrials.gov, databases of international and national respiratory and infectious diseases congresses by three independent investigators from January 01, 2020 to June 01, 2022. The search terms included the combination of the following key words: coronavirus disease 2019, SARS-CoV-2, COVID-19, intensive care unit, ICU, anticoagulation, anticoagulant, thromboprophylaxis, heparin, mortality, venous thromboembolism, deep vein thrombosis, deep venous thrombosis, pulmonary embolism, bleeding.

Participant or population: Adults (age ≥ 18 years) with severe COVID-19 disease (objectively confirmed SARS-CoV-2) who were hospitalized in the ICU and received at least one anticoagulation regimen: prophylactic dose, intermediate dose, therapeutic dose of low molecular weighted or unfractionated heparin.

Intervention: Prophylactic dose, intermediate dose or therapeutic dose of low molecular weighted or unfractionated heparin.

Comparator: Placebo, or none.

Study designs to be included: Original prospective observational study or clinical trial irrespective of blinding and language.

Eligibility criteria: 1) enrolment of adults (age ≥ 18 years) with severe COVID-19 disease (objectively confirmed SARS-CoV-2) who were hospitalized in the ICU and received at least one anticoagulation regimen (prophylactic dose, intermediate dose, therapeutic dose of low molecular weighted or unfractionated heparin); 2) reporting on the outcomes of interest separately (short-term mortality, deep-vein thrombosis incidence, pulmonary embolosm incidence, arterial thrombosis incidence, major bleeding incidence, minor bleeding incidence); 3) design of prospective observational study or clinical trial.

Information sources: Online databases including PubMed, EMBASE, Web of Science, Cochrane Library Database, Clinicaltrials.gov, databases of international and national respiratory and infectious diseases congresses.

Main outcome(s): 1) short-term mortality (at the end of the follow-up period but no later than 30 days), 2) deep-vein thrombosis incidence; 3) pulmonary embolosm incidence; 4) arterial thrombosis incidence; 5) major bleeding incidence, 6) minor bleeding incidence.

Additional outcome(s): None.

Data management: Three researchers independently searched and evaluated the titles, abstracts, and full texts for relevant studies and extracted data from eligible ones. All duplicated search results were excluded. Any disagreement was resolved through discussion between the researchers or by the decision of a fourth researcher. Predefined variables were extracted independently from each study as follows: 1) study information (study design, first author, title, journal, publication data, and country); 2) characteristics of patients (age, gender,

hospital unit, number of study participants); 3) interventions (administration of anticoagulants, type and dose of anticoagulants); 4) outcomes of interest (mortality, rates and types of thrombotic or bleeding events separately).

Quality assessment / Risk of bias analysis: Overall risk of confounding, selection and reporting bias was assessed with ROBINS Tool. Funnel plots and Egger's test were performed to assess publication bias, where applicable.

Strategy of data synthesis: Analysis was carried in R v.4.1 using meta package. Because a number of studies had only one arm, the frequency of the end point was chosen as a measure of the effect size. Individual trials were considered as random effects, heterogeneity was assessed using the inverse variance method, restricted maximum-likelihood estimator (REML) was used to estimate τ^2. The random-effects model was adopted for all the endpoints. The overall proportion was calculated with logit transformation, clopper-pearson method was used to estimate confidence intervals. Dosage type was used for subgrouping for all the endpoints, for mortality the type of trial was also considered as a moderator, for venous thrombosis endpoint the usage of routine ultrasound was considered as a moderator. The effect size was estimated in each subgroup. Differences in effect size were assessed by Q test, assuming common τ^2 in subgroups since the amount of trials is small.

Subgroup analysis: Subgroup analysis included different anticoagulation regimens (prophylactic dose, intermediate dose, and therapeutic dose).

Sensitivity analysis: Sensitivity analysis was performed by the leave-one-out method.

Country(ies) involved: Russian Federation, France.

Keywords: COVID-19; ICU; thromboprophylaxis; anticoagulant; heparin; deep vein thrombosis; venous thromboembolism; pulmonary embolism.

Contributions of each author:
Author 1 - Svetlana Rachina - conceptualization, supervision, funding acquisition, review and editing of the manuscript.
Author 2 - Yuliya Belkova - Author 2 – conceptualization, investigation, original manuscript preparation.
Author 3 - Anastasia Shchendrygina - original manuscript preparation.
Author 4 - Aleksandr Suvorov - formal analysis.
Author 5 - Denis Bourgeois - original manuscript preparation.
Author 6 - Marina Karuk - investigation.
Author 7 - Violetta Sitnikova - investigation.
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