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Fibrinolytic therapy in patients with COVID-19 and ARDS: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction In COVID-19-related acute respiratory distress syndrome (ARDS), the clot play a role in gas exchange abnormalities. Fibrinolytic therapy can improve alveolar ventilation by restoring blood flow. In this systematic review and meta-analysis protocol, we aim to assess the safety and efficacy of fibrinolytic therapy in such a population.

Methods We will perform a systematic search in MEDLINE, EMBASE, Cochrane CENTRAL and LILACS databases without language restrictions for relevant randomised controlled trials (RCTs) and quasi-RCTs. Two review authors will independently perform data extraction and quality assessments of data from included studies. In case of divergence, a third author will be contacted. The Cochrane handbook will be used for guidance. If the results are not appropriate for a meta-analysis, a descriptive analysis will be performed.

Discussion This systematic review and meta-analysis protocol will provide current evidence about the safety and efficacy of fibrinolytic therapy in patients with COVID-19 and ARDS. These findings will provide if fibrinolytic therapy might be an option for a desperate clinical setting, where all medical efforts have been used.

PROSPERO registration number PROSPERO CRD42020187482.

Ethics and dissemination Ethics committee approval is not necessary. We intend to update the public registry, report any protocol amendments and publish the results in a widely accessible journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Cochrane Handbook and GRADE approach for summarising the evidence on the effects of fibrinolytic therapy will strengthen the review.
⇒ Well accepted standards for reporting systematic reviews will be followed.
⇒ This is a protocol for a systematic review and meta-analysis of fibrinolytic therapy in COVID-19 patients with acute respiratory distress syndrome that will include only randomised controlled trials (RCTs) and quasi RCTs.
⇒ A subgroup analyses will be performed including route of administration and dose of the pharmacological agent, heparin association, effect of heparin therapy measured by aPTT and incidence of intracranial haemorrhage.
⇒ Since cases of COVID-19 decreased and there are few clinical trials designed on this topic, there will be few data to assess.

INTRODUCTION

In late December 2019, several local health facilities reported clusters of patients with pneumonia of unknown cause that were epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China.[1] Deep sequencing analysis from lower respiratory tract samples indicated a novel coronavirus, which was named 2019 novel coronavirus. In severe cases, patients with COVID-19 develop acute respiratory distress syndrome (ARDS), sepsis and multiorgan failure.[2]

Fibrin deposition in the air spaces and lung parenchyma are consistently observed with ARDS and contribute to hyaline-membrane formation and subsequent alveolar fibrosis, leading to respiratory dysfunction. COVID-19 patients with ARDS present a highly activated coagulation cascade, with microthrombosis and macrothrombosis in the lung and in other organs. Furthermore, endothelial damage occurs, which disrupts pulmonary regulation, promotes ventilation-perfusion mismatch (the primary cause of initial hypoxaemia) and promotes thrombogenesis.[3] Moreover, fibrin deposition is the result of an imbalance of the coagulation and fibrinolytic pathways, and several therapeutic strategies have been explored to target the dysfunction of these systems in ARDS.[4]

In particular, the use of fibrinolytic therapy (including plasminogen activators) to limit ARDS progression and reduce ARDS-induced death has received strong support from animal models.[5] Human studies are limited,

although in a phase 1 clinical trial, Hardaway *et al*[6] showed that the administration of urokinase or streptokinase (SK) resulted in a significant improvement of PaO_2 level in patients with severe ARDS secondary to trauma or sepsis.

In COVID-19 pneumonia, clots play a direct and significant role in gas exchange and in multisystem organ dysfunction. The preserved lung compliance noted early during COVID-19 in some patients with bilateral airspace opacities suggests that the observed pulmonary infiltrates could represent areas of pulmonary infarct and haemorrhage. Therefore, fibrinolytic therapy could improve perfusion in previously occluded regions leading to blood redistribution in lung pathological areas.[7]

Fibrinolytic drugs include recombinant tissue plasminogen activator, SK and urokinase. These drugs are widely used in severe diseases such as pulmonary embolism, stroke and acute myocardial infarction. However, there is evidence in both animals and humans that fibrinolytic therapy in ARDS improves survival, which also points to fibrin deposition in the pulmonary microvasculature as a contributory cause of ARDS.[8–10]

The rationale for fibrinolytic therapy is the pathological fibrin deposition that reflects a dysfunctional clotting system, with enhanced clot formation and fibrinolysis suppression, related to tissue factor produced by alveolar epithelial cells and macrophages, and high levels of plasminogen activator inhibitor 1 produced by endothelial cells or activated platelets.[11] Previous data on fibrinolytic therapy in ARDS associated to the prothrombotic state and clinical findings with pulmonary occlusive disease in COVID-19 suggest that the use of fibrinolytic therapy may have an impact in the treatment of severe COVID-19 induced ARDS, when all medical efforts and clinical treatment options were exhausted.[12]

Objectives
To assess the efficacy and safety of fibrinolytic therapy in patients with COVID-19 19 and ARDS. Our research question aims to assess if fibrinolytic drugs, as a rescue therapy, could improve the PaO2/FiO2 ratio in COVID-19 patients with ARDS compared with standard of care (SOC) alone.

METHODS
This protocol is prospectively registered in the international prospective register of SRs PROSPERO database (CRD42020187482) and is based on the Cochrane handbook of interventions reviews. In addition, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols are used to report this protocol. We started in 2020 and we plan to finish in 2023.

Patient and public involvement
No patient involved.

Type of studies
We will include Randomised Controlled Trials (RCTs) and quasi RCTs.

We will exclude observational studies, case series, case reports and animal studies.

Type of participants
1. Inclusion criteria: patients ≥16 years old with confirmed COVID-19 19 by RT-PCR and presenting moderate and severe ARDS according to the Berlin criteria, either on non-invasive (NIV or HFNC) or invasive mechanical ventilation (<48 hours).
2. Exclusion criteria: patients with previous bleeding disorder, active bleeding, acute myocardial infarction, liver failure, haemodialysis, cardiac tamponade, uncontrolled hypertension, traumatic brain injury in the last 3 months, stroke, intracranial haemorrhage, on extracorporeal membrane circulation (ECMO), gastrointestinal and genitourinary bleeding in the last 3 weeks and pregnancy.

Type of interventions
1. Intravenous fibrinolytic therapy plus SOC compared with SOC alone.
2. Nebulised fibrinolytic therapy plus SOC compared with SOC alone.
3. SOC will be patients without fibrinolytic therapy. Also, the treatment will be according to the institution's protocol for COVID-19 related ARDS, including or not anticoagulation therapy with heparin.

Type of outcomes measures
Primary outcomes:
1. Absolute PaO_2/F_IO_2 change from baseline prior the intervention to day 1, day 2, day 3, day 4 and day 5 after intervention exposure
2. Number of ventilator-free days.
3. Number of major bleeding events defined by a haemoglobin concentration decrease of 2 g/L or more, retroperitoneal, or intracranial bleed, transfusion of two or more units of red blood cells, or fatal haemorrhagic events, as defined by International Society on Thrombosis and Hemostasis.

Secondary outcomes:
1. PaO_2/F_IO_2 ratio ≥200 mm Hg 48 hours after the intervention.
2. Increase in 50% of PaO_2/F_IO_2 ratio 48 hours after the intervention.
3. Oxygen-free days.
4. Improvement of SOFA score by ≥2 points.
5. Twenty-eight days in-hospital mortality.
6. Improvement ≥2 points in the WHO Clinical Progression Scale.
7. VR and Vd/Vt ratio to access changes in dead space secondary to pulmonary vascular obstruction.
8. Length of stay in the intensive care unit.
9. Length of stay in the hospital.

Search methods for identification of studies

We will perform a comprehensive search with no restrictions on the language of publication, country of origin or publication status. In addition, we may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers when necessary.

Electronic searches

We will search the following sources from inception of each database, using appropriate controlled vocabulary indexing and natural language search terms:
- ▶ Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 6) in the Cochrane Library.
- ▶ MEDLINE PubMed (1946 to date).
- ▶ Embase Elsevier (1974 to date).
- ▶ LILACS (Latin American and Caribbean Health Sciences Literature database; 1982 to date).
- ▶ ClinicalTrials.gov.
- ▶ WHO International Clinical Trials Registry.

Our planned search strategies for each respective database are outlined in online supplemental appendix 1.

Data collection and analysis
Selection of studies

Two authors (FS and LRdS) will independently evaluate the titles and abstracts of the studies identified using the search strategy for eligibility, and those meeting the inclusion criteria will be selected in the review. Any difference in opinion regarding the inclusion of studies will be resolved by discussion until a consensus is reached, or by referral to a third review author (MLD). We will include a graphical representation of the flow of citations reviewed during this review, as described in the PRISMA statement.[13]

Data extraction and management

Two authors (FS and LRdS) will independently extract the data from the identified trials using a standardised form to tabulate study design, patients baseline characteristics such as age, ethnicity, comorbidities, as well as review focused outcomes. In case of differences in opinion, a third author (MLD) will be contacted, and will solve the issue through a consensus process. If any data are missing in the studies, the main author will be contacted, and the omitted data will be requested. If there is no response from the author, the study will be excluded. For eligible trials recorded as complete in a clinical trial log, but without available results, we will again attempt to contact the corresponding author, and if there is no response, we will add the details to the table 'Characteristics of studies under evaluation'. We will collect data from each study for analyses of dichotomous outcomes, continuous outcomes and other types of outcome data as described in chapter 7.7 'Extracting study results' in the Cochrane Handbook for Systematic Reviews of Interventions.[14]

Assessment of risk of bias in included studies

Two investigators (FS and LRdS) will undertake assessment of the risk of bias of the included studies independently, with the following taken into consideration, as guided by the Cochrane Handbook for Systematic Reviews of Interventions[14]:
- ▶ Random sequence generation.
- ▶ Allocation concealment.
- ▶ Blinding of participants.
- ▶ Blinding of outcome assessment.
- ▶ Incomplete outcome data.
- ▶ Selective outcome reporting.
- ▶ Other sources of bias.

We will use the Cochrane 'Risk of Bias's tool in Review Manager (RevMan2014) which involves describing each of these domains as reported in the study and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias. Lack of blinding will be sufficient to label a study as at high risk of bias.

Measure of treatment effect

For continuous outcomes, we will report the mean difference (MD) with SD or, when necessary, the standardised mean difference. In case of dichotomous outcomes, we will calculate the risk ratio and OR with 95% CI.

Unit of analysis issues

We will determine appropriate units of analysis from the included studies.

Dealing with missing data

We will contact study authors via email whenever the outcome of interest is not reported, and the methods of the study suggest that the outcome was measured. We will do the same if not all data required for the meta-analysis are reported unless the missing data are SD. If SD data are not available, we will approximate these using standard estimation methods: from p values, standard errors or 95% CIs if these are reported, as detailed in the Cochrane Handbook for Systematic Reviews of Interventions.[14] Where it is impossible to estimate these, we will contact the study authors. Apart from imputations for missing SD, we will not conduct any other imputations. We will extract and analyse data for all outcomes using the available case analysis method.

Assessment of heterogeneity

We will assess clinical heterogeneity (which may be present even in the absence of statistical heterogeneity) by examining the included trials for potential differences between studies in the types of participants recruited, interventions or controls used, and the outcomes measured. We will assess statistical heterogeneity by visually inspecting the forest plots and by considering the χ^2 test (with a significance level set at $p<0.10$) and the I^2 statistic, which calculates the percentage of variability that is due to heterogeneity rather than chance, with I^2 values over 50% suggesting substantial heterogeneity.

Assessment of reporting biases

We will create a funnel plot to detect reporting biases if at least 10 studies are included in the meta-analysis. We will assess reporting bias as between-study publication bias and within-study outcome reporting bias. If we identify small studies with larger treatment effects, we plan to perform a sensitivity analysis excluding these studies.

Data synthesis

Where we consider included studies to be sufficiently similar, we will conduct a meta-analysis by pooling the appropriate data using Review Manager (RevMan2014). We will consider a random-effects approach to better estimate the effect size of the different studies with small sample sizes. If meta-analysis is not possible, we will present the results in a narrative form.

Subgroup analysis and investigation of heterogeneity

We expect that the variables below may introduce heterogeneity into the analyses. We will perform the following prespecified subgroup analyses for the primary outcomes to investigate this.

► Type, route of administration and dose of pharmacological agent (to observe if different medications and doses affect outcome).
► Patients with low dose or subtherapeutic heparin infusion during the 24 hours of fibrinolytic therapy drip.
► Patients on anticoagulation therapy with unfractionated heparin presenting aPTT levels below range, in range and above range for anticoagulation therapy after fibrinolytic therapy exposure.
► Patients with intracranial haemorrhage.
► Patients sings of pulmonary hypertension in the echocardiogram.

Sensitivity analysis

We will carry out sensitivity analyses for the following parameters.

► Excluding studies judged to be at high risk of bias for any domain.
► Excluding studies with missing data, where this cannot be supplied by the study authors.

Summary of findings and assessment of the certainty of the evidence

We will present the overall quality of the evidence for each outcome according to the GRADE approach, which takes into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity (directness of results).[15] For each comparison, two of review authors will independently rate the certainty of evidence for each outcome as 'high', 'moderate', 'low' or 'very low' using GRADEpro GDT. We will resolve any discrepancies by consensus, or, if needed, by arbitration by a third review author. For each comparison, we will present a summary of the evidence for the main outcomes in a summary of findings table, which provides key information about the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies, numbers of participants and studies addressing each important outcome, and the rating of the overall confidence in effect estimates for each outcome.

DISCUSSION

Along the pandemic, no benefit was observed when therapeutic anticoagulation with intravenously heparin was initiated after the onset of severe respiratory failure, suggesting that therapeutic anticoagulation is only effective if started before the accumulation of significant clot burden within the lung vasculature. Nonetheless, Dixon et al concluded that nebulised heparin might suggest less progression of lung injury and earlier return home in patients with ARDS.[16] In specific settings, ECMO has been indicated for COVID-19-related to ARDS, showing better outcomes. However, this device is not available in most clinical centres (mainly in low-middle-income countries). Currently, there are RCTs[17] assessing the potential role for fibrinolytic therapy to restore pulmonary microvascular patency, reduce dead space ventilation and improve oxygenation in COVID-19 respiratory failure with high risk of death.

Recently, a Hungarian and Polish research group[18] have published the first protocol for a prospective meta-analysis assessing the efficacy and safety of fibrinolytic therapy in COVID-19 patients with ARDS. They will include RCTs and prospective studies. In the other hand, our Brazilian group planned to assess only RCTs and quasi RCTs. Regardless of the study design, it is crucial to researchers understand better the role of fibrinolytic therapy in such population.

Therefore, it is important to analyse if fibrinolytic therapy might be an adequate rescue therapy for severely hypoxaemic patients who fail to improve their oxygenation despite all medical efforts.

Ethics and dissemination

Ethics committee approval is not necessary. We intend to update the public registry used in this review, report any important protocol amendments and publish the results in a widely accessible journal.

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