PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness and safety of fibrinolytic therapy in critically ill COVID-19 patients with ARDS: protocol for a prospective meta-analysis
AUTHORS	Kovács, Emőke; Dembrovszky, Fanni; Ocskay, Klementina; Szabó, László; Hegyi, Péter; Molnar, Zsolt; Tánczos, Krisztián

VERSION 1 – REVIEW

REVIEWER	Juffermans, Nicole Amsterdam UMC - Locatie AMC, Intensive Care
REVIEW RETURNED	04-Jul-2022

GENERAL COMMENTS	This is a study protocol intended to review findings of ongoing trials on the efficacy of fibrinolytics in COVID-19 ARDS. The study protocol is clear. The choice of a random effects model makes sense. Some questions that came up while reading are: - authors state that the deposition of fibrin in tissue contributes to impaired gas exchagne but actually this is due to clots in vessels? - authors may want to include the diagnostic criteria of COVID, ie. PCR proven? - the primary outcome parameter of interest appears to be PF ratio. Authors may want to make clear at what point in time they plan to evaluate PF ratio? As heme released from a dissolved clot may result in vasoconstriction which may worsen PF ratio after initial improvement. A transient decline in PF ratio has already been reported in a case serie previously.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

This is a study protocol intended to review findings of ongoing trials on the efficacy of fibrinolytics in COVID-19 ARDS. The study protocol is clear. The choice of a random effects model makes sense. Some questions that came up while reading are:

C1: - authors state that the deposition of fibrin in tissue contributes to impaired gas exchagne but actually this is due to clots in vessels?

A1: Thank you for pointing out the unclear formulation of the idea. We wanted to indicate that there are multiple mechanism involved in COVID-19 due to the systemic procoagulant state and direct lung injury that increases the appearance of both microthrombi and fibrin deposits.
See our correction below:

“This procoagulant state promotes the formation of microthrombi in vessels and together with the direct lung injury leading to fibrin deposits, these cause a mismatch in the ventilation/perfusion ratio resulting in perfusion defects and worsening of hypoxemia that might not be improved by mechanical ventilation alone.”

C2: - authors may want to include the diagnostic criteria of COVID, ie. PCR proven?

A2: We thank the reviewer for the suggestion. We clarified in our eligibility criteria that by the diagnosis of COVID-19 we mean laboratory confirmed diagnosis.

“Adult hospitalised patients with laboratory confirmed (PCR) COVID-19 infection and ARDS according to the Berlin criteria”

C3: - the primary outcome parameter of interest appears to be PF ratio. Authors may want to make clear at what point in time they plan to evaluate PF ratio? As heme released from a dissolved clot may result in vasoconstriction which may worsen PF ratio after initial improvement. A transient decline in PF ratio has already been reported in a case series previously.

A3: A very valid point, thank you. We have changed the parts concerned accordingly. We hypothesise that fibrinolytic therapy would restore partially the imbalance in fibrionolytic and antifibrinolytic processess and thus it would repair the endogen capacity of thrombus clearance.
As we think that fibrinolytic therapy should only be used as a rescue therapy In COVID-19 we are more concerned with the immediate effect of fibrinolytic therapy, thus we would like to include time points such as 24h, 48h, 72 h after and assess secondarily the more long term effects like 7 days or 14 days after fibrinolysis. We would like to emphasisze the dynamic of change in P/F ratio thus we did not choose only one timepoint. Additionally the choice of the timepoints is highly influenced by data availability.