Honore et al. Critical Care (2020) 24:599
https://doi.org/10.1186/s13054-020-03309-3

Critical Care

LETTER Open Access

TPE seems to be a treatment that may improve outcomes by effectively removing fibrin degradation products and restoring coagulation status: fact or fiction?

Patrick M. Honore*, Leonel Barreto Gutierrez, Luc Kugener, Sebastien Redant, Rachid Attou, Andrea Gallerani and David De Bels

Gucyetmez et al., noting that elevated D-dimer levels have been found as a predictor for mortality in patients with COVID-19 pneumonia, concluded that therapeutic plasma exchange (TPE) seems to be a treatment that may improve outcomes by effectively removing fibrin degradation products (FDPs) and restoring coagulation status [1]. We are not sure that the authors have demonstrated the point that they intended to make. They propose the use of TPE to remove FDPs, with the rationale that while unfractionated heparin (UFH) and low molecular weight heparin (LMWH) decrease production of FDPs, they cannot contribute to the metabolization of existing FDPs [1]. After propensity score matching, the mortality rate, in the patients with D-dimer level ≥ 2 mg/L, was 8.3% in patients who received TPE (TPE +) versus 58.3% in those who did not (TPE −), with no thromboembolic events detected in either sub-group [1]. While there was a reduction in the D-dimer levels in the TPE + group and not in the TPE − group, this cannot automatically be assumed to be the underlying cause of the decreased mortality rate. The cause of death is important information that has been omitted from this paper. Furthermore, "treating the numbers" does not necessarily equate to an improvement in the status of the patient. It is also important to note that TPE has the potential to cause harm by diluting or attenuating the patient's adaptive response to infection via depletion of immunoglobulins and complement components 3 and 4 [2]. In the case of patients with COVID-19, TPE will remove the protective antibodies formed by the patient, which is not desirable. Indeed, TPE may not restore immune homeostasis but may rather aggravate immunoparalysis [3]. Finally, given the variety of additional treatments (e.g., antiviral drugs, cytokine filters, steroids) that the patients in the study received, how can one be certain of which treatment(s) ultimately influenced mortality? A randomized controlled trial is needed to truly assess the therapeutic efficacy of TPE in patients with COVID-19 and coagulation activation. All patients should receive standard supportive intensive care without any of the recently proposed treatments for COVID-19, with the exception of dexamethasone. The treatment group would receive three daily sessions of TPE. The prognostic model at admission, the daily severity measure, and outcome measures including detection of thromboembolic events and mortality would be clearly defined by the investigators as in any good quality intensive care trial.

This comment refers to the article available at https://doi.org/10.1186/s13054-020-03215-8.

* Correspondence: Patrick.Honore@CHU-Brugmann.be
ICU Department, Centre Hospitalier Universitaire Brugmann-Brugmann University Hospital, Place Van Gehuchtenplein, 4, 1020 Brussels, Germany

Authors' response

Bulent Gucyetmez

Dear Editor,

We would like to thank Honore et al. for their considerable comments. Firstly, we should emphasize three important points about our study: (1) we investigated the effect of therapeutic plasma exchange (TPE) on overall mortality, not mortality predictors, (2) we emphasized that "major thromboembolic events" were not detected, not only thromboembolic events, and (3) we did not mention the cause of deaths because all of them were multi-organ failure (MOF) caused by COVID-19 [1]. Even if "major thromboembolic events" are not detected, patients will be under risk in terms of micro-embolisms as long as their D-dimer levels are high and this could be a reason for MOF.

In the study, 95% and 80% of deaths were in GII and GIIb respectively although all therapies except TPE were similar. Additionally, in propensity score matching (PSM), 14 covariates including "the usage of steroid, interleukin blocker and cytokine filter" were matched [1]. Therefore, we think that the result of PSM is acceptable evidence for the effect of TPE on mortality in patients with high D-dimer level although the number of patients are limited.

On the other hand, references which are used by Honore et al. actually support our results [2, 3]. Namely, Rimmer E et al. mentioned the benefits of TPE before its harmful effects in the introduction section. Moreover, despite the possible rare adverse effects of TPE, they concluded that the mortality was decreased by TPE in adult patients with sepsis [2]. In another reference that 54 patients were included, 41 of them were administered steroid plus immunosuppressive agents. Nevertheless, authors emphasized that "88.9% of procedures were carried out without complications" and they opined that "Lower leucocyte counts could have affected increased susceptibility to infections; however, it is difficult to attribute them exclusively to TPE procedures" [3]. Additionally, fresh frozen plasma (FFP) was administered at 1/4 ratio with albumin during TPE in both studies [2, 3]. Dilution is more expected in this technique. Yet, we only used FFP by calculating estimated plasma volume while performing TPE. Lastly, it should not be forgotten that dexamethasone, which was mentioned as a proposed treatment by Honore et al., is also an immunosuppressive agent [4].

The main treatments of COVID-19 pneumonia are antiviral and anticoagulation therapies. However, we still strongly believe that "TPE should be featured as a part of the treatment especially in COVID-19 pneumonia patients with a high risk of thrombosis".

Abbreviations

TPE: Therapeutic plasma exchange; FDPs: Fibrin degradation products; UFH: Unfractionated heparin; LMWH: Low molecular weight heparin; TPE +: Patients who received TPE; TPE −: Patients who did not receive TPE

Acknowledgements

None.

Authors' contributions

PMH, SR, and DDB designed the paper. All authors participated in drafting and reviewing. All authors read and approved the final version of the manuscript.

Funding

None.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare to have no competing interests.

Received: 27 August 2020 Accepted: 22 September 2020
Published online: 06 October 2020

References

1. Gucyetmez B, Atalan HK, Sertdemir I, Cakir U, Telci L, COVID-19 Study Group. Therapeutic plasma exchange in patients with COVID-19 pneumonia in intensive care unit: a retrospective study. Crit Care. 2020;24(1):492. https://doi.org/10.1186/s13054-020-03215-8.
2. Rimmer E, Houston BL, Kumar A, Abou-Setta AM, Friesen C, Marshall JC, et al. The efficacy and safety of plasma exchange in patients with sepsis and septic shock: a systematic review and meta-analysis. Crit Care. 2014; 18(6):699. https://doi.org/10.1186/s13054-014-0699-2.
3. Szczeklik W, Wawrzycka K, Włudarczyk A, Sega A, Nowak I, Seczyńska B, et al. Complications in patients treated with plasmapheresis in the intensive care unit. Anaesthesiol Intensive Ther. 2013;45(1):7–13. https://doi.org/10.5603/AIT.2013.0002..
4. Giles AJ, Hutchinson M-KND, Sonnemann HM, Jung J, Fecci PE, Ratnam NM, et al. Dexamethasone-induced immunosuppression: mechanisms and implications for immunotherapy. J Immunother Cancer. 2018;6:51.

Publisher's Note