Effectiveness and safety of continuous plasma filtration adsorption (CPFA) treatment in patients with septic shock

Efectividad y seguridad de la plasma-filtración-adsorción continua (CPFA) en pacientes con shock séptico

To the Editor

The availability of continuous plasma filtration adsorption (CPFA) to treat patients with septic shock created a lot of expectations at

the time. However, after several randomized clinical trials, there is tremendous uncertainty on the efficacy and safety profile of CPFA in these patients. The objective of this letter is to review the information available on this issue and establish evidence-based recommendations regarding its clinical application.

Therefore, we started by analyzing the systematic review conducted by Poole and D'Arrigo[1] updated until October 2021. Only randomized clinical studies of patients with septic shock and short/mid-term mortality data were included (primary clinical endpoint). The synthesis of evidence was conducted using a conventional meta-analysis (random effects model) and sequential analysis (Trial Sequential Analysis [TSA]).[2] The risk of study bias was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB2).[3] The quality of the body of evidence and the formulation of recommendations was performed using GRADE approach.[4] Details on the methodology, results, and references can be found in the Electronic Supplementary Data (ESD).

The meta-analysis included 3 randomized clinical trials[5–7] with a total of 341 patients diagnosed as septic shock. The 3 trials were stopped before they could ever reach the predetermined sample size on grounds of futility,[5] increased early mortality in the experimental branch[6] or indirectly through the COMPACT-2 results.[7]

In the conventional meta-analysis (Table 1, Fig. 1) a non-significant trend can be seen towards an increased mortality rate in the experimental arm at 28 and 90 days followed by significant excess mortality at 3 days. The information available on non-critical outcomes (like shock duration, ICU stay, hemodynamic instability) was scarce and did not allow an overall synthesis.

The level of certainty of evidence available was considered moderate due to inaccuracy,[5] which did not allow us to discard a small protective effect. Sequential analysis (TSA) allowed us to discard, however, a significant reduction (>25%) of the risk of death at 28 days.

The increased mortality rate reported within the first 3 days deserves some reflection. In the first place, this estimate refers to a clinical outcome based on data (not predefined) and, therefore, is hindered by a high risk of bias. Also, at 90 days, excess mortality dropped nominally down to 6% (RR, 1.06; 95%CI between 0.87 and 1.30; non-significant *P* value). Excess early mortality did not reach statistical significance in the sequential analysis (95% confidence interval between 0.84 and 3.62), which is suggestive that it was a random maximum.

Despite this loss of statistical significance, the possible increased early mortality rate reported is worrying and deserves careful attention. The hypothetical early deaths described could be associated with the fact that extracorporeal blood purification therapies are being received. The pathophysiological nexus here could be the hemodynamic instability associated with the application of the technique,[8] which has demonstrated to increase mortality in the critically ill patient setting.[9] We should mention that, in the protocol of the 3 clinical trials, the early administration of this technique was being sought after (not beyond the first 12 h after diagnosis), and that the early application of renal replacement techniques (RRT) in critically ill patients is associated with more hemodynamic complications and no survival benefits.[10] As a matter of fact, investigators from the COMPACT-2 trial suggested that patients who do not need RRT to treat acute kidney injury (AKI) seem to be more susceptible to the deleterious effects of this technique.[6]

In conclusion, although statistically and formally a small protective effect cannot be ruled out, the 3 trials available suggest that CPFA is associated with excess mortality in the mid-term (moderate level of certainty) without evidence of improvement in other clinical outcomes. Also, if we take into consideration the cost associated with the intervention (some US$ 3000 per patient plus the work overload of the healthcare personnel), we will see that the risk-benefit ratio is truly unbalanced towards risk. Therefore, a strong recommendation should be made against the generalized use of CPFA in patients with septic shock.

Although the risk-benefit ratio is clearly unfavorable for the entire group of patients with septic shock, the existence of certain subgroups who may benefit from treatment cannot be discarded like patients who need RRT due to AKI. Conducting a meta-analysis of individual data could be a useful tool in the identification process of these different subgroups.

Table 1 Results of meta-analysis.

	RR (95%CI)			I^2	D^2
	Fixed effects	DerSimonian	TSA (DS)		
28-day mortality rate*	1.19 (0.93—1.53)	1.22 (0.88—1.68)	1.22 (0.81—1.82)	0.37 (0—0.69)	0.41
90-day mortality rate	1.06 (0.86—1.30)	1.06 (0.87—1.30)	1.06 (0.84—1.35)	0 (0—0.60)	0
3-day mortality rate	1.75 (1.10—2.77)	1.74 (1.10—2.76)	1.74 (0.84—3.62)	0 (0—0.60)	0

Abbreviations: 95%CI, 95% confidence interval; DS, DerSimonian-Laird; RR, relative risk; TSA, Trial Sequential Analysis.
* Main clinical outcome.

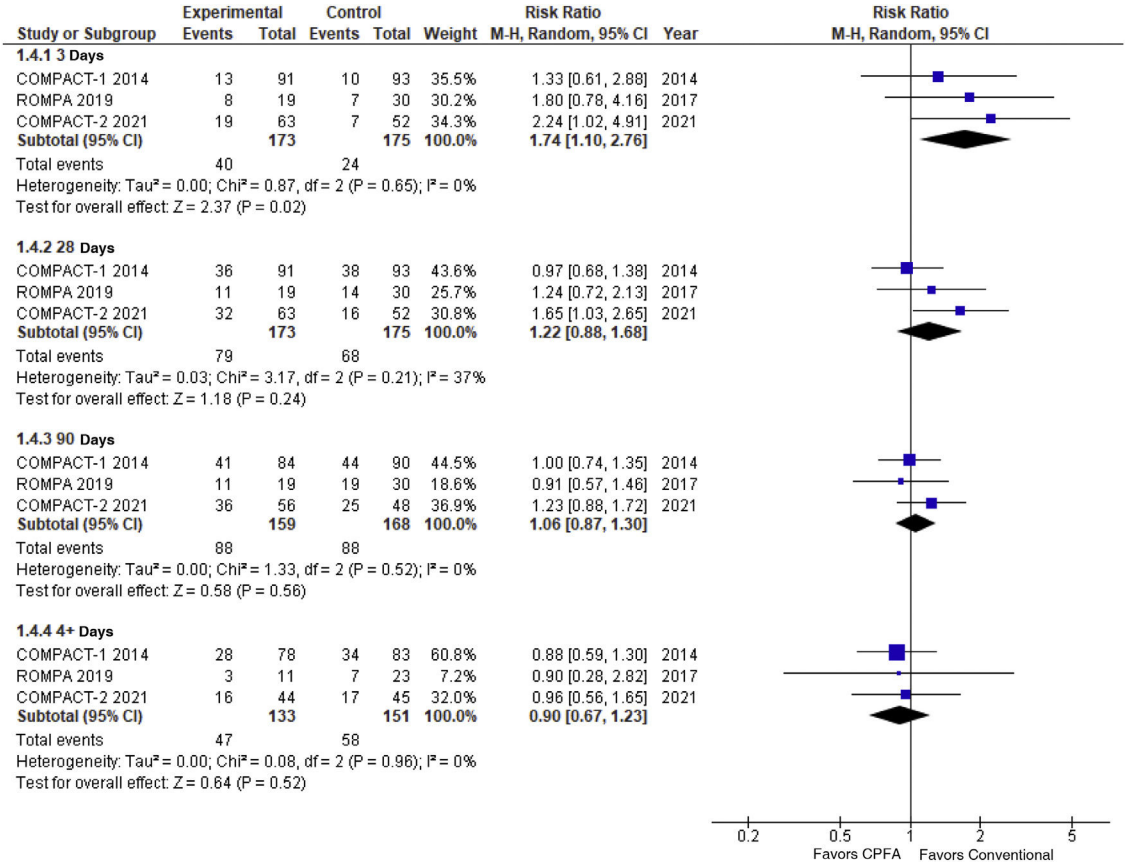

Figure 1 Results of the conventional meta-analysis, random effects.

Appendix A. Supplementary data

ESD related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.medine.2022.10.004.

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Are ICU nurses able to achieve their ventilation goals when bagging a patient? A pilot study

¿Son las enfermeras de la UCI capaces de alcanzar sus objetivos de ventilación cuando ventilan manualmente a un paciente? Un estudio piloto

Dear Editor:

Adequate ventilatory management of mechanically ventilated patients should be standard of care as it is essential to optimize therapy and minimize the risk of lung injury.[1,2] Therefore, not only the fine-tuning of mechanical ventilation settings should be a goal, but also high-quality manual ventilations should be delivered. Manual bag ventilation is a routine intervention in most ICUs,[3,4] and its quality is usually assumed to be adequate. However, as this is a provider-dependent non-controlled procedure (in terms of volume and/or pressure delivered) in actual practice, it is possible that current ventilation provided by nurses, when intermittent bagging mechanically ventilated patients, do not achieve the predefined goals.[5,6]

In our ICU, manual bag ventilation is usually performed before, during and after bronchial secretions aspiration as standard of care in every intubated and mechanically ventilated patient.[7] This study aims to compare, in terms of delivered volumes and ventilation rate (VR), standard manual ventilation (SMV) to ventilation guided by a handheld ventilation feedback device (VFD). We hypothesized that blinded SMV deliver volumes and VR out of the standard goals. The use of a VFD would help ICU nurses deliver adequate ventilation, and thus potentially reduce related risks.

We conducted a prospective, randomized, and crossover study in a 10-bed ICU at a University Hospital in northwest Spain in July 2021. Eligible study participants were ICU nurses. Each participant randomly performed one blinded and one guided test during manual bag ventilation before, during, and after bronchial secretions aspiration within routine clinical practice (Supplementary Fig. 1). Each test lasted 1 min. Endotracheally intubated and deeply sedated adult patients without respiratory pathology were eligible for inclusion. Participation was voluntary, written informed consent was obtained from all participants and from patients or from their legal representatives if the clinical situation prevented it. The study was performed in accordance with the amended Declaration of Helsinki. The Research Ethics Committee of Santiago-Lugo approved the study (ref. no. CAEG 2021/233). During the guided test, ICU nurses were provided with real-time feedback on the quality of manual ventilation. Neither training nor written instructions about the VFD was provided to the participants. However, a short oral 1-minute explanation was made to every participant before the tests. To perform the ventilation sequences the VFD (EOlife®, Archeon medical, Besançon, France) was inserted between the bag (Ambu® Mark IV Adult, Ballerup, Denmark) and a heat and moisture exchanger filter (ClearTherm™, Intersurgical Ltd, Wokingham, UK) before the endotracheal tube (Supplementary Fig. 2). Data on ventilation parameters were recorded with EOlife® software (Archeon medical, Besançon, France). For each test mean tidal volume (V_T), minute ventilation (V'_e), and mean VR were recorded. We considered V_T from 6 to 8 mL/kg of predicted body weight (PBW) and VR between 8 and 13 min^{-1} to be acceptable for these patients.[1,2] Correct ventilation performance was defined by both V_T and VR within the target range. Once both tests were completed, demographic characteristics of the participants were also recorded.

Thirty-five ICU nurses were enrolled into this study. Twenty-eight were women (80.0%). Mean participants' age was 38.0 ± 9.6 years and their average working experience in ICU was 7.6 ± 7.7 years (Supplementary Table 1). We recorded 35 blinded SMV sequences and 35 manual ventilation sequences guided with a VFD. V_T and V'_e were significantly lower during guided ventilation test. There were no significant differences in mean VR between groups (Table 1). By analyzing the performance of the 1-min ventilation sequences, we found a significant improvement of ventilation performance with the use of a VFD. Ventilation sequences with both V_T and VR within the target range were only achieved during guided tests (Fig. 1).

Our clinical impression that blinded SMV deliver volumes and VR clearly out of the goals motivated this study. Although this is a preliminary pilot study, to our knowledge, it is the first to evaluate the quality of usual care manual bag ventilation, in terms of delivered volumes and VR, performed by ICU nurses on real-life patient using a VFD. Our results are somewhat concerning. When delivered blinded SMV, experienced ICU nurses did not perform ventilations correctly, basically VR was out of the target range.