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Hemoadsorption in critically ill patients with or without COVID-19: A word of caution

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The use of extracorporeal blood purification therapies in critically ill patients, in particular in sepsis and septic shock [1], has been suggested as a potential treatment since decades but its effects are still controversial. Moderate certainty evidence suggested no difference in mortality in septic patients randomized to polymyxin B immobilized fiber column therapy, the most studied hemoadsorption system [2]. The certainty of evidence on the use of other devices was very low [2].

The use of hemoadsorption was also reported in patients with acute respiratory distress syndrome (ARDS) [3,4], a disease characterized by severe systemic inflammation, that could theoretically profit from adsorption of pro-inflammatory mediators. Similarly, the use of Cytosorb® hemoperfusion was suggested to treat severely ill patients due to the novel coronavirus SARS-CoV-2 disease (COVID-19). Recently, a randomized single-center trial was published on the topic, the 'Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation' (CYCOV) trial [5]. The study randomly assigned patients with severe COVID-19 pneumonia requiring venovenous extracorporeal membrane oxygenation to receive 72 h of Cytosorb® cytokine hemoadsorption or no treatment [5]. The trial showed no significant difference in the primary outcome (interleukin 6 concentrations) but found an increase in the 30-day mortality for the cytokine adsorption group (14 of 17 [82.3%] Cytosorb® vs. 4 of 17 [23.5%] control, $p < 0.001$). Various multiple regression and post-hoc analyses were performed to further detail these findings, not showing any statistically significant factor related to survival other than Cytosorb® treatment [5].

The CYCOV trial adds important outcome and safety data to the Cytosorb® literature and COVID-19 treatment evidence but is not the first randomized study to evoke deleterious effects of hemoadsorption extracorporeal therapies. The largest randomized controlled trial performed so far with Cytosorb® included mechanically ventilated patients with severe sepsis or septic shock and acute lung injury or ARDS [4]. The authors reported a higher 60-day mortality (secondary outcome) in patients undergoing cytokine adsorption (21 of 47 patients [44.7%] Cytosorb® vs. 13 of 50 [26%] control, $p = 0.039$) [4]. More deaths were also found in the 2 largest randomized trials on polymyxin B hemoadsorption: the EUPHRATES trial (110 of 219 [50.2%] polymyxin

B vs. 94 of 223 [42.2%], $p = 0.10$) [6] and ABDOMIX trial (40 of 119 [33.6%] vs. 27 of 113 [23.9%] $p = 0.10$) [7].

The effects of hemoadsorption devices on immunity, inflammation, micronutrients, electrolytes, and drugs concentrations as well as activity remain largely uninvestigated and could be associated to harmful outcomes. Removal of some antibiotics, immunosuppressors, and antiepileptics through hemoadsorption devices including Cytosorb® was reported by various studies [8–13]. A randomized animal study found that hemoadsorption with CytoSorb® increased to a clinically significant extent the clearance of 5 among 17 tested anti-infective agents, including fluconazole, linezolid, liposomal amphotericin B, Posaconazole, and teicoplanin [12]. Another recent in-vitro study found that remdesivir and its main active metabolite were rapidly eliminated by the CytoSorb® adsorber device and the simultaneous application should be discouraged in clinical practice [14]. The interactions between hemoadsorption therapies with effective COVID-19 drugs such as dexamethasone or humoral antibody-mediated immunity remain unknown.

Those findings and hypotheses suggest that further high-quality randomized trials are needed before the implementation of hemoadsorption devices in clinical practice in critically ill patients with or without COVID-19.

Disclosures

None.

Declaration of Competing Interest

The authors declare that they have no competing interests. The study and the authors did not receive any financial support.

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