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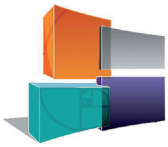

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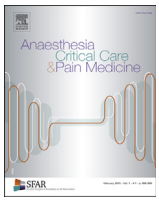

Editorial

Haemoperfusion with polymyxin B membrane: Recent results for an old debate!

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Sepsis is a super inflammatory response secondary to severe infection, which continues to lead the cause of mortality in intensive care (ICU) patients, especially when a shock is present [1]. Among the reasonable strategies proposed to reduce the mortality, removing the factors responsible for such inflammatory response sounds logic. The early antibiotic and surgical treatments are supposed to be the hallmark treatment of infection cause, especially if it is associated with supportive therapies to maintain the organ functions. The recommendations of the Surviving Sepsis Campaign have demonstrated the efficiency of a supportive therapeutic strategy to improve the outcome and to limit the iatrogenic consequences [2]. Among the complex underlying mechanisms leading to organ failure in septic shock [3], endotoxin (EDTX) appears one of the major stimulating factors [4]. This was deeply investigated both in experimental animal studies with *iv* large injected dose of EDTX and human studies using low dose of EDTX [5]. EDTX activates the systemic inflammation via a well-recognised pathway to generate a systemic inflammatory response [6]. The mechanistic process has been described and therapies blocking EDTX interaction with immune cells have been tested. Unfortunately, the ACCESS RCT testing a synthetic lipid A antagonist blocking LPS binding with MD2-TLR4 receptor failed to improve the outcome at day 28 in severe sepsis, [7] motivating other approaches to reduce the level of EDTX. Among the possibilities, the removal of plasma EDTX became the more plausible. This was technically possible considering the development of continuous renal replacement therapies. After the disappointment of the effect of regular dose of filtration rate [8] and of high volume haemofiltration [9] to improve outcome in severe sepsis or septic shock, it was necessary to apply another concept. The binding of EDTX on specifically design Polystyrene fiber filters coated with polymyxin B was developed by a Japanese company [10]. This technique was routinely used for several years in Japan to treat severe septic shock [11]. After publishing solid data proving the concept and numerous clinical reports supporting the interest for such a method, the demonstration of outcome benefit in septic shock in RCTs became essential. The first pilot RCTs was reported several years ago in a limited number of patients [12], with haemodynamic improvement but with no clear reduction in LPS level measured by the limulus amoebocyte technique, a sensitive bioassay technique. The first RCTs testing PMX haemoperfusion was reported in JAMA in 2009 in a small cohort of 64 severe sepsis and septic shock related to peritonitis [13]. This trial was designed to demonstrate the benefit of PMX treatment on haemodynamic patterns as a primary end point. Mean arterial pressure increased with a significant decrease in vasopressor requirements in the PMX treated group. The observed reduction mortality in the treated group (32%) was significant in comparison with the conventional group (53%) using unadjusted hazard ratio [13]. This benefit in mortality allowed the committee to interrupt earlier the trial, arguing the ethical concerns. In an editorial, JL Vincent argued that mortality rate did not differ at 28 days when odds ratio of the crude mortality was applied ($P = .13$) [14]. It can then be concluded that mortality was delayed in the PMX group, but not reduced. This debate on the potential of PMX haemoperfusion continued after the publication of the French RCT ABDOMIX in peritonitis-induced septic shock in 2015 [15]. This RCT enrolled 243 patients having septic shock within the 12 hours after emergency surgery. The PMX treatment consisted in 2 sessions of PMX and the primary outcome was the mortality at 28 days. After checking the quality of surgery and completion of 2 full session of PMX, there was no signal in favour of a reduction in mortality rate in the PMX treated group [15]. This study has been completed by an ancillary study on plasma cytokines levels. No significant modifications in 17 plasma cytokine levels could be observed, suggesting a modest modification in systemic inflammatory process [16]. Among the published critiques or comments, the absence of plasma LPS levels determination, the non-blinded PMX arm, the estimated relatively low severity of the patients were the most important. All of these potential limits were supposed to be solved by the recently published RCTs EUPHRATES in the JAMA October issue [17]. This trial started in September 2010 and was completed in June 2016, enrolling 450 patients (224 PMX treated vs. 226 in sham haemoperfused). After protocol adjustment on severity selection, 146 PMX patients were tested in comparison with 148 sham haemoperfused patients. The patients' selection was based on the presence of septic shock associated with a MODS score > 9 and an endotoxin activity higher than 0.60. The primary end point was the mortality at 28 days among all

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patients and among patients randomised with MODS more than 9. The Authors concluded: "Among patients with septic shock and high endotoxin activity, polymyxin B haemoperfusion treatment plus conventional medical therapy compared with sham treatment plus conventional medical therapy did not reduce mortality at 28 days". Taken together with the most recent meta-analysis [18], the use of PMX at the proposed "dose" and timing cannot be recommended to improve septic shock outcome. The authors of EUPHRATES have recently published their exploratory post-hoc analysis focused on a specific EDTX level-defined subgroup of patients [19]. The PMX treated patients with an EDTX activity between 0.06 and 0.89 (n = 194) had a better survival rate than the sham haemoperfused patients. The editorial linked to this report explained the necessary extreme cautious in interpretation of these post-hoc analysis [20]. Does it mean that the "blood purification" game is over? Probably not for the following reasons: the theory of EDTX removal remains valid, even it is not translated in clinical benefit; EDTX neutralisation might be achieved using exogenous administration of lipo-proteins to detoxify the blood; the extra-corporeal methods with specific cartridges might have a bigger surface in contact with blood, avoiding the risk of the system saturation in presence of high level of EDTX. This could be achieved by the use of microbeads multiplying the surface exchange allowing to fix more EDTX before being saturated. The later technique is under development but has not been clinically evaluated. The adapted "dose" of PMX haemoperfusion, the appropriate use for patients with high endotoxin activity, in presence of high of inoculum, at the earliest time possible might be the next step for such an approach. In conclusion, if blood purification in sepsis remains a valid approach, the current efficacy of LPS/cytokine elimination using different membranes and haemoperfusion rate cannot be recommended to reduce the mortality in absence of positive RCTs.

Disclosure of interest

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