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Letter to the Editor

CytoSorb therapy for infective endocarditis: Expectations and a question of patient phenotype?

Terapia CytoSorb en endocarditis infecciosa: ¿expectativas y una cuestión de fenotipo de pacientes?

As we write this letter, we have just reviewed and discharged from our intensive care unit (ICU) one of our patients who had undergone aortic valve replacement one day earlier for native valve infective endocarditis (IE) to correct severe aortic regurgitation caused by *Streptococcus sanguinis* infection and vegetations, diagnosed against a background of unintentional weight loss, malaise and night sweats. He had a rapid and uncomplicated operation with short cardiopulmonary bypass (CPB) and aortic cross clamp (ACC) times, a mild inflammatory response as judged by routinely measured biochemical parameters, no major haemodynamic problems and required only low-dose norepinephrine support postoperatively. Apart from mild acute kidney injury (AKI alert), there are no organ dysfunction issues and we have every reason to believe that he will make a full recovery.

We have a hospital approved policy for the indication of CytoSorb® (CytoSorbents Inc., Princeton, NJ, USA) therapy for IE surgery and this was considered for this patient. However, the uneventful course of the operation, in particular the absence of significant vasoplegia before, during and after the operation, led us to adopt a wait-and-see approach and ultimately to decide not to use this promising approach. Although we are enthusiastic proponents of CytoSorb therapy in hyperinflammatory situations and are actively involved in evaluating the concept of multiple cytokine removal in high-risk cardiac surgery, many similar cases raise questions about the indications, benefits and even our expectations of such therapy. Would cytokine haemadsorption change the course of these patients' accelerated recovery, or could it cause harm to the delicate process of complex cytokine milieu required for healing and recovery from major surgical trauma?

Although only available in Spanish, the Spanish group's systematic review and meta-analysis of perioperative haemadsorption therapy in infective endocarditis is important to summarise our current understanding of the available evidence. It includes 3 RCTs and 6 observational studies, with the former dominated by the multicentre REMOVE trial from Germany and a reasonable overall population size of over 700 IE patients and a sizeable event rate for most outcome measures.[1] The analysis shows overall safety but no major benefit in terms of postoperative stay, incidence of postoperative renal failure or need for surgical revision. However, they do show a significant effect on some organ dysfunctions; notably, ventilation time was significantly reduced, as was the need for vasopressor support, a common indicator of haemodynamic instability and vasoreactivity. This observation is important as vasoplegia is a common problem in the postoperative course of cardiac surgery and therefore has a clinically significant impact.[2] The magnitude of this effect is likely to be underestimated, as two studies that expressed vasoactive requirements differently could not be included in the quantitative analysis. Many studies have shown improved haemodynamics with less inotropic support, usually expressed by the vasoactive inotropic score, when intraoperative haemadsorption was used.[3,4]

The lack of effect on kidney injury must be treated with caution, as no definition is given, but it is unlikely to have involved careful assessment of severity, duration and resolution according to advanced criteria. Mortality tended to be lower with an overall relative risk of 0.75, particularly in the observational studies, but this beneficial effect was negated by the result of the REMOVE trial with an overall *p*-value of 0.05, just on the border of conventional statistical significance.[5] Accordingly, the inclusion of another small observational study or RCT could swing the pendulum in either direction. However, the question remains whether we would have more confidence if *p*-values fell below 0.05, or whether we would bury this therapy forever if there was another negative result. At least there is a trend, albeit not statistically significant, towards lower mortality. We believe that much more convincing evidence is needed either way, with a judicious readjustment of our expectations. We suggest that this can only be achieved through a personalised medicine approach targeting those patients who are prone to or have hyperinflammation and cytokine/DAMP (damage associated molecular patterns)-mediated perioperative organ injury, which requires deeper identification of patient phenotypes.[6]

The first point relates to our usual problem of translating therapies that are successful in the laboratory and model experiments into the real world of clinical practice.[7] There are several challenges, including excluding patients who would not benefit from the therapy and including patients whose perioperative course is complicated by hyperinflammation. Including the former (like our patient above) or excluding the latter population will both reduce the effect size and lead to an underestimation of the therapeutic potential. In addition, the therapy needs to be given a chance to work, so the relative timing, magnitude of the inflammatory response and the onset and duration of haemadsorption need to be matched. We also need to be more selective about our outcome measures. Certainly, hard outcomes are of interest, but haemadsorption targeting cytokine and toxin removal is unlikely to solve problems associated with primarily non-cytokine mediated inflammatory responses such as neutrophil-derived redox species production, platelet activation, direct lung atelectasis, neurological and cognitive dysfunction induced by embolisation, or multiple organ dysfunction due to hypotension, bleeding, or tissue hypoxia due to reduced oxygen delivery. Conversely, excessive systemic inflammatory response syndrome (SIRS) may contribute to both systemic and pulmonary complications, and the demonstrated effects of haemadsorption on ventilation times and vasoplegia are important endpoints in this regard.

The huge qualitative and quantitative differences in the individual inflammatory response of humans to a given stimulus are well known and explain one of the main paradigms in cardiac surgery regarding the contribution of the SIRS response to cardiac surgical outcomes, both in routine and IE settings. At one end of the spectrum is the population similar to our patient above: with limited SIRS and improved recovery, while at the other end of the spectrum is the "hot endocarditis phenotype" with predominant vasodilation, shock, vasoplegia, multiple organ dysfunction, prolonged ICU stay and significant morbidity and mortality. This phenotype can be identified by preoperative factors (although our preoperative risk scores are notoriously poor predictors of actual outcomes).[8] In addition, whole blood assays to endotoxin or other defined stimuli could identify individuals with an enhanced cytokine release profile

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by measuring individual and cytokine balance preoperatively.[9] In addition, genetic, proteomic and metabolic phenotyping has been advocated for patient stratification for the general surgical pathway and could be highly relevant in the cardiac surgery, and particularly, the IE population.[10] Similarly, haemodynamic criteria could be better used to identify the hyperinflammatory phenotype, for example early signs of vasoplegia after sternotomy or initiation of CPB. We strongly believe that it is this population that would largely benefit from timely and sufficient duration of haemadsorption. Although the safety of the therapy has been widely demonstrated in the field of cardiac surgery, it is unlikely to provide patient benefit in the population with a low SIRS profile.[11] In other words, a patient-tailored approach including patient selection, timing and dosing is of paramount importance when deciding to use haemadsorption. However, postoperative continuation of haemadsorption therapies should be considered depending on clinical parameters.[12]

We thank the authors for undertaking this important analysis and agree with their conclusion that haemadsorption may allow better control of postoperative inflammatory activity in cardiac surgery for IE. However, we also acknowledge that the inflammatory response to cardiac surgery remains at a crossroads as a leading theory, as fundamental translational science, and as a therapeutic potential for significant patient benefit. It is time to re-evaluate all these aspects through a modern and comprehensive consensus conference covering basic science and clinical evidence, under multi-society auspices, that should truly define the nature, components and contribution of SIRS to perioperative complications in both routine and endocarditis surgery.[13] This discussion should delineate the multi-cytokine response, trajectory and pro-anti-inflammatory balance in IE and the best approaches to maximise the potential benefits of anti-inflammatory agents and broader haemadsorption. Until these provide definitive evidence, we should carefully evaluate any future advances in the field as we continue to learn from both successes and failures.

Conflict of interest

The authors declare that they have no conflict of interest. Daniel Wendt and Harriet Adamson are full-time employees of CytoSorbents Europe GmbH, Berlin.

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