Commentary

The place of early haemoperfusion with polymyxin B fibre column in the treatment of sepsis

Claudio Ronco

Director, Department of Nephrology, Dialysis and Transplantation, San Bortolo Hospital, Vicenza, Italy

Corresponding author: Claudio Ronco, cronco@goldnet.it

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See related research by Kushi *et al.* in this issue [http://ccforum.com/content/9/6/R653]

Abstract

Direct haemoperfusion with polymyxin B-immobilized fibre (PMX-F) is a promising treatment for Gram-negative sepsis in critically ill patients. Indeed, it has been used routinely in Japan for a decade. Recent evidence presented in this journal suggests that PMX-F can have a positive impact on outcome in patients with sepsis, although other reports in the literature have presented confusing or even conflicting results. This commentary considers whether the available evidence allows us to establish an appropriate role for PMX-F treatment in sepsis and what further work is needed.

Introduction

A few years ago a new device for extracorporeal removal of circulating endotoxin entered the market (Toraymixin; Toray Industries, Osaka, Japan). The device uses polystyrene fibres coated with polymyxin B (which adheres via covalent bonds) that are incorporated in a sorbent column; this column is then used in an extracorporeal haemoperfusion circuit. The device is intended to be used as an adjuvant therapy, adsorbing endotoxin and other products and possibly improving the altered immunohomeostasis characteristic of Gram-negative sepsis in critically ill patients. A report by Kushi and coworkers [1] presents important evidence for a positive impact of the device on outcome in septic patients.

Several other reports have been published, but these have often presented confusing or conflicting results [2-5]. Nevertheless, polymyxin B-immobilized fibre (PMX-F) has been used routinely in Japan since 1995, and more than 50,000 septic patients have been treated. So, is it now possible to determine a clear role of PMX-F treatment in the therapy of sepsis? What work has been done thus far, and what must be added to the research agenda if we are to complete our evaluation?

Safety

The proposal that the toxic molecule polymyxin B, bound to fibres, be placed in contact with circulating blood promptly led to concerns about safety and biocompatibility. This is logical because use of haemoperfusion devices has been reported to result in thrombocytopenia and leucocytopenia. There was additional concern that polymyxin B could be released into the circulation. However, these fears were laid to rest when data indicating excellent biocompatibility were reported [6-8]. Nevertheless, PMX-F treatment is contra-indicated in patients in whom the use of heparin would cause uncontrolled bleeding or in whom adequate anticoagulation cannot safely be achieved, such as those with haemophilia or with known hypersensitivity to heparin or PMX-F.

Performance

The PMX-F cartridge has been studied *in vitro* and in animals and humans. Several reports demonstrated efficient removal of entotoxin from blood passing through the sorbent bed. Also, flow distribution in the cartridge has been shown to be homogeneous and to utilize all available surface for adsorption [9].

Indications

Sepsis and septic shock are common among critically ill patients. Also, a systemic inflammatory response syndrome may present as a primary cause of multiple organ failure.

In this setting continuous renal replacement therapy has been used to achieve adequate blood purification. Proposed use of these techniques for additional removal of proinflammatory mediators and endotoxin products has attracted increasing interest. However, only small quantities of proinflammatory substances have been identified in the filtrate during

PMX-F = polymyxin B-immobilized fibre.

continuous haemodiafiltration. There are various ways to increase the extracorporeal removal of proinflammatory mediators. One is to perform haemofiltration with high volumes (6 l/hour for 4–8 hours/day) using standard haemofiltration membranes. Another is to employ membranes with greater permeability and utilize plasmafiltration techniques. A third option is to use sorbent devices in haemoperfusion techniques. PMX-F treatment is indicated for use in patients with sepsis or septic shock caused by Gram-negative bacteria. Because of the high affinity of PMX-F for endotoxin, the rationale underlying extracorporeal therapy would be to remove circulating endotoxin by adsorption, thus preventing progression of the biological cascade of sepsis [10,11].

Patient selection

The primary goal of most studies was to test the ability of the cartridge to remove components of Gram-negative bacteria in the hope of improving outcome, but patient selection for the trials has been very difficult. In fact, in those studies in which Gram-negative sepsis was presumed, such infection was confirmed only occasionally. This has made the majority of studies either nonsignificant or at least underpowered, limiting the validity of the evidence for use of PMX-F treatment in Gram-negative sepsis. Statistically significant results and sufficient statistical power require the recruitment and study of greater numbers of patients with true Gram-negative infection. Unfortunately, it is difficult to determine at the time of enrolment whether a patient really has Gram-negative infection, and one must often wait at least 48 hours for culture results. Moreover, no organism is cultured in approximately 30% of patients with overt clinical sepsis. A number of studies might have failed to yield statistically significant findings because of nonspecific patient selection.

End-points

The definition of end-points for studies of PMX-F treatment is generally difficult and problematic. If the therapy is considered an adjuvant tool to prevent progression down the slippery slope of multiple organ syndrome resulting from a biochemical cascade of mediators, then we can compare PMX-F treatment with high-dose steroids. Both therapies may be important, especially at the beginning of the syndrome, but they do not have a causative approach or remove the origin of sepsis. In this setting, physiological end-points such as reduction in vasopressor support, improvement in haemodynamics and reduction in severity scores have been used more than solid outcome measures. Nevertheless, some studies have reported improvement in organ damage, and even improvement in survival.

The biological versus the clinical clock

Despite the biological rationale and the apparently excellent performance of the cartridge, an intriguing issue arises when definitive testing of this technology is performed. Over the time course of sepsis, we can distinguish between a biological and a clinical clock. The first starts when infection begins and fragments of Gram-negative bacteria invade the host. At this point, immediate intervention with a treatment designed to remove the substance initiating sepsis would probably result in blockade of the humoral response and the subsequent biochemical cascade. In contrast, the clinical clock starts only after the first signs and symptoms appear and patients exhibit the initial sepsis syndrome. At this point humoral and tissue derangement has already begun and organ damage may occur momentarily if not yet present. In these circumstances, intervention with extracorporeal therapy can only result in possible organ protection from further insults; it cannot achieve effective blockade of the syndrome.

What's next?

It would be reasonable to follow at least some of the following steps. The aim should be to synchronize the biological and the clinical (diagnostic) clocks. To achieve this we must work on possible early markers of Gram-negative sepsis that could be used to identify patients at risk and make the case for early application of PMX-F therapy. Gene polymorphisms for expression of different molecules could be one avenue to explore. Furthermore, we must analyze the types of sepsis, some of which are almost inevitably sustained by Gram-negative bacteria, as in the case of peritonitis. In such cases it may be logical to apply the therapy based on the assumed presence of infection. The latter approach has been undertaken by a group of investigators coordinated by two centers, including ours, in the EUPHAS (Early Use of Polymixin-B Hemoperfusion in Abdominal Sepsis) study. The study was begun a year ago and will complete enrolment during the next 12 months. This multicentre randomized controlled study should provide a definitive answer regarding the efficacy of PMX-F treatment, because it has been designed with an adequate sample size and with strict indications for specific clinical conditions.

Conclusion

There is a good biological rationale for the PMX-F device, and it represents a potential therapy for patients with early Gram-negative sepsis. Some technical and clinical issues have been resolved, but more work must be done. The EUPHAS study should significantly enhance our understanding of the real efficacy of this therapy.

Competing interests

The author(s) declare that they have no competing interests.

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