Extracorporeal therapy using microbeads to treat refractory septic shock by removing excessive reactive oxygen species

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Introduction

Sepsis, a life-threatening condition characterized by organ dysfunction stemming from a dysregulated host response to infection. Central to the detrimental effects in sepsis are reactive oxygen species (ROS), including superoxide, hydrogen peroxide, hydroxyl radical, and hypochlorous acid. These species are produced rapidly and ubiquitously at the onset of sepsis by immune cells through a process known as oxidative burst. Ceria nanoparticles (CeNPs) offer a broad-spectrum catalytic activity against various ROS types rendering them ideally suited for combating sepsis-related ROS. Thus, we propose a novel approach: continuously passing blood through a column composed of microbeads with CeNPs (Figure 1). This technique aims to eliminate a significant volume of various extracellular ROS types, thereby robustly mitigating the oxidative stress associated with sepsis. To our knowledge, this method of utilizing CeNPs in an extracorporeal blood purification system has not been previously attempted, marking a pioneering step in sepsis management.

Methods and Materials

The mesocellular silica foams (MCF) microbeads were synthesized using a modified template method, while the cerium oxide nanoparticles (CeNP) were synthesized in an aqueous phase using 6-aminohexanoic acid (Figure 2, left). CeNP-loaded MCF microbeads (CeMCF) were obtained by mixing CeNPs solution with MCF microbeads (Figure 2, right). To enhance hemocompatibility, microbeads were coated with polyvinylpyrrolidone (PVP, Figure 3). Male Sprague-Dawley rats (n = 7 each group) were used in animal experiments. Rats were anesthetized, intubated, and mechanically ventilated, and cannulated in the right common carotid artery, right common femoral artery, and left common femoral vein, and circuit was set up using tubing, a peristaltic pump, and a microbead cartridge (Figure 5a-c). A lethal dose of lipopolysaccharide (5 mg/kg) was intravenously injected. Resuscitation with intravenous normal saline (30 ml/kg) and norepinephrine (upto 1 mcg/kg/min) were performed. Hemoperfusion with PVP-CeMCF (Group 1: treatment) or PVP-MCF (Group 2: sham) was performed for 4 hours at a flow rate of 1.5 ml/min. No hemoperfusion was performed in the standard care group (Group 3: standard care only).

Figure 1

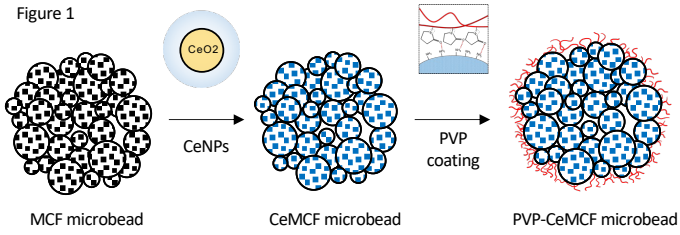


Figure 2

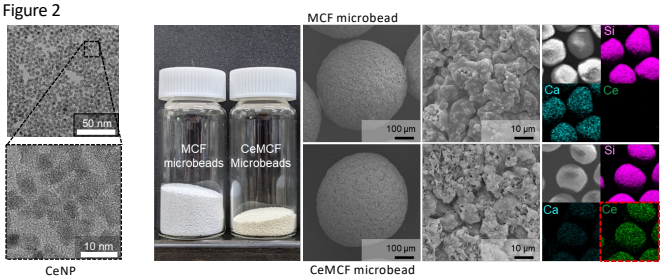


Figure 3

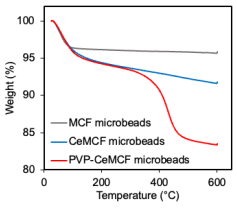


Figure 4

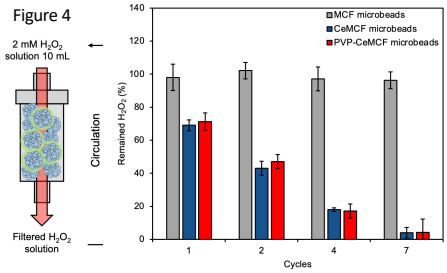
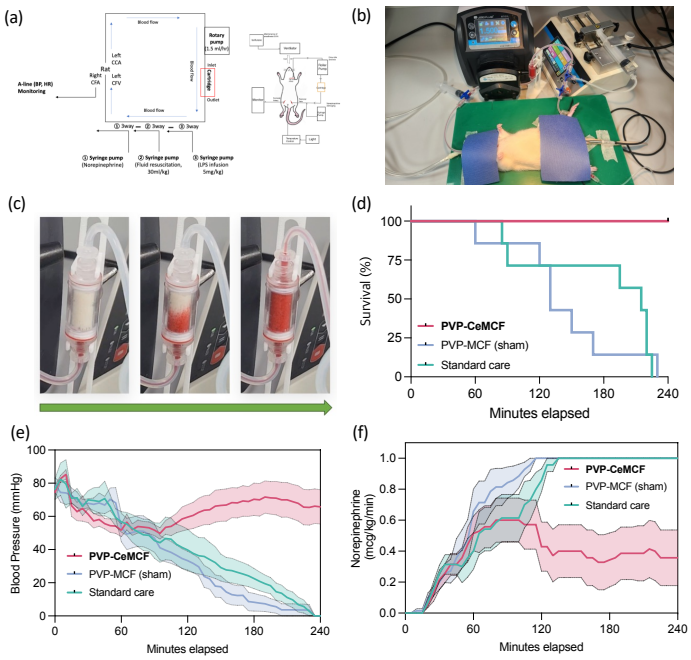


Figure 5



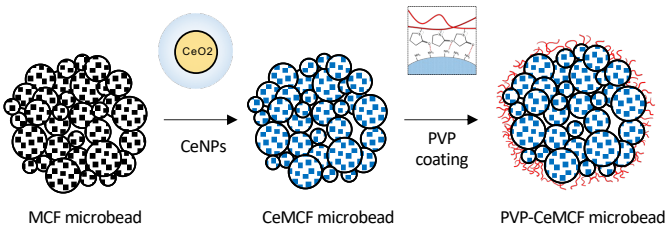
Results

MCF with a size of about 500 micrometers and high surface area (244.73 m2/g) and pore volume (0.56 cm3/g) were synthesized. 1 g of MCF was mixed with 5 mg/mL CeNPs, resulting in 100% loading efficiency (Ce 12.54 wt% in CeMCF microbeads). The resulting CeMCF microbeads had sufficient reactive oxygen species scavenging properties in hydrogen peroxide and hydroxyl radical assays, with CeMCF exhibiting up to 90% scavenging efficiency at a concentration of 10mg. In cartridge system tests, CeMCF microbeads showed significant hydrogen peroxide removal efficiency, with approximately 40% removal after 1 cycle, 50% after 2 cycles, and 96% after 7 cycles, while MCF microbeads showed no significant removal (Figure 4).

In refractory septic shock animal model, the treatment significantly improved the survival rate compared to the control group (100% in PVP-CeMCF group, 0% in PVP-MCF group, and 0% in standard care group , p-value < 0.001, Figure 5d). The PVP-CeMCF (treatment) group showed better recovery from refractory septic shock with reduced vasopressor dosage, while the PVP-MCF (sham control) and standard care (negative control) group remained refractory to the maximum dose of vasopressor and eventually succumbed (p-value < 0.001 for both MAP and norepinephrine dose, Figure 5e and 5f).

Conclusions

In pursuit of this novel strategy, we have engineered porous silica-based microbeads impregnated with Ceria nanoparticles, formulating therapeutically active microbeads adept at ROS removal. A hemoperfusion column cartridge composed of these microbeads was subsequently developed. To rigorously evaluate the effectiveness of this innovative treatment, we constructed a refractory septic shock animal model, characterized by a 100% mortality rate within hours despite established intensive care interventions, including mechanical ventilation, fluid resuscitation, and vasopressor administration. Our hemoperfusion experiments in this model exhibited a remarkable 100% survival rate, accompanied by notable improvement of hemodynamic profiles. This investigation thus unveils the potential viability and efficacy of extracorporeal catalysis in the realm of sepsis therapy. Our findings suggest that hemoperfusion with PVP-CeMCF microbeads could be a promising therapy option for septic shock treatment.



PVP-CeMCF

PVP-MCF (sham)

Standard care