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Drag-reducing polyethylene oxide improves microcirculation after hemorrhagic shock

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ABSTRACT

Background: Despite resuscitation after trauma, microcirculatory abnormalities are known to persist in post-shock multiorgan dysfunction. The high-molecular weight polymer polyethylene oxide (PEO) ($>10^6$ Da), a classic drag-reducing polymer, can improve hemorrhagic shock (HS)–induced hemodynamic abnormalities in rats.

Materials and methods: We examined the effects of PEO on microcirculation and on changes in multiple organs after shock. After the spinotrapezius muscle was prepared, HS was induced in Sprague–Dawley rats. Drug administration (normal saline or PEO) was performed 2 h after shock followed by infusion of shed blood.

Results: The velocity, blood flow, and functional capillary density in the shock + PEO group were significantly higher than those in the shock + normal saline group. Moreover, the kidney, liver, and lung function was improved, resulting in prolonged survival time. Our findings indicate that intravenous infusion of PEO can ameliorate shock-associated organ dysfunction and prolong survival time in severe HS, which may be a result of increased arteriolar blood velocity, blood flow, and functional capillary density.

Conclusions: PEO could have potential clinical application in the treatment of shock-induced multiorgan dysfunction.

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1. Introduction

Hemorrhage and uncontrolled hemorrhagic shock (HS) are the major causes of morbidity and mortality after multiple traumas [1], and most deaths related to hemorrhage occur within 6 h after the hemorrhage starts [2]. Abnormalities in microcirculation are major contributing factors to the development of post-shock multiple-organ dysfunction syndrome [3]. The current treatment of HS focuses on maintaining sufficient tissue perfusion and vital organ function with early and adequate fluid replenishment. Recently, the effects of certain types of polymers in shock models have come to light. These blood-soluble polymers have a relatively linear structure with a molecular mass $> 10^6$ Da and belong to the

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class of so-called drag-reducing polymers (DRPs) [4–7]. DRPs have been shown to reduce resistance to turbulent flow in pipes and increase flow velocity, which is known as the "Toms effect" [8]. Polyethylene oxide (PEO), a classic DRP, has been tested in the vascular system of experimental animals in the past few decades [4,7,9–11]. These tests revealed that the intravenous administration of nanomolar concentrations of PEO in different experimental animal models yields beneficial hemodynamic effects, including increased cardiac output and improved tissue, and organ perfusion [4,6,7]. In addition, treatment with PEO was shown to improve oxygen consumption after resuscitation from lethal HS [7]. However, the exact mechanisms responsible for the salutary effects of PEO in microcirculation remain to be fully understood. In this study, we investigated the effects of intravenous administration of a PEO-based DRP on arteriolar blood velocity, blood flow, and functional capillary density (FCD) of the spinotrapezius muscle in a rat model of HS. Moreover, the effects of the DRP on the function of the kidney, liver, and lung and on survival time after HS were examined.

2. Materials and methods

2.1. Reagents

PEO with a molecular weight of 5000 kDa (Sigma–-Aldrich, St. Louis, MO) was chosen as the test DRP. It was dissolved in saline and then dialyzed against saline for 24 h using a membrane with a 50-kDa molecular weight cutoff (Spectrum Laboratories Inc). After dialysis, the PEO solution was diluted to 1000 ppm with pyrogen-free sterile normal saline (NS) containing 0.05 mg/mL of gentamicin [7] and stored at 4°C. The 1000-ppm solution was diluted again to 10 ppm at about 1 h before the animal experiment [9]. The average molecular weight of the dissolved PEO was 4,988,362 ±,525,233 Da, as characterized by gel permeation chromatography. In the vehicle control (NS) group, NS containing the same concentration of gentamicin was used.

2.2. Surgical preparation

All the experiments conducted here were in accordance with the Guidelines of the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication no. 85-23, revised 1996) and were approved by the Animal Care and Use Committee of Southern Medical University. All animals had free access to food and water until the day of the experiment. Male Sprague–Dawley rats weighing 180–220 g (8 wks) were anesthetized by intraperitoneal injection of pentobarbital sodium (65 mg/kg, the blood pressure was stabilized 1 h after the specimen for microcirculation was prepared). Additional doses of pentobarbital were administered as needed to maintain adequate anesthesia. The left femoral artery and vein were cannulated with a PE-50 cannula. Mean arterial pressure (MAP) was recorded continuously through the left femoral artery cannula with the PowerLab registration equipment (AD Instruments, Sydney, Australia), whereas the left femoral vein catheter was used for intravascular injections. The right femoral artery was used for intermittent blood withdrawal. Body temperature was maintained at 37°C by a warm-water heating pad.

2.3. Spinotrapezius muscle preparation and microcirculation measurement

To observe the microcirculation of the rats, the RBC velocity in arterioles (Va) and venules (Vv), and the diameters and blood flow of the arterioles (Fa) and venules (Fv) were recorded. The left spinotrapezius muscle was partially exteriorized using a modification of the procedure originally described by Gray [12]. A total of 48 rats were used in this study. The rats were transferred to a Plexiglass viewing platform, and rectal temperature was maintained at 37°C via circulation of warm water within the platform. The excised muscle flap was moistened with Kreb's Ringer bicarbonate solution. The muscle was placed dorsal side up on the platform and spread till it reached its physiological length via sutures at the lateral margins. Finally, the muscle was covered with Saran plastic film (Dow Corning, Midland, MI) to minimize desiccation and atmospheric gas exchange. Then, the third-order vessels (diameter, 20–35 μm) were selected and imaged under an upright microscope (Zeiss Axio Scope A1 Microscope) equipped with a high-speed camera (record, 5000 × 2; Optronis, Kehl, Germany) and a high-definition camera (GE1900, 1920 × 1080, 30 fps, CCD, mono; Vision Technologies, ALLIED, Stadtroda, Germany). Vessel diameter and centerline RBC velocity were measured and used to calculate volume flow (Q) as follows: $Q = \pi \times Vm/1.6 \times (D/2)^2$, where Vm is the mean velocity, and D is the vessel diameter. Vm is calculated as the centerline RBC velocity divided by 1.6 for vessels with a diameter > 10 μm [13]. The high-definition camera was used to record the RBC movements in the capillaries for at least 10 s, using a previously described method [14] with slight modification. Generally, a field that had a large vessel or readily distinguishable vascular network geometry was chosen as the origin; capillaries were considered functional when they contained moving RBCs. FCD was estimated by counting the number of capillaries (12–16 in total) that contained moving RBCs during a 10-s observation period.

Before intravenous infusion of PEO or NS, the baseline microcirculation parameters were measured during a 2-min control period. Other measuring points were set at the initial stage of shock, 1 h, and 2 h after shock, initial stage of resuscitation, and 1 h and 2 h after infusion (Fig. 1).

2.4. Reproduction of a severe HS model with resuscitation

To establish the shock model, blood was withdrawn from the catheter placed in the femoral artery into a syringe containing diluted heparin solution (125 units/mL, 0.1 mL/1 mL blood volume) to achieve a decrease in MAP to 40 mm Hg within 10 min. To maintain the MAP at around 40 mm Hg in the next 120 min, additional blood was removed or added as needed. Blood was preserved at room temperature without special treatment, and then, drugs were administered intravenously within 10 min. This was followed by reinfusion of shed blood in the next 10 min (Fig. 1). The animals were then randomly divided into three groups [1]. The control (sham) group

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