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Additional therapy for septic shock

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Here is given results of treatment of sepsis complicated by acute sepsis and septic shock by means of human thrombomodulin and hemosorption. Human's recombinant thrombomodulin was utilized during disseminate intervascular coagulopathy and hemoperfusion at the time of septic shock. Thrombomodulin was injected in a patient's vein with the dose of 380unit/min during 30 minutes. hemoperfusion was carried out by means of the special sorbent which was made by "sewing" endotoxin's suppressing polymixin to the fibrins. Mentioned activities by means of hemoperfusion were used as complementary with the international treatment standards of sepsis.

Key Words: Sepsis,human s recombinant trombomodulin,septic shok, coagulopathy

Introduction:Septic shock has a high mortality risk despite the availability of various treatments. International guidelines for management of severe sepsis and septic shock have been published recently (1). In these guidelines, there are many recommendations for the best care of patients with severe sepsis and septic shock. Key recommendations and suggestions include early quantitative resuscitation of the septic patients during the first 6 hrs, blood cultures before antibiotic therapy, administration of broad-spectrum antimicrobials therapy within 1 hr, infection source control, initial fluid resuscitation with crystalloid and albumin, norepinephrine as the first-choice vasopressor, and so on.

Recently, drug therapies for sepsis have not fared well. Eli Lilly pulled Xigris (activated protein C) from the market in October 2012 following the negative results of the PROWESS-SHOCK trial (2). Therefore, few drugs are approved to treat sever sepsis and septic shock. In Japan, a new drug for treatment of disseminated intravascular coagulation (DIC) was approved by the Japanese Ministry of Health, Labor, and Welfare in 2008. This is a recombinant form of the anticoagulant protein thrombomodulin. In a phase III randomized controlled trial in japan, the rate of DIC resolution was significantly improved in the recombinant human thrombomodulin (rhTM) group than in the heparin group (3). For that reason, we use rhTM as an additional treatment in patients with sepsis-induced DIC. Another therapy for septic shock in Japan is endotoxin adsorption therapy by polymyxin B-immobilized fiber column hemoperfusion (PMX). In this article, we review rhTM and PMX therapy as additional treatments for septic shock.Recombinant human thrombomodulin (rhTM)

rhTM was developed for the treatment of patients with DIC in Japan. rhTM (380 U/kg, for 30min) is administered intravenously. rhTM suppresses thrombus formation by inhibiting thrombin coagulation activity and by activating protein C in complex with thrombin (4, 5). rhTM has concentration- dependent anticoagulant activity by conventional clotting tests. The concentration of rhTM required to inhibit thrombin activity was 50 times higher than that needed to inhibit thrombin generation. rhTM reduced the growth of the clot, however, it had little effect on the time to activate clotting. In addition, this effect of rhTM was completely abolished by anti-protein C antibody,

suggesting that rhTM attenuates blood clotting by reducing the level of generated thrombin through protein C activation (5). The safety and effectiveness of rhTM in the treatment of DIC was assessed in 3548 patients with DIC caused by infection (n=2516) or hematological malignancy (n=1032) by a post-marketing surveillance (6). The incidences of critical bleeding adverse reactions of rhTM in the patients with DIC caused by infection and hematological malignancy were 2.6% and 2.4%, and survival rates were 64.1% and 70.7%, respectively. We should carefully administer rhTM in patients with severe renal dysfunction or renal replacement therapy. In these cases, dose of rhTM must be reduced to 130 u/kg, because rhTM is excreted through kidneys. Further studies are needed to elucidate the effects of rhTM on sepsis-induced DIC.

PMX therapy

Endotoxin, an outer membrane component of gram-negative bacteria, plays an important role in the pathogenesis of septic shock. Polymyxin B, a cationic polypeptide antibiotic, has a strong affinity to endotoxin and is able to bind the lipid A portion of endotoxin through ionic and hydrophobic interactions. Intravenous administration of polymyxin B has significant nephrotoxic and neurotoxic effects. However, the covalent binding of polymyxin B onto the surface of the polystyrene-based carrier fiber inactivates the endotoxin in the blood without exerting toxicity. PMX is a method performed with a clinically applied adsorbent column (Toraymyxin 20R) containing 5 mg of polymyxin B per gram of polystyrene fiber with a priming volume of 135 mL (7). PMX has been used for the treatment of septic shock since 1994 in Japan. PMX adsorbed monocytes, activated neutrophils, and anandamide, as well as endotoxin through direct covalent bond, hydrophobic and ionic interactions, and hydrodynamics, and reduced the blood concentrations of inflammatory cytokines, plasminogen activator inhibitor 1 and adhesion molecules. PMX increased blood pressure and reduced the dosage requirement for vasopressive/inotropic agents (8). In phase 2 study, PMX-DHP therapy helped lower 28-day mortality from 53% to 32% when added to standard care (9). Multicenter randomized controlled trials of PMX therapy for septic shock are currently in progress in the USA and Europe. We believe that PMX therapy may be one of the additional treatments for septic shock.

Conclusion According to international guidelines for management of severe sepsis and septic shock, we start treatments in patients with severe sepsis and septic shock. In addition, we use rhTM in patients with sepsis-induced DIC and PMX therapy in patients with endotoxin shock as additional treatments for septic shock.

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მოყვანილია მძიმე სეფსისის და სეპტიკური შოკით გართულებული სეფსისის მკურნალობის შედეგები ადამიანის რეკომბინანტული თრომბომოდულინის და ჰემოსორბციის მეშვეობით.ადამიანის რეკომბინანტული თრომბომოდულინი გამოყენებული იყო დისსემინირებული სისხლძარღვშიდა კოაგულოპათიისას,ხოლო ჰემოპერფუზია-სეპტიკური შოკის დროს.ადამიანის რეკომბინანტული თრომბომოდულინი 380 ერთ/წთ დოზით 30 წუთის განმავლობაში შეჰყავდათ ავადმყოფის ვენაში.ხოლო ჰემოპერფუზიას აწარმოებდნენ სპეციალური სორბენტის მეშვეობით,რომელიც შექმნილი იყო ენდოტოქსინის შემბოჭავი პოლიმიქსინ-B ფიბრინის ბოჭკოებთან “მიკერებით.” აღნიშნული ღონისძიებები გამოყენებული იყო სეფსისის საერთაშორისოდ აღიარებული სტანდარტული მკურნალობის დამატებით და დადებითი შეფასება დაიმსახურა.