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EDITORIAL

Polymyxin B-immobilized fiber columns: A column to breathe new life into the treatment of interstitial lung disease?

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Abstract

Acute exacerbations of idiopathic pulmonary fibrosis (IPF) is a severe respiratory condition with high mortality rate. Direct hemoperfusion with polymyxin B-immobilized fiber columns (PMX-DHP) was originally introduced for the treatment of septic shock. Application of PMX-DHP to the treatment of acute exacerbations of IPF may improve oxygenation and survival of the patients with the disease. In addition to acute exacerbations of IPF, PMX-DHP has been applied to acute respiratory failure from various causes; an amyopathic dermatomyositis patient who developed rapidly progressive interstitial lung disease (ILD) with elevated anti-CADM-140/MDA5 autoantibody and a patient with severe amiodarone pulmonary toxicity. It is also demonstrated that PMX-DHP performed on the first day of steroid pulse therapy may improve the prognosis of patients with rapidly progressive ILDs in a case-control setting. PMX treatment decreases not only various circulating molecules but also inflammatory cells, in particular activated monocytes, producing such mediators. Although the incidence of acute exacerbations of IPF is too low for proper randomization, in order to test the effects of PMX-DHP on the disease, a cohort or case-control analytic study needs to be conducted, preferably from more than one center or research group.

Key words: Acute exacerbation; Idiopathic pulmonary fibrosis; Polymyxin B; Hemoperfusion; Interstitial lung disease

Core tip: Application of direct hemoperfusion with polymyxin B-immobilized fiber columns (PMX-DHP) to the treatment of acute exacerbations of idiopathic pulmonary fibrosis may improve oxygenation and survival of the patients with the disease. PMX-DHP performed on the first day of steroid pulse therapy may improve the prognosis of patients with rapidly progressive interstitial lung diseases in a case-control setting. PMX treatment decreases not only various circulating molecules but also inflammatory cells, in particular activated monocytes, producing such mediators. In order to test the effects of PMX-DHP on the disease, a cohort or case-control analytic study needs to be conducted, preferably from more than one center or research group.

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PMX-DHP TO BREATHE NEW LIFE INTO THE TREATMENT OF ILD

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial lung disease (ILD) of unknown cause that usually affects middle-aged and older adults. Although the natural history of IPF was thought to be a steady, gradual, and predictable decline in lung function over years, some patients may experience an accelerated phase of rapid clinical decline. When these acute declines develop without clinically apparent infection, left heart failure, pulmonary embolism, or other identifiable cause, the episodes of acute deterioration have been termed acute exacerbations of IPF[1]. In spite of the intensified therapy with broad-spectrum antibiotics, high dose glucocorticoids, and mechanical ventilation, the hospital mortality rate was as high as 78% in one study[2]. The estimates of incidence and mortality rates of acute exacerbation of IPF are discordant among different studies, probably due to substantial variations in the definition of acute exacerbation. Among them Japanese patients with IPF seem to suffer from acute exacerbation much more frequently than patients of other ethnic backgrounds[3-6].

Direct hemoperfusion through a membranous polymyxin B fiber column (PMX-DHP) is an extracorporeal technique to effectively reduce blood endotoxin levels during sepsis. The addition of PMX-DHP to conventional therapy reduced mortality in a population with severe sepsis and/or septic shock due to intra-abdominal Gram-negative infections[7]. PMX-DHP also improved the circulatory disturbance, oxygenation, and mortality in patients with ARDS[8,9]. Since then, PMX-DHP has been applied to rapidly progressive ILDs associated with various disorders (Table 1). Seo *et al*[10] applied PMX-DHP to the treatment of acute exacerbations of IPF for the first time. They successfully treated 4 of 6 patients through administration of PMX-DHP in addition to glucocorticoid therapy. The results of a study of a large and diverse cohort treated with PMX-DHP demonstrated that PMX-DHP might improve oxygenation and survival in IPF patients with acute exacerbation[11]. In addition to acute exacerbations of IPF, PMX-DHP has been applied to acute respiratory failure from various causes. An amyopathic dermatomyositis patient who developed rapidly progressive ILD with elevated anti-CADM-140/MDA5 autoantibody was successfully treated with PMX-DHP after being resistant to combined steroid and immunosuppressant therapy[12]. A patient with severe amiodarone pulmonary toxicity was also successfully treated with PMX-DHP and completely recovered, in which the patient's severe respiratory failure improved with the reduction of amiodarone and monodesethylamiodarone serum levels[13]. Hara *et al*[14] reported that PMX-DHP would be a safe and effective therapy for rapidly progressive ILDs of different etiologies resistant to initial high-dose glucocorticoid therapy. Since all of these previous reports were observational case series without controls, case-control studies were needed. We then tried to determine the effects of PMX-DHP on the prognosis of the patients with rapidly progressive ILDs in a case-control setting. A retrospective study of the clinical records of consecutive 26 patients with acute exacerbation of IPF or rapidly progressive ILDs treated in our institute demonstrated that PMX-DHP performed on the first day of steroid pulse therapy may improve the prognosis of patients with these diseases[15].

PMX treatment decreases not only various circulating molecules including monocyte chemotactic protein 1, metalloproteinase (MMP) -9, tissue inhibitor of MMP-1, neutrophil elastase, interleukin (IL)-8, IL-9, IL-12, IL-17, PDGF, and VEGF[9,14,16,17] but also inflammatory cells, in particular activated monocytes, producing such mediators[18,19]. These results suggest that removal of proinflammatory, profibrotic, and proangiogenic cytokines by PMX-fibers may improve oxygenation in the patients with rapidly progressive ILD or acute exacerbations of IPF. If the removal of these molecules were delayed, acute lung injury would progress into irreversible fibrosis resulting in fatal respiratory failure. The improved prognosis seen in the patients treated with the simultaneous administration of PMX-DHP with

Table 1 Representative reports of PMX-DHP for the treatment of intersititial lung diseases

Ref.	Publication year	Case		Comments
		n	Underlying disease	
Seo *et al*[10]	2006	6	IPF, acute exacerbation	The first trial
Abe *et al*[11]	2012	160	IPF, acute exacerbation (73)	The largest cohort study
Teruya *et al*[12]	2013	1	Amyopathic dermatomyositis	Decrease in anti-CADM140/MDA5 antibody titer observed
Sato *et al*[13]	2013	1	Amiodarone lung injury	Reduction of amiodarone and its derivative observed
Hara *et al*[14]	2011	33	Rapidly progressive ILD Resistant to steroid pulse therapy	Decrease in serum MCP-1 observed
Takada *et al*[15]	2014	26	IPF, acute exacerbation Rapidly progressive ILD	The first case-control study

IPF: Idiopathic pulmonary fibrosis; CADM: Clinically amyopathic dermatomyositis; MDA: Myeloma differentiation antigen; ILD: Interstitial lung disease; MCP-1: Monocyte chemotactic protein 1; PMX-DHP: Direct hemoperfusion with polymyxin B-immobilized fiber columns.

steroid pulse therapy may support this hypothesis.

Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients[20]. Although the best evidence is obtained from properly designed randomized controlled trials, the incidence of acute exacerbations of IPF is too low for proper randomization. In order to test the effects of PMX-DHP on the disease, a cohort or case-control analytic study needs to be conducted, preferably from more than one center or research group. Furthermore, a prospective study with predetermined eligibility criteria and outcome measures should be designed.

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