

Effect of Platelet-Activating Factor Antagonist (TCV-309) on Survival in the Canine Double Lung Transplantation Model

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Fourteen adult mongrel dogs were subjected to sequential double lung transplantation. The animals were assigned randomly to three experimental groups. Four dogs served as the control group (no treatment). Four other dogs were flushed with 4°C University of Wisconsin (UW) solution (UW flush group). The remaining six dogs were treated with platelet-activating factor antagonist (TCV-309) (PAF-antagonist group). None of the animals in the control group or the UW flush group survived more than 6 hours after transplantation. In contrast, all of the dogs in the PAF-antagonist group were extubated. The mean survival in this group was 5.2 days. PAF-antagonist (TCV-309) preserved lung function and improved survival in the canine sequential double lung transplantation model.

Key words ; double lung transplantation, platelet-activating factor (PAF),

Introduction

Experimental studies of lung transplantation usually employ a single lung transplantation model. However, in these studies, it is necessary to perform contralateral pneumonectomy, or pulmonary arterial ligation to estimate the function of the transplanted lung. In the canine double lung transplantation model, it is possible to assess the function of the transplanted lung directly, but survivals are few^{1),2)}. Recently, in single lung transplantation, PAF (Platelet-Activating Factor)-antagonist has been shown to preserve lung function in the canine model^{19),20)}. The purpose of this study is to determine whether the PAF-antagonist (TCV-309) would improve survival in the canine double lung transplantation model.

Materials and Methods

The dogs were assigned randomly to one of three experimental groups. In four dogs, sequential double lung transplantation was performed without treatment

(control group). Four other dogs were received the flushed grafts with 4°C University of Wisconsin (UW) solution (30 ml/kg, 25 cmH₂O) through the pulmonary artery cannula (UW flush group). The remaining six dogs were treated with PAF-antagonist (TCV-309). Donor dogs were treated with 600 µg/kg PAF-antagonist intravenously during harvest (200 µg/kg one shot, and then 400 µg/kg/30 minutes continuously) without UW solution flushing. Recipient dogs received 600 µg/kg PAF-antagonist during transplantation (200 µg/kg one shot, and then 400 µg/kg/30 minutes continuously) (PAF-antagonist group).

Harvesting of the donor lung :

Fourteen adult mongrel dogs weighing 9-17 kg were anesthetized with intravenous administration of pentobarbital (25 mg/kg) and ventilated with a Harvard ventilator. With the dogs in the supine position, a median sternotomy was performed and heparin (500 units/kg) was administered intravenously, and then the heart-lung block was extracted.

The right and left bronchi were divided at the distal side of two cartilage rings from the carina. The right and left main pulmonary arteries were divided at the bifurcation of the common pulmonary artery. The left atrium was separated carefully to right and left.

Transplantation and immunosuppression :

A weight-matched dogs were anesthetized as same manner with donor dogs to be used as recipient. The first side single lung transplantation was performed through a lateral thoracotomy at the fifth intercostal space. Anastomosis of the atrium, main pulmonary artery and main bronchus was respectively performed with 5-0, 6-0 and 4-0 Prolene continuous sutures. The thorax was closed and a chest tube was left in place. Then, the second side single lung transplantation was performed in the same fashion. Extracorporeal circulation was not used.

Cyclosporine (20 mg/kg/day, im) and azathioprine (1

Table 1

Dog	Weight (kg)		ischemic time (min)		survival time (hour)	outcome
	Donor	Recipient	of graft lung			
(1) controls						
No.1	10	11	right	40	1	Cardiac failure
No.2	11	12	left	110	0	Bleeding
No.3	10	11	right	35	5	Cardiac failure
No.4	9	11	left	45	4	Cardiac failure
			right	120		Cardiac failure
			right	45		Cardiac failure
			left	180		Cardiac failure
(2) UW solution flush						
No.1	12	13	left	30	0	Arrest
No.2	12	13	right	/	0	Arrest
No.3	11	15	right	40	4	Pulmonary edema
No.4	11	14	left	/	6	Pulmonary edema
			right	35		Pulmonary edema
			right	90		Pulmonary edema
			left	30		Pulmonary edema
			right	80		Pulmonary edema
(3) PAF-antagonist						
No.1	10	11	left	65	21 days	Prostration
No.2	11	14	right	200	12	Cardiac failure
No.3	17	17	left	70	4 days	Prostration
No.4	11	12	right	210	13	Bleeding
No.5	10	10	left	60	2 days	Prostration
No.6	11	10	right	165	3 days	Prostration
			left	60		Prostration
			right	230		Prostration
			left	55		Prostration
			right	190		Prostration
			left	55		Prostration
			right	190		Prostration

UW : University of Wisconsin

PAF : Platelet-activating factor

mg/kg/day, po) were administered after transplantation for the lifespan of the dogs. All dogs were maintained according to the National Society Medical Research Principles of Laboratory Animal Care.

Results

The ischemic time was 30 to 70 minutes in the first lung, and 80 to 230 minutes in the second lung. None of the animals in the control group or the UW flush group survived more than 6 hours after transplantation. In the control group, three dogs died with cardiac failure due to pulmonary dysfunction and one dog died with bleeding. In the UW flush group, two dogs died of pulmonary edema and two died of a cardiac arrest due to lung dysfunction. In contrast, all of the dogs in the PAF-antagonist group were extubated, and the mean survival time was 5.2 days (range : 0.5-21 days).

Discussion

The successful single lung transplantation technique was published by Vieth et al. using dog model in 1970³⁾, and in

clinically by Cooper et al. in 1987⁴⁾. The first clinical double lung transplantation was performed by Patterson et al.⁵⁾ in 1988. In the early days of the double lung transplantation, the bronchial anastomosis was performed at the trachea. This resulted in serious tracheal complications due to anastomotic ischemia. So recently, the sequential double lung transplantation has been performed⁶⁾. Experimental double lung transplantation using dog model was little successful, because the surgical injury was too much for dogs^{11,2)}. In this study, three dogs in PAF-antagonist group survived more than 10 days, and one of them survived for 3 weeks. It is suggested that PAF-antagonist preserved the lung function and made surgical damage less.

Platelet-activating factor (PAF) was found to be released from antigen-sensitized basophils⁷⁾. It has been shown to be produced from a variety of inflammatory cells including neutrophils⁸⁾, monocytes⁹⁾, eosinophils¹⁰⁾, macrophages¹¹⁾, lymphocytes¹²⁾, platelets¹³⁾, and also endothelial cells¹⁴⁾. The systemic effect of the PAF includes hypotension¹⁵⁾, pulmonary hypertension¹⁶⁾, increased airway resistance¹⁷⁾, and increased vascular permeability¹⁸⁾. PAF is detected in a variety of physiologic conditions including acute inflammation, endotoxic shock, and acute allergic disease. In single lung transplantation, PAF-antagonist has been shown to preserve lung function in the canine

after 24-hours preservation^{19),20)}. In our study, PAF-antagonist improved outcome. It is suggested that PAF-antagonist prevented not only the reperfusion lung injury, but the surgical damage. I guess that there are some cytoprotective effect in PAF-antagonist, however it is not clear in this study.

UW solution has an electrolyte composition similar to the intracellular fluid and contains antioxidants, stable nontoxic colloid, and lactobionate and raffinose, all of which protect the organ from cold injury. In canine experiments, UW solution made it possible to preserve lung grafts for 24 hours in single lung transplantation model^{21),22)}, liver grafts for 48 hours²³⁾, and pancreas²⁴⁾, and kidney grafts for 72 hours²⁵⁾. In this study, UW solution was not shown to be efficacious in the preservation of the lung for sequential double transplantation. However, further examination will be required, to make sure the effects of UW solution for canine double lung transplantation.

In conclusion, PAF-antagonist (TCV-309) made the survival time long in the canine double lung transplantation model.

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