PROSTAGLANDIN E1 INCORPORATED IN LIPID MICROSPHERES (LIPO-PGE1) REDUCED THE ISCHEMIA / REPERFUSION-INDUCED SPINAL CORD INJURY IN RATS BY INHIBITING NEUTROPHIL ACTIVATION

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Objective
To examine whether lipo-prostaglandin E1(Lipo-PGE1) reduces spinal cord injury (SCI) in rats by inhibiting neutrophil activation after the transient ischemia.

Introduction
Ischemic spinal cord injury is an important pathologic mechanism leading to the paraplegia observed after surgery to repair aortic aneurysms. Activated neutrophils play a pivotal role in the development of ischemia/reperfusion (I/R)-induced tissue injury. Consistent with this theory, we have recently demonstrated that leukocytopenia significantly inhibited the neutrophil accumulation as well as the severity of the motor disturbances seen after transient ischemia of the spinal cord. It has been reported that PGE1 reduced the production of cytokine-induced neutrophil chemoattractant in endotoxin-induced rat liver injury. The pharmacological effects of Lipo PGE1 has been shown to be more effective than PGE1 alone. These observations strongly suggest that Lipo-PGE1 reduces I/R-induced spinal cord injury by inhibiting neutrophil activation.

Methods
In rats, spinal cord ischemia was induced by using a balloon catheter placed into aorta. The balloon catheter inflated for 20 minutes. After the transient ischemia,motor disturbances were evaluated by using Tarlov’s motor scale and inclined plane test. Histological examination of spinal cord was performed by using hematoxylin-eosin staining 24 hours after the ischemia. Tissue levels of myeloperoxidase (MPO) as an index of neutrophil accumulations and cytokines, including tumor necrosis factor-α (TNF-α) were measured in following experimental groups: (A) Sham-operation; (B) Control; (C) Lipo-PGE1-treatment (2microg/kg, iv) were administered intravenously 5 minutes before aortic occlusion. Control rats received saline instead of Lipo-PGE1

Results
Pretreatment with Lipo-PGE1 significantly reduced motor disturbances compared with those in control animals.(Figure 1) Histological damage were markedly reduced in animals given Lipo-PGE1. Furthermore, the increases in the tissue levels of TNF-α and MPO activity in the ischemic part of the spinal cord were significantly reduced in animals that received Lipo-PGE1.(Figure 2)

Discussion & Conclusions
The present study strongly suggest that Lipo-PGE1 reduced the I/R-induced SCI by inhibiting neutrophil activation. The therapeutic mechanism(s) of Lipo-PGE1 might depend on its inhibitory effect on the production of TNF-α, which is a potent activator of neutrophils.

It has been known that neutrophils play a role in I/R-induced tissue injury by releasing various inflammatory mediators, which are capable of damaging endothelial cells. Consistent with this theory, we have recently demonstrated that leukocytopenia significantly inhibited the neutrophil accumulation as well as the severity of the motor disturbances seen after transient ischemia of the spinal cord in the present model. These observations suggested that the neutrophil accumulation was causes rather than effects of the transient ischemia-induced spinal cord injury. Thus, Lipo-PGE1 may attenuate the motor disturbances probably by inhibiting the neutrophil accumulation in ischemic spinal cord tissue in the present study, because the increase of the MPO activity in ischemic spinal cord tissue was significantly reduced by administration of Lipo-PGE1,

TNF-α is a potent proinflammatory cytokine and contributes to activated leukocyte-induced endothelial injury. PGE1 has been shown to inhibit the production of TNF-α by lipopolysaccharides-stimulated peripheral blood mononuclear cells. Consistent with these observations, PGE1 attenuated the transient ischemia-induced increases in tissue level of TNF-α and subsequent neutrophil accumulation in the spinal cord tissue of rats in the present study.

Lipo-PGE1 is a safe drug that is already used in the clinical setting, such as Buerger disease, arteriosclerosis obliterans, and peripheral vascular disease and has few known side-effects, even at relatively high dosages. Taken together,Lipo-PGE1 appears to have potential as a therapeutic agent for prevention of SCI in patients undergoing aortic aneurysm repair.

Figure 1
Change in neurologic score,inclined plane test,during first 7days after transient ischemia of the spinal cord. Open circles are control animals. Closed circles are animals given lipo-PGE1. * means S.D., **p<.01 vs control

Figure 2
Effect of lipo-PGE1 on MPO,TNF-α activity at L1 level in ischemia/reperfusion spinal cord respectively 24hours,3hours after transient ischemia. *means S.D., **p<.01 vs sham, ***p<.01 vs control

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48th Annual Meeting of the Orthopaedic Research Society
Poster No: 0645