

Effect of Inhaled Tacrolimus on Cytokines & Other Indicators of Ischemia Reperfusion Injury in Rat Lung Transplant Model

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Patients that receive a lung transplant have a 5-yr survival rate of only approximately 50% percent. This survival is significantly lower compared to other solid organ transplants. One major cause for early death after lung transplantation is primary graft failure. Ischemia reperfusion (I-R) injury is one of the major contributors to the development of primary graft failure. Underlying mechanisms of ischemic injury includes production of reactive oxygen species and up-regulation of NADPH, NFκB, nitric oxide synthase and adhesion molecules. During reperfusion these changes induce activation of neutrophils and platelets and together with the NO signaling pathway, lead to vascular damage with increase pulmonary vascular resistance and vascular permeability. I-R injury manifests clinically as diffuse pulmonary edema, with impaired oxygenation and decreased lung compliance. It also has been shown that this can predispose the allograft to the development of acute rejection.

It is hypothesized that the presence of nanoparticle Tacrolimus in the donor lung prior to donor cardiac arrest and procurement will attenuate the ischemia reperfusion injury after transplantation. This hypothesis will be tested using an established orthotopic left lung transplant model in rat. Study design: The donor in the treatment group will be pretreated with a dose of inhaled nanoparticle Tacrolimus prior to lung harvest and the graft will be stored for a 12 or 18 hour period of cold ischemia at 4 deg C in an inflated state. After transplantation the recipient will be sacrificed after 2 or 4 hours, which will constitute the reperfusion period. At the time of sacrifice, blood, BAL and lung tissue will be obtained and examined for: ABG, cytokine assay, Flow cytometry, MPO activity, wet to dry ratio and Tacrolimus drug level. It is hypothesized that there will be a down regulation in pro-inflammatory cytokines, decreased activation of macrophages and neutrophils in the graft, lowered MPO activity, improved wet to dry weight ratio and ABG in the treated group when compared to a donor group not receiving the inhaled drug.