Reduction of Primary Graft Dysfunction using Cytokine Adsorption During Organ Preservation and after Lung Transplantation

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Abstract

Despite advancements, Primary Graft Dysfunction (PGD) mortality and a lack of donor organs both continue to hinder lung transplantation. We looked at cytokine adsorption as a treatment for Acute Respiratory Distress Syndrome (ARDS) donor lungs since ARDS restricts the use of donor lungs. Using lipopolysaccharide, it caused mild to moderate ARDS in 16 donor pigs. Then, during Ex Vivo Lung Perfusion (EVLP) and/or post-transplantation utilizing extracorporeal hemoperfusion, the treatment of the lungs was performed with or without cytokine adsorption. The medication dramatically reduced post-transplant immune cell counts as well as cytokine levels during EVLP. The incidence of PGD was dramatically decreased in treated mice, and histology showed fewer symptoms of lung damage during both treatment periods. Overall, lung transplantation with cytokine adsorption was successful in restoring lung function and lowering PGD.

Keywords: Primary graft dysfunction • Lung transplantation • Acute lung injury

Introduction

Organ transplantation is still a crucial weapon in the arsenal of treatments for advanced illness, but the field is still constrained by a lack of available organs. The World Health Organization (WHO) notes that just 10% of the world's need for organ transplantation is being satisfied, which it considers to be a public health disaster. The availability of donor organs continues to constrain lung transplantation, leading to waiting list deaths. There are estimates that just 40% of potential donor lungs are chosen for transplantation due to donor lung injury and concern for impending Primary Graft Dysfunction, in striking contrast to the 83% of potential donor kidneys that are transplanted. Despite scientific progress, PGD continues to be the main cause of early death and is a major factor in the development of Chronic Lung Allograft Dysfunction (CLAD), which is the main cause of late mortality. Due to lung damage, rejected donor lungs are frequently considered irreversible. Acute Lung Injury (ALI) and the more severe Acute Respiratory Distress Syndrome (ARDS) stand as a frequent cause of severe respiratory failure among other factors that might harm donor lungs, such as aspiration, infection, or neurogenic edema. An inflammatory injury at the alveolar capillary barrier and edema in the airspaces define the damage. Interleukin-6 (IL-6) and other cytokines, such as interleukin-1 (IL-1), and Tumor Necrosis Factor (TNF), are essential signalling molecules that start, increase, and maintain inflammatory reactions both locally and systemically in ALI and ARDS. Orthotopic heart transplantation has been demonstrated to benefit from cytokine reduction via adsorption, and delayed graft function after kidney transplantation has also been shown to decrease.

Despite evidence that cytokine adsorption does not improve patient survival in septic shock, there is still disagreement on its effectiveness. By lowering the amounts of cytokines like IL-6, IL-1, and TNF, cytokine adsorbers have been used to treat sepsis or ALI. Although cytokine adsorbers are being researched for their potential in ARDS patients, their ability to save donor lungs from ARDS damage for subsequent transplantation has not been completely investigated. Previous transplantation models have used healthy lungs exposed to extended cold ischemia, but cytokine adsorption in a model of ARDS-damage to the donor before organ retrieval has not previously been assessed. Ex Vivo Lung Perfusion (EVLP) is a cutting-edge method for evaluating donor lungs that had previously been deemed undesirable. It has been employed in the successful transplant of lungs that had been EVLP-evaluated. Recently, cytokine adsorption has been tested in pre-clinical conditions in conjunction with EVLP and used as a treatment for healthy lungs exposed to prolonged cold ischemia storage. The restoration of the tissue from exposure to protracted ischemia by cytokine adsorption would allow for longer transportation durations and ease the scheduling of surgeries given that the tissue was healthy at its origin. This would be distinct from looking at lungs that were already damaged at the time of ex-plantation in an effort to increase the number of donor lungs that are still viable for transplant.

In the study, cytokine adsorption is used in the recipient during and after the transplant to assess the potential for transplanting lungs with ARDS, with the PaO_2/FiO_2 ratio serving as the primary endpoint to assess lung function. Using an extracorporeal cytokine hemoadsorber, this treatment was either given in two stages-at EVLP and post-transplantation or it was given only after the transplant (one-step treatment).

Discussion

The study investigates the use of a cytokine adsorber to treat ARDS-damaged lungs and prepare the organs for donation. The outcomes point to the utilization of a cytokine adsorber.

i. recovers pulmonary function and inflammation during EVLP.
ii. restores pulmonary function and reduces inflammation in the 48 hour follow-up post-transplantation.
iii. was correlated with a decreased incidence of PGD in recipients.

The importance of this method is based on the interest in repairing damaged lungs. Cross-circulation can help heal damaged human lungs, but it can be difficult to put xenogeneic or allogenic cross-circulation into practise. In contrast, using EVLP is a tried-and-true technique that by itself can lessen acute lung injury. EVLP is capable of treating healthy lungs subjected to prolonged cold ischemia storage when used in conjunction with a cytokine adsorber. However, the results of employing cytokine adsorption on ARDS-damaged lungs that are then transplanted and assessed for Primary Graft Dysfunction (PGD), the gold standard for determining the effectiveness of possible therapies in the clinic, have not been studied using this technique.

In order to address this, donor lungs that had an ARDS injury from LPS were transplanted and given cytokine adsorption therapy. After being administered intravenously, LPS, which is made from gram-negative bacteria's outer membrane, damages the lung's endothelial cells. An additional factor driving the breakdown is a systemic inflammatory response. The endothelium lining of the lung's vessel walls interacts with the bacterial toxin to cause programmed cell death, which is thought to be crucial to sepsis pathogenesis. Given that the condition has the potential to be clinically translated. This method of producing ARDS has been investigated in large animal models. Other methods of inducing ARDS, such as recurrent lavage and oleic acid, also cause lung disease but do so by using pathways that are not the same as those identified in ARDS patients in humans. The use of endotoxins has benefits such as technical repeatability and a pathophysiology similar to clinical ARDS. Given the significant number of organs that are rejected owing to acute lung injury, using an LPS-induced ARDS model gives an opportunity to investigate the extension of the donor pool. Numerous factors, including infection, neurogenic edema, and trauma, can lead to the development of ARDS. Damage to the central nervous system results in high stress that sets off ARDS in neurogenic edema.

Despite the variations in these diseases' etiologies, they all cause damage to the lung epithelium, which raises permeability and causes pathological pulmonary edoema and a failure of the lung to properly exchange gases. To test treatments that lessen or completely reverse the harm brought on by cellular injury, an ARDS model that accurately mimics this pathology must be used. The focus on prolonged cold ischemia storage in other EVLP and cytokine adsorption research has led to the conclusion that lung tissue may be perfused for longer but has not addressed a scenario in which the lung is already injured. The problem of improving donor tissue injured before storage would be addressed by the resemblance of LPS-induced ARDS to a clinical situation of acute lung injury mixed with the current context of an additional cytokine adsorber. Pathologically, ARDS has previously been defined by diffuse alveolar damage in which hyaline membranes distinctively line alveolar spaces. Edema and alveolar hemorrhage may be present as endothelial cells and pneumocytes undergo necrosis. In the model included in the study, mild hyaline membrane formation was observed in the tissue obtained following LPS administration. Further evidence of ARDS onset was supplemented by the blinded scoring conducted, which graded samples based on proteinaceous debris, thickening of the alveolar walls, hemorrhage, and atelectasis, and showed significant histological damage in LPS-treated lungs as compared to controls. Additionally, all donors' levels of early response cytokines specifically, IL-6, IL-8, IL-1, and TNF-dramatically increases after receiving LPS. It has been previously noted that ARDS causes an increase in these cytokines. TNF-, IL-1, IL-6, IL-8, and IL-18, proinflammatory cytokines, have even been proposed as indicators of morbidity and mortality in ARDS. TNF-, a proinflammatory cytokine that functions downstream of pattern recognition receptors and has been implicated in the aetiology of ARDS, has also been examined for its potential role in morbidity and death in ARDS.

The transplanted lungs are observed for 48 hours to test the effectiveness of the adsorption; it discovered that both the one-step and two-step approaches resulted in higher hemodynamic stability and a decreased requirement for inotropic support. This is consistent with research on cytokine adsorption in patients with septic shock, in whom the therapy resulted in lower noradrenaline levels. Additionally, a randomized controlled experiment in septicemia indicated that lowering IL-6 levels reduced inflammation. Recipients in the model were shown to have lower cytokine levels, and the treated groups' neutrophil and total white blood cell counts both decreased significantly. Since clinical investigations have demonstrated elevated IL-6 and TNF in the plasma and BALF samples of those who do not survive as well as a link between IL-6 and more time spent on breathing, decreasing cytokine levels are especially crucial in ARDS.

The inflammatory response in ARDS is mediated by activated macrophages, which release TNF, which in turn activates neutrophils and, along with other mediators, causes the recruitment of inflammatory cells to the alveoli.Histological analysis of the study's treated lung tissue revealed a decline in accumulated immune cells. This supports the conclusion that cytokine adsorption aids in the reduction of inflammation. It is important to note that the lung injury score for the one-step treatment was comparable to the scores for the two-step and control groups, and this difference was reflected in the TUNEL staining. This would suggest that the cytokine adsorber, when given both during EVLP and post-transplantation as opposed to only after transplantation, has an additive impact. It's interesting to note that after 2 hours of EVLP, the graft in one recipient in the two-step treatment group dramatically edematized the lungs. Following EVLP, the trachea could be drained of up to 1.2 litres of fluid, and during the transplant, adjustments were made to fit the expanded graft into the patient's chest. Nearly all of the edema had been reabsorbed by the conclusion of the post-transplant monitoring period, and the graft displayed excellent gas exchange capacity and no symptoms of PGD, indicating that the cytokine adsorption was particularly significant during hemoperfusion post-transplant. These cases of septicemia and edema show how the inclusion of a cytokine adsorber may help restore unacceptably damaged donor lungs in the crucial days just after transplantation. Given the mortality linked to PGD, indicated by PaO_2/FiO_2 ratios up to three days after surgery, the days after lung transplantation are crucial. In this investigation, two of four one-step treated recipients and five of six two-step treated recipients had no PGD at all with the addition of a cytokine adsorber in the first 12 hours following transplantation. In comparison, five out of six recipients who were not treated developed severe grade 3 PGD. Again, when compared to the rate of PGD in the one-step therapy group, the two-step treatment appears to have an additive effect. When comparing the PaO_2/FiO_2 ratios at the conclusion of the experiment, this additive impact of therapy in both EVLP and post-transplant (the two-step group) with respect to post-transplant alone (one-step group) is further highlighted. The two-step recipients are much higher than the one-step alone, in addition to the fact that both groups have improved in comparison to the non-treated recipients. Leukocyte numbers in particular were dramatically reduced in the treated animals' immune cell populations. As a result, when the donor organ begins to receive re-perfusion in the early post-transplantation phase, the body may be more amenable to accepting a new organ. The decreased incidence of PGD could be attributed to the lower immune response provided by a cytokine adsorber.

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