Distinct Phthophysiologic Mechanisms of Septic Acute Kidney Injury: Role of Immune Suppression and Apoptosis

So-Young Lee[1], Hee-Young Lee[2], Yoon-Suk Go[2]
Sang-Kyung Jo[2], Won-Yong Cho[2], Hyoung-Kuy Kim[2]

Department of Nephrology[1] Eulji University Hospital Seoul Korea
Department of Nephrology[2] Korea University Hospital Seoul Korea

Introduction: Sepsis is the most common cause of acute kidney injury (AKI) in critically ill patients and the presence of AKI is known to be associated with worse prognosis. However, the mechanisms leading to AKI in sepsis remain elusive and is thought to be caused mostly by altered renal hemodynamics. In addition, sepsis is traditionally considered as an excessive systemic inflammatory response, however, several clinical trials that inhibit inflammation were found to have no effect and according to recent observations, sepsis induced organ dysfunction might be associated with paradoxical immune suppression. The purpose of this study was to examine the pathophysiology of septic AKI focusing on immune suppresion and apoptosis of kidney and/or immune cells by providing on-site quantitative comparison between septic vs ischemia/reperfusion (I/R) induced AKI, a well known disease mediated by activation of innate immunity.

Methods: At 24 hrs after cecal ligation & puncture (CLP) or I/R injury, biochemical, histologic kidney injury and cytokine profiles in plasma, kidney were compared. Apoptosis of immune cell and renal cell was assessed by TUNEL staining and quantified by measurement of activity of caspase 3 in spleen and kidneys. We also examined the effect of caspase 3 inhibition on apoptosis of immune cell, renal tubular cell as well as on renal function. Finally, we observed CD4+CD25+regulatory T cell (Tregs) frequency and the effect of depletion of these cells in renal function was examined in septic mice and compared with that in I/R mice where depletion of these cells was associated with worse renal function.

Results: Despite comparable degree of renal dysfunction, acute tubular necrosis or inflammation were hardly observed in septic kidneys. However, tubular cell apoptosis was prominent and the number of TUNEL positive cells and caspase 3 activity showed a positive correlation with plasma creatinine. Pretreatment with caspase 3 inhibitor resulted in attenuation of renal dysfunction with reduced apoptosis. In assessment of systemic immune status, septic AKI was associated with increased anti-inflammatory cytokine, IL-10 in plasma and kidneys and also showed massive immune cell apoptosis with increased relative percentage of Tregs. In contrast to I/R injury that depletion of Tregs aggravates renal injury, depletion of these cells resulted in significant renoprotective effect.

Conclusion: Our data showed a link between apoptosis, immune suppression and kidney dysfunction during sepsis and suggest that inhibition of apoptosis might be useful to decrease mortality or organ dysfunction. Future studies are needed to clarify the exact pathophysiology of this devastating disease to develop various strategies to improve overall prognosis in sepsis.

Key Words: 패혈증, 급성 신손상, 아포프토시스
Sepsis, Acute kidney injury, Apoptosis, Immune suppression