패혈증성 급성 신손상에서 덱사메타손의 효과

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Dexamethasone Attenuates Septic AKI by Reducing Immune Cell and Renal Tubular Cell Apoptosis

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Background: Sepsis is the most common cause of acute kidney injury (AKI) with high mortality in critically ill patients whereas our understanding of pathogenesis and treatment for septic AKI has remained limited. According to surviving sepsis campaign, low dose glucocorticosteroids (GCs) can be used in septic shock patients and it also has been known to reduce renal dysfunction in rat endotoxemia model. The purpose of this study was to investigate the pathophysiology of septic AKI and the effect of GCs in septic mice.

Methods: Sepsis was induced by cecal ligation and puncture (CLP) method in 8-10wk-old C57BL/6 mice. Saline or dexamethasone (DEX) dissolved in saline was administered right after CLP. We examined hemodynamic, biochemical and histological changes in a time-course manner. Blood pressure (BP) was measured using tail-cuff plethysmography every hour, and echocardiograms were taken at 0, 6, 12 and 24hr in un-anaesthetized mice. Apoptosis was assessed by TUNNEL staining and caspase-3 activity in kidney, spleen and heart tissue.

Results: CLP resulted in mixed gram negative and positive bacterial peritonitis with multiple organ dysfunction (elevated LDH, ALT, creatinine), and mortality at 24hr was 21.7%. Mean arterial BP was significantly decreased (91±10 to 64±19 mmHg, $p<0.01$), starting at 3hr after CLP. Fractional shortening (FF) that estimates cardiac systolic function increased and remained high until 24hr (from 54.8±1.1 at baseline to 60.8±3.6% at 24 hr), suggesting that CLP induced hyperdynamic "warm shock". Serum creatinine started to increase 12hr after CLP, from 0.22±0.03 at baseline to 1.2±0.14 mg/dL at 24hr. In contrast to heart, where there was no apoptosis, massive immune cell apoptosis were observed in spleen even at 3hr after CLP. Renal tubular apoptosis was also prominent in cortex and outer medulla, while there was no evidence of tubular necrosis or inflammation. DEX treatment had no effect on BP or FF. However mice with CLP+DEX showed significantly reduction of immune cell and renal cell apoptosis and this was associated with significantly lower mortality and reduced serum creatinine level.

Conclusion: These results suggest that immune cell apoptosis as well as renal cell apoptosis play an important role in the mortality and organ dysfunction in sepsis. The therapeutic potential of GC is thought to be mediated by their direct antiapoptotic effect on immune and renal cells, but not by an effect on hemodynamic parameters.

Key Words: 패혈증, 급성 신손상, 덱사메타손
Sepsis, Acute kidney injury, Dexamethasone