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만성신부전 동물 모델에서 phosphodiesterase 5 길항제와 N-acetylcysteine이 방사선 조영제 유발 신병증에 미치는 영향

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Renal Protective Effects of Phosphodiesterase-5 Inhibitor on Radiocontrast-Induced Nephropathy in Chronic Kidney Disease

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Backgrounds: Radiocontrast agent causes damage to the kidney by contracting renal arterioles and by direct toxic effect to tubular epitheliums. Phosphodiesterase-5 inhibitors (PDEi-5) are known to have not only vasodilative but also anti-oxidative effect. We investigate whether PDEi-5 ameliorates radiocontrast induced nephropathy (CIN) and N-acetylcysteine (NAC) has benefits and/or synergistic effects with PDEi-5 in rat model of chronic kidney disease.

Methods: 48 male SD rats were performed 5/6 nephrectomy and divided into 4 groups: vehicle, PDEi-5 (1.5 mg/kg) treated group, NAC (60 mg/kg) treated group, and combination group. All rats received drugs 4 times every 12 hrs. Radiocontrast agent (Iopromide 10 ml/kg) was injected 1 hour after 3rd injection. Blood and 24 hours urine were taken every 48 hrs for 6 days. Rats were sacrificed at 2nd and 6th day of experiment. Serum NGAL, cystatin C, BUN, and creatinine were measured and creatinine clearances were calculated. The expression of iNOS, eNOS, MCP-1, and nitrotyrosine were measured and TUNEL stains were performed in kidney.

Results: There were no significant changes of BUN and creatinine levels among groups. PDEi-5 (0.43±0.13 mg/ml/100 g) and NAC group (0.39±0.79 mg/ml/100 g) had significant improvements of creatinine clearance compared to vehicle group (0.25±0.87 mg/ml/100 g) at 6th day. Serum NGAL significantly decreased in PDEi-5 (68.3±5.5 vs 82.79±11.25 ng/mL, 64.1±10.1 vs 83.6±7.6 ng/mL) and NAC group (58.3±19.6 vs 82.79±11.25 ng/mL, 53.8±19.3 vs 83.6±7.6 ng/mL) compared to vehicle group at 2nd and 4th day respectively. Serum cystatin C also significantly decreased in PDEi-5 (5.28±0.9 ng/mL) and NAC group (5.8±0.66 ng/mL) compared to vehicle group (7.53±1.3 ng/mL) at 2nd day. At 2nd day, eNOS expression was significantly decreased in PDEi-5 group.

MCP-1 and nitrotyrosine expression decreased in PDEi-5 and Combination group at 2nd day. TUNEL stain showed decreased apoptosis in PDEi-5 and combiantion group but not in NAC group at 2nd day. At 6th day, there were no differences in TUNEL staining among the groups.

Conclusion: these results suggest that PDE-5i may prevent and ameliorate CIN via anti-oxidative and anti-apoptotic potentials, but there were no synergic effects of combination of PDE-5i and NAC on CIN.

Key Words: 방사선 조영제
Phosphodiesterase-5 inhibitor, N-acetylcysteine, Contrastmedia