CO TREATMENT OF BOSENTAN & VALSARTAN ATTENUATES RENAL INJURY IN UNILATERAL URETERAL OBSTRUCTED MICE.

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INTRODUCTION:

Both endothelin-1 (ET-1) and the renin-angiotensin system (RAS) may play important roles in renal fibrosis in the obstructed kidney. However, there have been few clear demonstrations of a relationship between their activation and additive or synergistic roles in renal fibrosis. We investigated the protective roles and relationship between renal RAS and ET-1 in unilateral ureteral obstruction (UUO) mice.

METHODS:

8-week-old male C57BL/6 mice were divided into seven groups: sham, bosentan+sham, valsartan+sham, vehicle+UUO, bosentan+UUO, valsartan+UUO, and valsartan+bosentan+UUO. Valsartan and bosentan were administered orally using an NG tube (valsartan 10 mg/kg/day, bosentan 100 mg/kg/day for 8 days, after which the molecular and structural kidney parameters were evaluated. Bosentan treatment elevated plasma renin activity, renal renin, and AT1R expression in UUO mice.

RESULTS :

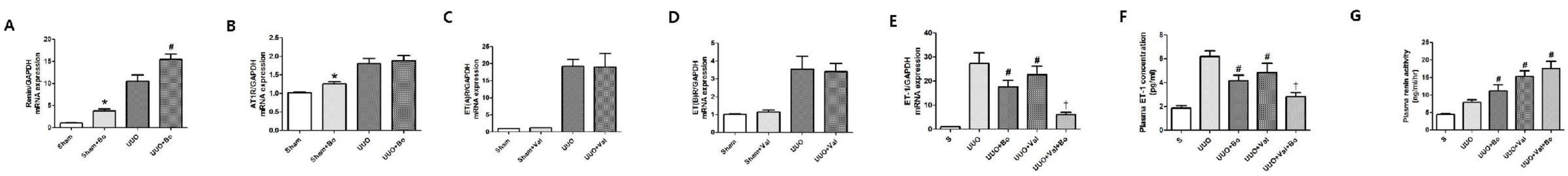

Figure 1. Relationship between ET-1 and RAS. Bosentan treatment increased the mRNA expression of renin in sham and UUO kidneys (A). It also elevated the mRNA expression of AT1R in sham kidneys. However, there were no significant differences in mRNA expression of AT1R in UUO kidneys (B). Valsartan treatment did not affect renal ET(A)R or ET(B)R mRNA expression in UUO kidneys (C and D). Bosentan and valsartan significantly reduced renal ET-1 mRNA expression and plasma levels of ET-1 compared to vehicle-treated UUO mice. Co-treatment with bosentan and valsartan significantly reduced renal ET-1 mRNA expression and plasma levels of ET-1 compared to single-treated UUO mice (E and F). Plasma renin activity (PRA) was higher in UUO mice than in sham mice. Plasma renin activity (PRA) was higher in valsartan- and bosentan-treated UUO mice compared to vehicle-treated UUO mice (G). * $P < 0.05$, vs. sham, # $P < 0.05$, vs. UUO, † $P < 0.05$, vs. single treatment in UUO.

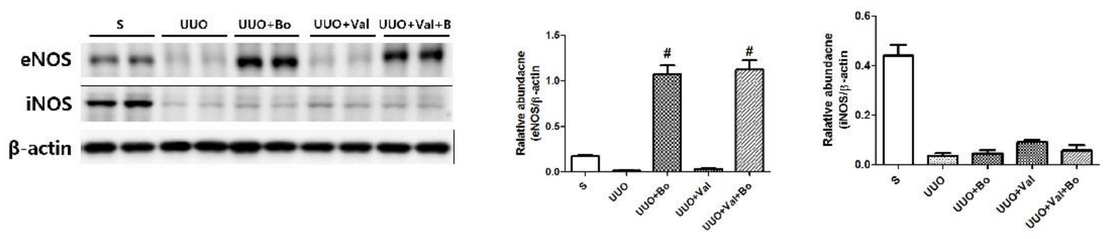

Figure 2. Representative kidney tissue sections immunostained for eNOS and iNOS. UUO kidneys showed decreased expression of eNOS and iNOS in vehicle-treated mice. Bosentan treatment increased eNOS expression in the kidneys. In addition, co-treatment of bosentan and valsartan increased eNOS expression. # $P < 0.05$, vs. UUO.

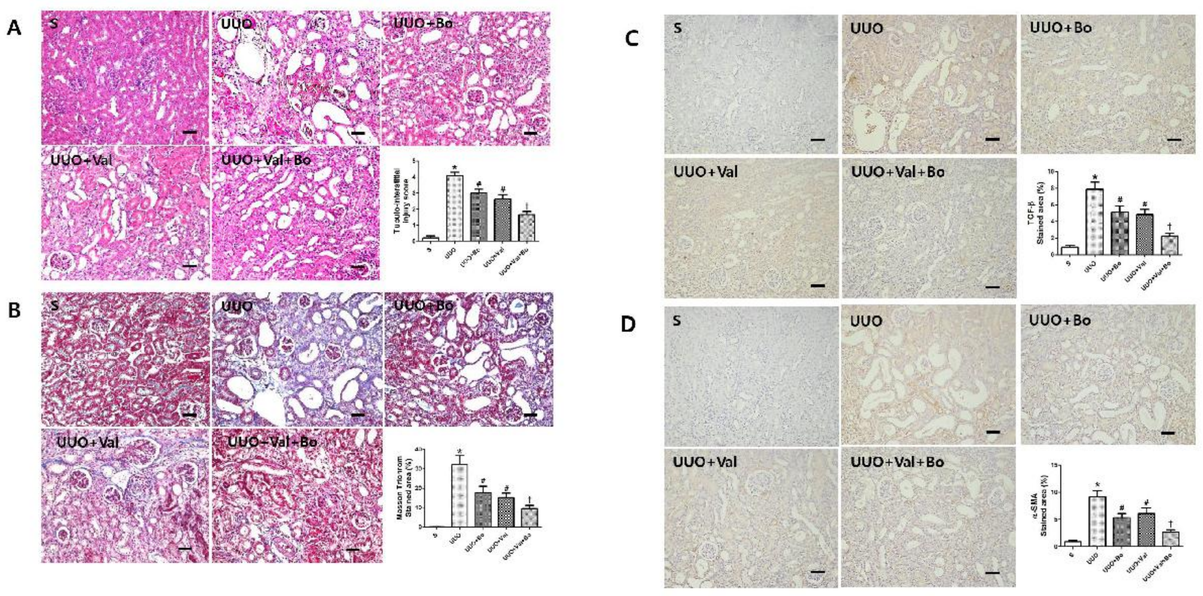

Figure 3. Representative kidney tissue sections with H&E staining, Masson's trichrome staining, and immunostaining for TGF-β α-SMA. (A) Bosentan and valsartan treatment significantly reduced renal injury scores in UUO kidneys. Co-treatment with bosentan and valsartan reduced renal injury scores significantly compared to single treatments (B) The blue-stained fibrotic area of the kidney was greater in vehicle-treated UUO mice than in sham mice, and co-treatment with bosentan and valsartan reduced the fibrotic area significantly in UUO kidneys compared to single treatments (C and D). The α-SMA-positive area (dark brown, C) of the kidney and TGF-β-positive area (dark brown, D) were greater in vehicle-treated UUO mice than in sham mice. Bosentan and valsartan treatment significantly reduced the α-SMA- and TGF-β-positive areas in UUO kidneys (N), as did co-treatment, compared to single treatments. * $P < 0.05$, vs. Sham, # $P < 0.05$, vs. UUO, † $P < 0.05$, vs. single treatment in UUO.

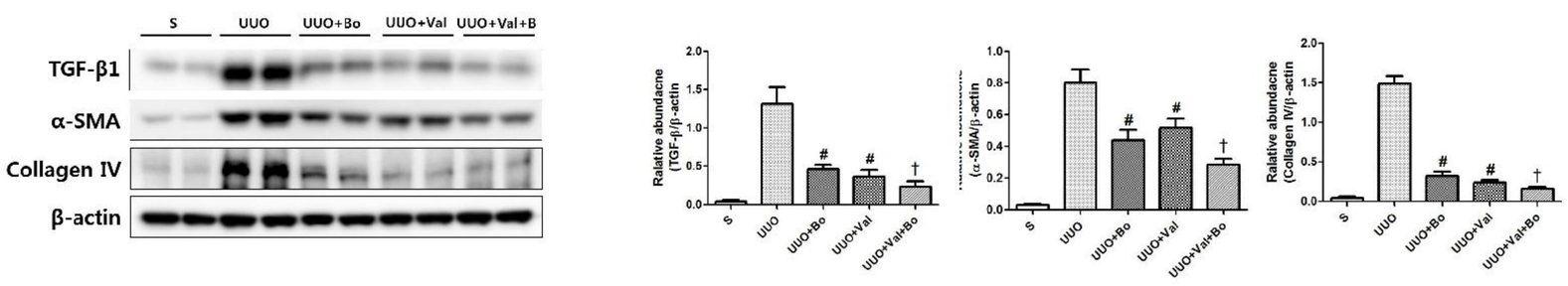

Figure 4. Representative kidney tissue sections immunostained for TGF-β, α-SMA, and collagen IV. The levels of TGF-β, α-SMA, and collagen IV were greater in vehicle-treated UUO mice than in sham mice, and bosentan and valsartan treatment significantly reduced the levels of each in UUO kidneys (N), as did co-treatment, compared to single treatments. # $P < 0.05$, vs. UUO, † $P < 0.05$, vs. single treatment in UUO.

CONCLUSION :

Bosentan and valsartan acted complementarily, and co-treatment with both drugs had an additive protective effect against renal fibrosis.

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