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Cardioprotective effect of losartan alone or in combination with remote ischemic preconditioning on the biochemical changes induced by ischemic/reperfusion injury in a mutual prospective study with a clinical and experimental animal arm

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Background: Losartan at therapeutic doses have beneficial cardiovascular protective effects. The aim of the study was to investigate possible cardio-protective effect of this drug alone or in combination with remote ischemic Preconditioning (RIPC) on the biochemical changes induced by ischemic/reperfusion injury (I/R) in a combined prospective study with a clinical and experimental animal arm.

Methods: Thirty consecutive patients undergoing elective percutaneous coronary intervention (PCI) were recruited. Patients were divided into three groups (10 each): Group-1: Control group which includes patients who were exposed to PCI without any preconditioning. Group-2: Patients who were maintained on losartan at a dose 50-100 mg/day for at least one month before undergoing PCI. Group-3: Patients who were maintained on losartan at a dose 20 mg/day for at least one month before the day of PCI that was preceded by RIPC. On the other hand; sixty adult male New Zealand white rabbits weighing 1500-2500 grams have been used in the experimental arm of the study. The rabbits were divided into 6 groups (n=10): Group I (control), Group II (sham), Group III (I/R as 30 min ischemia followed by 120 min reperfusion), Group IV (regular losartan 20 mg/kg for 40 days orally followed by I/R), Group V (I/R preceded by RIPC) and Group VI (exactly similar to groups IV in exposure to drug but I/R was preceded by RIPC). Biochemical parameters reflecting cardiac damage due to I/R were measured in blood for all clinical and experimental groups for comparison. These parameters included tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), nitric oxide (NO), troponin I (cTnI), creatine kinase MB (CK-MB) and C-reactive protein (CRP). In groups III, IV, V and VI blood sample were withdrawn following I/R.

Results: It was found that patients who received pretreatment with losartan before undergoing PCI and patients who received the drug and exposed to RIPC before doing PCI developed significant reduction ($P<0.05$) in serum levels of IL-6, TNF-α, CRP, cTnI and CK-MB associated with significant increase ($P<0.05$) in serum level of NO compared with corresponding values in patients who were exposed directly to PCI without losartan pretreatment and/or RIPC. In Group III, I/R induced significant elevation in all biochemical parameters except NO which was significantly reduced compared with control or sham groups. In Group IV, RIPC showed a protective effect against I/R injury as evidenced by significant reduction ($P<0.05$) in the levels of TNF-α, IL-6, CK-MB and CRP while the level of NO was significantly ($P<0.05$) increased compared with Group III. In Group V, losartan significantly ($P<0.05$) reduced the levels of TNF-α, IL-6 and CRP compared with Group III but no elevation in NO was recorded in the group. In Group VI, losartan combined with RIPC showed a possible synergistic protective effect as the levels of TNF-α, IL-6, CK-MB and CRP were significantly reduced ($P<0.001$) while NO significantly ($P<0.001$) increased compared with Group III.

Conclusions: Pretreatment with losartan combined with RIPC can exert a synergistic cardioprotective effects by reducing the possible biochemical changes related to ischemic reperfusion injury.

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