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Effect of Nicorandil, Bone Marrow-Derived Mesenchymal Stem Cells and Their Combination in Isoproterenol-Induced Heart Failure in Rats

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Abstract : Aim: The aim of the present study was to investigate whether combined nicorandil and bone marrow-derived mesenchymal stem cells (BMDMSC) treatment could offer an additional benefit in ameliorating isoproterenol (ISO)-induced heart failure in rats. Methods: ISO (85 and 170 mg/kg/day) was injected subcutaneously for 2 successive days, respectively. By day 3, electrocardiographic changes were recorded and serum was separated for determination of CK-MB level for confirmation of myocardial damage. Nicorandil (3 mg/kg/day) was then given orally with or without a single i.v. BMDMSC administration. Electrocardiography and echocardiography were recorded 2 weeks after beginning of treatment. Rats were then sacrificed and ventricles were isolated for estimation of vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF-α) and transforming growth factor-beta (TGF-β) contents, caspase-3 activity as well as inducible nitric oxide synthase (iNOS) and connexin-43 protein expressions. Moreover, histological analysis of myocardial fibrosis was performed and cryosections were done for estimation of homing of BMDMSC. Results: ISO induced a significant increase in ventricles/body weight ratio, left ventricular end diastolic (LVEDD) and systolic dimensions (LVESD), ST segment and QRS duration. Moreover, myocardial fibrosis as well as VEGF, TNF-α and TGF-β contents were significantly increased. On the other hand, connexin-43 protein expression was significantly decreased, while caspase-3 and iNOS protein expressions were significantly increased. Combined therapy provided additional improvement compared to cell treatment alone towards reducing cardiac hypertrophy, fibrosis and inflammation. Furthermore, combined therapy induced significant increase in angiogenesis and BMDMSC homing and prevented ISO induced changes in iNOS, connexin-43 and caspase-3 protein expressions. Conclusion: Combined nicorandil/BMDMSC treatment was superior to BMDMSC alone towards preventing ISO-induced heart failure in rats.

Keywords : fibrosis, isoproterenol, mesenchymal stem cells, nicorandil
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