PROPHYLACTIC VERSUS THERAPEUTIC POTENTIAL OF LOW-DOSE ERYTHROPOIETIN IN HYPOXIC EXPERIMENTAL DIABETIC NEPHROPATHY

Rehab H Ashour1, Abd El-Motaal M Fouda1, Fatma A Moustafa2, Manal I Fouda3, Farida M El-Banna1 and Mohamed A Saad1
1Mansoura Faculty of Medicine, Clinical Pharmacology Dept, Mansoura, Egypt, 2Mansoura Faculty of Medicine, Pathology Dept, Mansoura, Egypt, 3Mansoura Faculty of Medicine, Clinical Pathology Dept, Mansoura, Egypt

Introduction and Aims: The novel hypoxia theory of chronic kidney diseases (CKD) including diabetic nephropathy (DN) and its role in progression of renal injury is well documented. Erythropoietin (EPO), secreted primarily by renal cortical fibroblast-like cells in response to renal hypoxia, exerts a series of cytoprotective effects. The present study was formulated to test the role of endogenous EPO in relation to novel hypoxia theory in experimental DN and whether improving renal hypoxia could be achieved by low-dose rHuEPO with subsequent effects on DN progression.

Methods: Forty male SD rats were randomly divided into six groups: control naïve group (n=8), control-rHuEPO group (n=6), untreated streptozotocin (STZ) diabetic groups sacrificed both 20 (n=6) and 28 weeks (n=8) after induction of diabetes, EPO prophylactically-treated diabetic group (n=6, 150 U/kg, S.C., TIW), EPO therapeutically-treated diabetic group (n=6). EPO treatment was continued either for the 28 weeks (prophylactic intervention) or the last 8 weeks (therapeutic intervention). Albuminuria was evaluated every four weeks. Assessment was done by renal function tests, blood pressure measurement, renal vein oxygen tension (RV O2T) and electrolyte levels, plasma active-renin concentration (PRacC), endogenous EPO concentration by Rat EPO immunoassay ELISA kit, and complete hematological profile, together with renal histopathological examination using Periodic Acid-Schiff (PAS) and Masson trichrome-stained sections.

Results: STZ-induced diabetic rats developed progressive albuminuria, renal dysfunction, and significant glomerular changes 28 weeks after induction of diabetes. Contrarily to expectations and in spite of improving diabetic-renal hypoxia, administration of rHuEPO for 28 weeks led to marked albuminuria progression with profound increase of PRacC and plasma EPO concentration; together with picture of acute tubular injury on renal histopathological examination. EPO therapeutically-treated diabetic group showed some beneficial effects on DN progression manifested as significant decrease of plasma creatinine, final albuminuria by 27.8 % with significant increase of creatinine clearance, and significant improvement of RV O2T compared to untreated-diabetic control group at 28 weeks after induction of diabetes. These results were supported by significant decrease of glomerular changes score on histopathological examination. Plasma EPO concentration didn’t show significant change compared to untreated diabetic control groups.

Conclusions: In conclusion, prophylactic low-dose rHuEPO resulted in deterioration of DN together with increase in PRacC and plasma EPO concentration in spite of improved diabetic renal hypoxia. On the other hand, improvement was obtained in the diabetic group treated with EPO after 20 weeks of diabetes induction. It is possible that intervention with rHuEPO at this particular time interrupts the cycle of renal hypoxia-endogenous EPO secretion and thus prevents DN progression. In addition, this study has questioned the new dilemma about a renoprotective role of low-dose rHuEPO in the setting of chronic renal injuries and proved that this low-dose rHuEPO led to elevation of blood pressure and hematocrit even when used only for 8 weeks.

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