

## **Melatonin improves therapeutic potential of mesenchymal stem cells- derived exosomes against renal ischemia-reperfusion injury in rats**

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**Background:** Renal ischemia-reperfusion injury (RIRI) is one of the main causes for acute kidney injury (AKI). Many previous attempts failed to adopt a suitable treatment regimen for AKI. Recently, combined melatonin (Mel) and mesenchymal stem cell (MSC)-derived exosomes (Exo) therapy gave a promising therapeutic option for acute liver ischemic injury, however this treatment approach has not been tested against RIRI yet.

**Aim:** This study tested the hypothesis that administration of exosomes derived from MSCs preconditioned with Mel gave best protection against RIRI as compared to therapy by MSCs or exosomes derived from non-preconditioned MSCs. Materials and Methods: Female adult rats (n = 50) equally divided into control group, sham group, RIRI group (induced by bilateral renal arteries clamping), RIRI + MSCs group (1 x10<sup>6</sup> bone marrow derived MSCs), RIRI + Exo group (250 µg Exo derived from non-preconditioned MSCs), and RIRI + Mel + Exo group (250 µg Exo derived from Mel preconditioned MSCs). MSCs or Exo was bilaterally injected once in each renal artery during reperfusion.

**Results:** The obtained results revealed notable improvement in RIRI following all treatment (MSCs, Exo, and Exo+Mel) with best improvement in Exo+Mel group as evidenced by: 1) decreased kidney injury histopathological score; 2) reduced blood levels of kidney damage markers [blood urea nitrogen (BUN) and creatinine]; 3) declined oxidative stress status (MDA level, HIF1 $\alpha$  gene, and NOX2 protein); 4) increased anti-oxidant status (HO1 gene, and SOD, CAT, GPx activities); 5) declined apoptosis (caspase 3 activity and mRNA, and PARP1, Bax genes), 6) induced anti- apoptotic effect (Bcl2 gene); 7) inhibition of inflammation (decreased ICAM1, IL1 $\beta$ , NF $\kappa$ B and increased IL10 genes); 8) improved regeneration (bFGF, HGF and SOX9 proteins); and 9) enhanced angiogenesis (VEGF gene).

**Conclusion:** Treatment with exosomes derived from MSCs preconditioned with melatonin gave best protective effect against renal ischemia-reperfusion injury as compared to therapy by non-preconditioned MSCs or their exosomes.

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