Acute treatment with bone marrow-derived mononuclear cells attenuates the organ injury and dysfunction induced by haemorrhagic shock in the rat

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Recent evidence suggests that stem cells such as bone marrow-derived mononuclear cells (BMMNC) have a dual role as they have both regenerative and paracrine properties. It is hypothesised that proteins such as IL-8, VEGF, SDF-1 and HGF; which are secreted by stem cells *in vivo* may be protective in animal models of ischemia and reperfusion injury (IRI) [1]. Here we investigate the effects of BMMNC on the multiple organ failure induced in a rat model of haemorrhagic shock (HS). Male Wistar rats were anaesthetised using sodium thiopentone (120 mg/kg i.p. maintained using ~10 mg/kg i.v. when required) and cannulation of the trachea, carotid artery and jugular vein was performed. The anaesthetised rats were then subjected to haemorrhage by withdrawing blood via the cannula in the carotid artery to reduce mean arterial pressure to 35 ± 5mmHg for 90 min. This was followed by resuscitation with 20 ml/kg Ringer's lactate administered over 10 min and 50% of the shed blood over 50 min, both administered via the cannula in the jugular vein. Rats were sacrificed 4 h after the onset of resuscitation. BMMNC were freshly isolated from rat tibias and femurs using Ficoll density gradient centrifugation and BMMNC (1×10^7 cells per rat in 1 ml/kg PBS, i.v.) were administered on resuscitation. Administration of BMMNC in HS-rats was found to significantly attenuate renal dysfunction, and hepatic and neuromuscular injury when compared to vehicle (PBS) treated HS-rats (Data is mean ± SEM, analysed using one-factorial ANOVA and Dunnett's post test, $P<0.05$). Arterial blood gas analysis was performed at the end of the experiment to quantify the degree of metabolic acidosis induced by HS. HS-rats treated with BMMNC were less acidotic when compared to HS-rats treated with PBS (base deficit: 1.77 ± 1.73mM vs. -3.90 ± 1.19mM, Data is mean ± SEM, analysed using two-factorial ANOVA and Bonferroni's post test, $P<0.05$). Thus, administration of BMMNC on resuscitation attenuates the multiple organ failure associated with HS in the rat. In order to investigate the possible mechanism by which BMMNC mediate this protection, western blot analysis was performed on lung and liver samples obtained from rats 4 h after the onset of resuscitation. It was found that Akt expression was significantly increased (Data expressed as mean fold difference when compared to sham ± SEM, Lung: 0.48 ± 0.08 vs. 0.74 ± 0.08. Liver: 0.66 ± 0.71 vs. 1.07 ± 0.12, analysed using one-factorial ANOVA and Dunnett's post test, $P<0.05$) and NF-κB expression was halved (Lung: 2.33 ± 0.12 vs. 1.10 ± 0.28. Liver: 2.29 ± 0.12 vs. 1.10 ± 0.18) in samples obtained from HS-rats treated with BMMNC when compared to HS-rats treated with PBS. This suggests that BMMNC may activate anti-apoptotic signalling pathways thus protecting organs against the IRI induced by HS.

Di Santo S et al., Novel cell-free strategy for therapeutic angiogenesis: in vitro generated conditioned medium can replace progenitor cell transplantation, PLoS ONE 4(5): e5643, 2009.