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# Umbilical cord stem cell-derived exosomes have neuroprotective potential in a model of preterm white matter injury

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**Objective:** Survivors of preterm birth are at risk to suffer from white matter injury (WMI) leading to subsequent neurodevelopmental deficits. Preterm-specific WMI is characterized by a disruption of normal developmental myelination of the brain. In animal models of WMI, Wharton's jelly mesenchymal stem/stromal cells (WJ-MSC) derived from umbilical cords restore normal myelination, in part through the release of cell-derived extracellular vesicles like exosomes. We aimed to test the therapeutic potential of WJ-MSC-derived exosomes in an animal model of preterm WMI.

**Study Design:** We isolated exosomes from WJ-MSC culture supernatants using serial centrifugation. Consistent with the etiology of WMI in preterm infants, we introduced brain injury in 3-day old rat pups with lipopolysaccharide i.p. and unilateral carotid artery cauterization followed by hypoxia (8% O2). As a treatment, animals received an intranasal administration of infrared-labeled exosomes which were traced inside the bodies of the animals. In a short-term experiment, we analyzed cortical apoptosis and myelination using TUNEL-assay, real-time RT-PCR and Western blot. In a long-time experiment, we tracked the survival and learning capacity of the animals using the Morris water maze assay.

**Results:** Intranasally administered exosomes rapidly translocated to the brain and arrived within 30 min after administration. Treated animals exhibited reduced cortical apoptosis and diminished hypomyelination 9 days after brain injury as the exosomes rescued the loss of myelin basic protein ($p<0.05$). Exosome treatment doubled the animal's overall survival rate ($p<0.01$) and improved their learning capacity ($p<0.05$) 1 month after WMI.

**Conclusion:** Treatment with WJ-MSC-derived exosomes improves survival, partially restores normal developmental myelination and alleviates associated neurodevelopmental deficits. Intranasal administration of WJ-MSC-derived exosomes represents a minimally-invasive and effective treatment for WMI.