Abstract

Background: Although traumatic brain injury (TBI) is a significant cause of morbidity and mortality worldwide, there have been few significant therapeutic advances in recent years. Preclinical studies have explored the potential of adipose-derived stem cells (ADSCs) to improve neural function and reduce brain damage in animal models following TBI. This systematic review aims to assess and synthesize the current evidence on the efficacy of ADSCs in animal models with induced TBI.

Methods: Following PRISMA guidelines, we systematically searched *Scopus*, *PubMed*, *Web of Science*, and *Cochrane Library* from inception to July 7, 2024, for original, English-language studies on animal models of induced TBI treated with ADSCs. We excluded *in vitro*, *in silico*, studies involving humans, and conference abstracts. Risk of bias was assessed using the SYRCLE tool.

Results: Twenty-two studies met the inclusion criteria. The most common routes of ADSC administration were intravenous and intracerebral injections, typically given within 24 hours of induced TBI. Histological and neuroimaging assessments showed reduced tissue swelling and interstitial fluid accumulation in ADSC-treated animals, indicating decreased brain vasogenic edema. ADSC treatment also reduced neuroinflammation markers, suggesting lower activation of astrocytes and microglia around the injury site associated with M2 microglial phenotype polarization. Enhanced neurogenesis was observed, particularly in the hippocampus, with markers like BrdU and NeuN indicating improved neuron formation. Consistent cognitive and motor improvements were also noted, with treated animals showing shorter escape times and path lengths in spatial memory tests (e.g., Morris Water Maze) and better motor coordination in beam tests.

Conclusion: The available pre-clinical *in vivo* evidence indicates that ADSC-based therapies have the potential to mitigate neuroinflammation, reduce brain edema, enhance neurogenesis, and improve functional outcomes following induced TBI. Clinical studies are warranted to investigate the use of ADSCs in the treatment of TBI in humans.

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