

**Letter to Editor**

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# Perseus-The Protector of Mankind: Mesenchymal Stem Cell Transplantation may be a Promising Treatment for Neurological Diseases

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To the Editor;

We read with great interest that the article by professor Davut BOZKAYA entitled "A New Hope in the Treatment of Intraventricular Haemorrhage in Preterm Infants: Mesenchymal Stem Cells" in Turkish Neurosurgery 32(2):344-346, 2022. <https://doi.org/10.5137/1019-5149.JTN.34850-21.2>" (3). In this article, professor Davut BOZKAYA drew the conclusion that "Mesenchymal stem cell (MSC) transplantation may be a promising treatment for premature infants to reduce morbidity and mortality after intraventricular bleeding (IVH). However, a need exists for studies that evaluate the optimal application route, dose and time of administration, as well as its efficacy and safety".

MSCs are widely used in clinical applications (11,12). It could be envisioned that MSCs transplantation may be a promising treatment for Neurological diseases. Current research highlights MSCs applications in modulating neurogenesis, angiogenesis, and immune regulation, particularly through their capacity to promote progenitor cell differentiation. Notably, preclinical and clinical trials demonstrate therapeutic efficacy in premature infants with bronchopulmonary dysplasia (BPD) and hypoxic-ischemic encephalopathy (HIE). For instance, human umbilical cord blood-derived MSCs (UCB-MSCs) have shown marked neuroprotective effects in severe intraventricular hemorrhage (IVH) models, significantly reducing brain injury and post-hemorrhagic hydrocephalus (PHH) incidence in rodent studies (1-3). These findings underscore MSC therapy's potential to mitigate morbidity and mortality in IVH patients.

Stem cell therapy is another medical revolution after drug and surgical medication (11,12). Emerging evidence suggests MSCs transplantation holds significant promise for treating neurological diseases. MSCs are a class of cells with significant self-renewal and multi-lineage differentiation properties and MSCs characterized by immune regulation, suppression of inflammation and promotion of angiogenesis. They are favorable for the treatment of various diseases and injuries (4-8,11). MSCs therapies were anticipated to repair the structure and function of diseased or damaged tissues via direct cell replacement and/or paracrine effect (10). MSCs suppress T-lymphocyte proliferation and the inflammatory response, changing in the cytokine release of T cells (2,6). Due to, MSCs increase the production of anti-inflammatory cytokines, such as IL-10, while reducing the inflammatory cytokine release from dendritic cells, such as TNF- $\alpha$ , interleukin12 (IL-12) and interferon- $\gamma$ , in IVH patients (1,9). It is indicated that the inflammatory reaction caused by Neurological injury disease is a crucial factor (6,11), MSCs can affect immune cells proliferation, differentiation, activation and inflammatory cytokine secretion by cells interaction and secretion of soluble immune regulatory factors and inhibit the proliferation of T cells and microglia, regulate dendritic cells, monocytes and macrophages and natural killer (NK) cells to Suppress the inflammatory response. MSCs secret a variety of cytokines and growth factors through paracrine, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (BFGF), hepatocyte growth factor (HGF), that could stimulate peripheral mature endothelial cells proliferation and migration, improve the microenvironment of ischemic tissue to participate in angiogenesis (11,12).

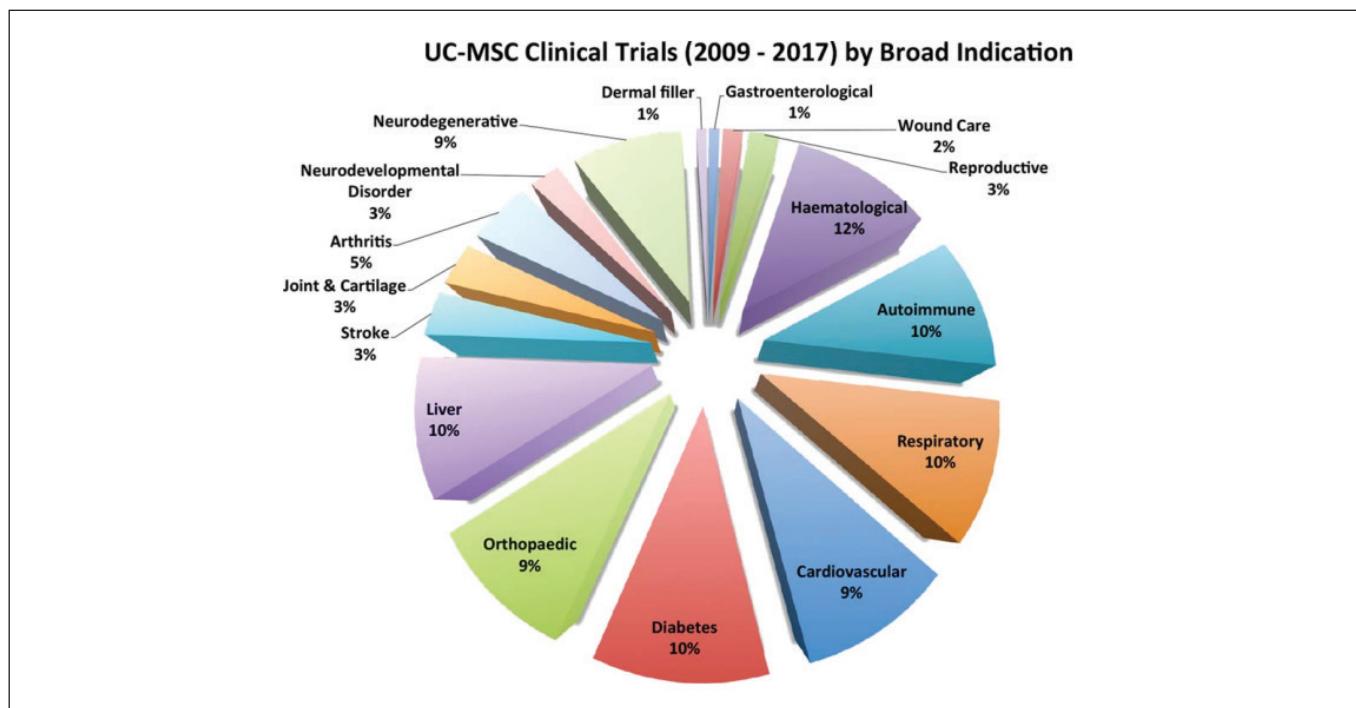


Figure 1: Representative applications of UCB-MSCs (Quoted from Reference 2).

We agree with the conclusions drawn from professor Davut BOZKAYA, and propose these questions to advance MSC research. Elucidating these aspects will facilitate protocol standardization and enhance therapeutic outcomes. Further investigation into dosage optimization, treatment timing, and mechanism validation remains imperative for clinical translation. Some challenges require resolution to standardize MSC therapeutics, such as administration optimization: Is intravenous infusion the optimal delivery route? Potential pulmonary sequestration may reduce therapeutic efficacy. Have recent studies explored alternative administration strategies? And the next question: what is the mechanism behind the therapeutic effect of MSCs? Cell replacement or paracrine-mediated microenvironment modulation? or something else? We look forward the reply. These questions awaiting to reply so as to better conduct relevant research and provide support for the application of MSCs. To solving these problems will benefit the further standardization of MSCs therapy and to improve MSCs therapy.

Despite the positive features of MSCs, there are many unanswered questions concerning IVH cases, such as the method of administration, dose and optimal timing, the mechanism of MSCs therapeutic effect, is cell replacement or something else? These all need to be studied in depth.

#### Declarations

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#### AUTHORSHIP CONTRIBUTION

Study conception and design: HD  
 Draft manuscript preparation: HD, YW, BH  
 Critical revision of the article: HD  
 Other (study supervision, fundings, materials, etc...): HD, YW  
 All authors (HD, YW, BH) reviewed the results and approved the final version of the manuscript.

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