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Editorial Commentary

Mesenchymal stem cell therapy for neonatal intraventricular hemorrhage: a long way to go?

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Comment on: Ahn SY, Chang YS, Sung SI, *et al.* Mesenchymal Stem Cells for Severe Intraventricular Hemorrhage in Preterm Infants: Phase I Dose-Escalation Clinical Trial. Stem Cells Transl Med 2018;7:847-56.

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The goal of neonatal medicine is intact survival, or to prevent the complications and improve the neurodevelopmental outcome of these vulnerable population. Intraventricular hemorrhage (IVH) is one of the most common and devastating morbidities among the preterm infants, especially those born as very low birth weight infants (VLBWI) (1). The severity of IVH is known to be inversely correlated with neurodevelopmental outcomes, and most of the infants affected by severe (grade 3 or 4) IVH die or develop neurodevelopmental sequelae. Currently, there is no effective therapeutic approach for severe IVH.

In 1982, Nakahata *et al.* found the existence of stem cells in umbilical cord blood (2). Since then, therapeutic use of the stem cell has been drawing attention in clinical settings. In the field of perinatal medicine, Cotton and colleagues performed a trial to administer autologous umbilical cord blood (UCB) stem cells to moderate or severe hypoxic-ischemic encephalopathy, and they reported the improved intact survival rate at the age of 3 years (3). In 2014, the researchers from Korea, the same authors of below mentioned paper, has reported the favorable results of phase 1 clinical trial of mesenchymal stem cells (MSCs) therapy for bronchopulmonary dysplasia, showing the attenuation of the disease severity (4). In addition, recent systematic review of preclinical studies of MSCs for bronchopulmonary dysplasia suggested therapeutic benefit (5).

The paper being referenced in this editorial (published in the *Stem Cells Translational Medicine* on June 24, 2018) shows that intraventricular transplantation of allogeneic human UCB-derived MSCs into preterm infants with severe IVH is safe and feasible (6).

This study is a phase 1, open-label, single-arm, single-center trial to evaluate the safety and feasibility of intraventricular allograft transplantation of UCB derived MSCs into premature infants with severe IVH. They used *ex vivo* cultured allogeneic, unrelated, human-blood-derived mesenchymal stem cells (hUCB-MSCs) which they described previously [CD45-, CD14-, CD34-, and human leukocyte antigen (HLA)-DR-negative, and are also CD73-, CD105-, and CD90-positive (4)]. The patients with the ultrasonographic diagnosis of severe IVH (≥grade 3) whose gestational age was 23–34 weeks were enrolled into the study between the study period 2014 and 2015. This was the dose-escalation trial, thus the first three cases received low dose of MSCs (5×10^6 cells/kg) and the following six cases received high dose of MSCs (1×10^7 cells/kg) via intraventricular injection under direct ultrasound guidance. Regarding the safety, no serious adverse events (SAE) directly associated with intraventricular hUCB-MSCs treatment in both lower and higher dosages group until discharge, including death and anaphylaxis. However, there were other SEA associated with preterm birth reported in the study population, including BPD (9/9), NEC (2/9), ROP (2/9), Late-onset sepsis (1/9), and inguinal hernia operation (4/9).

Another problem of cell therapy for the brain is the risk of abnormal cell proliferation and tumor formation after transplantation (7), however, the risk of tumorigenesis

of the MSCs has not been assessed in this study. The assessment for the risk of formation of abnormal neural circuits which can be the cause of seizure is also lacking. Thus, further longitudinal follow-up study regarding safety is indispensable.

In terms of the efficacy of the treatment, 5 cases of 9 recruited patients needed ventriculoperitoneal shunting before first NICU discharge. In addition, 2 cases of the remaining 4 patients without shunting did show massive ventriculomegaly at corrected 36–40 weeks' gestation. In the previous report which reviewed the natural history of 248 VLBWI with IVH, 34% of the patients with severe IVH (≥ grade 3) received surgical treatment for progressive ventricular dilatation and 18% of the patients with severe IVH died (8). In this study, 4 out of 6 patients in the high dose group required ventriculoperitoneal shunting due to posthemorrhagic hydrocephalus, this outcome might not be much different to the natural history. In addition, the inflammatory cytokine levels of cerebrospinal fluid in the adult IVH patients were reported to peak at 3–6 days post bleeding (9). Besides, the timing of MSCs administration in the current study was median 12 (range, 7–15) days post IVH, those might be too late if aiming for anti-inflammatory effects.

Thus, further feasibility study for both safety and efficacy might be needed for clinical application.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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