Turk Neurosurg 32(2):344-346, 2022

Case Report

DOI: 10.5137/1019-5149.JTN.34850-21.2

Received: 21.04.2021
Accepted: 25.05.2021

Published Online: 06.12.2021

A New Hope in the Treatment of Intraventricular Haemorrhage in Preterm Infants: Mesenchymal Stem Cells

Davut BOZKAYA[1], Burak CERAN[1], Esra OZMEN[1], Esin OKMAN[1], Evrim ALYAMAC DIZDAR[1], Serife Suna OGUZ[1], Ikbal OK BOZKAYA[2]

[1]Ankara City Hospital Child Health and Diseases, Division of Neonatology, Ankara, Turkey
[2]Ankara City Hospital Child Health and Diseases, Division of Pediatric Hematology, Ankara, Turkey

Corresponding author: Davut BOZKAYA ✉ drbozkaya@gmail.com

ABSTRACT

To date, there has been no effective treatment to prevent brain damage in premature infants or to prevent the development of post-hemorrhagic hydrocephalus (PHH) after severe intraventricular hemorrhage (IVH). Therefore, new, safe and effective treatment methods need to be developed to improve the prognosis of IVH, for which morbidity and mortality rates are high. Recent studies have shown that the strong immunomodulatory properties of mesenchymal stem cells (MSCs) have an anti-inflammatory effect after IVH, inhibiting the development of PHH and decreasing apoptosis and gliosis, thus improving the self-renewal ability of neuronal tissues. For this reason, MSCs transplantation after IVH is a promising treatment method. In this article, we present a case of grade-III IVH who recovered after MSCs transplantation.

KEYWORDS: Intraventricular haemorrhage, Mesenchymal stem cells, Premature infant, Treatment

INTRODUCTION

The increase in the survival rate of extremely preterm infants in recent years has led to an increase in the number of severe intraventricular bleeding (IVH) (11). The risk and severity of intraventricular haemorrhage are directly related to the degree of immaturity (9,13,14). The incidence of mortality and morbidity (seizure, cerebral palsy and growth retardation) increases due to PHH, which is a frequent complication of severe IHV (4,10). Currently, there is no effective treatment to reduce brain damage in premature infants or to prevent the development of PHH after severe IVH. Therefore, new, safe and effective treatment methods need to be developed to improve the prognosis of IVH in terms of morbidity and mortality.

In recent years, MSCs applications, which are thought to play a role in the growth and differentiation of root and precursor cells, angiogenesis and immune modulation, have come to the agenda. Several preclinical and clinical studies have shown promising results, with MSCs transplantation in premature infants developing bronchopulmonary dysplasia (BPD) and hypoxic ischemic encephalopathy (HIE) (2,6,8). Human umbilical cord blood (UCB), which is the origin of MSCs, has been shown to reduce brain damage and PHH development significantly when transplanted to severe IVH-developing rats (1-3). We report a case of severe IVH (grade-III) treated with MSCs transplantation.

CASE REPORT

This study was approved by the Department of Organ, Tissue Transplantation and Dialysis Services of the Turkish Ministry of Health (No: 56733164/203, Date: 25.08.2018). Consent was obtained from the family for the publication of the case.

The male infant was delivered by caesarean section at 27 weeks and 5 days gestational and weighed 950 grams. The fifth minute Apgar score was seven. On the second day, while he was receiving CPAP, respiratory distress increased; conse-

Davut BOZKAYA : 0000-0001-5548-7387
Burak CERAN : 0000-0001-5914-5325
Esra OZMEN : 0000-0001-6661-3473
Esin OKMAN : 0000-0002-0846-4032
Evrim ALYAMAC DIZDAR : 0000-0001-8956-0917
Serife Suna OGUZ : 0000-0002-1870-0983
Ikbal OK BOZKAYA : 0000-0002-7666-8731

quently, he was intubated and surfactant was applied. On the third postnatal day, medical treatment was performed for hemodynamically significant patent ductus arteriosus (PDA). In the control cranial USG of the patient whose ductus was not closed despite two cycles of medical therapy, grade-III IVH was detected (Figure 1A, B). In the follow-up phenobarbital and levatiracetam treatments were initiated because he had a generalized seizure After obtaining the necessary consent and permission from the Department of Organ Tissue Transplantation and Dialysis Services of the Ministry of Health, it was decided to perform MSCs transplantation on the patient. On the sixth day, after detecting bleeding, UCB-derived MSCs (1 x 10^7/kg intraventricular and 1 x 10^7/kg intravenous) were administered with cranial ultrasound. After treatment, weekly cranial USG and head circumference were performed. Control cranial (cranial or cranial) USG was reported to be normal in the fourth week of administration. In the follow-up, on the 133rd postnatal day, the cranial MRI report showed normal ventricles and hemosiderin accumulation in the parenchyma. The patient did not have any seizures and discontinued his anti-epileptic treatment. On the 163rd postnatal day, she was discharged in generally good condition and normal neurological examination. The patient is now two years old, and her development is compatible with that of her peers.

DISCUSSION

Mesenchymal stem cell transplantation is a promising treatment in neonatal diseases with complex multifactorial etiology, such as BPD, IVH and HIE, which have had no effective treatment until now.

MSCs suppress T-lymphocyte proliferation and the inflammatory response, changing in the cytokine release of T cells (5). 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-α, interleukin (IL) 12 and interferon-γ, in IVH patients. This may prevent PHH due to inflammation after IVH. On the other hand, MSCs increase angiogenesis, myelination and the ability of neurons to re-synapse with the neurotropic factors they secrete. They also minimise neuronal loss by decreasing gliosis and cell death after IVH (1,7,9,12).

Despite the positive features of mesenchymal stem cells, there are many unanswered questions concerning IVH cases, such as the method of administration, dose and optimal timing. In animal studies, during the acute period of IVH (2–7 days), it has been reported to be given locally (intraventricular) in stable cases and intravenously in unstable cases (11). Yet no human studies on the timing and method of administration have been performed. In the 2019, there is a phase-1 study

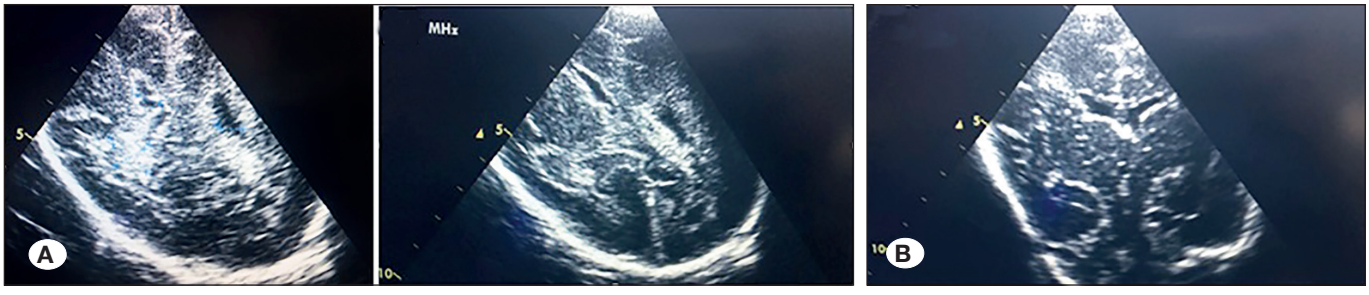

Figure 1: Serial images of brain injury induced by intraventricular hemorrhage **A)** Representative coronal-view images of a cranial ultrasonogram obtained before, **B)** representative coronal-view images of a serial cranial ultrasonogram obtained after.

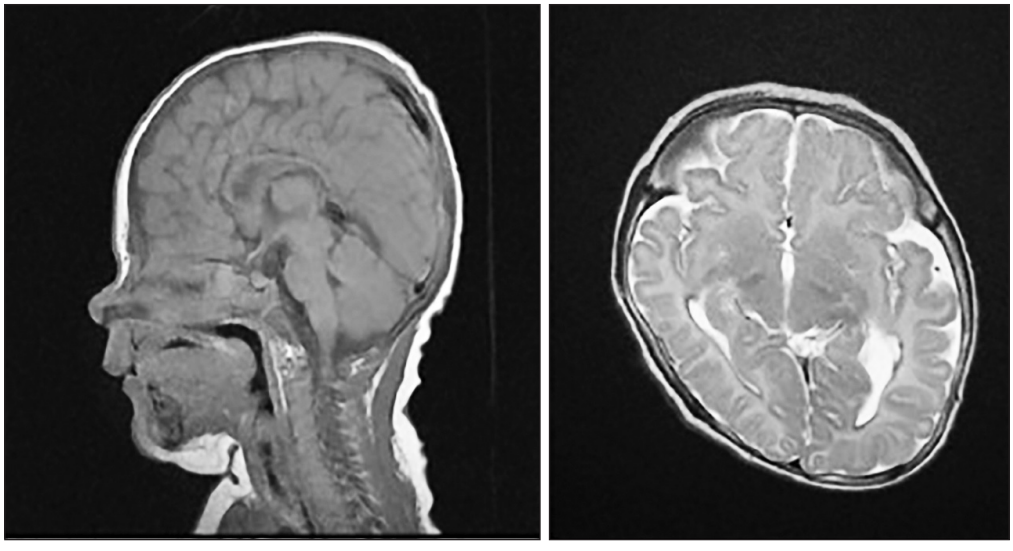

Figure 2: Control cranial MR imaging on day 133.

on human by Ahn et al. In this study, 1 x 10^7 cells/kg (high dose-6 cases) and 5 x 10^6 cells/kg (low dose-3 cases) MSCs transplantation was applied, and similar results were obtained in both applications (13). However, since there were only nine cases, no definite recommendation was made regarding the dose and route of administration.

In our case, after six days of IVH, we applied 1 x 10^7 cells/kg intravenous and intraventricular MSCs transplantation. After the treatment, haemorrhage in the cranial ultrasound showed gradual improvement, no parenchymal bleeding area was observed at the fourth week and the ventricular index regressed to normal dimensions. The patient did not develop neurological deficits and was discharged without antiepileptic treatment, which was started due to seizure at the beginning of IVH.

CONCLUSION

Mesenchymal stem cell transplantation may be a promising treatment for premature infants to reduce morbidity and mortality after 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.

AUTHORSHIP CONTRIBUTION

Study conception and design: DB

Data collection: DB, EO

Analysis and interpretation of results: DB, EO

Draft manuscript preparation: DB, IOB

Critical revision of the article: DB, SSO

Other (study supervision, fundings, materials, etc...): DB, IOB, EAD

All authors (DB, BC, EO, EO, EAD, SSO, IOB) reviewed the results and approved the final version of the manuscript.

REFERENCES

1. Ahn SY, Chang YS, Park WS: Mesenchymal stem cells transplantation for neuroprotection in preterm infants with severe intraventricular hemorrhage. Korean J Pediatr 57:251-256, 2014
2. Ahn SY, Chang YS, Sung DK, Sung SI, Ahn JY, Park WS: Pivotal role of brain-derived neurotrophic factor secreted by mesenchymal stem cells in severe intraventricular hemorrhage in newborn rats. Cell Transplant 26:145-156, 2017
3. Ahn SY, Chang YS, Sung SI, Park WS: Mesenchymal stem cells for severe intraventricular hemorrhage in preterm infants: Phase I dose-escalation clinical trial. Stem Cells Transl Med 7:847-856, 2018
4. de Vries LS, Groenendaal F, Liem KD, Heep A, Brouwer AJ, van 't Verlaat E, Benavente-Fernández I, van Straaten HL, van Wezel-Meijler G, Smit BJ, Govaert P, Woerdeman PA, Whitelaw A; ELVIS study group: Treatment thresholds for intervention in posthaemorrhagic ventricular dilation: A randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 104:F70-F75, 2019
5. Kim ES, Chang YS, Choi SJ, Kim JK, Yoo HS, Ahn SY, Sung DK, Kim SY, Park YR, Park WS: Intratracheal transplantation of human umbilical cord blood-derived mesenchymal stem cells dose-dependently attenuates hyperoxia-induced lung injury in neonatal rats. Cell Transplant 20:1843-1854, 2011
6. Kim YE, Park WS, Ahn SY, Sung DK, Chang YS: Intratracheal transplantation of mesenchymal stem cells attenuates hyperoxia-induced lung injury by down-regulating, but not direct inhibiting formyl peptide receptor 1 in the newborn mice. PloS one 13:e0206311, 2018
7. Park WS, Ahn SY, Sung SI, Ahn JY, Chang YS: Mesenchymal stem cells: The magic cure for intraventricular hemorrhage? Cell Transplant 26:439-448, 2017
8. Park WS, Ahn SY, Sung SI, Ahn JY, Chang YS: Strategies to enhance paracrine potency of transplanted mesenchymal stem cells in intractable neonatal disorders. Pediatr Res 83:214-222, 2018
9. Payne AH, Hintz SR, Hibbs AM, Walsh MC, Vohr BR, Bann CM, Wilson-Costello DE; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network: Neurodevelopmental outcomes of extremely low-gestational-age neonates with low-grade periventricular-intraventricular hemorrhage. JAMA Pediatrics 167:451-459, 2010
10. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, Hale EC, Newman NS, Schibler K, Carlo WA, Kennedy KA, Poindexter BB, Finer NN, Ehrenkranz RA, Duara S, Sánchez PJ, O'Shea TM, Goldberg RN, Van Meurs KP, Faix RG, Phelps DL, Frantz ID 3rd, Watterberg KL, Saha S, Das A, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network: Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics 126:443-456, 2010
11. Sung DK, Chang YS, Ahn SY, Sung SI, Yoo HS, Choi SJ, Kim SY, Park WS: Optimal route for mesenchymal stem cells transplantation after severe intraventricular hemorrhage in newborn rats. PloS one 10:e0132919, 2015
12. Thebaud B: Stem cell-based therapies in neonatology: A new hope. Arch Dis Child Fetal Neonatal Ed 103:F583-F588, 2018
13. Thorp JA, Jones PG, Clark RH, Knox E, Peabody JL: Perinatal factors associated with severe intracranial hemorrhage. Am J Obstet Gynecol 185:859-862, 2001
14. Walsh MC, Bell EF, Kandefer S, Saha S, Carlo WA, D'angio CT, Laptook AR, Sanchez PJ, Stoll BJ, Shankaran S, Van Meurs KP, Cook N, Higgins RD, Das A, Newman NS, Schibler K, Schmidt B, Cotten CM, Poindexter BB, Watterberg KL, Truog WE: Neonatal outcomes of moderately preterm infants compared to extremely preterm infants. Pediatr Res 82:297-304, 2007