BÖLÜM 19

HİPOKSİK BEYİN HASARINDA KÖK HÜCRE TEDAVİSİ

Özlem ATEŞ YAMAN [1]
Nihal OLGAÇ DÜNDAR [2]

GİRİŞ

Hipoksi dokuya taşınan oksijen miktarında azalma, iskemi ise dokuya glikoz ve oksijen ulaştırılmasını engelleyen kan akımındaki parsiyel veya tam yokluktur. Her yaş grubunda birçok faktör hipoksi ve reperfüzyonun eşlik ettiği veya etmediği iskemi ile beyin hasarı gelişmesine neden olabilir. Asfiksi, arrest, şok, kanama, travma, enfeksiyonlar, tromboembolik ve metabolik olaylar hipoksik iskemik beyin hasarı nedenleri arasında sayılabilir.[1,2]

Her yaş grubunda önemli bir morbidite ve mortalite nedenidir. Uzun dönemde bilişsel ve motor alanda sekel gelişmesine neden olabilir. Hipoksi ve iskemiye en hassas organ olan beyinde aynı anda birçok yolakta gelişen biyokimyasal olaylar zinciri hücre hasarına giden süreci başlatır. Patofizyolojisinin iyi anlaşılması, erken dönemde tedavi stratejilerinin geliştirilerek beynin hasardan korunması amacına ulaşmak için gereklidir. Olguların yakın nörolojik izlemi ve yardımcı görüntüleme tetkikleri ile hasarın ciddiyeti ve prognoz üzerine etkilerine dikkat edilerek en uygun tedavi yaklaşımı belirlenmeye çalışılmalıdır.

Rejeneratif tıp alanındaki son klinik araştırmalar, hipoksik iskemik ensefalopatide ve inme, kardiyak arrest gibi diğer hipoksik iskemik atakların neden olduğu yenidoğan dönemi dışındaki beyin hasarı için olası bir tedavi olarak embriyonik kök hücrelerin incelenmesine odaklanmıştır. Embriyonik kök hücreler hematopoietik, sinir veya mezenkimal kök hücrelere farklılaşma potansiyeline sahiptir.[3,4] Mezenkimal kök hücreler, nöronal dokuya dönüşüm yerine parakrin etki ile yeni beyin hücrelerinin oluşumunu uyarır böylece nörorejeneratif ve immün modüle edici etkileri nedeniyle beyin hasarının tedavisinde kullanılır.[5,6]

Hipoksik beyin hasarında kök hücre tedavisi, yenidoğanda hipoksik iskemik ensefalopatide ve yenidoğan dışı iskemik beyin hasarında olmak üzere iki alt bölümde incelenmiştir.[47]

HİPOKSİK İSKEMİK ENSEFALOPATİ

Hipoksik iskemik ensefalopati (HİE) yenidoğanlarda perinatal asfiksiye bağlı gelişen fizyolojik, hücresel ve moleküler değişikliklerle seyreden beyin hasarıdır. Hipoksik-iskemik ensefalopati 1-6/1000 canlı doğumda görülür.[7] Etkilenen be-

[1] Uzm. Dr., İzmir Tepecik Eğitim ve Araştırma Hastanesi Çocuk Nöroloji Kliniği, ORCID iD :0009-0001-9414-2231
[2] Prof. Dr., İzmir Katip Çelebi Üniversitesi Tıp Fakültesi Çocuk Nörolojisi BD., ORCID iD:0000-0002-5902-3501

nik çalışmalar, 3.6×10^4 ila 4.3×10^7 mezenkimal KH /kg arasında değişen IV dozlarının kemirgenlerde önemli davranış kazanımları sağladığını göstermektedir.[86] Bir çalışmada, yenidoğanın hipoksik iskemik bir modelinde fare başına 0,5 x 10^6 mezenkimal KH verildiğinde lezyon boyutunda önemli bir azalma ve sensorimotor fonksiyon gelişimi kaydedilmiştir. Dozu $0,25\times10^6$ mezenkimal KH'ye düşürmenin sensorimotor performans veya gri/beyaz cevher korunması üzerinde anlamlı bir etkisinin olmadığını, dozu $1,0\times10^6$'ya yükseltmenin ise sensorimotor fonksiyonda veya lezyon boyutunun küçülmesinde ek iyileştirmeler sağlamadığını göstermiştir.[87] Bir faz I çalışmasında, 0.5, 1.0 ve 1.5×10^6 allojenik umblikal kord kan KH/kg IV transfüzyonunun güvenli olduğu ve kronik inme hastalarında davranış kazanımları olduğu gösterilmiştir. İnmeli sıçanlarda iskemiden iki gün sonra sıçan başına $2x10^6$ umblikal kord kan KH IV uygulamasının güvenli olduğu ve nöroproteksiyon sağladığı saptanmıştır.[88] İskemik yaralanmadan bir gün sonra umblikal kord kan KH (1×10^6 veya 4×10^6) IV enjeksiyonunun inmeli sıçanlarda nörolojik hasarı azalttığı gösterilmiştir.[89]

Kombine Tedavi

Kardiyak arreste bağlı beyin hasarında, mezenkimal KH ile tedavi edilen sıçanlar, iskemiden sonra 2 saat boyunca terapötik hipotermi ile tedavi edilenlere kıyasla daha iyi veya eşdeğer fonksiyonel sonuçlar gösterirken hipoterminin bu patolojide mezenkimal KH tedavisinin faydalarını artırdığı bulunamamıştır.[78] İskemik inmeli sıçanlarda, 5 dakika boyunca 0.6 mL/dk infüzyon hızında soğuk salin (4°C) enjeksiyonu ile iskemi sonrası hipotermi, mezenkimal KH'nin reperfüzyon hasarı üzerindeki terapötik etkilerini artırabilir.[90] İskemiden yedi gün sonra, umblikal kord kan KH'lerin ve eritropoietinin kombine kullanımının inmeli sıçanlarda güçlü nörojenik ve anjiyogenik etkilere sahip olduğu gösterilmiştir.[91]

Sonuç olarak; hipoksik iskemi aracılı beyin hasarı hücre ve doku düzeyinde birçok mekanizmaların birbiri ile etkileşimleri neticesinde gelişen bir durum olup, çeşitli etiyolojilerde sekel gelişimine hatta ölüme neden olabilmektedir. İnme geçirdikten sonra iskemik dokuda iyileşmenin gerçekleşebilmesi ve hastanın kaybettiği fonksiyonlarını geri kazanılabilmesi için kök hücre uygulamaları umut verici görünmektedir. Bununla birlikte, hücre tipi seçimi, hücre dozu, uygulama yolu ve hasta özellikleri dahil olmak üzere optimal parametreler belirsizliğini korumakta ve önerilen yöntemlerin etkilerini en üst düzeye çıkarmak için daha fazla araştırmaya ihtiyaç bulunmaktadır.

KAYNAKLAR

1. Aksu T TB. Yenidoğanda Hipoksik İskemik Ensefalopati. In: Tatlı B ÖM, editor. Yenidoğan Nörolojisi. 1. ed2016. p. 19-41.
2. K G. Yenidoğan Bebekte Hipoksik İskemik Ensefalopati2010.
3. Fleiss B, Guillot PV, Titomanlio L, Baud O, Hagberg H, Gressens P. Stem cell therapy for neonatal brain injury. Clinics in perinatology. 2014;41(1):133-48.
4. Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. Nature reviews Immunology. 2008;8(9):726-36.
5. van Velthoven CT, Kavelaars A, van Bel F, Heijnen CJ. Mesenchymal stem cell transplantation changes the gene expression profile of the neonatal ischemic brain. Brain, behavior, and immunity. 2011;25(7):1342-8.
6. Wagenaar N, Nijboer CH, van Bel F. Repair of neonatal brain injury: bringing stem cell-based therapy into clinical practice. Developmental medicine and child neurology. 2017;59(10):997-1003.
7. Shankaran S. Neonatal encephalopathy: treatment with hypothermia. Journal of neurotrauma. 2009;26(3):437-43.
8. Wang Q, Lv H, Lu L, Ren P, Li L. Neonatal hypoxic-ischemic encephalopathy: emerging therapeutic strategies based on pathophysiologic phases of the injury. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2019;32(21):3685-92.
9. van Bel F, Groenendaal F. Birth asphyxia-induced brain damage: the long road to optimal reduction and prevention! Pediatric Medicine. 2020;3.
10. Ristovska S, Stomnaroska O, Danilovski D. Hypoxic Ischemic Encephalopathy (HIE) in Term and Preterm Infants. PRILOZI. 3922;43(1):77-84.

11. Executive summary: Neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. Obstetrics and gynecology. 2014;123(4):896-901.
12. DuPont TL, Chalak LF, Morriss MC, Burchfield PJ, Christie L, Sánchez PJ. Short-term outcomes of newborns with perinatal acidemia who are not eligible for systemic hypothermia therapy. The Journal of pediatrics. 2013;162(1):35-41.
13. Andersen M, Andelius TCK, Pedersen MV, Kyng KJ, Henriksen TB. Severity of hypoxic ischemic encephalopathy and heart rate variability in neonates: a systematic review. BMC pediatrics. 2019;19(1):242.
14. Ahearne CE, Boylan GB, Murray DM. Short and long term prognosis in perinatal asphyxia: An update. World journal of clinical pediatrics. 2016;5(1):67-74.
15. Murray DM. Biomarkers in neonatal hypoxic-ischemic encephalopathy-Review of the literature to date and future directions for research. Handbook of clinical neurology. 2019;162:281-93.
16. Douglas-Escobar M, Weiss MD. Hypoxic-ischemic encephalopathy: a review for the clinician. JAMA pediatrics. 2015;169(4):397-403.
17. Juul SE, Ferriero DM. Pharmacologic neuroprotective strategies in neonatal brain injury. Clinics in perinatology. 2014;41(1):119-31.
18. Gilles F, Gressens P, Dammann O, Leviton A. Hypoxia-ischemia is not an antecedent of most preterm brain damage: the illusion of validity. Developmental medicine and child neurology. 2018;60(2):120-5.
19. Jeffrey JN, Joseph JV. Chapter 16 - Encephalopathy of Prematurity: Clinical-Neurological Features, Diagnosis, Imaging, Prognosis, Therapy. 2018:425-57.e11.
20. Laptook AR. Birth Asphyxia and Hypoxic-Ischemic Brain Injury in the Preterm Infant. Clinics in perinatology. 2016;43(3):529-45.
21. Michniewicz B, Szpecht D, Sowińska A, Sibiak R, Szymankiewicz M, Gadzinowski J. Biomarkers in newborns with hypoxic-ischemic encephalopathy treated with therapeutic hypothermia. Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery. 2020;36(12):2981-8.
22. Abate BB, Bimerew M, Gebremichael B, Mengesha Kassie A, Kassaw M, Gebremeskel T, et al. Effects of therapeutic hypothermia on death among asphyxiated neonates with hypoxic-ischemic encephalopathy: A systematic review and meta-analysis of randomized control trials. PloS one. 2021;16(2):e0247229.
23. Shankaran S, Pappas A, McDonald SA, Vohr BR, Hintz SR, Yolton K, et al. Childhood outcomes after hypothermia for neonatal encephalopathy. The New England journal of medicine. 2012;366(22):2085-92.
24. Lee CYZ, Chakranon P, Lee SWH. Comparative Efficacy and Safety of Neuroprotective Therapies for Neonates With Hypoxic Ischemic Encephalopathy: A Network Meta-Analysis. Frontiers in pharmacology. 2019;10:1221.
25. Aly H, Elmahdy H, El-Dib M, Rowisha M, Awny M, El-Gohary T, et al. Melatonin use for neuroprotection in perinatal asphyxia: a randomized controlled pilot study. Journal of perinatology : official journal of the California Perinatal Association. 2015;35(3):186-91.
26. Frymoyer A, Juul SE, Massaro AN, Bammler TK, Wu YW. High-dose erythropoietin population pharmacokinetics in neonates with hypoxic-ischemic encephalopathy receiving hypothermia. Pediatric research. 2017;81(6):865-72.
27. Wu YW, Mathur AM, Chang T, McKinstry RC, Mulkey SB, Mayock DE, et al. High-Dose Erythropoietin and Hypothermia for Hypoxic-Ischemic Encephalopathy: A Phase II Trial. Pediatrics. 2016;137(6).
28. Pazos MR, Mohammed N, Lafuente H, Santos M, Martínez-Pinilla E, Moreno E, et al. Mechanisms of cannabidiol neuroprotection in hypoxic-ischemic newborn pigs: role of 5HT(1A) and CB2 receptors. Neuropharmacology. 2013;71:282-91.
29. Barks JDE, Liu Y, Wang L, Pai MP, Silverstein FS. Repurposing azithromycin for neonatal neuroprotection. Pediatric research. 2019;86(4):444-51.
30. Gonzales-Portillo GS, Reyes S, Aguirre D, Pabon MM, Borlongan CV. Stem cell therapy for neonatal hypoxic-ischemic encephalopathy. Frontiers in neurology. 2014;5:147.
31. Ankrum JA, Ong JF, Karp JM. Mesenchymal stem cells: immune evasive, not immune privileged. Nature biotechnology. 2014;32(3):252-60.
32. Ahn SY, Park WS, Sung SI, Chang YS. Mesenchymal stem cell therapy for intractable neonatal disorders. Pediatrics and neonatology. 2021;62 Suppl 1:S16-s21.
33. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8(4):315-7.
34. Prockop DJ, Kota DJ, Bazhanov N, Reger RL. Evolving paradigms for repair of tissues by adult stem/progenitor cells (MSCs). Journal of cellular and molecular medicine. 2010;14(9):2190-9.
35. Mueller M, Kramer BW. Stem cells and Bronchopulmonary Dysplasia - The five questions: Which cells, when, in which dose, to which patients via which route? Paediatric respiratory reviews. 2017;24:54-9.
36. Nitkin CR, Rajasingh J, Pisano C, Besner GE, Thébaud B, Sampath V. Stem cell therapy for preventing neonatal diseases in the 21st century: Current understanding and challenges. Pediatric research. 2020;87(2):265-76.
37. Wang Y, Long W, Cao Y, Li J, You L, Fan Y. Mesenchymal stem cell-derived secretomes for therapeutic potential of premature infant diseases. Bioscience reports. 2020;40(5).
38. Yoshimoto M, Koenig JM. Stem Cells: Potential Therapy for Neonatal Injury? Clinics in perinatology. 2015;42(3):597-612.
39. Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: past, present, and future. Stem cell research & therapy. 2019;10(1):68.

40. Mirzaei H, Sahebkar A, Sichani LS, Moridikia A, Nazari S, Sadri Nahand J, et al. Therapeutic application of multipotent stem cells. Journal of cellular physiology. 2018;233(4):2815-23.
41. Phuc PV, Ngoc VB, Lam DH, Tam NT, Viet PQ, Ngoc PK. Isolation of three important types of stem cells from the same samples of banked umbilical cord blood. Cell and tissue banking. 2012;13(2):341-51.
42. Weiss ML, Troyer DL. Stem cells in the umbilical cord. Stem cell reviews. 2006;2(2):155-62.
43. Ballen KK, Barker JN, Stewart SK, Greene MF, Lane TA. Collection and preservation of cord blood for personal use. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2008;14(3):356-63.
44. Malgieri A, Kantzari E, Patrizi MP, Gambardella S. Bone marrow and umbilical cord blood human mesenchymal stem cells: state of the art. International journal of clinical and experimental medicine. 2010;3(4):248-69.
45. Ringdén O, Okas M, Uhlin M, Uzunel M, Remberger M, Mattsson J. Unrelated cord blood and mismatched unrelated volunteer donor transplants, two alternatives in patients who lack an HLA-identical donor. Bone marrow transplantation. 2008;42(10):643-8.
46. Rocha V, Labopin M, Sanz G, Arcese W, Schwerdtfeger R, Bosi A, et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. The New England journal of medicine. 2004;351(22):2276-85.
47. Serrenho I, Rosado M, Dinis A, C MC, Grãos M, Manadas B, et al. Stem Cell Therapy for Neonatal Hypoxic-Ischemic Encephalopathy: A Systematic Review of Preclinical Studies. International journal of molecular sciences. 2021;22(6).
48. Cotten CM, Murtha AP, Goldberg RN, Grotegut CA, Smith PB, Goldstein RF, et al. Feasibility of autologous cord blood cells for infants with hypoxic-ischemic encephalopathy. The Journal of pediatrics. 2014;164(5):973-9.e1.
49. Tsuji M, Sawada M, Watabe S, Sano H, Kanai M, Tanaka E, et al. Autologous cord blood cell therapy for neonatal hypoxic-ischaemic encephalopathy: a pilot study for feasibility and safety. Scientific reports. 2020;10(1):4603.
50. Penny TR, Pham Y, Sutherland AE, Mihelakis JG, Lee J, Jenkin G, et al. Multiple doses of umbilical cord blood cells improve long-term brain injury in the neonatal rat. Brain research. 2020;1746:147001.
51. Hu C, Li L. Preconditioning influences mesenchymal stem cell properties in vitro and in vivo. Journal of cellular and molecular medicine. 2018;22(3):1428-42.
52. Park WS, Ahn SY, Sung SI, Ahn JY, Chang YS. Strategies to enhance paracrine potency of transplanted mesenchymal stem cells in intractable neonatal disorders. Pediatric research. 2018;83(1-2):214-22.
53. Hu Y, Chen W, Wu L, Jiang L, Qin H, Tang N. Hypoxic preconditioning improves the survival and neural effects of transplanted mesenchymal stem cells via CXCL12/CXCR4 signalling in a rat model of cerebral infarction. Cell biochemistry and function. 2019;37(7):504-15.
54. Ding DC, Chang YH, Shyu WC, Lin SZ. Human umbilical cord mesenchymal stem cells: a new era for stem cell therapy. Cell transplantation. 2015;24(3):339-47.
55. Zhou X, Gu J, Gu Y, He M, Bi Y, Chen J, et al. Human Umbilical Cord-Derived Mesenchymal Stem Cells Improve Learning and Memory Function in Hypoxic-Ischemic Brain-Damaged Rats via an IL-8-Mediated Secretion Mechanism Rather than Differentiation Pattern Induction. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology. 2015;35(6):2383-401.
56. Zhang X, Hirai M, Cantero S, Ciubotariu R, Dobrila L, Hirsh A, et al. Isolation and characterization of mesenchymal stem cells from human umbilical cord blood: reevaluation of critical factors for successful isolation and high ability to proliferate and differentiate to chondrocytes as compared to mesenchymal stem cells from bone marrow and adipose tissue. Journal of cellular biochemistry. 2011;112(4):1206-18.
57. Yoder MC, Mead LE, Prater D, Krier TR, Mroueh KN, Li F, et al. Redefining endothelial progenitor cells via clonal analysis and hematopoietic stem/progenitor cell principals. Blood. 2007;109(5):1801-9.
58. Chakkarapani AA, Aly H, Benders M, Cotten CM, El-Dib M, Gressens P, et al. Therapies for neonatal encephalopathy: Targeting the latent, secondary and tertiary phases of evolving brain injury. Seminars in fetal & neonatal medicine. 2021;26(5):101256.
59. Ahn SY, Chang YS, Sung DK, Sung SI, Park WS. Hypothermia broadens the therapeutic time window of mesenchymal stem cell transplantation for severe neonatal hypoxic ischemic encephalopathy. Scientific reports. 2018;8(1):7665.
60. Park WS, Sung SI, Ahn SY, Yoo HS, Sung DK, Im GH, et al. Hypothermia augments neuroprotective activity of mesenchymal stem cells for neonatal hypoxic-ischemic encephalopathy. PloS one. 2015;10(3):e0120893.
61. Herz J, Köster C, Reinboth BS, Dzietko M, Hansen W, Sabir H, et al. Interaction between hypothermia and delayed mesenchymal stem cell therapy in neonatal hypoxic-ischemic brain injury. Brain, behavior, and immunity. 2018;70:118-30.
62. Yu Y, Yan Y, Luo Z, Luo P, Xiao N, Sun X, et al. Effects of human umbilical cord blood CD34(+) cell transplantation in neonatal hypoxic-ischemia rat model. Brain & development. 2019;41(2):173-81.
63. Zhang X, Zhang Q, Li W, Nie D, Chen W, Xu C, et al. Therapeutic effect of human umbilical cord mesenchymal stem cells on neonatal rat hypoxic-ischemic encephalopathy. Journal of neuroscience research. 2014;92(1):35-45.
64. Donega V, Nijboer CH, van Velthoven CT, Youssef SA, de Bruin A, van Bel F, et al. Assessment of long-term safety and efficacy of intranasal mesenchymal stem cell treatment for neonatal brain injury in the mouse. Pediatric research. 2015;78(5):520-6.
65. van Velthoven CT, Kavelaars A, van Bel F, Heijnen CJ. Nasal administration of stem cells: a promising novel route to treat neonatal ischemic brain damage. Pediatric research. 2010;68(5):419-22.

66. Kabatas S, Civelek E, Savrunlu EC, Kaplan N, Boyalı O, Diren F, et al. Feasibility of allogeneic mesenchymal stem cells in pediatric hypoxic-ischemic encephalopathy: Phase I study. World journal of stem cells. 2021;13(5):470-84.
67. Nabetani M, Mukai T, Shintaku H. Preventing Brain Damage from Hypoxic-Ischemic Encephalopathy in Neonates: Update on Mesenchymal Stromal Cells and Umbilical Cord Blood Cells. American journal of perinatology. 2022;39(16):1754-63.
68. Kabataş S, Civelek E, İnci Ç, Yalçınkaya EY, Günel G, Kır G, et al. Wharton's Jelly-Derived Mesenchymal Stem Cell Transplantation in a Patient with Hypoxic-Ischemic Encephalopathy: A Pilot Study. Cell transplantation. 2018;27(10):1425-33.
69. Yang J, Ren Z, Zhang C, Rao Y, Zhong J, Wang Z, et al. Safety of Autologous Cord Blood Cells for Preterms: A Descriptive Study. Stem cells international. 2018;2018:5268057.
70. Fu X, Hua R, Wang X, Wang P, Yi L, Yu A, et al. Synergistic Improvement in Children with Cerebral Palsy Who Underwent Double-Course Human Wharton's Jelly Stem Cell Transplantation. Stem cells international. 2019;2019:7481069.
71. Novak I, Walker K, Hunt RW, Wallace EM, Fahey M, Badawi N. Concise Review: Stem Cell Interventions for People With Cerebral Palsy: Systematic Review With Meta-Analysis. Stem cells translational medicine. 2016;5(8):1014-25.
72. Chen L, Zhang G, Gu Y, Guo X. Meta-Analysis and Systematic Review of Neural Stem Cells therapy for experimental ischemia stroke in preclinical studies. Scientific reports. 2016;6:32291.
73. Tang Y, Yu P, Cheng L. Current progress in the derivation and therapeutic application of neural stem cells. Cell death & disease. 2017;8(10):e3108.
74. Oh JH, Jung CR, Lee MO, Kim J, Son MY. Comparative analysis of human embryonic stem cell-derived neural stem cells as an in vitro human model. International journal of molecular medicine. 2018;41(2):783-90.
75. Zhang S, Lachance BB, Moiz B, Jia X. Optimizing Stem Cell Therapy after Ischemic Brain Injury. Journal of stroke. 2020;22(3):286-305.
76. Donega V, Nijboer CH, van Tilborg G, Dijkhuizen RM, Kavelaars A, Heijnen CJ. Intranasally administered mesenchymal stem cells promote a regenerative niche for repair of neonatal ischemic brain injury. Experimental neurology. 2014;261:53-64.
77. van Velthoven CT, Kavelaars A, Heijnen CJ. Mesenchymal stem cells as a treatment for neonatal ischemic brain damage. Pediatric research. 2012;71(4 Pt 2):474-81.
78. Chung TN, Kim JH, Choi BY, Jeong JY, Chung SP, Kwon SW, et al. Effect of Adipose-Derived Mesenchymal Stem Cell Administration and Mild Hypothermia Induction on Delayed Neuronal Death After Transient Global Cerebral Ischemia. Critical care medicine. 2017;45(5):e508-e15.
79. Achyut BR, Varma NR, Arbab AS. Application of Umbilical Cord Blood Derived Stem Cells in Diseases of the Nervous System. Journal of stem cell research & therapy. 2014;4.
80. Zhao Q, Hu J, Xiang J, Gu Y, Jin P, Hua F, et al. Intranasal administration of human umbilical cord mesenchymal stem cells-conditioned medium enhances vascular remodeling after stroke. Brain research. 2015;1624:489-96.
81. Liang CC, Liu HL, Chang SD, Chen SH, Lee TH. The Protective Effect of Human Umbilical Cord Blood CD34+ Cells and Estradiol against Focal Cerebral Ischemia in Female Ovariectomized Rat: Cerebral MR Imaging and Immunohistochemical Study. PloS one. 2016;11(1):e0147133.
82. Shiao ML, Yuan C, Crane AT, Voth JP, Juliano M, Stone LLH, et al. Immunomodulation with Human Umbilical Cord Blood Stem Cells Ameliorates Ischemic Brain Injury - A Brain Transcriptome Profiling Analysis. Cell transplantation. 2019;28(7):864-73.
83. Gonzales-Portillo GS, Sanberg PR, Franzblau M, Gonzales-Portillo C, Diamandis T, Staples M, et al. Mannitol-enhanced delivery of stem cells and their growth factors across the blood-brain barrier. Cell transplantation. 2014;23(4-5):531-9.
84. Balaguer Rosello A, Bataller L, Lorenzo I, Jarque I, Salavert M, González E, et al. Infections of the Central Nervous System after Unrelated Donor Umbilical Cord Blood Transplantation or Human Leukocyte Antigen-Matched Sibling Transplantation. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2017;23(1):134-9.
85. Sarmah D, Agrawal V, Rane P, Bhute S, Watanabe M, Kalia K, et al. Mesenchymal Stem Cell Therapy in Ischemic Stroke: A Meta-analysis of Preclinical Studies. Clinical pharmacology and therapeutics. 2018;103(6):990-8.
86. Vu Q, Xie K, Eckert M, Zhao W, Cramer SC. Meta-analysis of preclinical studies of mesenchymal stromal cells for ischemic stroke. Neurology. 2014;82(14):1277-86.
87. Donega V, van Velthoven CT, Nijboer CH, van Bel F, Kas MJ, Kavelaars A, et al. Intranasal mesenchymal stem cell treatment for neonatal brain damage: long-term cognitive and sensorimotor improvement. PloS one. 2013;8(1):e51253.
88. Liang CC, Lee TH, Chang SD. Effect of umbilical cord blood stem cells transplantation on bladder dysfunction induced by cerebral ischemia in rats. Taiwanese journal of obstetrics & gynecology. 2016;55(5):672-9.
89. Lin W, Hsuan YC, Lin MT, Kuo TW, Lin CH, Su YC, et al. Human Umbilical Cord Mesenchymal Stem Cells Preserve Adult Newborn Neurons and Reduce Neurological Injury after Cerebral Ischemia by Reducing the Number of Hypertrophic Microglia/Macrophages. Cell transplantation. 2017;26(11):1798-810.
90. Wei W, Wu D, Duan Y, Elkin KB, Chandra A, Guan L, et al. Neuroprotection by mesenchymal stem cell (MSC) administration is enhanced by local cooling infusion (LCI) in ischemia. Brain research. 2019;1724:146406.
91. Hwang S, Choi J, Kim M. Combining Human Umbilical Cord Blood Cells With Erythropoietin Enhances Angiogenesis/Neurogenesis and Behavioral Recovery After Stroke. Frontiers in neurology. 2019;10:357.