Turkish Archives of Pediatrics

REVIEW
DOI: 10.5152/TurkArchPediatr.2021.21006

Breast milk stem cells: Are they magic bullets in neonatology?

Sinem Gülcan Kersin, Eren Özek

Division of Neonatology, Department of Pediatrics, Marmara University School of Medicine, İstanbul, Turkey

ABSTRACT

Each mammal produces milk specific to its newborn that meets all nutritional needs. Breast milk is not only a secretory product but is also a complex liquid containing several components that provide enteral nutrition. The stage of lactation, the fullness of the breast, the feeding of the baby, and the health of the mother during the breastfeeding period cause differences in the composition of breast milk. Although the positive effects of breast milk on the physical and intellectual development of a child in the short and long term have been known for centuries, its mechanism has not been elucidated. Stem cells are defined as the cells that possess specific markers and have not undergone differentiation. Under suitable conditions and stimuli, they can differentiate into desired cells. The detection of stem cells, whose exact origin is not known, in breast milk and their demonstration in the baby's body have prompted the necessity of exploring the possible role of stem cells in the treatment of diseases. In this review, breast milk-derived stem cells and their possible role in neonatology are discussed.

Keywords: Bronchopulmonary dysplasia, human breast milk, hypoxic-ischemic encephalopathy, intraventricular hemorrhage, necrotizing enterocolitis, stem cell

Introduction

Each mammal produces milk that is unique for its newborn. The specific components in milk satisfy the nutritional requirements of the newborn. Although the beneficial effects of breast milk on the basic physical and intellectual development of a child in the short and long term have been known for centuries, the mechanism remains elusive. The mechanism by which breast milk consumed in the early period of life confers protection against diseases occurring in the later period of life warrants investigation.

Breast milk is not simply a product that provides enteral nutrition for the infant but is also a complex fluid with more than 200 well-known components (1). With advances in analytical techniques, the number of recognized components has increased. Breast milk contains thousands of cells per milliliter (2). Milk is constituted by several substances in various phases, including solutions, colloids, membranes, membrane-bound globules, and living cells. Breast milk composition is variable among women. The stage of lactation, the degree of breast fullness, breastfeeding and breastmilk removal, the growth rate of the infant and its needs, the health of the mother, and the environment cause differences in the composition of breast milk (2,3). Milk regulates immunity in the newborn and at infancy through the inherent bioactive and immunological components and confers protection against infections (4). Recent studies have revealed that components in the breast milk establish communication with other cells in the development and regulation of the innate and acquired immune system (5). Breast milk also contains certain biologically active elements, such as exosomes, that were not previously recognized. Exosomes are small vesicles that function in intercellular signaling, inflammation, cell adhesion, and immune response (6). In an in vitro study conducted by Lanik et al. (7), the positive effects of breast milk on the proliferation and growth of mouse and human enterocytes were shown. The symbiotic relationship between breast milk and

Corresponding Author:
Sinem Gülcan Kersin
✉sinemgulcan@hotmail.com
Received: 07.01.2021
Accepted: 26.01.2021
turkarchpediatr.org

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Cite this article as: Kersin SG, Özek E. Breast milk stem cells: are they magic bullets in neonatology? Turk Arch Pediatr 2021; 56(3): 187-91.

its natural hosts has led to the formulation of the notion that breast milk is a living system or an organ (2,3). Researchers have suggested that breast milk can be used in combination with traditional drug therapies.

Stem Cells and Progenitor Cells of Breast Milk

Stem cells are the most versatile cells, which exhibit specific markers and possess the ability to differentiate into lineages, i.e., the cells and tissues of different body organs, under favorable conditions and stimuli. To consider a cell as a stem cell, it is necessary that the cell fulfill the following characteristics (8):

- The ability to self-renew or to create at least one similar cell that bears the characteristics of the original cell
- The ability to differentiate from a single cell into multiple serial cells (multilineage differentiation)
- The ability to perform functional reconstruction of a particular tissue in vivo

Different classifications of stem cells have been defined. The most accepted classifications are as follows (9):

- Embryonic stem cells
- Non-embryonic stem cells
  - Hematopoetic stem cells
    - Bone marrow stem cells
    - Peripheral blood stem cells
    - Umbilical cord blood stem cells
  - Stromal (mesenchymal) stem cells
  - Other stem cells resident in organs

The cell composition of breast milk can be accurately evaluated using new methods developed for the identification and separation of biological fluids, such as multicolor flow cytometry. The exact source of human breast milk stem cells that can differentiate into multilineages is unknown (2,10). Stem cells in breast milk were first described in 2007. Cregan et al. (11) reported the presence of the general stem cell marker nestin in term breast milk, which is a neural, bone marrow, pancreatic, and epithelial stem cell marker. Except for probiotic bacteria, cells of eukaryotic origin found in breast milk stem cells are examined after classification into two groups, namely blood- and breast-derived cells. The blood-derived group includes immune cells and hematopoietic stem cells; the breast-derived cells include lactocytes and myoepithelial cells (12).

As expected, breast milk contains cytokeratin (CK) 18-positive luminal epithelial cells synthesizing milk protein and beta-casein-positive lactocytes. In a healthy breastfeeding period, 98% of the breast milk can consist of these cells (13). Along with mature epithelial cells, there are also precursors and stem cells in breast milk. It is hypothesized that the mammary glands, which carry the role of milk-secreting organs after a lactation-free period, reveal hidden progenitor cells via activation of intracellular signaling pathways (14). Cregan et al. (11) also reported the stem cell marker, CK5+, in the lactating mammary gland in a cell culture experiment.

A mammary stem cell marker, α6 integrin (CD49f), and an epithelial progenitor cell marker, p63, were detected in cell cultures obtained from breast milk by Sani et al. (15). In an in vitro study conducted by Thomas et al. (16), it was reported that these cells not only exhibited stem cell markers but also possessed multipotent properties, could undergo self-renewal, and differentiated at least two epithelial lineages of cells that produce milk proteins, such as CK18+ lumen cell or CK14+ myoepithelial cell (17).

The detection of the most pluripotent, multilineage human embryonic stem cells in breast milk, which can differentiate into various cell types, had a considerable impact on science (18). In a study conducted by Hassiotou et al. (2), undifferentiated pluripotent stem cells expressing SSEA4, TRA-1-60, and TRA-1-81 were detected in breast milk, and they showed that these cells could differentiate into epithelial cells, such as lactocytes and myoepithelial cells, and milk-secreting proteins. Sani et al. (15) observed that mesenchymal stem cells expressed CD44, CD90, CD271, and CD146 in the majority of cultures, and a subpopulation also expressed the embryonic stem cell markers of Oct4, Sox2, TRA 60-1, Nanog, and CK18+ lumen epithelial cells, which can differentiate into adipocytes and osteoblasts. Similarly, in the study conducted by Hosseini et al. (18), human breast-derived stem cells expressed mesenchymal and embryonic markers.

In a study on breast milk stem cells of premature and term babies conducted by Briere et al. (19), stem cell marker values were not significantly different between the groups, but the stem cell markers SOX2, Nanog, CD90, and CD105 were expressed more in preterm milk than term milk. Although the reason is not fully explained, it is assumed that the symbiotic relationship between mother and baby continues during breastfeeding, and there are changes in stem cells and gene expression levels according to the infant's needs (20).

There is no evidence available on the exact origin of breast milk stem cells. In a review authored by Hassiotou and Hartmann (2), the presence of CD34+ hematopoietic stem/progenitor cells originating from the mother's bloodstream has been demonstrated in colostrum and breast milk. Similarly, few studies suggest that blood-derived stem cell markers in breast milk originate from hematopoietic stem cells, whereas certain studies have reported that the origin is attributable to maternal blood circulation (21). Human breast milk stem cells remain to be elucidated, and the mechanisms by which stem cells exist in breast milk in the postnatal period warrant investigation.

Breast Milk and Microchimerism

Microchimerism is the presence of a small number of cells or DNA that originate from another individual that are genetically distinct from the cells of the host individual (22). Maternal-fetal and fetal-maternal microchimerism occur most commonly in pregnancy, and it is also known to occur during breastfeeding (22). The mechanism by which these cells affect the baby remain unknown. In an animal experiment, Hassiotou et al. (23) reported that stem cells in breast milk could pass through the infant gastrointestinal system and provided complete functionality in the target tissue. In another study performed by Abd Allah et al. (24), fluorescently dyed purified milk stem cells were shown to be present in various organs of the offspring. Aydın et al. (25) showed that maternal cells detected in the blood and brain of pups differentiated into glial and neuronal cell types in the brain.

Pregnancy-induced microchimerism cells can be detected in the offspring's bloodstream for several years. During the lactation period, maternal stem cells are not considered pathological by the immune system, bypass the gastrointestinal tract, and contribute to optimizing neonatal and infant immune development and tissue growth/repair (26). The roles of these mysterious cells and many other unknown cells are still under investigation.

Breast Milk Stem Cells and Their Role in the Treatment of Neonatal Disease

Stem cells play crucial roles, such as direct differentiation into the required cell types, paracrine function, and secretion of factors to change the behavior of cells and repair tissue (27). In regenerative medicine, multiple studies have been conducted on stem cells and their effect on tissue repair, wound healing, and cancer. There are also studies reporting that paracrine activities of stem cells are more important for repair than their differentiation potential (27).

Stem cells obtained from different sources and stem cell-derived therapies have shown considerable potential in the treatment of different diseases affecting neonates. Breast milk stem cells are unlikely to be tumorigenic, demonstrate relatively easier accessibility, and invasive techniques are not required for their acquisition (10).

One of the most surprising effects of breast milk stem cells has been shown in stroke. In a review published on the application of stem cell therapy for abrogating stroke-induced neuroinflammation by Stonesifer et al. (28), it was found that breast milk stem cells differentiated into astrocytes and reduced damage by stimulating the suppression of peripheral immune invasion via secreting growth factors, such as vascular endothelial growth factor and hepatocyte growth factor. In another study conducted by Okazaki et al. (29), mesenchymal stem cells were used within a period of 3-24 hours after stroke, and an increase in the expression of anti-apoptotic Bcl-2 and survivin proteins with a 50% reduction of the ischemic area was observed.

Hypoxic-ischemic encephalopathy (HIE), which is characterized by a sudden decrease in blood flow and consequent impairment in the tissue oxygenation of the brain in newborns, is one of the conditions in which neonatologists encounter considerable challenges. The neuroprotective approach is the most effective strategy available in the management of HIE to protect the developing newborn brain from reperfusion damage. It is hypothesized that the cytokines, bioactive molecules, and growth factors secreted by stem cells can limit the damage indirectly via paracrine effect, as reported in stroke studies, and can enable the recovery of functions by increasing neurogenesis (30). In animal models of HIE studies conducted by van Velthoven et al. (31,32), mesenchymal stem cells were administered via different routes, such as intravenous, intranasal, and intracranial, and a reduction in hypoxic damage was observed. Zhang et al. (33) showed that intraventricular transplantation of umbilical cord blood mesenchymal stem cells into rats with hypoxia-ischemia-induced brain damage reduced apoptosis and improved neurological functions. Autologous umbilical cord blood has been used worldwide in hematology, endocrinology, neurological diseases, cerebral palsy, and treatment of HIE (34). In a study conducted by Huang et al. (35), human umbilical cord mesenchymal stem cell transplantation was shown to improve neurological and extrapyramidal functions and emotional reaction in adult patients with HIE. In a pilot study including six newborns with severe HIE, umbilical cord blood was collected in the delivery room, and umbilical mesenchymal stem cell infusion was performed along with the continuation of therapeutic hypothermia. Neurofunctional development of four babies was reported to be normal without any impairment at 18 months of age (36). There have been no studies conducted using breast milk stem cells in HIE thus far. Promising results in the management of HIE, considering the importance of plasticity in newborn brains, will continue to pave the way for conduction of further studies.

The role of stem cells is presently under investigation to develop an alternative approach in the treatment for certain issues owing to prematurity, such as intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), and necrotizing enterocolitis (NEC). In an observational study involving preterms with severe IVH, human breast milk was provided intranasally. It was reported that the need for surgical intervention because of progressive ventricular dilatation and posthemorrhagic hydrocephalus was less in the intranasal breast milk group, and it was effective in limiting brain damage (37). A phase I dose-escalation clinical trial conducted by Ahn et al. (38) on nine premature infants with severe IVH reported that the treatment with allogeneic human umbilical cord-derived mesenchymal stem cells via intraventricular route was tolerated and safely feasible.

Bronchopulmonary dysplasia, which is a chronic lung disease, continues to be a major cause of neonatal morbidity and mortality worldwide. Inflammatory responses mediated by proinflammatory cytokines are crucial in the development of BPD (39). In an animal study in which BPD was developed experimentally, van Haaften et al. (40) showed that intratracheal bone marrow-derived mesenchymal stem cells suppressed inflammation, improved lung functions, and prevented irreversible hyperoxia-induced neonatal lung injury via paracrine effect of stem cells. In a phase I dose-escalation trial conducted by Chang et al. (39), human umbilical cord blood-derived mesenchymal stem cells were transplanted in preterm infants at high risk for BPD via an intratracheal route, and the authors found that BPD severity was markedly decreased. In the phase II trial of children with severe BPD, aged 0-1 years, intravenous administration of human umbilical mesenchymal stem cells with an additional low- or high-dose infusion along with the traditional supportive treatments was performed. The 24-month follow-up results are expected to be published this year (41). No studies have been conducted thus far using breast milk stem cells directly in BPD; however, breast milk stem cells have a potential applicability in this area.

Necrotizing enterocolitis, which is an acquired, life-threatening disease characterized by inflammation, loss of villi and epithelial cells, and intestinal necrosis, is one of the major issues of prematurity. Although the immaturity and microbial colonization of intestines, innate immune response, and reperfusion injury are attributable factors, the pathogenesis of this disease is obscure (42). There are several studies in the literature on breast milk-derived exosomes that significantly decrease the incidence and severity of experimental NEC (43). The role of mesenchymal

Table 1. The most recent stem cell studies in the literature on newborns

Study	Phase / Route	Stem cell type	Disease	Effect
Zhang et al. (33)	Animal/intraventricular	hUC-MSCs and cord blood mononuclear cells	HIE	↓ Cellular apoptosis, number of activated astrocytes Recovery of long-term spatial memory
Tsuji et al. (36)	Phase II clinical trial/ intravenous	Autologous hUC-MSCs	HIE	Feasible and safe
Ahn et al. (38)	Phase I dose-escalation clinical trial/intraventricular	Allogeneic hUC-MSCs	IVH	Feasible and safe
Keller et al. (37)	Phase I clinical trial/ intranasal	BMSCs	IVH	↓ Incidence of severe neurodevelopmental outcome
Kim et al. (46)	Animal/intraventricular	hUC-MSCs	IVH	↓ MAPK and STAT pathways ↓ microglial activation during IVH
Chang et al. (39)	Phase I clinical trial/ intratracheal	hUC-MSCs	BPD	↓ BPD severity in transplant group
Wu et al. (41)	Phase II dose-escalation trial on children aged 0-1 year	hUC-MSCs	BPD	Feasible and safe for severe BPD
Moreira et al. (47)	Animal/intranasal	hUC-MSCs	BPD	↓ Pulmonary vascularization ↓ Chronic inflammation ↑ Tissue healing ↑ Alveolar development
McCulloh et al. (48)	Animal/intraperitoneal	AF-MSC exosomes, bone marrow-derived MSC exosomes, AF-NSC exosomes, E-NSC exosomes	NEC	↓↓ Experimental NEC
Pisano et al. (45)	Animal/intraperitoneal, enteral	BMSC extracellular vesicles	NEC	↓ Incidence and severity of experimental NEC
Borhani-Haghighi et al. (49)	Animal	BMSCs	Spinal cord injury	↓ Apoptosis and inflammation at the site of injury

AF-MSC: amniotic fluid-derived mesenchymal stem cell; AF-NSC: amniotic fluid-derived neural stem cell; BMSC: breast milk-derived stem cell; BPD: bronchopulmonary dysplasia; E-NSC: neonatal enteric stem cell; HIE: hypoxic-ischemic encephalopathy; hUC-MSC: human umbilical cord mesenchymal stem cell; IVH: intraventricular hemorrhage; MAPK: mitogen-activated protein kinase; MSC, mesenchymal stem cell; NEC: necrotizing enterocolitis; STAT1: signal transducer and activator of transcription 1.

stem cells is also being investigated in the treatment of NEC. In an animal study conducted by Zani et al. (44), the authors reported that amniotic fluid stem cells improved survival, clinical status, and gut functions via modulation of stromal cells and enhanced repair of the damaged intestine via paracrine effect related to a COX-2 dependent mechanism. In a recent animal study conducted by Pisano et al (45), the offspring were randomly divided into the breastfed group without injury, the NEC group, the group that received human breast milk-derived extracellular vesicles once intraperitoneally, and the group that received human breast milk-derived extracellular vesicles orally at each feed. The results showed that none of the pups fed with breast milk had NEC, and the incidence of NEC was significantly lower in the intraperitoneally administered group than the enteral group. No human studies have been conducted using breast milk stem cells directly in NEC, although it is well known that breast milk prevents the development of NEC.

Conclusion

Stem cells from different sources are being investigated in many neonatal disorders, and they demonstrate promising applicability. There are many unknown aspects regarding breast milk stem cells. With advances in technology and scientific research, further data can be obtained regarding breast milk stem cells, and they may be hopefully used in the treatment of IVH, NEC, and HIE.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.G.K.; Design - S.G.K.; Supervision - E.O.; Materials – S.G.K.; Data Collection and/or Processing - S.G.K.; Analysis and/or Interpretation - S.G.K.; Literature Review - S.G.K., E.O.; Writing - S.G.K.; Critical Review - E.O.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Blanc B. Biochemical aspects of human milk--comparison with bovine milk. World Rev Nutr Diet 1981; 36: 1-89. [Crossref]
2. Hassiotou F, Hartmann PE. At the dawn of a new discovery: The potential of breast milk stem cells. Adv Nutr. 2014; 5: 770-8. [Crossref]
3. Witkowska-Zimny M, Kaminska-El-Hassan E. Cells of human breast milk. Cell Mol Biol Lett 2017; 22: 11. [Crossref]
4. Henrick BM, Yao XD, Nasser L, Roozrogousheh A, Rosenthal KL. Breastfeeding behaviors and the innate immune system of human milk: Working together to protect infants against inflammation, HIV-1, and Other Infections. Front Immunol 2017; 8: 1631. [Crossref]
5. Cacho NT, Lawrence RM. Innate immunity and breast milk. Front Immunol 2017; 8: 584. [Crossref]
6. Hock A, Miyake H, Li B, et al. Breast milk-derived exosomes promote intestinal epithelial cell growth. J Pediatr Surg 2017; 52: 755-9. [Crossref]
7. Lanik WE, Xu L, Luke CJ, et al. Breast milk enhances growth of enteroids: An ex vivo model of cell proliferation. J Vis Exp 2018; 132: 56921. [Crossref]

8. Weissman IL. Translating stem and progenitor cell biology to the clinic: Barriers and opportunities. Science 2000; 287: 1442-6. [Crossref]
9. Ateş U. Kök hücrelerin sınıflandırılması [Let's familiarize ourselves with the stem cell]. FNG& Bilim Tıp Transplantasyon Dergisi 2016; 1: 19-28. [Crossref]
10. Hassiotou F, Beltran A, Chetwynd E, et al. Breastmilk is a novel source of stem cells with multilineage differentiation potential. Stem Cells 2012; 30: 2164-74. [Crossref]
11. Cregan MD, Fan Y, Appelbee A, et al. Identification of nestin-positive putative mammary stem cells in human breastmilk. Cell Tissue Res 2007; 329: 129-36. [Crossref]
12. Briere CE, McGrath JM, Jensen T, Matson A, Finck C. Breast milk stem cells: Current science and implications for preterm infants. Adv Neonatal Care 2016; 16: 410-9. [Crossref]
13. Hassiotou F, Geddes DT, Hartmann PE. Cells in human milk: State of the science. J Hum Lact 2013; 29: 171-82. [Crossref]
14. Shackleton M, Vaillant F, Simpson KJ, et al. Generation of a functional mammary gland from a single stem cell. Nature 2006; 439: 84-8. [Crossref]
15. Sani M, Hosseini SM, Salmannejad M, et al. Origins of the breast milk-derived cells; An endeavor to find the cell sources. Cell Biol Int 2015; 39: 611-8. [Crossref]
16. Thomas E, Zeps N, Cregan M, Hartmann P, Martin T. 14-3-3σ (sigma) regulates proliferation and differentiation of multipotent p63-positive cells isolated from human breastmilk. Cell Cycle 2011; 10: 278-84. [Crossref]
17. Wobus AM. Potential of embryonic stem cells. Mol Aspects Med 2001; 22: 149-64. [Crossref]
18. Hosseini SM, Talaei-Khozani T, Sani M, Owrangi B. Differentiation of human breast-milk stem cells to neural stem cells and neurons. Neurol Res Int 2014; 2014: 807896. [Crossref]
19. Briere CE, Jensen T, McGrath JM, Young EE, Finck C. Stem-Like Cell Characteristics from breast milk of mothers with preterm ınfants as compared to mothers with term ınfants. Breastfeed Med 2017; 12: 174-9. [Crossref]
20. Alsaweed M, Lai CT, Hartmann PE, Geddes DT, Kakulas F. Human Milk Cells Contain Numerous miRNAs that May Change with Milk Removal and Regulate Multiple Physiological Processes. Int J Mol Sci 2016; 17: 956. [Crossref]
21. Fan Y, Chong YS, Choolani MA, Cregan MD, Chan JK. Unravelling the mystery of stem/progenitor cells in human breast milk. PLoS One 2010; 5: e14421. [Crossref]
22. Sarkar K, Miller FW. Possible roles and determinants of microchimerism in autoimmune and other disorders. Autoimmun Rev 2004; 3: 454-63. [Crossref]
23. Hassiotou F, Heath B, Ozal O, et al. Breastmilk stem cell transfer from mother to neonatal organs. The FASEB Journal. 2014; 28: 216.4 [Crossref]
24. Abd Allah SH, Shalaby SM, El-Shal AS, et al. Breast milk MSCs: An explanation of tissue growth and maturation of offspring. IUBMB Life 2016; 68: 935-42. [Crossref]
25. Aydın MŞ, Yiğit EN, Vatandaşlar E, Erdoğan E, Öztürk G. Transfer and integration of breast milk stem cells to the brain of suckling pups. Sci Rep 2018; 8: 14289. [Crossref]
26. Hanson LA. The mother-offspring dyad and the immune system. Acta Paediatr 2000; 89: 252-8. [Crossref]
27. Dittmer J, Leyh B. Paracrine effects of stem cells in wound healing and cancer progression. Int J Oncol 2014; 44: 1789-98. [Crossref]
28. Stonesifer C, Corey S, Ghanekar S, Diamandis Z, Acosta SA, Borlongan CV. Stem cell therapy for abrogating stroke-induced neuroinflammation and relevant secondary cell death mechanisms. Prog Neurobiol 2017; 158: 94-131. [Crossref]
29. Okazaki T, Magaki T, Takeda M, et al. Intravenous administration of bone marrow stromal cells increases survivin and Bcl-2 protein expression and improves sensorimotor function following ischemia in rats. Neurosci Lett 2008; 430: 109-14. [Crossref]
30. van Velthoven CT, Kavelaars A, Heijnen CJ. Mesenchymal stem cells as a treatment for neonatal ischemic brain damage. Pediatr Res 2012; 71: 474-81. [Crossref]
31. van Velthoven CT, Kavelaars A, van Bel F, Heijnen CJ. Repeated mesenchymal stem cell treatment after neonatal hypoxia-ischemia has distinct effects on formation and maturation of new neurons and oligodendrocytes leading to restoration of damage, corticospinal motor tract activity, and sensorimotor function. J Neurosci 2010; 30: 9603-11. [Crossref]
32. 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. Pediatr Res 2010; 68: 419-22. [Crossref]
33. Zhang J, Yang C, Chen J, et al. Umbilical cord mesenchymal stem cells and umbilical cord blood mononuclear cells improve neonatal rat memory after hypoxia-ischemia. Behav Brain Res 2019; 362: 56-63. [Crossref]
34. Boruczkowski D, Pujal JM, Zdolińska-Malinowska I. Autologous cord blood in children with cerebral palsy: A review. Int J Mol Sci 2019; 20: 2433. [Crossref]
35. Huang L, Zhang C, Gu J, et al. A Randomized, placebo-controlled trial of human umbilical cord blood mesenchymal stem cell infusion for children with cerebral palsy. Cell Transplant 2018; 27: 325-34. [Crossref]
36. Tsuji M, Sawada M, Watabe S, et al. Autologous cord blood cell therapy for neonatal hypoxic-ischaemic encephalopathy: A pilot study for feasibility and safety. Sci Rep 2020; 10: 4603. [Crossref]
37. Keller T, Körber F, Oberthuer A, et al. Intranasal breast milk for premature infants with severe intraventricular hemorrhage-an observation. Eur J Pediatr 2019; 178: 199-206. [Crossref]
38. 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 2018; 7: 847-56. [Crossref]
39. Chang YS, Ahn SY, Yoo HS, et al. Mesenchymal stem cells for bronchopulmonary dysplasia: Phase 1 dose-escalation clinical trial. J Pediatr 2014; 164: 966-72.e6. [Crossref]
40. van Haaften T, Byrne R, Bonnet S, et al. Airway delivery of mesenchymal stem cells prevents arrested alveolar growth in neonatal lung injury in rats. Am J Respir Crit Care Med 2009; 180: 1131-42. [Crossref]
41. Wu X, Xia Y, Zhou O, et al. Allogeneic human umbilical cord-derived mesenchymal stem cells for severe bronchopulmonary dysplasia in children: Study protocol for a randomized controlled trial (MSC-BPD trial). Trials 2020; 21: 125. [Crossref]
42. Eaton S, Zani A, Pierro A, De Coppi P. Stem cells as a potential therapy for necrotizing enterocolitis. Expert Opin Biol Ther. 2013; 13: 1683-9. [Crossref]
43. Chen W, Wang X, Yan X, Yu Z, Zhang J, Han S. The emerging role of exosomes in the pathogenesis, prognosis and treatment of necrotizing enterocolitis. Am J Transl Res 2020; 12: 7020-33.
44. Zani A, Cananzi M, Fascetti-Leon F, et al. Amniotic fluid stem cells improve survival and enhance repair of damaged intestine in necrotising enterocolitis via a COX-2 dependent mechanism. Gut 2014; 63: 300-9. [Crossref]
45. Pisano C, Galley J, Elbahrawy M, et al. Human Breast milk-derived extracellular vesicles in the protection against experimental necrotizing enterocolitis. J Pediatr Surg 2020; 55: 54-8. [Crossref]
46. Kim S, Kim YE, Hong S, et al. Reactive microglia and astrocytes in neonatal intraventricular hemorrhage model are blocked by mesenchymal stem cells. Glia 2020; 68: 178-92. [Crossref]
47. Moreira A, Winter C, Joy J, et al. Intranasal delivery of human umbilical cord Wharton's jelly mesenchymal stromal cells restores lung alveolarization and vascularization in experimental bronchopulmonary dysplasia. Stem Cells Transl Med 2020; 9: 221-34. [Crossref]
48. McCulloh CJ, Olson JK, Wang Y, et al. Treatment of experimental necrotizing enterocolitis with stem cell-derived exosomes. J Pediatr Surg 2018; 53: 1215-20. [Crossref]
49. Borhani-Haghighi M, Navid S, Mohamadi Y. The Therapeutic potential of conditioned medium from human breast milk stem cells in treating spinal cord injury. Asian Spine J 2020; 14: 131-8. [Crossref]