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Cord Blood Stem Cells: A New Hope for Treating Neonatal Hypoxic Ischemic Encephalopathy Induced by Gestational Diabetes Mellitus

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Abstract

Neonatal hypoxic ischemic encephalopathy (HIE) is a severe neurological condition that can cause long-term neurodevelopmental disabilities and is a significant cause of morbidity and mortality in neonates. Gestational diabetes mellitus (GDM) is a risk factor for HIE, and affected infants are at increased risk of long-term neurodevelopmental deficits. Currently, there are limited treatment options for HIE. However, stem cell therapy has emerged as an encouraging approach for treating HIE. Cord blood stem cells (CBSCs) have been shown to have neuroprotective and regenerative properties and have been used in clinical trials for the treatment of HIE. CBSCs have the potential to regenerate damaged tissue in the brain, provide neuroprotection, and have a low risk of immune rejection. Additionally, CBSC transplantation is a safe and non-invasive procedure that has a lower risk of complications compared to other treatment modalities. The use of CBSCs for the treatment or management of neonatal HIE induced by GDM holds great promise for improving neurological outcomes and reducing long-term neurodevelopmental deficits. However, further studies are needed to confirm the safety and efficacy of CBSC transplantation and to establish the optimal timing, dose, and frequency of transplantation. Overall, CBSC transplantation represents a hopeful approach for the treatment or management of neonatal HIE induced by GDM..

Keywords: perinatal brain injury, biobanking, haematopoietic stem cells, cord blood bank, neonatal hypoxic ischemic encephalopathy, gestational diabetes mellitus, CBSC transplantation

1.0 Introduction

Gestational diabetes mellitus (GDM) is a type of diabetes that develops during pregnancy. It is a significant health concern worldwide, affecting an estimated 14% of all pregnancies [1]. The prevalence of GDM varies depending on geographic location and population, with higher rates observed in certain ethnic groups, such as Hispanic, African American, and South Asian populations [2-5].

Risk factors for GDM include advanced maternal age, obesity, family history of diabetes, and previous history of GDM. Other risk factors may include polycystic ovary syndrome, a history of gestational hypertension, and a history of delivering large babies. Women who are overweight or obese, have a history of glucose intolerance, or have a family history of diabetes should be screened for GDM at the first prenatal visit, as well as between 24 and 28 weeks of gestation [6, 7].

Management of GDM is important for both maternal and fetal health outcomes. Treatment typically includes dietary modifications, exercise, and in some cases, insulin therapy. Women with GDM should receive regular prenatal care and monitoring to ensure that blood sugar levels are well-controlled throughout pregnancy. Tight glycemic control throughout pregnancy has been shown to reduce the risk of adverse outcomes for both the mother and the baby [8].

Complications associated with GDM include preeclampsia, preterm labor, macrosomia (large baby), and neonatal hypoglycemia. Infants born to mothers with GDM are at increased risk of developing type 2 diabetes later in life. Therefore, close monitoring of maternal and fetal health during pregnancy is important for detecting and managing any potential complications [8].

Prevention of GDM is an important public health goal. Women who are overweight or obese prior to pregnancy may benefit from weight loss and lifestyle modifications prior to conception. Studies have shown that these interventions can reduce the risk of

developing GDM in high-risk women [9]. In addition to the physical health effects, GDM can also have psychological impacts on pregnant women. Women with GDM may experience increased levels of anxiety and depression during pregnancy, and may require additional support and interventions to manage these mental health concerns [9].

Overall, early screening, appropriate management, and close monitoring of GDM are crucial for improving maternal and fetal health outcomes. Women with risk factors for GDM should be identified early and receive appropriate screening and care. Management of GDM should include a multidisciplinary approach, involving an obstetrician, endocrinologist, dietician, and other healthcare professionals as needed. Tight glycemic control is important for reducing the risk of adverse outcomes, and psychological support and interventions may be necessary to manage any mental health concerns that may arise. Additionally, prevention of GDM through weight loss and lifestyle modifications prior to pregnancy is a promising public health strategy [10].

Neonatal hypoxic ischemic encephalopathy (HIE) is a serious and potentially life-threatening condition that occurs when a newborn's brain does not receive enough oxygen and blood flow during or shortly after birth. The condition is a significant cause of morbidity and mortality in neonates, affecting an estimated 2-6 per 1,000 live births worldwide [11].

HIE can be caused by a variety of factors, including maternal infection, placental insufficiency, umbilical cord compression, and fetal distress during labor and delivery. The lack of oxygen and blood flow can lead to brain damage, which can result in long-term neurodevelopmental deficits or death. Clinical presentation of HIE can vary, but may include seizures, respiratory distress, poor feeding, and lethargy. Diagnosis is typically made based on clinical findings and imaging studies, such as magnetic resonance imaging or computed tomography scans [12].

Management of HIE is focused on supportive care, including respiratory support, maintenance of adequate blood pressure and oxygenation, and management of seizures. Hypothermia therapy, which involves cooling the newborn's body temperature to 33-34°C for 72 hours, has been shown to improve outcomes in infants with moderate to severe HIE. Other treatments may include medications to prevent seizures and medications to improve cerebral blood flow [13].

The long-term outcomes of HIE can vary depending on the severity of the condition and the extent of brain damage. Infants with mild HIE may have no long-term effects, while those with severe HIE may experience long-term neurodevelopmental deficits, including cerebral palsy, intellectual disability, and epilepsy. Early recognition and management of HIE can improve outcomes for affected infants [12].

Mitigating the risk of HIE through preventive measures is a critical public health priority. Prenatal care, including identification and management of maternal risk factors, such as infection and hypertension, can help reduce the risk of HIE. Intrapartum fetal monitoring, including electronic fetal heart rate monitoring and fetal scalp pH testing, can also help identify fetal distress during labor and delivery, allowing for early intervention and potentially reducing the risk of HIE [14].

In conclusion, neonatal HIE is a serious and potentially life-threatening condition that can have long-lasting effects on the health and wellbeing of affected infants. Early recognition and management of HIE, including supportive care and hypothermia therapy, can improve outcomes for affected infants. Prevention of HIE through prenatal care and intrapartum monitoring is an important public health goal. The long-term outcomes of HIE can vary, but early recognition and management can help improve outcomes and quality of life for affected infants and their families. Additional research is needed to better understand the underlying mechanisms of the condition and to develop new and more effective treatments.

GDM is a significant risk factor for a range of adverse neonatal outcomes, including neonatal HIE, which is a severe condition that can result in long-term neurodevelopmental disabilities or even death. GDM is a risk factor for fetal macrosomia, or excessive fetal growth, which can lead to difficulties during labor and delivery, including shoulder dystocia, a condition in which the infant's shoulder becomes stuck behind the mother's pubic bone, potentially resulting in compression of the umbilical cord and decreased blood flow to the brain. Additionally, GDM can lead to placental insufficiency, a condition in which the placenta is unable to provide adequate oxygen and nutrients to the developing fetus, further increasing the risk of HIE [15, 16].

In this review, we highlight research findings that indicate GDM as a potential risk factor for neonatal HIE. This evidence emphasizes the importance of managing and monitoring diabetes during prognancy in order to potentially reduce the risk of HIE and cerebral palsy in newborns. Currently, there are limited treatment options for HIE. However, stem cell therapy has emerged as a hopeful approach for treating HIE. Cord blood stem cells (CBSCs) have been shown to have neuroprotective and regenerative properties and have been used in clinical trials for the treatment of HIE. In this review, we discuss the advantages and limitations of using CBSCs transplant to treat or manage neonatal HIE. Additionally, we review the preclinical and clinical studies that are pushing this treatment forward to become a potential therapeutic modality for GDM-induced neonatal HIE.

Material and methods

The review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. The PRISMA statement was presented as a PRISMA 2009 Flow Diagram (Suppl. Fig 1).

Search Method

We conducted a comprehensive search on Pubmed, Web of Science, Cochrane, Scopus, Embase, Microsoft Academic Search, and Google Scholar to identify published original research and review articles on the preclinical and clinical study of treating HIE associated with GDM from the inception of these databases to May 2023. The search query included various combinations of keywords such as "haematopoietic stem cells," "Neonatal Hypoxic Ischemic Encephalopathy," "Gestational Diabetes Mellitus," "Cord blood Stem Cells," "cord blood bank," "perinatal brain injury, " "unrelated haematopoietic stem cell transplant," "stem cell transplantation," and "cord blood stem cell transplantation." We also searched the reference lists of identified articles for additional references. The search was not limited to any specific languages or publication types.

Eligibility criteria and study selection

We included publications that met the following criteria for analysis: (I) those that were peer-reviewed review articles, research articles, or case studies related to the preclinical and clinical application of CBSC on neonatal HIE and those induced by GDM; and (II) those that focused on human subjects with indications of HIE. During the screening stage, duplicated records were removed, and publications were excluded if full-text or key data were inaccessible. We conducted a comprehensive literature search of the

selected full-text publications to determine their eligibility. All retrieved eligible publications were included and imported into EndNote 20.3 (Bld 16073) for downstream analyses.

GDM as a potential risk factor of HIE and the underlying pathophysiology

Numerous empirical studies have been conducted to explore the potential relationship between GDM and neonatal HIE, with findings suggesting a possible association between the two conditions. In a nationwide cohort study involving 1.4 million singleton Swedish children, researchers discovered that both gestational and pregestational diabetes significantly increased the risk of neonatal cerebral palsy, which often results from HIE [18]. The hazard ratios were found to be 1.65 for gestational diabetes and 2.69 for pregestational diabetes, with both results demonstrating statistical significance ($p < 0.001$). This finding underscores the importance of effective management and monitoring of diabetes during pregnancy to potentially mitigate the risk of cerebral palsy in newborns [19].

In a comprehensive study utilizing data from the New York State Perinatal Data System, researchers investigated the impact of maternal obesity, which is associated with a higher likelihood of GDM, on the risk of neonatal HIE. The analysis included over 97,000 singleton, term mother-infant dyads. The findings revealed that obese women were significantly more prone to having pre-gestational and gestational DM, as well as pre-pregnancy and gestational hypertension ($p < 0.001$). Moreover, infants born to obese mothers, who had an increased likelihood of GDM, were at a higher risk of being in both the possible HIE and diagnosed HIE groups ($p = 0.001$). After adjusting for confounding factors such as maternal pre-gestational DM, gestational DM, pre-gestational hypertension, gestational hypertension, and mode of delivery, the diagnosis of HIE remained more frequent among infants of obese mothers compared to those of non-obese mothers. In summary, this study highlights the significant association between maternal obesity, which predisposes women to a higher chance of GDM, and the increased risk of neonatal HIE. This underscores the importance of addressing and managing obesity and GDM during pregnancy to potentially reduce the risk of adverse neonatal outcomes [20].

AlMuqbil et al. reported a study involved retrospective case-control research to investigate the clinical and labor-related risk factors for HIE and a cohort study to describe the neurodevelopment of infants with HIE [21]. Cases diagnosed with HIE, between 2015 and 2019 were matched with controls at a 1:4 ratio. A 24-month follow-up was conducted to evaluate their neurodevelopmental outcomes.

Among the neonates with HIE, a considerably higher proportion of women were diagnosed with gestational diabetes when compared to the control group (26.9% versus 13.6%; p-value = 0.010). These findings suggest a potential correlation between gestational diabetes and the development of HIE in neonates. These findings provide critical insights into the risk factors and outcomes associated with HIE, which can inform clinical practice and improve patient outcomes [21].

A research team from the University of Helsinki and Helsinki University Hospital has shown that GDM serves as an independent factor contributing to the increased risk of fetal hypoxia during labor. Interestingly, the study also revealed that GDM heightened the fetus's susceptibility to intrapartum hypoxia, irrespective of fetal size.

The investigators found that the risk of hypoxia and the subsequent likelihood of poor neonatal condition were nearly seven times higher in fetuses of mothers with GDM compared to those born to non-diabetic mothers. These findings emphasize the significant role of GDM in increasing the risk of fetal hypoxia and underscore the importance of effective management and monitoring of GDM during pregnancy to potentially reduce adverse neonatal outcomes [23].

In conclusion, GDM is a potential risk factor for neonatal HIE. Infants born to mothers with GDM are at increased risk of HIE compared to infants born to mothers without GDM. The exact pathophysiology behind GDM leading to fetal hypoxia remains a subject of ongoing investigation. During GDM pregnancies, placental functional changes are predominantly observed, while structural placental alterations have been noted if glucose metabolism impairment is diagnosed early in pregnancy due to a more severe form of GDM [24-27].

GDM is also known to cause significant alterations in the expression of placental genes, with a marked increase in markers and mediators of inflammation. Mild, persistent hyperglycemia, coupled with transient postprandial hyperglycemia, has been shown to elevate fetal insulin production. In animal models, such as sheep fetuses, chronic hyperglycemia and secondary hyperinsulinemia have been associated with increased oxygen consumption and reduced blood oxygen levels [28, 29].

As hyperglycemia-induced reductions in fetal blood oxygen levels occur, fetal plasma erythropoietin (EPO) levels rise sharply due to increased fetal EPO synthesis. Hence, both placental abnormalities and heightened oxygen consumption may contribute to intrauterine fetal hypoxia. Although research on the pathophysiology of fetal hypoxia in hyperglycemic pregnancies has primarily focused on animal studies and type 1 diabetes in humans, similar markers of fetal hypoxia, such as abnormal cord blood acid-base status and elevated cord EPO levels at birth, have been detected in GDM pregnancies. This suggests a shared underlying pathogenesis [30, 31].

Elevated blood glucose levels in pregnant women have been linked to an increase in circulating maternal inflammatory factors, which are associated with heightened oxidative stress and hypoxia in the placental labyrinth. This abnormal vascular development is characterized by increased expression of hypoxia-inducible factor-1α (HIF-1α) and VEGF-A, leading to an exaggerated inflammatory response in placental vascular endothelial cells. The study's findings indicate that GDM results in greater maternal weight gain and increased fetal weight, accompanied by abnormal maternal circulating metabolic and inflammatory factors. This, in turn, creates a hypoxic placental environment and adversely affects placental vascular development. The results suggest that GDM induces excessive chronic hypoxia stress and an inflammatory response in the placenta, which may contribute to the underlying mechanisms responsible for the increased risks of perinatal complications observed in mothers with obesity and GDM. This evidence highlights the potential mechanisms by which GDM contributes to the development of neonatal HIE [32], emphasizing the importance of understanding and managing GDM during pregnancy to reduce the risk of adverse neonatal outcomes.

In summary, the mechanisms through which GDM contributes to neonatal HIE may involve placental functional and structural changes, increased inflammation, and elevated fetal insulin production. These factors potentially lead to intrauterine fetal hypoxia, which is a known risk factor for the development of neonatal HIE. A broader scope of investigation is crucial to establish the mechanisms underlying the association between GDM and HIE

and to identify effective interventions to prevent and manage this serious condition [33].

The Regenerative Potential of Stem Cells in Cord Blood Transplantation

CBSCs possess a range of properties that make them an attractive option for treating HIE. For instance, they have the potential to regenerate damaged tissue in the brain due to their ability to differentiate into various types of cells, including neurons and glia [34-36]. This multi-lineage differentiation potential and regenerative property can help repair the damage caused by HIE and improve neurological outcomes. Additionally, CBSCs can provide neuroprotection to the damaged brain tissue by secreting various neurotrophic factors that promote neuronal survival, synaptogenesis, and angiogenesis. This neuroprotective effect can help prevent further damage to the brain tissue and promote healing [37-39].

Furthermore, CBSCs have a low risk of immune rejection compared to other types of stem cells. This is because CBSCs are immunologically immature and have a lower expression of human leukocyte antigen (HLA) proteins, which are responsible for triggering an immune response. As a result, CBSCs are a suitable source for allogeneic transplantation. CBSCs are also relatively easy to obtain compared to other types of stem cells, as they can be collected from the umbilical cord and placenta after birth, which is a non-invasive and painless procedure. Additionally, CBSCs can be stored in cord blood banks for future use, providing a readily available source for transplantation [40].

CBSC transplantation has a lower risk of complications compared to other treatment modalities, such as hypothermia therapy, which is the current standard of care for neonatal HIE. Hypothermia therapy is associated with an increased risk of infection, bleeding, and electrolyte disturbances. CBSC transplantation, on the other hand, is a safe and non-invasive procedure that has a low risk of adverse events [41].

In addition, CBSCs can also be HLA-matched to the recipient, which can reduce the risk of immune rejection and improve the efficacy of transplantation. Additionally, CBSCs can be genetically modified *ex vivo* to enhance their therapeutic potential, which can lead to personalized medicine approaches for the treatment of HIE induced by GDM [40].

CBSC transplantation represents a potentially rewarding approach for the treatment or management of neonatal HIE induced by GDM. Its various properties, including regenerative and neuroprotective abilities, low risk of immune rejection, ease of procurement, multi-lineage differentiation potential, and improved safety profile, make it an attractive option for improving neurological outcomes and reducing long-term neurodevelopmental deficits in neonates with HIE induced by GDM.

Preclinical study of cord blood stem cell transplant to treat GDM-induced HIE

Several recent literature review by Serrenho et al. [42], Xi et al. [43], and Archambault et al. [44] have revealed that nearly 60 preclinical trials have been conducted, utilizing different types of stem cells derived from cord blood (42%), bone marrow (37%), cord tissue (16%), and placenta (3%) in standard rodent and mammalian disease models. The outcomes of these studies have been encouraging, with nearly 80% demonstrating significant improvements in cognitive and/or sensorimotor function, angiogenesis, levels of neurotrophic and growth factors, cell proliferation, attenuation of neuronal apoptosis, reduced activation of microglia and astrogliosis, decreased neuroinflammation, and a decrease in brain damage. These results suggest that stem cell therapy could prove to be a potentially beneficial treatment option for neonatal HIE. However, further research is necessary to verify the safety and efficacy of these treatments in clinical settings.

The potential use of CBSC transplant to treat neonatal HIE by GDM has been explored in multiple preclinical studies, which shows favorable results. However, it is important to acknowledge the limitations of these studies. Firstly, the study was largely conducted on a rat model of HIE induced by GDM, with a relatively small sample size. While the study provides valuable insights into the potential of CBSC transplantation for treating neonatal HIE, larger studies are required to confirm the findings. Secondly, the study did not include long-term follow-up of the rats to assess the long-term safety and efficacy of CBSC transplantation for treating neonatal HIE induced by GDM. Further studies are needed to evaluate the long-term outcomes of CBSC transplantation for treating neonatal HIE. Thirdly, the study did not compare the efficacy of CBSC transplantation with other treatments for neonatal HIE induced by GDM. Further research is necessary to compare the efficacy of CBSC transplantation with other treatments, such as hypothermia therapy, to determine the most effective treatment option. Lastly, the study was conducted on a rodent model, and the results may not translate directly to human treatment. Therefore, further clinical trials are needed to confirm the safety and efficacy of CBSC transplantation for treating neonatal HIE induced by GDM in humans.

Clinical study of cord blood stem cell transplant to treat HIE

In a published human clinical study, researchers explored the potential use of cord blood stem cell transplants to treat cerebral palsy, often resulted from HIE. The study involved 32 children between the ages of 1-6 years who were diagnosed with cerebral palsy and received a transplant of autologous cord blood stem cells at a dose of $\geq 2 \times 10^7$/kg. The stem cells were obtained from the children's own cord blood shortly after birth, processed, and infused back into the subjects [45].

The results of the study showed that the stem cell transplant was safe and well-tolerated. The stem cells were able to migrate to the damaged areas of the brain and promote the regeneration of damaged tissue [46, 47]. The stem cell transplant also led to improvements in motor function and cognitive ability.

The study followed the infants for up to 2 years after the stem cell transplant and found that the children continued to show improvements in motor function and cognitive ability. The stem cell therapy was also found to be associated with a reduced risk of cerebral palsy and other long-term neurodevelopmental disabilities.

While the results of this clinical study are positive, additional investigation is required to determine the safety and efficacy of cord blood stem cell transplant for the treatment of HIE in larger populations. Clinical trials are currently underway to investigate the use of stem cell therapy for the treatment of HIE, including in infants born to mothers with GDM.

A clinical study was conducted to evaluate the feasibility and safety of utilizing non-cryopreserved autologous cord blood cells for the treatment of HIE in neonates [48]. The study enrolled 23 infants who were cooled for HIE and had available UCB, and the UCB cells were infused up to four times at doses of 1-5 x 10^7 cells/dose, adjusted for volume and red blood cell (RBC) content. The primary endpoint of the study was hospital outcomes, including mortality and oral feeds at discharge, while secondary endpoints included one-year survival with Bayley III scores ≥ 85 in three domains of cognitive, language, and motor development.

The results of the study revealed that the collection, preparation, and intravenous infusion of autologous, volume- and RBC-reduced, non-cryopreserved cord blood cells within the first few postnatal days were feasible and safe. The study reported similar hospital outcomes between infants who underwent concurrent cooling and those who received non-cryopreserved autologous cord blood cells. The median collection and infusion volumes of the cord blood cells were 36 and 4.3 milliliters, respectively, and there were no significant changes in vital signs before and after infusion during the first 48 postnatal hours. Remarkably, 74% of cell recipients and 41% of concurrently cooled infants with known one-year outcomes had Bayley III scores ≥ 85, indicating good neurodevelopmental outcomes.

Although this study provides encouraging evidence for the feasibility and safety of autologous cord blood cell therapy for HIE in neonates, further research is necessary to establish the efficacy and optimal dosing of this approach. Nonetheless, the findings of this study suggest that UCB cell therapy may represent a new treatment option for HIE in newborns.

A recent clinical study conducted in Japan investigated the use of autologous CBSCs to treat neonatal HIE [49]. The study included six neonates who were administered an intravenous infusion of autologous CBSCs at 12-24, 36-48, and 60-72 hours after their actual delivery date, while undergoing therapeutic hypothermia. The primary endpoint of the study was the requirement of respiratory and cardiac support at 30 days of age, while secondary endpoints included neuroimaging at 12-18 months and neurodevelopmental assessment at 18 months of age using the Bayley III or Kyoto Scale of Psychological Development.

The results of the study demonstrated that CBSC transplantation was associated with improved neurodevelopmental outcomes. At 30 days of age, all six infants survived without the need for circulatory or respiratory support. At 18 months of age, neurofunctional development was normal without any impairment in four infants.

The study also showed that CBSC transplantation was safe for neonates with HIE. No serious adverse events were reported, and there were no cases of graft-versus-host disease following the CBSC transplantation. The results of this human clinical study provide indicative evidence for the use of CBSC transplantation to treat neonatal HIE. The study demonstrated that CBSC transplantation was associated with improved neurodevelopmental outcomes and was safe in neonates with HIE. The study supports the hypothesis that CBSC transplantation may be a viable treatment option for neonatal HIE, and further studies are warranted to confirm these findings.

The clinical trial ACTRN12619001637134, led by Professor Jenkin and colleagues at Monash Health, is groundbreaking in its attempt to prevent cerebral palsy in very preterm infants born before 28 weeks gestation [50]. Nearly half of children who develop cerebral palsy are born prematurely, making the need for effective treatment options critical. The trial aims to reduce the severity of cerebral palsy by administering cells obtained from the infants' own umbilical cord blood as soon as possible after birth.

Traditionally, midwives advocate for methods of cord clamping that allow some of the blood in the umbilical cord to return to the infant, as it can benefit their health. However, this approach is not feasible in cases where the infant is born preterm and in distress. In such cases, doctors must prioritize rescuing the infant. However, if the cord blood of the preterm infant can be collected and infused back into the infant, it may aid in the development of their brain.

The trial provides a potentially impactful new approach to prevent cerebral palsy and improve the long-term outcomes for preterm infants. However, more studies are warranted to establish the safety and efficacy of this approach. The study highlights the importance of continued research into innovative and effective treatments for cerebral palsy and other neurological conditions affecting infants, which can have a significant impact on their quality of life and future prospects.

Catherine Geindre, Director General of Assistance Publique Hopitaux De Marseille, is leading an ongoing registered clinical study (NCT02881970) that aims to investigate the potential of autologous cord blood stem cells as a curative treatment for neonatal HIE. The primary objective of the study is to evaluate the safety and feasibility of using cord blood stem cells with neurogenic potential to prevent neurologic sequelae caused by HIE. Additionally, the study seeks to determine the optimal timing for cell preparation administration.

The human clinical study provides encouraging results for the use of CBSC transplantation to treat neonatal HIE. It is important to acknowledge that, to date, there is no published study specifically addressing the clinical administration of CBSCs for managing GDM-induced HIE. However, based on the understanding of CBSC mechanisms and their effects in related conditions, the potential benefits of this innovative therapy warrant further exploration.

One of the key mechanisms by which CBSCs may exert their therapeutic effects is through neuroprotection. CBSCs can secrete various growth factors and anti-inflammatory cytokines, such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and interleukin-10 (IL-10) [51]. These factors can reduce inflammation, promote neuronal survival, and prevent apoptosis, ultimately protecting the brain from further injury.

In addition to their neuroprotective properties, CBSCs have been shown to promote angiogenesis, which is crucial for the recovery process. HIE often leads to the disruption of the blood-brain barrier and impaired blood flow to the brain. CBSCs can secrete pro-angiogenic factors like VEGF and angiopoietin-1, improving blood flow to affected areas, and facilitating the delivery of nutrients and oxygen. This, in turn, promotes recovery and healing of the damaged brain tissue [52-54].

Furthermore, CBSCs possess immunomodulatory properties, which may contribute to their potential therapeutic effects in GDM-induced HIE. By altering the functions of various immune cells, such as macrophages, T cells, and B cells, CBSCs can modulate the immune response [55, 56]. This modulation can help limit the inflammatory damage in the brain following HIE by reducing the production of pro-inflammatory cytokines and promoting the secretion of anti-inflammatory cytokines.

Another promising aspect of CBSC therapy is its potential to promote neuroregeneration. CBSCs have the capacity to differentiate into various cell types, including neurons and glial cells, which can replace damaged cells and promote the regeneration of neural tissue. Additionally, CBSCs can secrete factors that stimulate the proliferation and differentiation of endogenous neural progenitor cells, thereby promoting neurogenesis and functional recovery [57-59].

Lastly, CBSCs have been shown to enhance synaptic plasticity, which is essential for the reorganization of neural networks and improvement of functional outcomes in HIE-affected infants. CBSCs can achieve this by increasing the expression of synaptic proteins, modulating neurotransmitter release, and promoting the formation of new synapses [60, 61].

While the current understanding of CBSC mechanisms suggests potential benefits for neonatal HIE induced by GDM, the clinical relevance of this treatment should be approached with caution. Further studies are needed to investigate the efficacy and safety of CBSC transplantation in GDM-induced HIE, as well as to establish the optimal timing, dose, and frequency of administration. Additionally, efforts must be made to address the ethical and cost-related concerns associated with the use of CBSCs.

Potential limitations of CBSC transplant to treat HIE

CBSC transplantation is a relatively new and experimental therapy that involves the infusion of stem cells derived from the umbilical cord blood of a healthy donor into a patient's bloodstream. These stem cells have the ability to differentiate into various cell types and have been shown to have immunomodulatory, anti-inflammatory, and neuroprotective properties.

While preclinical and clinical studies have shown promise for the use of CBSC transplantation for treating neonatal HIE, it is important to carefully consider the potential risks and limitations associated with the procedure. Some of the potential risks and limitations include:

Safety concerns: The safety of CBSC transplantation for treating neonatal HIE induced by GDM has not been extensively studied. There is a risk of adverse events and complications, including infection, graft-versus-host disease, immune reactions, tumor formation, and rejection.

Timing: The optimal timing for CBSC transplantation for treating neonatal HIE induced by GDM is not yet established. It is unclear whether the procedure should be performed immediately after birth or delayed until the onset of symptoms.

Dose and frequency: The optimal dose and frequency of CBSC transplantation for treating neonatal HIE induced by GDM are not yet established. It is unclear how many cells should be transplanted, how often the procedure should be performed, and how many total treatments are necessary.

Cost: CBSC transplantation is an expensive procedure, and the cost may be a barrier to access for many families.

Ethical concerns: The use of CBSCs raises ethical concerns related to the use of human tissue and the potential exploitation of vulnerable populations.

Despite these potential risks and limitations, CBSC transplantation for treating neonatal HIE induced by GDM remains an area of active research and development. Further studies are needed to establish the safety and efficacy of the procedure, as well as the optimal timing, dose, frequency, and long-term outcomes. Close monitoring and follow-up are essential to detect and manage any potential complications.

Concluding remarks

Cord blood stem cell therapy has shown promise as a potential treatment for HIE induced by GDM in both preclinical and clinical studies. However, expanded research is necessary to determine the safety and efficacy of this treatment and to identify the optimal timing and dosing of stem cell therapy.

Future directions for the use of cord blood stem cell transplant to treat HIE induced by GDM may include:

Optimizing the timing of stem cell therapy: Studies have shown that the timing of stem cell therapy may be critical for its effectiveness. The optimal time window for stem cell therapy after the diagnosis of HIE induced by GDM is not yet clear, and subsequent inquiries should be conducted to determine the best timing for this treatment.

Identifying the optimal dosing of stem cell therapy: The optimal dose of stem cells required to promote neuroprotection and tissue regeneration in the brain is not yet known. Future studies will need to investigate the optimal dose required to achieve the best outcomes and to minimize any potential side effects.

Investigating combination therapies: Stem cell therapy may be used in combination with other therapies to enhance its effectiveness. Hypothermia therapy, which involves cooling the body temperature of the newborn, is currently the standard of care for the treatment of HIE induced by GDM. Future studies may investigate the use of stem cell therapy in combination with hypothermia therapy or other neuroprotective agents to further improve outcomes.

Exploring the use of allogeneic stem cells: Autologous cord blood stem cells, which are collected from the infant's own umbilical cord blood shortly after birth, are currently the most commonly used type of stem cell in clinical studies. However, allogeneic stem cells, which are collected from a donor other than the recipient, may also hold promise as a potential treatment for HIE induced by GDM. Future research may investigate the use of allogeneic stem cells to further explore the potential of this treatment.

In conclusion, while CBSC therapy has shown promise as a potential treatment for HIE induced by GDM, in-depth examination is essential to determine the safety and efficacy of this treatment and to identify the optimal timing and dosing of stem cell therapy. Future directions may include optimizing the timing and dosing of stem cell therapy, investigating combination therapies, and exploring the use of allogeneic stem cells to further improve outcomes.

Author contributions

Concept or design: Leung CK, Leung HC, Yeung CF

Acquisition of data: Leung CK, Leung HC, Yeung CF

Analysis or interpretation of data: Leung CK, Leung HC, Yeung CF

Drafting of the manuscript: Leung CK, Leung HC, Yeung CF

Critical revision of the manuscript for important intellectual content: Leung CK, Leung HC, Yeung CF

Leung CK, Leung HC, Yeung CF had full access to the data, contributed to the study, approved the final version for publication, and took responsibility for its accuracy and integrity.

Conflicts of interest

The author reports no conflicts of interest in this work.

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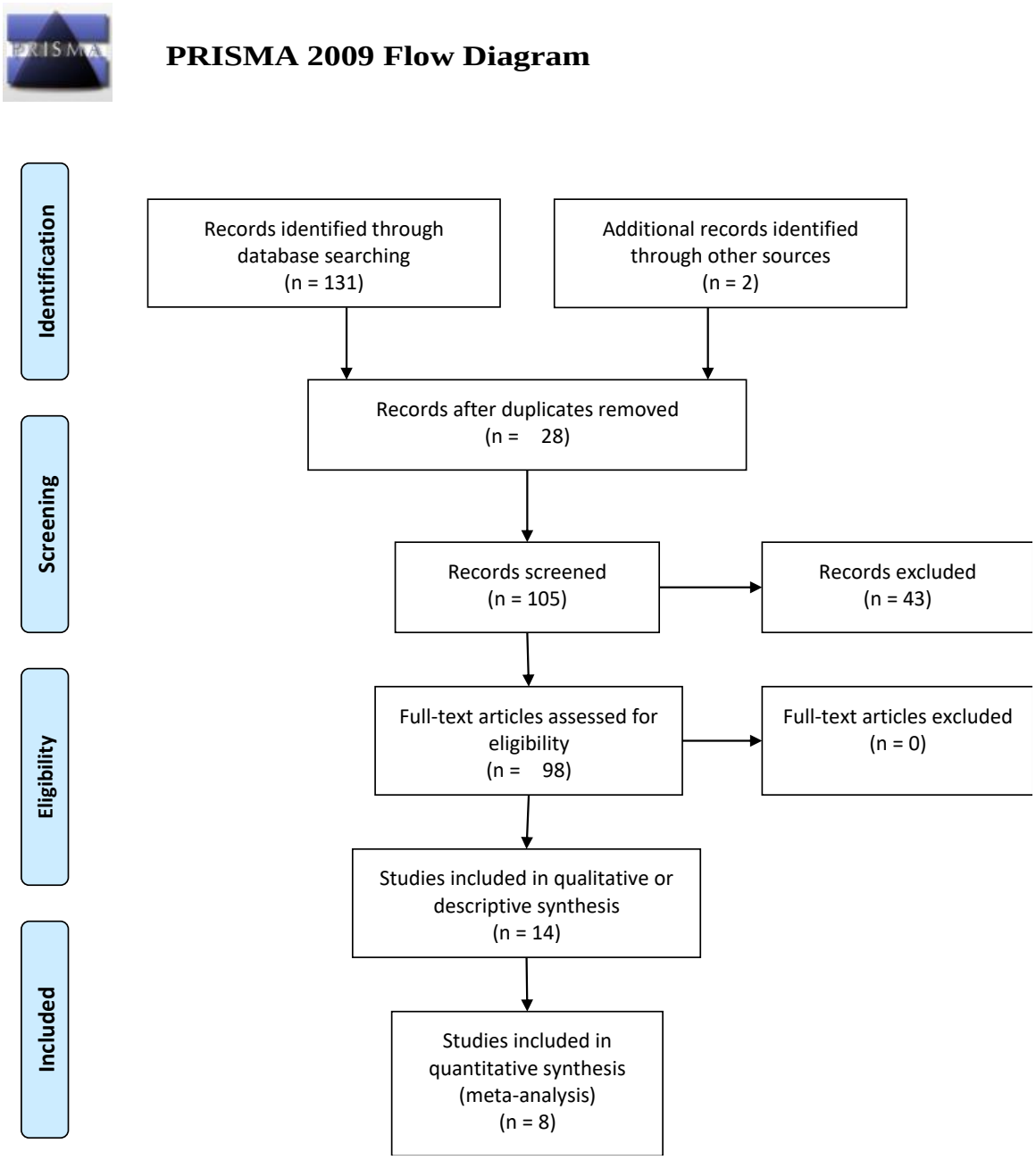
Ethics approval

Not applicable

Abbreviations

HSCT: Hematopoietic stem cells transplantation; BM: Bone marrow; CBB: Cord blood bank; CBT: Cord blood transplant; CBU: Cord blood unit; HLA: Human leukocyte antigens

Suppl. Fig. 1 PRISMA flow diagram



Reference:

1. Mazumder T, Akter E, Rahman SM, Islam MT, Talukder MR. Prevalence and Risk Factors of Gestational Diabetes Mellitus in Bangladesh: Findings from Demographic Health Survey 2017-2018. Int J Environ Res Public Health. 2022;19(5).
2. Zhu H, Zhao Z, Xu J, Chen Y, Zhu Q, Zhou L, et al. The prevalence of gestational diabetes mellitus before and after the implementation of the universal two-child policy in China. Front Endocrinol (Lausanne). 2022;13:960877.
3. Zhou T, Du S, Sun D, Li X, Heianza Y, Hu G, et al. Prevalence and Trends in Gestational Diabetes Mellitus Among Women in the United States, 2006-2017: A Population-Based Study. Front Endocrinol (Lausanne). 2022;13:868094.
4. Pokharel P, Pokhrel KM, Lamichhane P, Khanal K, Rawal S. Prevalence of Gestational Diabetes Mellitus in Nepal: A Systematic Review and Meta-analysis. J Nepal Health Res Counc. 2022;20(1):12-20.
5. Meyer BN, Cash HL, Uso A, Eliapo-Unutoa I, Ropeti R, Muasau-Howard B. Gestational Diabetes Mellitus Prevalence, Screening, and Treatment Practices in American Samoa, 2016. Hawaii J Health Soc Welf. 2022;81(7):185-92.

6. Song S, Zhang Y, Qiao X, Duo Y, Xu J, Peng Z, et al. ALT/AST as an Independent Risk Factor of Gestational Diabetes Mellitus Compared with TG/HDL-C. Int J Gen Med. 2022;15:115-21.
7. Benhalima K, Van Crombrugge P, Moyson C, Verhaeghe J, Vandeginste S, Verlaenen H, et al. Risk factor screening for gestational diabetes mellitus based on the 2013 WHO criteria. Eur J Endocrinol. 2019;180(6):353-63.
8. Tsakiridis I, Giouleka S, Mamopoulos A, Kourtis A, Athanasiadis A, Filopoulou D, et al. Diagnosis and Management of Gestational Diabetes Mellitus: An Overview of National and International Guidelines. Obstet Gynecol Surv. 2021;76(6):367-81.
9. Homayouni A, Bagheri N, Mohammad-Alizadeh-Charandabi S, Kashani N, Mobaraki-Asl N, Mirghafurvand M, et al. Prevention of Gestational Diabetes Mellitus (GDM) and Probiotics: Mechanism of Action: A Review. Curr Diabetes Rev. 2020;16(6):538-45.
10. Szmuilowicz ED, Josefson JL, Metzger BE. Gestational Diabetes Mellitus. Endocrinol Metab Clin North Am. 2019;48(3):479-93.
11. Russ JB, Simmons R, Glass HC. Neonatal Encephalopathy: Beyond Hypoxic-Ischemic Encephalopathy. Neoreviews. 2021;22(3):e148-e62.
12. Yildiz EP, Ekici B, Tatli B. Neonatal hypoxic ischemic encephalopathy: an update on disease pathogenesis and treatment. Expert Rev Neurother. 2017;17(5):449-59.
13. Chiang MC, Jong YJ, Lin CH. Therapeutic hypothermia for neonates with hypoxic ischemic encephalopathy. Pediatr Neonatol. 2017;58(6):475-83.
14. Bonifacio SL, Hutson S. The Term Newborn: Evaluation for Hypoxic-Ischemic Encephalopathy. Clin Perinatol. 2021;48(3):681-95.
15. Rossi AC, Prefumo F. Antepartum and intrapartum risk factors for neonatal hypoxic-ischemic encephalopathy: a systematic review with meta-analysis. Curr Opin Obstet Gynecol. 2019;31(6):410-7.
16. Kureshi A, Khalak R, Gifford J, Munshi U. Maternal Obesity-Associated Neonatal Morbidities in Early Newborn Period. Front Pediatr. 2022;10:867171.
17. Parums DV. Editorial: Review Articles, Systematic Reviews, Meta-Analysis, and the Updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Guidelines. Med Sci Monit. 2021;27:e934475.
18. Bano S, Chaudhary V, Garga UC. Neonatal Hypoxic-ischemic Encephalopathy: A Radiological Review. J Pediatr Neurosci. 2017;12(1):1-6.
19. Villamor E, Tedroff K, Peterson M, Johansson S, Neovius M, Petersson G, et al. Association Between Maternal Body Mass Index in Early Pregnancy and Incidence of Cerebral Palsy. JAMA. 2017;317(9):925-36.
20. Monaco-Brown M, Munshi U, Horgan MJ, Gifford JL, Khalak R. Association of Maternal Obesity and Neonatal Hypoxic-Ischemic Encephalopathy. Front Pediatr. 2022;10:850654.
21. AlMuqbil M, Alanazi J, Alsaif N, Baarmah D, Altwaijri W, Alrumayyan A, et al. Clinical Characteristics and Risk Factors of Neonatal Hypoxic-Ischaemic Encephalopathy and Its Associated Neurodevelopmental Outcomes During the First Two Years of Life: A Retrospective Study in Saudi Arabia. Int J Gen Med. 2023;16:525-36.
22. Martinello K, Hart AR, Yap S, Mitra S, Robertson NJ. Management and investigation of neonatal encephalopathy: 2017 update. Arch Dis Child Fetal Neonatal Ed. 2017;102(4):F346-F58.
23. Tarvonen M, Hovi P, Sainio S, Vuorela P, Andersson S, Teramo K. Intrapartal cardiotocographic patterns and hypoxia-related perinatal outcomes in pregnancies complicated by gestational diabetes mellitus. Acta Diabetol. 2021;58(11):1563-73.
24. Jarmuzek P, Wielgos M, Bomba-Opon D. Placental pathologic changes in gestational diabetes mellitus. Neuro Endocrinol Lett. 2015;36(2):101-5.
25. Madazli R, Tuten A, Calay Z, Uzun H, Uludag S, Ocak V. The incidence of placental abnormalities, maternal and cord plasma malondialdehyde and vascular endothelial growth factor levels in women with gestational diabetes mellitus and nondiabetic controls. Gynecol Obstet Invest. 2008;65(4):227-32.
26. Radaelli T, Varastehpour A, Catalano P, Hauguel-de Mouzon S. Gestational diabetes induces placental genes for chronic stress and inflammatory pathways. Diabetes. 2003;52(12):2951-8.
27. Desoye G, Hauguel-de Mouzon S. The human placenta in gestational diabetes mellitus. The insulin and cytokine network. Diabetes Care. 2007;30 Suppl 2:S120-6.
28. Philips AF, Dubin JW, Matty PJ, Raye JR. Arterial hypoxemia and hyperinsulinemia in the chronically hyperglycemic fetal lamb. Pediatr Res. 1982;16(8):653-8.
29. Roberts KA, Riley SC, Reynolds RM, Barr S, Evans M, Statham A, et al. Placental structure and inflammation in pregnancies associated with obesity. Placenta. 2011;32(3):247-54.
30. Beneventi F, Locatelli E, Cavagnoli C, Simonetta M, Lovati E, Lucotti P, et al. Effects of uncomplicated vaginal delivery and epidural analgesia on fetal arterial acid-base parameters at birth in gestational diabetes. Diabetes Res Clin Pract. 2014;103(3):444-51.
31. Teramo KA, Widness JA. Increased fetal plasma and amniotic fluid erythropoietin concentrations: markers of intrauterine hypoxia. Neonatology. 2009;95(2):105-16.
32. Li HP, Chen X, Li MQ. Gestational diabetes induces chronic hypoxia stress and excessive inflammatory response in murine placenta. Int J Clin Exp Pathol. 2013;6(4):650-9.
33. Nancy Laval MP, Hamza Talsmat, Bohdana Marandyuk, Pia Wintermark, Ala Birca, Elana Pinchefsky, Sophie Tremblay. Exposure to maternal diabetes during pregnancy is associated with worse short-term neonatal and neurological outcomes following perinatal hypoxic-ischemic encephalopathy. PrePrint (Research Square). 2022.
34. Markiewicz I, Sypecka J, Domanska-Janik K, Wyszomirski T, Lukomska B. Cellular environment directs differentiation of human umbilical cord blood-derived neural stem cells in vitro. J Histochem Cytochem. 2011;59(3):289-301.
35. Chung DJ, Choi CB, Lee SH, Kang EH, Lee JH, Hwang SH, et al. Intraarterially delivered human umbilical cord blood-derived mesenchymal stem cells in canine cerebral ischemia. J Neurosci Res. 2009;87(16):3554-67.
36. Buzanska L, Machaj EK, Zablocka B, Pojda Z, Domanska-Janik K. Human cord blood-derived cells attain neuronal and glial features in vitro. J Cell Sci. 2002;115(Pt 10):2131-8.
37. Schira J, Falkenberg H, Hendricks M, Waldera-Lupa DM, Kogler G, Meyer HE, et al. Characterization of Regenerative Phenotype of Unrestricted Somatic Stem Cells (USSC) from Human Umbilical Cord

Blood (hUCB) by Functional Secretome Analysis. Mol Cell Proteomics. 2015;14(10):2630-43.
38. Berlet R, Anthony S, Brooks B, Wang ZJ, Sadanandan N, Shear A, et al. Combination of Stem Cells and Rehabilitation Therapies for Ischemic Stroke. Biomolecules. 2021;11(9).
39. Zhao J, Chen N, Shen N, Zhao H, Wang D, Shi J, et al. Transplantation of human umbilical cord blood mesenchymal stem cells to treat a rat model of traumatic brain injury. Neural Regen Res. 2012;7(10):741-8.
40. CK L. An overview of cord blood stem cell transplantation in Hong Kong. Journal of Medical Science. 2022;91(3).
41. Shi PA, Luchsinger LL, Greally JM, Delaney CS. Umbilical cord blood: an undervalued and underutilized resource in allogeneic hematopoietic stem cell transplant and novel cell therapy applications. Curr Opin Hematol. 2022;29(6):317-26.
42. Serrenho I, Rosado M, Dinis A, C MC, Graos M, Manadas B, et al. Stem Cell Therapy for Neonatal Hypoxic-Ischemic Encephalopathy: A Systematic Review of Preclinical Studies. Int J Mol Sci. 2021;22(6).
43. Xi Y, Yue G, Gao S, Ju R, Wang Y. Human umbilical cord blood mononuclear cells transplantation for perinatal brain injury. Stem Cell Res Ther. 2022;13(1):458.
44. Archambault J, Moreira A, McDaniel D, Winter L, Sun L, Hornsby P. Therapeutic potential of mesenchymal stromal cells for hypoxic ischemic encephalopathy: A systematic review and meta-analysis of preclinical studies. PLoS One. 2017;12(12):e0189895.
45. Sun JM, Song AW, Case LE, Mikati MA, Gustafson KE, Simmons R, et al. Effect of Autologous Cord Blood Infusion on Motor Function and Brain Connectivity in Young Children with Cerebral Palsy: A Randomized, Placebo-Controlled Trial. Stem Cells Transl Med. 2017;6(12):2071-8.
46. Ullah M, Liu DD, Thakor AS. Mesenchymal Stromal Cell Homing: Mechanisms and Strategies for Improvement. iScience. 2019;15:421-38.
47. Zhou Y, Shao A, Xu W, Wu H, Deng Y. Advance of Stem Cell Treatment for Traumatic Brain Injury. Front Cell Neurosci. 2019;13:301.
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. J Pediatr. 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. Sci Rep. 2020;10(1):4603.
50. Malhotra A, Novak I, Miller SL, Jenkin G. Autologous transplantation of umbilical cord blood-derived cells in extreme preterm infants: protocol for a safety and feasibility study. BMJ Open. 2020;10(5):e036065.
51. Neuhoff S, Moers J, Rieks M, Grunwald T, Jensen A, Dermietzel R, et al. Proliferation, differentiation, and cytokine secretion of human umbilical cord blood-derived mononuclear cells in vitro. Exp Hematol. 2007;35(7):1119-31.
52. Watt SM, Gullo F, van der Garde M, Markeson D, Camicia R, Khoo CP, et al. The angiogenic properties of mesenchymal stem/stromal cells and their therapeutic potential. Br Med Bull. 2013;108(1):25-53.
53. Lee C, Shim S, Jang H, Myung H, Lee J, Bae CH, et al. Human umbilical cord blood-derived mesenchymal stromal cells and small intestinal submucosa hydrogel composite promotes combined radiation-wound healing of mice. Cytotherapy. 2017;19(9):1048-59.
54. Rai V, Moellmer R, Agrawal DK. Stem Cells and Angiogenesis: Implications and Limitations in Enhancing Chronic Diabetic Foot Ulcer Healing. Cells. 2022;11(15).
55. Yang G, Fan X, Liu Y, Jie P, Mazhar M, Liu Y, et al. Immunomodulatory Mechanisms and Therapeutic Potential of Mesenchymal Stem Cells. Stem Cell Rev Rep. 2023:1-18.
56. Huang Y, Wu Q, Tam PKH. Immunomodulatory Mechanisms of Mesenchymal Stem Cells and Their Potential Clinical Applications. Int J Mol Sci. 2022;23(17).
57. Galieva LR, Mukhamedshina YO, Arkhipova SS, Rizvanov AA. Human Umbilical Cord Blood Cell Transplantation in Neuroregenerative Strategies. Front Pharmacol. 2017;8:628.
58. Bojanic C, To K, Zhang B, Mak C, Khan WS. Human umbilical cord derived mesenchymal stem cells in peripheral nerve regeneration. World J Stem Cells. 2020;12(4):288-302.
59. Sung MA, Jung HJ, Lee JW, Lee JY, Pang KM, Yoo SB, et al. Human umbilical cord blood-derived mesenchymal stem cells promote regeneration of crush-injured rat sciatic nerves. Neural Regen Res. 2012;7(26):2018-27.
60. Andres RH, Horie N, Slikker W, Keren-Gill H, Zhan K, Sun G, et al. Human neural stem cells enhance structural plasticity and axonal transport in the ischaemic brain. Brain. 2011;134(Pt 6):1777-89.
61. Shi Y, Nan C, Yan Z, Liu L, Zhou J, Zhao Z, et al. Synaptic Plasticity of Human Umbilical Cord Mesenchymal Stem Cell Differentiating into Neuron-like Cells In Vitro Induced by Edaravone. Stem Cells Int. 2018;2018:5304279.