

Review Article

Numerous Types of Stem Cells Possess Potential to Treat Congenital Hydrocephalus

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Abstract

Twenty-five percent of premature neonate's experience Intraventricular Hemorrhage (IVH) and 10% of these events are complicated further by the occurrence of hydrocephalus. The number of infants at high risk for IVH and therefore Post Hemorrhagic Hydrocephalus (PHH), is rising due to improved survival rate of premature infants. Fetal onset hydrocephalus is a heterogeneous brain disorder involving Cerebrospinal Fluid (CSF) dynamics and is a result of both genetic and environmental factors. Mesenchymal stem cells present themselves as a potent therapeutic modality for brain injury based on their multipotency, anti-inflammatory, antioxidant and angiogenic functions. Numerous animal model clinical provide evidence that Mesenchymal Stem Cells (MSCs) can target nearly all mechanisms involved in the pathogenesis of hydrocephalus. Unrestricted somatic stem cells possess anti-inflammatory and immunomodulatory properties as well as release growth factors and cytokines with known neuroprotective and axonal growth promoting functions. Neural stem cells are self-sustaining, pluripotent cells that have the capability to correct brain maldevelopment, reduce brain damage, promote regeneration and repair via neurotrophic and immunomodulatory mechanisms and direct cell replacement. For these reasons, stem cells possess the potential to be an effective therapy and should be further researched.

Keywords: Stem Cells, Therapy; Congenital Hydrocephalus; Hydrocephalus; Intraventricular Hemorrhage; Mesenchymal Stem Cells

Abbreviations

APP: Amyloid Precursors Proteins; AQP: Aquaporin; AT: Adipose Tissue; BBB: Blood-Brain Barrier; BDNF: Brain-Derived Neurotrophic Factor; BM: Bone Marrow; BM-MSC: Bone Marrow-Derived Mesenchymal Stem Cells; CNS: Central Nervous System; CSF: Cerebrospinal Fluid; CTGF: Connective Tissue Growth Factor; ESC: Embryonic Stem Cells; ETV: Endoscopic Third Ventriculostomy; GDNF: Glial Cell Line-Derived Neurotrophic Factors; GMH: Germinal Matrix Hemorrhage; HLA: Human Leukocyte Antigen; 1H-MAS NMR: 1H high-Resolution Magic Angular Spinning Nuclear Magnetic Resonance; IGF -1: Insulin-like Growth Factor; IL: Interleukin; ISF: Interstitial Fluid; IVH: Intraventricular Hemorrhage; MMP -9: Metalloprotease-9; MRI: Magnetic Resonance Imaging; mRFP1: monomeric Red Fluorescence Protein; MSC: Mesenchymal Stem Cells; NK: Natural Killer; NSC: Neural Stem Cells; PHH: Post Hemorrhagic Hydrocephalus; ROP: Retinopathy Of Prematurity; SAE: Severe Adverse Effects; TGF- β : Transforming Growth Factor Beta; TNF- α : Tumor Necrosis Factor Alpha; UCB: Umbilical Cord Blood; USSC: Unrestricted Somatic Stem Cells; VEGF: Vascular Endothelial Growth Factor; VZ: Ventricular Zone

Introduction

Fetal onset hydrocephalus is a brain disorder involving CSF dynamics that can present itself in numerous ways due to various causes [1]. Severe intraventricular hemorrhage in premature infants can lead to hydrocephalus which has significant mortality rates and can lead to neurological disabilities [2]. Obstructive congenital hydrocephalus presents itself as ventriculomegaly and

increased intercranial pressure leading to an adverse effect on brain tissue by the skull and is associated with periventricular edema, ischemia and hypoxia, damage of white matter and glial reactions. [3]. Both genetic and environmental factors contribute to the development of fetal-onset hydrocephalus. Examples of contributing factors include vitamin B and folic acid deficiency, viral infection of ependyma, prematurity-related germinal matrix hemorrhage and IVH [4]. As of right now, only palliative treatments exist for fetal onset hydrocephalus, each with their own side effects [5]. The three current standards of treatment include ventricular shunts, extra ventricular drains and third ventriculostomy. Although shunts have been found to prevent further brain damage, they fail to solve the vital brain maldevelopment and neurological outcome associated with hydrocephalus [4]. 80-90% of neurologic impairment found in shunt-dependent neonates with fetal onset hydrocephalus is not reversed via surgery and 50% of shunts fail within 2 years. In regards to Endoscopic Third Ventriculostomy (ETVs), 20-50% of them close up within 5 years and exhibit high rates of infection [4,6].

Mesenchymal stem cells present themselves as a potent therapeutic modality for brain injury based on their multipotency, anti-inflammatory, antioxidant and angiogenic functions [2]. MSCs can be harvested at low cost and via minimal invasiveness from various sources including bone marrow, adipose tissue and umbilical cord blood [2]. Unrestricted somatic stem cells are another potential therapeutic modality for hydrocephalus. USSCs possess anti-inflammatory and immunomodulatory properties as well as release growth factors and cytokines with known neuroprotective and axonal growth promoting functions at higher levels than MSCs [5]. Neural stem cells are another type of stem cell that possess the potential to treat hydrocephalus. NSCs are self-sustaining, pluripotent cells that have the capability to correct brain maldevelopment, reduce brain damage, promote regeneration and repair via neurotrophic and immunomodulatory mechanisms and direct cell replacement [6]. This literary review summarizes current research on the application of stem cell-based therapy as a method of treatment for pediatric hydrocephalus including the epidemiology and pathophysiology of hydrocephalus, the current standard of care, why treatments have failed, the potential of numerous types of stem cells as a treatment for hydrocephalus and promising results from clinical trials.

Epidemiology

Approximately 1 to 3 newborns per 1000 live births are affected by fetal-onset hydrocephalus which is characterized by abnormal CSF flow accompanied by ventricular dilatation [4]. 25% of premature neonates experience IVH and 10% of these events are complicated further by the occurrence of hydrocephalus [5]. More than 50% of infants with severe IVH die or develop posthemorrhagic hydrocephalus [2]. The number of infants at high risk for IVH is rising due to improved survival rate of premature infants [2]. This is of concern because brain damage due to IVH, especially in periventricular white matter, is exacerbated to PHH and leads to higher rates of mortality and neurological morbidity including seizure, cerebral palsy and developmental retardation [2].

Pathophysiology

Fetal onset hydrocephalus is a brain disorder involving CSF dynamics [1]. Posthemorrhagic hydrocephalus is a result of either over secretion or impaired absorption of CSF [5]. Impaired absorption could be partially due to blood obstructing arachnoid villi which is associated with fibroproliferative response, inflammation and subependymal gliosis [5]. CSF hypersecretion and decreased absorption are associated with AQP1 and AQP4. AQP1 is primarily expressed along the choroid plexus epithelial lining. CSF production and intraventricular pressure is reduced due to loss of function of AQP1. AQP4 is primarily expressed along astrocyte foot processes surrounding capillaries and on the surface of ependymal cells lining the lateral and third ventricles. AQP4 serves to absorb CSF and ISF. Ventricular enlargement and increased intercranial pressure developed in knockout mice which suggests a protective role of AQP4 in preserving normal ventricular volume. Failure of AQP4 CSF resorption, rather than AQP1 mediated CSF production, in double knockout mice led to CSF accumulation in these mice. The importance of aquaporin channels in CSF homeostasis is emphasized by these observations. Free hemoglobin and iron contribute to inflammation in PHH and result in increased toll-like receptor expression which is associated with hypersecretion of CSF [5]. Severe intraventricular hemorrhage in premature infants can lead to hydrocephalus which has significant mortality rates and can lead to neurological disabilities [2]. IVH is a result of immature and developing blood vessels rupturing in the germinal matrix [5]. After IVH, inflammation within the subarachnoid space occurs due to the hemolysis of extravasated blood resulting in PHH. CSF resorption is impaired by obliterative arachnoiditis which is induced by inflammatory responses [7]. According to an NIH workshop on PHH, infants affected by IVH experience somatic growth impairment, motor dysfunction and neurocognitive deficiency [5].

Obstructive congenital hydrocephalus presents itself as ventriculomegaly and increased intracranial pressure leading to an adverse effect on brain tissue by the skull and is associated with periventricular edema, ischemia and hypoxia, damage of white matter and glial reactions [3]. Both genetic and environmental factors contribute to the development of fetal-onset hydrocephalus. Examples of contributing factors include vitamin B and folic acid deficiency, viral infection of ependyma, prematurity-related germinal matrix hemorrhage and IVH [4]. The induction of IVH in preterm infants can be attributed to multiple risk factors such as vaginal delivery, low Apgar score, respiratory-distress syndrome, pneumothorax, hypoxia, hypercapnia and infection. IVH leads to progressive PHH via the following pathway. Bleeding from the germinal matrix into the cerebral ventricles subsequently leads to hemolysis which then elevates the concentration of extracellular hemoglobin. The heme is degraded which then increases the concentration of bilirubin, carbon monoxide and free iron in CSF. Proinflammation, chemotaxis and apoptosis in intercranial hemorrhaging occurs due to cell-free hemoglobin. Dysfunction of arachnoid granulations caused by extravasated blood in CSF activating an inflammatory response in the microvascular barrier leads to reduced resorption of CSF. Imbalance in CSF resorption and production leads to retention of CSF and thus hydrocephalus [7]. In animal models, disruption of VZ in the cerebral aqueduct triggers stenosis and hydrocephalus. Similar pathology can be observed in humans [4]. VZ disruption affects the aqueduct and telencephalon resulting in the translocation of neural stem cells into fetal CSF and the formation of subependymal gray matter heterotopia which results from a failure of neuroblast migration during embryonic brain development. The arrival of macrophages and lymphocytes to the denuding zone is affiliated with the onset of VZ disruption which suggests that there is an inflammatory immune response associated with the profession and severity of hydrocephalus. Hydrocephalus causes brain-parenchymal injury in newborns via increased intracranial pressure, decreased cerebral perfusion, iron-induced free radical damage and inflammatory cytokine levels [7]. Cerebral abnormalities that result from the pathophysiology of PHH are irreversible (Fig. 1) [4].

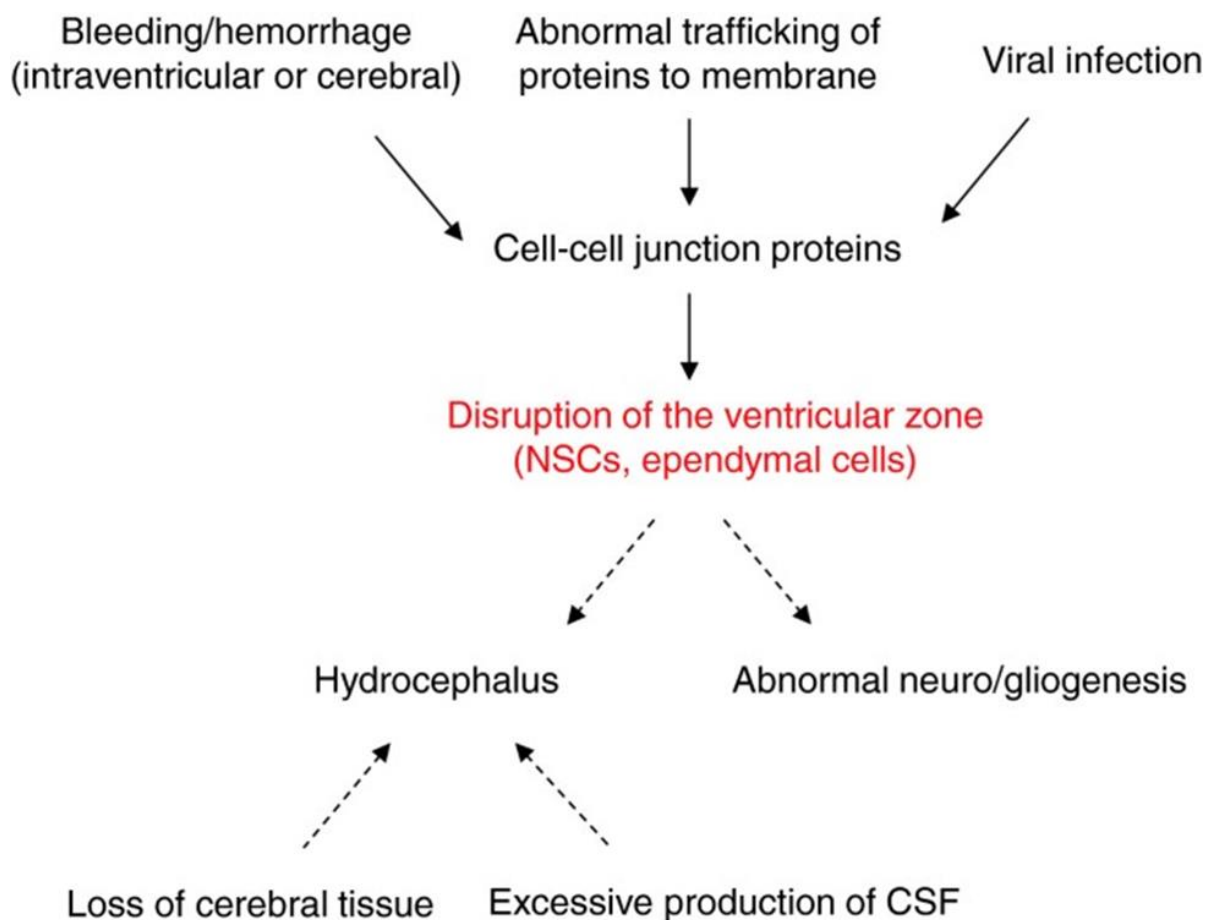


Figure 1: Numerous factors that contribute to the pathogenesis of hydrocephalus are depicted above. IVH or cerebral hemorrhage, abnormal trafficking of proteins to membrane and viral infection all impact cell-cell junction proteins which ultimately disrupt the ventricular zone leading to hydrocephalus. Hydrocephalus can also result from loss of cerebral tissue or excessive production of CSF [6].

Why Have Treatments Failed?

As of right now, only palliative treatments exist for fetal onset hydrocephalus, each with their own side effects [5]. The three current standards of treatment include ventricular shunts, extra ventricular drains and third ventriculostomy [3]. 50% of shunts fail within 2 years and the consequences of CSF proteins being shunted into a confined space are unknown. Shunts may generate auto-antibodies against specific CSF proteins which may ultimately alter neuronal physiology and exacerbate neurological deficits [6]. Other known complications of shunts include obstruction, infection, fracture, migraine, over drainage and underdrainage [3]. Although shunts have been found to prevent further brain damage, they fail to solve the vital brain maldevelopment and neurological outcome associated with hydrocephalus [4]. 80-90% of neurologic impairment found in shunt-dependent neonates with fetal onset hydrocephalus is not reversed via surgery [4]. In regard to Endoscopic Third Ventriculostomy (ETVs), 20-50% of them close up within 5 years and exhibit high rates of infection [6]. ETVs could also lead to adverse effects on neuroendocrine regulation and divert signaling molecules in CSF away from their targets [6].

Discussion

Mesenchymal stem cells, unrestricted somatic stem cells and neural stem cells are the three types of stem cells with the greatest potential of treating hydrocephalus. Mesenchymal stem cells exhibit great potential to treat hydrocephalus because they demonstrate potent immunomodulating abilities in the brain following a stroke or neonatal hypoxic ischemic encephalopathy which have similar pathologies [2]. MSCs can be harvested at low cost and via minimal invasiveness from various sources including bone marrow, adipose tissue and umbilical cord blood [4]. Umbilical cord blood is the most promising source due to its vast availability, high proliferation capacity and low immunogenicity [8]. A vital determinant of the efficacy of MSC therapy is donor age [8]. Numerous animal model clinical provide evidence that MSCs can target nearly all mechanisms involved in the pathogenesis of hydrocephalus. The potential downsides of using stem cells including, unwanted long-term effects, unwelcome interactions of the stem cells with the immune system and potential to promote tumorigenesis, must be investigated prior to conducting human clinical trials [4]. The safety of using stem cells as a therapeutic modality depend on numerous factors including differentiation status and proliferative ability of the grafted cells, timing of administration, route via which stem cells are administered and long-term survival of the graft [4]. Optimal transplantation route, timing and dosage of MSCs needs to be investigated [8].

Use of Stem Cells to Treat Hydrocephalus

Mesenchymal stem cells present themselves as a potent therapeutic modality for brain injury based on their multipotency, anti-inflammatory, antioxidant and angiogenic functions [2]. Anti-inflammatory effects of MSCs may include - immune modulation and delivery of various growth factors and cytokines such as VEGF, HGF, BDNF, GDNF and IL-10. Via secretion of these factors, MSCs may promote a shift from proinflammatory environment towards an anti-inflammatory, tolerant environment [2]. MSCs can differentiate into osteoblasts, chondroblasts, myocytes and adipocytes [4]. Neuronal progenitor cells, lung epithelial cells and renal tubular cells can also be derived via MSCs [4]. The tumorigenic potential of embryonic stem cells is not present in MSCs, which makes MSCs more favorable as a therapy [8]. MSCs are plastic adherent, positively express CD73, CD90 and CD105 and negatively express CD45, CD34, CD14, CD11b and HLA DR [8]. Mesenchymal stem cells exhibit great potential to treat hydrocephalus because they demonstrate potent immunomodulating abilities in the brain following a stroke or neonatal hypoxic ischemic encephalopathy which have similar pathologies [2]. MSCs can be harvested at low cost and via minimal invasiveness from various sources including bone marrow, adipose tissue and umbilical cord blood [2]. Umbilical cord blood is the most promising source due to its vast availability, high proliferation capacity and low immunogenicity [8]. UCB-derived MSCs are also predicted to be well tolerated based on their low expression of human leukocyte antigen major histocompatibility complex class I and their lack of major histocompatibility complex class II molecules [2]. Lack of histocompatibility complex class II antigen expression and the ability of MSCs to inhibit the proliferation and function of immune cells such as NK cells, dendritic cells and T and B lymphocytes, make MSCs immune privileged [8]. UCB-derived MSCs have decreased the effects of many disorders including bronchopulmonary dysplasia, acute respiratory distress syndrome and middle cerebral arterial occlusion via paracrine effects [2]. MSCs have multiple routes for transplantation. Intraventricular and intrathecal seem to be more optimal than intravenous and intraperitoneal approaches [8]. Although intravenous and intraperitoneal are less invasive, MSCs may be retained in organs other than the brain such as the lungs, liver, kidney and spleen [8]. Local transplantation via ventricular tap is favorable because the anterior fontanel is open in newborns [8].

Unrestricted somatic stem cells are another potential therapeutic modality for hydrocephalus. USSCs possess anti-inflammatory and immunomodulatory properties as well as release growth factors and cytokines with known neuroprotective and axonal growth promoting functions at higher levels than MSCs [5]. In numerous CNS injury models, USSCs have exhibited a higher neuroprotective and regenerative potential which may be attributed to the fact that USSCs are more primitive than MSCs and lack expression of HLA phenotypic markers that could cause rejection in xenographic transplantation [5]. In addition to their promising properties, USSCs possess the potential to stabilize the aquaporin water channels in the choroid plexus and ependymal wall ultimately reducing post-hemorrhagic hydrocephalus [5].

Neural stem cells are another type of stem cell that possess the potential to treat hydrocephalus. NSCs are self-sustaining, pluripotent cells that have the capability to correct brain maldevelopment, reduce brain damage, promote regeneration and repair via neurotrophic and immunomodulatory mechanisms and direct cell replacement [6]. NSCs are available in the embryonic and adult brain and can be transplanted allowing for migration, differentiation and integration into injured areas [6]. Healthy NSCs can replace radial glial cells, neural progenitors and neuroblasts that are lost during the hydrocephalic process [6]. Damage to the ventricular zone resulting from ventricular zone disruption could potentially be repaired by NSCs [6].

Results of Clinical Trials and Why/Why Not They Were Effective

Intraventricular hemorrhage was induced via injection of 100 microliters of blood into each lateral ventricle of Postnatal day 4 (P4) Sprague Dawley rats. Three groups were created: IVH treated with MSC transplant, IVH treated with fibroblast transplant and an IVH control group treated with a phosphate buffered saline injection. MSCs derived from human umbilical cord blood were intraventricularly transplanted at Postnatal day 6 (P6). Serial MRIs were performed on the 7th and 28th days post IVH induction. Behavioral function tests, specifically a negative geotaxis test, was performed on days 7, 14, 21 and 28. A rotarod test was performed between days 26 and 28. On postnatal day 32 (P32), histological and biochemical analyses were performed using brain tissues and CSF collected on days 14 and 28. Posthemorrhagic hydrocephalus development was prevented by intraventricular transplant of UCB-derived MSCs. Progression of ventricular dilatation was attenuated by stem cell transplantation. UCB-derived MSCs improved sensorimotor function and mitigated cell death and reactive gliosis in periventricular brain tissue. Delayed myelination and corpus callosum thinning induced by PHH was alleviated by stem cell transplantation. MSC transplantation significantly downregulated increased inflammatory cytokines such as IL-1 α , IL-1 β , IL-6 and TNF- α . The neuroprotective mechanism of UCB-derived MSCs could be attributed to the anti-inflammatory effects of these cells [2].

In a study conducted on rabbit pups, IVH was induced via glycerol and followed by injection of USSCs into the cerebral ventricles 18 hours later. On days 7 and 14, ventricular size decreased by approximately 60% in USSC treated pups in comparison to control pups. Cell infiltration and ependymal wall disruption were reduced by USSC treatment. AQP1's immune-reactivity and AQP4's expression in the ependymal wall was restored via USSC transplant. These effects were confirmed via mRNA analysis of dissected choroid plexus and ependymal tissue. IVH caused an increase in TGF- β isoforms, CTGF and MMP-9 mRNA and protein levels; treatment with USSCs brought these elevated levels back to normal. USSC injection also allowed for significant recovery of the IL-10 mRNA levels that were depleted due to IVH. Overall, USSCs enacted anti-inflammatory effects via suppression of TGF- β isoforms, CTGF and MMP-9, recovery of IL-10, restoration of aquaporins' expression towards baseline and reduction of hydrocephalus. This study presented some limitations. One limitation was that CSF turnover rate was not directly measured, so contributions of other routes of CSF elimination or production were not accounted for. In addition, beneficial correlations were established, however which factors are induced or released via USSCs to produce the overall effects is unknown. Lastly, optimal dosing was not examined [5].

In another animal trial conducted on mice, phenotypic inspection and genotyping were used to identify hyh and non-hydrocephalic mice. Bone marrow derived MSCs were obtained from mice expressing mRFP1. MSCs were then injected into the lateral ventricle of hydrocephalic mice when a severe form of the disease was observed. The MSC injected mice were compared to hydrocephalic mice injected with the vehicle and non-hydrocephalic littermates. Analysis of the neural cell populations and potential of trans differentiation took place. To detect metabolites and osmolytes correlated to hydrocephalus severity and outcome in the neocortex, 1H- MAS NMR spectroscopy was utilized. To simulate the periventricular astrocyte reaction conditions, an *in-vitro* assay was performed using BM-MSC under high TNF- α levels. The secretome in the culture was analyzed.

4 days post-transplant of MSCs, MSCs were observed to be undifferentiated and scattered into the astrocyte reaction present in the damaged neocortex white matter. No tissue rejection was detected. The neuroprotective effect of MSCs was observed based on reduction in apoptosis in the periventricular neocortex walls of mice in which MSCs were transplanted. Levels of metabolites and osmolytes such as taurine and neuroexcitotoxic glutamate in the neocortex decreased which is a sign of tissue recovery. BM-MSC exhibited an upregulation of cytokine and protein secretion which could explain immunomodulation, homing, vascular permeability and ultimately tissue recovery [3].

IVH was induced in a rodent model by bilateral injection of 80 microliters of blood into the cerebral ventricles. Blood was injected in the periventricular region in another model however only 15-65% of these rodents developed PHH. In another model clostridial collagenase was injected in the germinal matrix to induce GMH but no ventricular dilatation occurred. GMH was induced in another model via intraperitoneal injection of glycerol into preterm rabbits that were delivered at day 29 of gestation instead of day 32. Only 39% of the rabbit pups developed severe grade 3 or 4 IVH, which is the main cause of PHH in preterm infants. The finest model studied was one in which 200 microliters of dam's blood was injected into the cerebral ventricles of P4 rat pups. 100% of the rats developed severe IVH which was confirmed by MRI. 85% of these pups developed PHH that lasted for more than 4 weeks after induction of IVH. After these 4 weeks, rats exhibited impaired sensorimotor functions, augmented cell death, inflammation, delayed myelination in brain tissue and significant upregulation of inflammatory cytokines in CSF. An important feature of this model is that at birth and P10 rodent brains are compatible to fetuses at 24- and 40-weeks' gestation. Brain damage and PHH post-IVH have not been reduced via single agents such as decorin, colchicine, TGF- β blocker, non-steroidal anti-inflammatory drugs and bone morphogenic protein. TGF- β blocking factors did not improve neuromotor performance and failed to stop the progression of ventricular dilatation. In one newborn rabbit model, neurologic impairment, delayed myelination and reactive gliosis were attenuated by the inhibition of cyclooxygenase-2 in the inflammatory cascade induced by IVH. In another newborn rabbit model, restoration of oligodendrocyte maturation, myelination, astrocyte morphology and motor function were observed via inhibition of bone morphogenic factor. Neither of these treatments decreased the size of enlarged cerebral ventricles post IVH which suggests a multifaceted therapeutic agent is needed to treat PHH because modulating one factor is not sufficient. When MSCs were transplanted intraventricularly in P4 post-IVH rats, inflammatory cytokines in the brain decreased thus preventing the development of PHH. MSC transplant attenuated myelin basic protein and abnormal sensorimotor function as well as improved brain apoptosis. Paracrine anti-inflammatory effects seem to mediate the neuroprotective mechanism of MSCs. One limitation in this study is that definition, isolation and expansion techniques for MSCs must be established [7].

The optimal timing of MSC transplantation was investigated in a rat model. 100 microliters of blood was injected into each ventricle of P4 Sprague-Dawley rats to induce severe IVH. 1×10^5 UCB-derived MSCs in 10 microliters of normal saline were transplanted intraventricularly at day 2 (P6) or day 7 (P11). To determine the most effective time of transplantation, serial brain MRIs, negative geotaxis and rotarod tests were performed and brain tissues obtained on P32 underwent histological and biochemical analysis. The development of PHH, behavioral impairment, increased apoptosis and astrogliosis, reduced corpus callosum thickness and brain myelination and upregulation of inflammatory cytokines including IL-1 α , IL-1 β , IL-6 and TNF- α was significantly attenuated via transplantation of MSCs intracerebroventricular at P6 not P11. Significant neuroprotection via UCB-derived MSCs was only observed when they were transplanted early at 2 days (P6) during acute inflammation after induction of IVH but not at 7 days (P11). This observation could be attributed to the fact that low levels of inflammatory cytokines are present at P11 and are thus insufficient to induce the anti-inflammatory effects of MSCs [9].

A similar study was conducted using Sprague-Dawley rats to assess the optimal route for mesenchymal stem cell transplantation. On P4, severe IVH was induced via injection of 100 microliters of blood into each ventricle. MRI was used to confirm severe IVH at P5, followed by transplantation of 1×10^5 human UCB-derived MSCs by an IC route and 5×10^5 by an IV route at P6. Brain MRIs, rotarod tests and biochemical and histological analyses of brain tissue obtained at P32 were performed. Both transplantation methods were uniformly effective in preventing PHH. Although delivery efficacy was superior with IC, since therapeutic efficacy was the same in the IV route may be preferred. Administration via IV is less invasive and it may be difficult for clinically unstable, preterm infants to tolerate an invasive IC delivery. Improved rotarod tests at P31 and P32 with both routes of administration suggests that the neuroprotective effects of may persist into human adolescence [10].

A phase 1 human clinical trial was conducted using MSCs for severe IVH in pre-term infants. 9 patients participated in the clinical trial with a mean gestational age of 26.1 ± 0.7 weeks and birth weight of 808 ± 85 g at 11.6 ± 0.9 postnatal days. 3 female infants of the 9 received a low dose of MSCs 5×10^6 cells/kg while the remaining 6 male infants received a high dose of 1×10^7 cells/kg. Treatment was well tolerated and no patients experienced serious adverse effects, dose-limiting toxicities, or mortality attributable to MSC transplantation. Dose-limiting toxicities were defined by the following conditions: sudden death within 6 hours of MSC transplant, anaphylactic shock immediately after transplant, or the occurrence of brain tumor lesions after transplant. Adverse effects were classified to include shunt placement, death, culture-confirmed late-onset sepsis, corrective surgery for retinopathy of prematurity, seizure, or necrotizing enterocolitis. SAEs including sepsis, necrotizing enterocolitis, ROP requiring surgery, inguinal hernia requiring surgery, severe bronchopulmonary dysplasia and seizures were observed in 8 out of 9 patients. A ventriculoperitoneal shunt was administered to 5 out of the 9 infants with severe grade 4 IVH. Additional biomarkers must be identified to identify neuronal injury early. A previous study regarding brain-specific proteins in the CSF, infants with IVH and PHH exhibited significantly higher levels of glial fibrillary acidic protein levels than normal proteins. In PHH infants, an increase in concentrations of amyloid precursors proteins, soluble APP α and L1 cell adhesion molecule have been observed. To understand whether any biomarkers in the CSF can be used along with cranial ultrasonography, to predict neuronal injury, progress of PHH and poor neurodevelopmental outcomes, further research is needed. Via a bedside tap placed in open the anterior fontanel, MSCs were administered intraventricularly under ultrasonography guidance. All infants tolerated the procedure well and no complications were observed which suggests that local intraventricular transplantation of MSCs is safe and feasible in preterm infants with severe IVH and may be a better alternative than systemic intravenous transplantation. Further testing is needed to determine the optimal time and dosage of MSC transplantation. In addition, because symptoms of IVH such as developmental delay, cerebral palsy and cognitive impairment can persist into childhood, a follow-up is necessary to assess the safety of MSC transplant. Phase II of this clinical trial is currently underway [11].

Conclusion

Both genetic and environmental factors contribute to the development of fetal-onset hydrocephalus. Examples of contributing factors include vitamin B and folic acid deficiency, viral infection of ependyma, prematurity-related germinal matrix hemorrhage and IVH. Approximately 1 to 3 newborns per 1000 live births are affected by fetal-onset hydrocephalus which is characterized by abnormal CSF flow accompanied by ventricular dilatation. More than 50% of infants with severe IVH die or develop posthemorrhagic hydrocephalus. There is an urgent need for therapeutic modality to prevent PHH and attenuate brain damage post-severe IVH in preterm infants because no effective treatment currently exists. The current standard of care for hydrocephalus involves ventricular shunts, extra ventricular drains and third ventriculostomy. Each of these treatments come with numerous side effects. Known complications of shunts include obstruction, infection, fracture, migraine, over drainage and underdrainage and 50% of them fail within 2 years. 20-50% of ETVs close within 5 years and exhibit high rates of infection.

The three types of stem cells with the greatest potential of treating hydrocephalus include mesenchymal stem cells, unrestricted somatic stem cells and neural stem cells. Mesenchymal stem cells exhibit the greatest potential to treat hydrocephalus because they demonstrate potent immunomodulating abilities in the brain following a stroke or neonatal hypoxic ischemic encephalopathy which have similar pathologies. Umbilical cord blood is the most promising source due to its vast availability, high proliferation capacity and low immunogenicity. Numerous animal model clinical provide evidence that MSCs can target nearly all mechanisms involved in the pathogenesis of hydrocephalus. A phase I human clinical trial exhibits the great potential of MSCs to treat IVH and subsequently PHH. However, further research via a double-blind randomized control phase II clinical trial with follow-up evaluation is needed to prove the safety and efficacy of MSCs as a therapeutic strategy. Certain aspects of MSC therapy need to be investigated prior to deeming it an effective treatment including optimal transplantation route, timing and dosage.

Conflict of Interest

The authors have no conflict of interest to declare.

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