Journal of Rehabilitation Research and Practice

Devyaltovskaya et al., J Rehabil Res Pract. 2024;5(1):33-36.

Case Report

Cell therapy with autologous mesenchymal stem cells for premature baby with neonatal sepsis and bronchopulmonary dysplasia: Case report

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Received date: July 29, 2024
Accepted date: September 05, 2024

Abstract

Background: Mesenchymal stem cells (MSCs) have significant regenerative and anti-inflammatory potential; therefore they are widely used in medical practice. Neonatology is becoming a new area of clinical application of MSCs, including pathology treatment of premature newborns.

Objective: In the presented case report are demonstrated the results of cell therapy of bronchopulmonary dysplasia (BPD) with autologous MSCs in premature newborns who have suffered from neonatal sepsis.

Methods: The patient was conducted with two intravenous injections of biomedical cellular product (BMCP) "Human mesenchymal stem cells" in addition to standard treatment.

Results: The presented clinical case demonstrates the effectiveness of autologous umbilical cord MSCs in the medical prevention of severe forms of BPD. The immunomodulatory effect of umbilical cord MSCs provided a favorable outcome of early onset neonatal sepsis (EONS).

Conclusion: The inclusion of autologous MSCs in the therapy of premature babies with neonatal sepsis and developing BPD is a safe and effective treatment.

Keywords: Mesenchymal stem cells, Neonatal sepsis, Bronchopulmonary dysplasia, Newborn

Introduction

Bronchopulmonary dysplasia (BPD) remains the most common disease in premature newborns, associated with immature lung injury under the influence of supplemental oxygen and mechanical ventilation [1]. "Classical BPD" is observed in premature newborns who have not received surfactant treatments. It is characterized by pulmonary fibrosis due to oxygen toxicity and volumetric/barometric trauma caused by mechanical ventilation. A new or "mild" form of BPD is observed in children born at 29 weeks of gestation, and is characterized by disordered pulmonary development due to prematurity [2]. The frequency of BPD development depends on many factors: birthweight, gestational age, gender, chorioamnionitis, maternal smoking, fetal state of lung development, surfactant deficiency, mechanical ventilation in the neonatal period, the parameters and duration of respiratory support, asphyxia, congenital pneumonia, patent ductus arteriosus [3]. The risk of developing BPD increases with a decrease in body weight and gestational age. Infants with BPD can have various long-term consequences, such as bronchial asthma, frequently appearing respiratory infections [4]. Infants with persistent pulmonary x-ray findings of parenchymal injury who continue

to receive respiratory support are classified according to the therapy required for targeted saturation range (SpO_2) of 90%–95% [5,6]. Newborns continue to receive respiratory support.

The mortality rate is high in children with very low birth weight (VLBW). VLBW survivors have an increased risk of disease development, including BPD [7]. These conditions are found in every fourth child with a birth weight up to 1500 grams [4]. Septic condition can be found occasionally in patients with BPD which is increased in relation to VLBW. Sepsis interrupts lung development and leads to induction/progression of BPD through involvement of inflammation, oxidative stress, and damage to the endothelium of blood vessels in the lungs [8,9]. The incidence of sepsis within the first 72 hours of life (early-onset sepsis, EONS) is approximately 2–3.5% among infants born at less than 28 weeks' gestation [8].

Mesenchymal stem/stromal cells (MSCs) and MSC-derived exosomes have multidimensional effects in attenuating inflammation and tissue destruction while also aiding in reparative responses, and they may serve as adjunctive therapies to prevent neonatal sepsis and BPD [8]. MSCs have anti-apoptotic, anti-inflammatory, and antifibrous properties, which makes cell therapy a perspective direction for the treatment of BPD and sepsis [10].

Cell therapy based on MSCs is considered as a new promised tool to treat pathology in adults and newborns. The therapeutic effect of umbilical cord MSCs resulted in 40% decrease mortality rate of EONS [11]. Previous experimental studies propose an increase in the effectiveness of antibiotic therapy for septic conditions while taking antibiotics and MSCs [12].

A report would be presented on the case of a premature baby with neonatal sepsis and BPD. Autologous umbilical cord -derived MSCs for cell therapy were used in State Institution the Republican Scientific and Practical Center «Mother and Child», Minsk, Republic of Belarus. The form of written informed consent of the child's mother to receive umbilical cord tissues of a newborn for preparing MSCs was obtained (Approved by Protocol of the Ethical Committee of the State Institution the Republican Scientific and Practical Center «Mother and Child» No. 3 dated May 05, 2022). Autologous MSCs from umbilical cord were prepared in State Institution «Republican Center for Transfusiology and Medical Biotechnologies», Ministry of Health the Republic of Belarus. The form of written informed consent of the legal representative/mother for the injection of MSCs to a premature baby at risk of developing BPD was obtained (Approved by Protocol of the Ethical Committee of the State Institution the Republican Scientific and Practical Center «Mother and Child» No. 2 dated March 23, 2022).

Case Report

A premature male infant P.M. was born on 05/04/2022 with 29/2-week gestational age via cesarean section due to preterm premature rupture of membranes (pPROM) from a 22-year-old mother (2 gravida, 1 para) who suffered from gestational hypothyroidism. Respiratory Distress Syndrome (RDS) prophylaxis with dexamethasone once was carried out. The amniotic fluid was clear. Preterm infant had a birthweight 1400 grams, length 37 cm, head circumference 28 cm, chest circumference 25 cm. His Apgar score in the 1st minute was 6. Patient was required for mechanical ventilation. Surfactant replacement therapy with poractant alfa (CUROSURF 280 mg CHIESI FARMACEUTICI, S.p.A.) was administered one day. With diagnosis: respiratory distress syndrome, respiratory failure, prematurity 29/2 weeks' infant was admitted to the neonatal intensive care unit (NICU) where he stayed for 27 days. He was also diagnosed with neonatal sepsis.

Neonatal intensive care unit

While assessing the acid-base blood parameters, the infant was diagnosed with metabolic lactate - acidosis on the 1st day of life. The complete blood count on the 1st day of life showed the Iteration Index 0.29. Red blood cells (RBC) were within normal limits: erythrocytes – 3.56×10^{12}/l, hemoglobin – 136 g/l. The biochemical blood tests revealed indicators of inflammation: C-reactive protein - 15.4 mg/l, procalcitonin - 52.5 ng/ml.

Chest X-ray revealed signs of pneumonia in the upper right lobe and interstitial pulmonary edema on the 2nd and 3rd days of life, signs of bilateral pneumonia on the 7th day of life, signs of pneumonia in the upper right lobe, interstitial pulmonary edema on 7th day. Brain ultrasound examination performed on the 1st and 8th days of life showed brain tissue immaturity.

On the 15th day of life erythrocytopenia 2.91×10^{9}/l; decrease of hemoglobin to 100.5 g/l was noted in the complete blood count (CBC). On the 26th day of life eosinophils increased - 15%. In the biochemical blood tests on the 15th and 26th days of life there was no increase in procalcitonin and c-reactive protein levels. Patient's cultures for bacteria remained negative.

The therapy of EONS included antibacterial therapy (17 days, meropenem for 8 days), total parenteral nutrition (11 days), hematological supply (14 days), prevention of fungal infection. The child received respiratory support for 27 days (17 days of mechanical ventilation, 10 days of NIPPV - non-invasive positive pressure ventilation). Symptomatic therapy: caffeine (intravenously), vitamin D. For the purpose of immunoprotection the patient was administered human immunoglobulin intravenously.

Morphofunctional immaturity and generalized congenital infectious process as well as prolonged mechanical ventilation contributed to the formation of BPD. Inhalation therapy of obstructive syndrome caused by BPD included ipratropium bromide + fenoterol; budesonide.

Infant condition was severe without negative dynamics. There were episodes of bronchospasm due to emerging BPD, respiratory failure. Auscultatory breathing was carried out in all lung fields symmetrically. Hemodynamics is relatively stable without support. Based on decision of the consultation and the presence of informed consent obtaining from the mother, 05/25/22, on the 21st day of birth the patient has got the first injection of biomedical cellular product (BMCP) "Human mesenchymal stem cells" at a dose of 2 million cells (1.29 million cells per 1 kg of body weight) intravenously in addition to standard treatment. Baby body weight was 1547 grams. No patient reaction to the introduction of MSCs was observed.

The pediatric department for premature newborns

On the 28th day of life the child was transferred to the pediatric department for premature newborns of the Republican Scientific and Practical Center "Mother and Child" with a diagnosis of EOS (pneumonia, carditis). BPD new form, respiratory failure, Hydropericardium, Prematurity 29 weeks, VLBW, Encephalopathy of premature mixed genesis. Anemia of premature mixed genesis.

Table 1. Schedule of autologous mesenchymal stem/stromal cells application to child P.M.

Injection of MSCs	First	Second
Age	21st day of birth	54th day of birth
Body weight	1547 grams	2130 grams
Dose	2 million cells	4 million cells
Number of cells per 1 kg of body weight	1.29 million cells	1.88 million cells

The patient continued to receive antibiotic therapy for 6 days and partial parenteral nutrition. BPD treatment included inhalation (ipratropium bromide; budesonide); spironolactone.

Diagnostic examinations at 1st month of life, X-ray examination revealed signs of BPD. Infant was diagnosed with a delay in general development rate due to encephalopathy of prematurity, previous somatic pathology and prematurity at 29 weeks. VLBW. Bilateral calicoectasia. EONS (pneumonia, carditis) in anamnesis. BPD prematurity, new form, mild in anamnesis. Retinopathy of prematurity, initial regression phase, Lactase deficiency, Gastroesophageal reflux disease, Patent foramen ovale, Anemia of prematurity.

Before the second introduction of MSCs at the 38th week of gestational age a CBC and biochemistry were performed for patient. All parameters were within normal limits. The infant was nursed in a crib on a joint stay with his mother. His condition was satisfactory without oxygen support. Newborn's reflexes and muscle tone were reduced. Accessory muscle breathing was observed. Duration of oxygen dependence totally amounted to 41 days.

No markers of an inflammatory response were found in the biochemistry. Patient cultures for bacteria remained negative. Based on the decision of the consultation and the informed consent obtaining from the mother, 06/27/22, on the 54thday of birth patient was performed the reintroduction of BMCP at a dose of 4 million cells (1.88 million cells per 1 kg of body weight) intravenously in addition to standard treatment. Infant's body weight was 2130 grams. No reaction to the introduction of MSCs was observed.

Child was discharged at a gestational age of 38/3 weeks (55 days of life) from the pediatric department for premature newborns to the outpatient stage of medical care in a satisfactory condition, one day after cell therapy.

Discussion

BPD is associated with a high risk of life–threatening complications - acute and chronic respiratory failure, protein-energy deficiency, pulmonary hypertension, "pulmonary heart"; it is characterized by regression of clinical manifestations with age with prolonged persistence of residual morphological changes in the lungs and subclinical disorders of the functional parameters of external respiration. Mortality in BPD is about 3% in the first year of life. In premature infants with BPD and pulmonary hypertension, the death rate reaches 10-40%, with BPD at home ventilation – up to 20% [13]. Existing therapeutic approaches include effective oxygen support, antenatal corticosteroids, surfactant treatments [1]. Cell therapy based on MSCs is considered as a new promising method for BPD prevention and treatment [14]. Experimental studies have shown the possibility of improving the alveoli structure, preventing arrested alveolar growth, and restoring lung alveolarization and vascularization under the MSCs action [4]. Clinical achievements in newborn treatment of BPD at the NICU have significantly improved survival of premature infants with VLBW and extremely low birth weight (ELBW). At the same time, mortality from sepsis is high and varied from 17% to 46 % [15,16], especially in the cohort of premature infants with ELBW. According to various authors, from 4 to 14% of all neurological outcomes in newborns with VLBW and ELBW are caused by neonatal sepsis [17], and included disabilities like cerebral palsy, visual or hearing impairments, and cognitive problems. Neonatal sepsis is linked to various adverse outcomes, including respiratory complications, bronchopulmonary dysplasia, nutritional and growth issues, and immunological dysfunction [17,18]. A systemic inflammatory response that develops in this case causes multiple organ dysfunction and can cause hypoperfusion, hypoxia and brain damage by free radicals, which leads to poor long-term neurological outcomes [19]. Premature infants transferred from the delivery room to the NICU immediately where frequently exposed started antimicrobial therapy. However, the antibiotics therapy in newborns may increases the frequency of superinfection, necrotizing enterocolitis and dysbiosis but also leads to multidrug resistance.

Clinical use of MSCs in premature newborns with BPD can provide regeneration of lung tissue, development of vascular blood flow in the lungs, normalization of immune reactivity, which ultimately allows us to figure on a favorable outcome in the treatment of patients with severe infection or sepsis. The use of autologous MSCs is associated with fewer ethics-associated controversies and is therefore one of the preferred therapy options for neonatal infectious diseases [20,21].

Despite the effectiveness MSC-based cell therapy has some contraindications: mother's positive markers of infectious hepatitis, human immunodeficiency virus, tuberculosis, bronchopulmonology diseases. Limitations for MSCs implication are children with gestational age older than 32 weeks with genetic and chromosomal diseases; congenital malformations of the lungs; which need for palliative care; intraventricular hemorrhage of the IV degree; pulmonary hemorrhage; the presence of markers of acute inflammatory processes, non-sterile blood culture, positive inoculations on flora from 3 different anatomical loci.

Although the results coming from dozens of clinical trials employing MSCs are encouraging, the common clinical use of MSCs is still under development and is not a routine procedure [22]. MSCs have been universally considered safe, however continuous monitoring and prolonged follow-up should be the focus of future research to realize more effective schedule of cell administration, and to avoid the possible limitations and complications of cell therapy [23].

Conclusion

The presented clinical case demonstrates the effectiveness and safety of autologous umbilical cord MSCs in addition to standard therapy for the medical prevention of severe form of BPD and EONS. The described clinical case substantiates the possibility of clinical application of cell therapy using MSCs in septic conditions in premature newborns. Integration of the cell therapy into routine clinical practice will help to decrease immature child's mortality and disability.

Funding

The study was supported by the Ministry of Health of the Republic of Belarus (grant No. 20220684).

Conflict of Interest

The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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