Potential Therapy Intrathracheal Uses Umbilical Cord Blood Mesencimal Stem Cell Derivatives As The Latest Strategy For The Treatment Of Dysplasia Broncopulmonary In Premature Infants In Indonesia : A Literature Review

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ABSTRACT

Indonesia is the 5th country with the highest premature birth rate in the world. Multifactorial complications in premature babies whose lungs are not yet fully developed in the form of respiratory distress syndrome, one of which is bronchopulmonary dysplasia, can hinder their growth and development in the future. Bronchopulmonary dysplasia (Bronchopulmonary dysplasia/BPD) is one of the most common causes of morbidity in premature infants. Globally, the incidence of BPD varies widely from 10% -89%. Utilization of stem cells or stem cells has become one of the futuristic approaches in treating diseases related to tissue engineering. The study found that Mesenchymal Stem Cells (MSC/Mesenchymal Stem Cells) which are multipotent and have the ability to differentiate into cells derived from the mesoderm lineage, can be a renewable step in repairing tissues in the lungs, BPD is no exception. Compared to adult stem cells, the use of embryonic stem cells, especially Mesenchymal Stem Cells (MSC) from umbilical cord blood, has the potential to self-renewal and differentiate into several types of cells in an unlimited way. MSC from cord blood has advantages including, 1) easy collection process, 2) rapid proliferation, 3) fast processing at a relatively cheap price compared to other sources, 4) minimal risk of disease transmission and rejection, 5) and safer for mother and child. MSC transplantation has potential as a therapy for BPD by acting as a "paracrine factory" that can detect and respond to cues in the microenvironment and the site of injury. However, the potential of MSC in BPD still needs to be explored further considering its enormous benefits. There needs to be holistic collaboration between health workers and researchers so that this method can be realized. Further research on side effects, therapeutic doses, and long-term effects of therapy is expected to complement the challenges that are still present today.

Keywords: Premature Infants, Bronchopulmonary dysplasia/BPD, Mesenchymal, Stem Cells

1. INTRODUCTION

Children are the most valuable treasure compared to gold. Therefore, the state needs to pay special attention to its potential, including in the health sector. Unfortunately, the number of premature births is a problem that has caught the world's attention. Data shows that there are around 15 million premature babies born each year with Indonesia itself being the 5th country with the highest premature birth rate in the world, after India, China, Nigeria and Pakistan.[1] Multifactorial complications in premature babies whose lungs have not yet developed fully developed form of respiratory distress syndrome, one of which is bronchopulmonary dysplasia, which can inhibit its growth and development in the future. Bronchopulmonary dysplasia (Bronchopulmonary dysplasia/BPD) is one of the most common causes of morbidity in premature infants. Globally, the incidence of BPD varies widely from 10% -89%. However, in the majority of studies in North America, Asia, and Oceania, one third or more of very premature infants developed BPD. In Asia, the incidence of BPD varies between 18-82%, while in Oceania it is between 30-62%.[2] Based on these data, BPD is one of the complications of premature babies that needs great attention, especially in its management.

According to the American Lung Association,[3] BPD is a chronic lung disease in neonates, especially premature babies and requires oxygen therapy. Infants with BPD experience damage to the lungs and bronchi, causing dysplasia of the alveoli. Another definition according to Bancalari & Jain,[4] BPD is a chronic lung disease caused by several factors. These factors include airway immaturity which can lead to impaired lung growth, and can also affect the airways and blood vessels in the lungs.

Until now, there is no definite treatment that can return lung function to normal in infants with BPD.[5] The current management of BPD focuses more on supporting lung growth and optimizing its function, limiting further injury, and detecting possible complications.[6] Studies have found that the administration of exogenous surfactants has not shown positive results in reducing the incidence of BPD.[7] On the other hand, the use of pharmacological drugs such as diuretics, bronchodilators, and corticosteroids has not shown any prevention or long-term clinical improvement in the baby's lungs.[6,7] In fact, if left unchecked, this condition can develop into asthma and early-onset emphysema with age, thus interfering with the growth and development of the baby later in life.[5] Therefore, a futuristic approach that can improve alveolar and vascular function microscopy in infants with BPD is potentially direct i is a new step in the treatment of BPD in Indonesia.

Today, the utilization of stem cells or stem cells has become a futuristic approach in the treatment of diseases related to tissue engineering.[8] Studies have found that Mesenchymal Stem Cells (MSCs) are multipotent and have the ability to differentiate into cells derived from the mesoderm lineage, can be a renewable step in repairing lung tissue, including BPD.[8] Stem cell therapy cultured from umbilical cord blood (UCB) can produce extracellular vesicles that can repair lungs with BPD through the paracrine pathway.[9] In addition, administration of therapy via the local intratracheal route is the best option in transferring stem cells into the lungs.[9] This tissue engineering method is expected to repair alveoli and microvessels in infants with BPD in Indonesia.

2. CONTENTS

2. 1 **Bronchopulmonary Dysplasia**

Bronchopulmonary dysplasia (Bronchopulmonary Dysplasia/BPD) is defined as a developmental disorder of the alveolar and immature lung capillaries, requiring treatment with supplemental oxygen.[5] The terminology used to diagnose and classify the severity of BPD can be seen in Table 1. Generally, this condition is found in babies who are born prematurely due to complications from injuries from the use of ventilator machines and ROS (Reactive Oxygen Species) in the lungs, thereby stimulating inflammatory response indicated by increased proinflammatory cytokines such as interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)-alpha.[11] This situation is also induced by several growth factors such as transforming growth factor (TGF) and angiogenic factors such as vascular endothelial growth factor (VEGF) and angiopoietin.

Table 1 Definitions for BPD Diagnosis and Severity Assessment

	Gestational Age	
	<32 Weeks	≥ 32 Weeks
Examination Time	36 weeks after HPHT or postnatally	>28 days and <56 days postnatally
	Oxygen therapy >21% for 28 days	
Mild BPD	Room air at 36 weeks HPHT/postnatal	Room air at 56 postnatal days
Moderate BPD	Requires 30% O2 at 36 weeks of HPHT/postnatal	Requires 30% O2 at 56 days postnatal
Severe BPD	Requires ≥30% O2 and/or pressure ventilation at 36 weeks of HPHT/postnatally	Requires ≥30% O2 and/or pressure ventilation at 56 days of HPHT/postnatal

2. 2 **Stem Cells**

Stem cell therapy has become one of the most potential treatments for challenging newborn illnesses, such as BPD, in regards to ethics, safety, and therapeutic applicability.[9] This ability to differentiate into diverse cell types makes it useful as a therapy for tissue regeneration.[8] Based on the source and nature, the selection of stem cell types can be classified as follows in Table 2. Compared with adult stem cells, the use of embryonic stem cells, especially Mesenchymal Stem Cells (MSC) from umbilical cord blood, has the potential to self-renewal and differentiate into several types of cells are not limited. MSC from cord blood has advantages including, 1) easy collection process, 2) rapid proliferation, 3) fast processing

at a relatively cheap price compared to other sources, 4) minimal risk of disease transmission and rejection, 5) and safer for mother and child.[9]

Table 2 Potential and Sources of Stem Cells for Regenerative Therapy

Stem cell	Source		Potency
Embryonic	Morula		Totipotent
	Blastosis		The pluripotency
Fetal	Fetus		Multipoten, Pluripoten
	Extrafetal tissue	Placenta (amnion, chorion)	Multipoten, Pluripoten
		Amniotic fluid	Multipoten, Pluripoten
		Wharton jelly from the umbilical cord	Multipoten, Pluripoten
		Umbilical cord blood	Multipoten
Mature	Spinal cord mesenchymal stem cells		Multipoten, Pluripoten
	Other organs and tissues (adipose tissue, skin, striated muscle, heart, liver, nervous tissue, blood, etc.)		Multipotent, oligopotent, bipotent and unipotent
Induced	Somatic differentiated cell		The pluripotency

Previously, MSC was thought to work by differentiating into reparative MSC derivatives. However, this hypothesis is no longer used[13] . The main mechanism of MSC currently involves paracrine factors that can trigger endogenous recovery. A large number of studies have shown that MSCs can secrete a wide variety of growth factors and immunomodulating cytokines.[9] MSCs can also secrete extracellular vesicles (EV), these vesicles carry a variety of macromolecules, such as proteins, lipids, and nucleic acids, which transmit signals to cells. and can cause changes in cell function[14]. Several studies have proven that conditioned MSC medium can improve hyperoxyl lung injury in animal models of BPD[15]. This finding proves that the therapeutic effect on BPD is more related to its paracrine effect than to its regenerative effect.[9] According to Omar and colleagues in 2022, an animal model of BPD transplanted with MSC experienced alveolar repair and pulmonary vascular remodeling[16]. Specifically, MSCs can provide (i) anti-inflammatory effects, namely decreasing proinflammatory cytokines such as MIF macrophages, IFN-γ, TGF-β, and TNF-α, (ii) antifibrotic effects, namely decreasing collagen density, MMP, and elastin expression, and increased VEGF, MMP-2, vessel density, and angiogenesis, and (iii) improved lung function and accelerated recovery with decreased injury-related protein markers BPD, CX3CL1, TNF-α, TIM-1, hepassocin, neprilysin, osteoprotegerin, and LIF , and increased alveolar septal width and septal crest density.

In MSCs transplanted locally or systemically as a therapy, anti-inflammatory, anti-apoptotic, antioxidant, antifibrotic, antibacterial, and even membrane permeability stabilization effects were found through the secretion of soluble paracrine molecules and extracellular vesicles (exosomes) or mitochondrial transfer from MSCs to cells. hosts [17]. Cytoprotective paracrine factors secreted by MSCs also vary in various animal models. In animal models of BPD, vascular endothelial growth factor (VEGF) secreted by transplanted human MSCs can induce VEGF expression in hosts in hyperoxic lungs.[9] When VEGF is present in transplanted MSCs or contained in EVs of MSCs was blocked by transfection of small interfering RNA for human VEGF, this action apparently also blocked the beneficial protective effect of the transplanted MSCs.

In a phase I clinical trial conducted by Chang et al., in 2014, a significant decrease in tracheal aspirate levels of IL-6, IL-8, MMP-9, TNF-α, and TGF-β1 was found on 7th day compared to initial levels or on the 3rd day post-transplantation, as well as lower severity of BPD in recipients.[18] Then in a phase II clinical trial conducted by Ahn et al.,[9] it was found that intratracheal MSC transplantation was relatively safe and could be performed and obtained significant improvements. significant in premature infants at 23-24 weeks' gestation.

The choice of MSC transplantation method locally into the alveoli of the lungs also requires special attention. The systemic intravenous route has several drawbacks, such as the possibility of pulmonary embolism and the difficulty of targeting specific injury sites.[9] Intratracheal transplantation is potentially the best step in stem cell transplantation into the

lung. This is supported by a study which states that this method has succeeded in transmitting UCB-derived MSCs and has been proven safe and feasible in phase 1 clinical trials in infants recorded for up to 2 years later.

3. CONCLUSION

Based on the things that have been mentioned before, MSC transplantation has the potential to be a therapy for BPD by working as a "paracrine factory" that can detect and respond to cues in the microenvironment and the location of injury. In addition, this method also produces various paracrine factors that have various repair functions, such as anti-inflammatory, anti-apoptotic, antioxidant, anti-fibrotic, and antibacterial. This is in contrast to pharmacological therapy which tends to lead to polypharmacy, but does not provide significant results.[9] The use of UCB-derived MSCs with intratracheal transplantation has the potential to be used as the latest step in the treatment of BPD in premature infants in Indonesia.

However, the potential of MSC in BPD still needs to be explored further considering its enormous benefits. There needs to be holistic collaboration between health workers and researchers so that this method can be realized. Further research regarding side effects, therapeutic doses, and long-term effects of therapy is expected to complement the challenges that are still present today. It is hoped that intratracheal therapy using UCB-derived MSC as the latest strategy for treating BPD in premature babies in Indonesia can be a step for the nation towards Golden Indonesia 2045.

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