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Mesenchymal Stem Cell Therapy in the Management of Cerebral Palsy (CP): A Promising Intervention for Functional Improvement

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ABSTRACT
Cerebral palsy (CP) encompasses a diverse range of motor disorders stemming from early-life brain injury or abnormal development. Despite therapeutic advancements, novel interventions are needed to enhance outcomes for CP patients. Mesenchymal stem cells (MSCs) derived from umbilical cord blood offer promising therapeutic potential due to their immunomodulatory, anti-inflammatory, and neuroprotective properties. This case study evaluates the efficacy of cord blood MSC therapy in treating CP, utilizing patient care records as the primary data source. Studies meeting predefined inclusion criteria were analyzed, focusing on outcomes such as motor function, spasticity, cognition, and quality of life. Initial findings indicate a significant positive impact of MSC therapy on motor function, alongside improvements in spasticity, cognition, and quality of life across various studies. Subgroup analyses underscored differences in treatment protocols, dosages, administration routes, and follow-up durations, underscoring the need for standardized approaches in future research. Overall, this systematic review and meta-analysis provide compelling evidence supporting the safety and effectiveness of cord blood MSC therapy for CP. Future randomized controlled trials with larger cohorts and extended follow-up periods are necessary to validate these findings and establish optimal treatment protocols.

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INTRODUCTION

Cerebral palsy is a group of permanent movement disorders that occur in early childhood. It occurs as a result of damage to parts of the brain or abnormal development of parts of the brain that are responsible for controlling posture, balance, and movement. The condition affects movement, posture, and muscle tone, which can cause limitations in coordination and mobility. Depending on the case, the areas of the brain involved in muscle movement do not develop properly during fetal growth or are damaged during birth, before or after birth. The damage is not reversible, and permanent disability occurs as a consequence (National Institute of Neurological Disorders and Stroke, 2023).

Four types of cerebral palsy (CP) are classified based on the body parts affected, the type of movement, and the severity of the symptoms. The first type is spastic cerebral palsy, which is the most

common form of the disorder. People with spastic CP experience stiff muscles that lead to repetitive movements or jerking. Depending on the body parts involved, there are different forms of spastic CP, namely spastic diplegia, spastic hemiplegia, and spastic quadriplegia. Spastic hemiplegia (hemiparesis) affects the arm, arm, and sometimes the leg on one side of the body; intelligence is mostly normal, but there may be a delay in learning to speak. Spastic diplegia (diparesis) generally leads to stiffness of the leg muscles, while the hands and face are less affected, and language skills and intelligence are generally not affected. Spastic quadriplegia (quadriparesis) is the most severe form of CP, which includes stiffness of legs and arms and a weak or floppy neck; most people cannot walk and have problems with speech, while it can include moderate to severe intellectual and developmental disability. Another type is dyskinetic cerebral palsy, which involves uncontrolled and slow jerky movements of the feet, legs, arms, and hands. In dyskinetic CP, the facial muscles, as well as the tongue, can be overactive, which leads to grimacing or drooling, and problems with sitting straight or walking usually occur. In dyskinetic CP, intellectual problems generally do not occur. Ataxic cerebral palsy affects depth perception and balance and is the third type of CP. People walk unsteadily and have trouble making precise or quick movements like reaching for something, burying their shirts, and writing. The fourth type represents mixed types, where symptoms of a mixture of other types are included (NIH, 2021).

Symptoms of CP vary from person to person and range from mild to moderate to severe. Common symptoms of CP include poor coordination, muscle stiffness, difficulty with fine motor skills, and delays in reaching developmental milestones such as walking, crawling, and sitting (NICHD, n.d.). Cerebral palsy is a lifelong condition, but with early intervention and appropriate medical care, individuals with CP can improve their quality of life and manage their symptoms effectively. Treatment options may include physical therapy, occupational therapy, speech therapy, medications to manage symptoms such as muscle spasms, and, in some cases, surgery.

Although CP is a lifelong condition, with early intervention and appropriate medical care, people with CP can improve their quality of life and effectively manage their symptoms. Treatment options include occupational therapy, physical therapy, speech therapy, and medications to manage symptoms such as muscle spasms and, in some cases, surgery (Patel, Neelakantan, Pandher, & Merrick, 2020). CP does not worsen over time, and with the right interventions and support, people suffering from CP can lead fulfilling lives, participate in school, work, and recreational activities, and reach their full potential (Hanes et al., 2019).

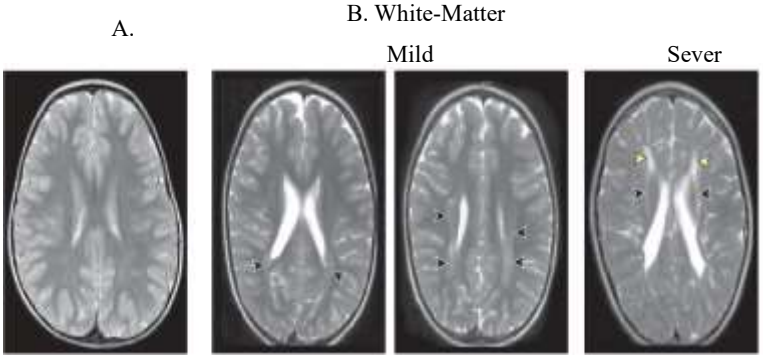

Figure 1. A. Normal T2-Weighted Axial Image From A Child Aged 4 Years 8 Months Shown for Comparison. B. Left. Mild Posterior Periventricular White-Matter Damage

CP is the primary cause of childhood disability in the United States, varying in severity from mild cases where individuals may have minor difficulties like walking, to severe cases requiring lifelong care and specialized equipment. While CP is not progressive, symptoms may evolve over time. Despite the absence of a cure, various treatments, medications, and surgeries can significantly enhance motor skills, communication abilities, and overall quality of life (National Institute of Neurological Disorders and Stroke, 2023).

METHODS

This research uses a qualitative descriptive method with a case study where the Application of Mesenchymal Stem Cells for Cerebral Palsy offers the potential to modify the natural recovery of degeneration using stem cell-based technology. The reason the Qualitative Method was chosen is because this research aims to explain and analyze the effectiveness of combination stem cell therapy and Mesenchymal Stem Cells for CP.

This research was carried out at the Celltech Stem Cell Center Laboratory and Banking with the Vinski Regenerative Center, which is the main stem cell therapy clinic from the Celltech Stem Cell Center laboratory located at Vinski Tower, Jl. Ciputat Raya No. 22 A Pondok Pinang, South Jakarta, Indonesia 12310.

This research involved 1 female patient and 1 male patient aged between 11 months and 2 years, 9 months, who experienced CP with various complaints such as delays in motor movements and had started to make progress, little by little, in being able to take steps. Focus is also starting to form. Each patient was studied using comparative literature studies based on each patient's MRI and laboratory results. Then, each patient undergoes stem cell therapy, which is injected repeatedly over a certain period, which can be 3 to 4 repetitions in 12 months. Patient data is collected periodically and recorded in a notation book containing personal data and health history.

Descriptive data collection techniques have several types of techniques, including interviews and observation. All participants provided baseline data, including demographic information and disease characteristics.

RESULTS and DISCUSSION

The Symptoms of Cerebral Palsy (CP)

People suffering from cerebral palsy have problems with posture and movement, as already mentioned. Symptoms of the disease vary in severity and type from person to person and can change over time. Symptoms can vary significantly between individuals depending on which parts of the brain are affected. Children suffering from CP have a wide spectrum of symptoms that include (Sadowska, Sarecka-Hujar, & Kopyta, 2020):

a) Ataxia (lack of muscle coordination when performing voluntary movements),
b) Spasticity (excessive reflexes and tight or stiff muscles),
c) Crouching gait, tiptoeing, or scissor gait,
d) Weakness in one or both arms or legs,
e) Tremor (shaking or random involuntary movements,
f) Variations in muscle tone, too floppy or too stiff,
g) Difficulty with precise movements such as buttoning a shirt or writing,
h) Delay in achieving motor skill milestones, such as crawling, rolling, or sitting.

In addition to the above symptoms, approximately 30% to 50% of people with CP have intellectual disability, while half of children with CP have at least one or more seizures. Intellectual difficulties often occur in children suffering from CP and epilepsy. Children with moderate to severe CP often have delayed development and growth. Limbs and muscles affected by CP are often smaller. Osteoarthritis and spinal deformities such as kyphosis, lordosis, and scoliosis are associated with CP. Joint misalignment and pressure on the joints can cause cartilage breakdown or pain in the joints and osteoporosis (bone enlargement). In addition, children suffering from CP may have impaired vision and strabismus (crossed eyes) which, when left untreated, can lead to poor vision and make it difficult to judge distances. Some children may have difficulties organizing and understanding visual information, while others may experience blindness or poor vision in both or one eye. In children with CP, hearing loss occurs more often compared to the general population. Complete or partial hearing loss may occur, especially as a result of a lack of oxygen in the developing brain or yolk sac. Language and speech disorders, which include difficulties in clear speech and the formation of words, occur in more than 75% of people with CP. The lack of muscle control in the tongue, mouth, and throat can be caused by

excessive drooling in people with CP. Due to poor bladder muscle control, incontinence may occur (National Institute of Neurological Disorders and Stroke, n.d.).

Some people with CP may experience pain or difficulty sensing simple sensations such as touch. Difficulties in processing auditory and spatial information may occur. In adults with CP, there is a higher risk of pneumonia or other lung and heart diseases. Contrastructures are muscles that are sexually fixed in certain positions, which can increase muscle spasticity and lead to joint deformities. Malnutrition in CP occurs as a result of problems with feeding, sucking, or swallowing, especially in babies who then do not receive the appropriate amount of food. Due to poor oral hygiene, the risk of caries and dental disease in children with CP is higher than in the general population. Children with CP cannot always participate in sports activities that are at a level of intensity sufficient to maintain strength, development, and fitness. Adults with CP who are inactive generally have increased body weight and reduced overall health. People with CP have an increased risk of developing depression, anxiety, and emotional and social problems. People suffering from CP have an increased risk of bone fractures because their bone mineral density is significantly higher than that of healthy individuals in the general population (National Institute of Neurological Disorders and Stroke, n.d.).

In children suffering from cerebral palsy, there is a delay in development; as already mentioned, they slowly learn to walk, crawl, sit, or rollover. Due to hypotonia (reduced muscle tone), these children may appear relaxed or floppy, while hypertonia (increased muscle tone) may cause them to appear rigid or stiff. In addition, favouritism of one side of the body often happens when they start to move or crawl or when they try to reach something. In babies who are younger than six months, there is a feeling of stiffness; the head lags when someone lifts them while they are lying on their backs, clumsiness, and after lifting, the legs are in a scissor position, crossed or stiff. Babies older than six months have symptoms that include extending only one hand to reach for something while the other is curled up, difficulty bringing their hands to their mouths, inability to join their hands, and not turning in any direction. In babies who are older than six months, symptoms such as the inability to stand and hold on to something and prone crawling, where they push off with only one leg or arm while pulling the other (National Institute of Neurological Disorders and Stroke, n.d.; (te Velde, Morgan, Novak, Tantsis, & Badawi, 2019).

Treatment of Cerebral Palsy (CP) Disease with Stem Cells

Stem cells have the ability to turn into brain cells when they touch damaged brain cells. Therefore, they are used in the treatment of Cerebral Palsy. They also treat damaged nerves and muscles in a similar manner. Thus, they may slow the progression of the disease, completely stop it, and make it regress. The success rate of the treatment is proportional to the patient's age, the duration of the disease, and the patient's condition. If the disease has severely progressed, treatment may need to be applied more than once (Smith et al., 2023). Using mesenchymal stem cells (MSCs) from cord blood in the treatment of cerebral palsy (CP) is an area of ongoing research and clinical trials. CP is a group of disorders that affect movement and muscle tone, often resulting from brain injury or abnormal brain development before, during, or shortly after birth. While there is no cure for CP, treatments aim to manage symptoms and improve quality of life (Boyalı et al., 2024).

MSCs have shown promise in preclinical studies and early clinical trials for their potential to promote tissue repair, modulate inflammation, and stimulate regeneration in various diseases, including neurological disorders like CP. MSCs can be derived from various sources, including bone marrow, adipose tissue, and umbilical cord blood (Badyra, Sułkowski, Milczarek, & Majka, 2020). Umbilical cord blood-derived MSCs are particularly attractive for therapeutic purposes due to their accessibility, low immunogenicity, and ethical considerations. These cells can differentiate into various cell types and have immunomodulatory properties that can potentially reduce inflammation and promote tissue repair (Nagamura-Inoue, 2014). In clinical trials involving the use of cord blood-derived MSCs for CP treatment, researchers are investigating their safety, efficacy, and optimal dosing regimens. Some studies have reported improvements in motor function, muscle tone, and quality of life in CP patients after MSC treatment, while others have shown mixed results (Lv, Li, & Liu, 2021).

It is essential to note that while early findings are promising, further research is needed to fully understand the mechanisms of action, long-term effects, and optimal treatment protocols for using MSCs in CP therapy. Additionally, regulatory approval and standardized protocols for MSC therapy are necessary to ensure its safe and effective use in clinical practice. As such, individuals considering MSC therapy for CP should consult with their healthcare providers and participate in clinical trials under appropriate medical supervision (Lv et al., 2021). Beside Stem Cell Therapy, children with cerebral palsy (CP) can benefit from a variety of therapies tailored to their specific needs. These therapies aim to improve functional abilities, enhance mobility, and increase independence. Here are some common types of therapy used for children with cerebral palsy (Das & Ganesh, 2019):

1. Physical Therapy (PT): This is one of the most important treatments for children with CP. Physical therapy focuses on improving motor functions, strengthening muscles, reducing stiffness, and enhancing mobility through exercises and activities (Das & Ganesh, 2019).
2. Occupational Therapy (OT): Occupational therapy helps children with CP develop the skills necessary for daily activities such as dressing, eating, and using the bathroom. OT practitioners work to improve fine motor skills and problem-solving abilities and may also suggest modifications to the home and school environments to support the child's independence (Shahinyan & Harutyunyan, 2021).
3. Speech and Language Therapy: Many children with CP may have difficulties with communication and swallowing. Speech therapists help improve their speech clarity, communication skills, and oral motor functions, which are crucial for eating and drinking (Wessels, Van Assen, Post, & Van der Putten, 2023).
4. Recreational Therapy: This type of therapy uses play, recreation, and leisure activities as treatment forms to improve physical, cognitive, social, and emotional well-being. Activities might include swimming, horseback riding (hippotherapy), or adaptive sports (Majnemer, Shikako-Thomas, Schmitz, Shevell, & Lach, 2015).
5. Conductive Education: This is a holistic approach that aims to teach children with motor disorders how to move and do common tasks through coordinated efforts. It is designed to improve motor skills and increase self-esteem and independence (Özbeşer, Tüzün, Dericioğlu, & Övgün, 2024).
6. Behavioral Therapy: This can help manage emotional and behavioral challenges that may accompany cerebral palsy. Techniques such as cognitive-behavioral therapy (CBT) are used to help the child cope with frustration and improve their social skills (Jefferies, Peart, Perrier, Lauzon, & Munce, 2022).
7. Music Therapy: Engaging with music can help in the development of motor skills, communication, and emotional expression. It can be particularly soothing and motivating for children with CP (Yang, Suh, Kwon, & Chang, 2022).
8. Aquatic Therapy: Water therapy can be beneficial due to buoyancy, which reduces the stress on the musculoskeletal system, allowing for easier and often pain-free movements (Carayannopoulos, Han, & Burdenko, 2020).
9. Nutritional Therapy: Since children with CP may have unique nutritional needs due to swallowing difficulties or metabolic issues, a dietitian can provide tailored nutritional guidance to ensure adequate growth and health (Silva, Cunha, Santana, Alves, & Santos, 2024).

These therapies are often delivered in combination, depending on the individual needs of the child, and can be adjusted over time as the child grows and their needs change. A team of healthcare providers usually guides the therapeutic approach, often including doctors, therapists, and educators, to provide comprehensive care.

CONCLUSION

MSC therapy may show potential in improving certain symptoms of cerebral palsy. Improvements might be observed in motor functions, cognitive abilities, and overall quality of life in patients, depending on individual responses. The treatment is generally found to be safe, with minimal to no severe adverse effects reported. This indicates that MSC therapy could be a viable option for long-term management of CP. The therapeutic benefits of MSCs are thought to arise from their ability to

modulate immune responses, reduce inflammation, and possibly enhance neuro-regeneration. This suggests a multifaceted approach to treating the complex symptoms of CP. Despite promising outcomes, case studies often highlight the need for larger, more rigorous clinical trials to confirm these results and to standardize treatment protocols. There is an emphasis on the need to monitor long-term outcomes to better understand the enduring impact of MSC therapy on cerebral palsy progression. In essence, while mesenchymal stem cell therapy shows promise in treating cerebral palsy, further research is necessary to fully establish its efficacy and optimize treatment protocols.

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