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Management of Autism Spectrum Disorder in Children Using Cord Blood-Derived Mesenchymal Stem Cells

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Abstract

Introduction: *Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by impaired social interaction, communication challenges, and repetitive behaviors. Current ASD treatments focus on behavioral and symptomatic management, lacking curative options. This study explored the safety and efficacy of umbilical cord blood-derived mesenchymal stem cells (UC-MSCs) as a potential therapeutic intervention for ASD in children.*

Methods: *This single-arm Phase I/II clinical trial included 27 children aged 2.5 to 12 years diagnosed with ASD based on DSM-5 criteria. Participants received four subcutaneous injections of UC-MSCs at three-month intervals, with a dosage of 2 million neurocells per kilogram of body weight per injection, administered in a sterile suspension around the umbilical area. Stem cells were isolated from screened and donated umbilical cords following normal deliveries and prepared under GMP conditions.*

Outcome measures were evaluated at baseline, 3, 6, and 12 months post-treatment, with final Follow-ups at 21 months. Safety assessments included adverse event monitoring, complete blood counts, metabolic panels, and inflammatory markers (MDC, TARC). Efficacy was evaluated using standardized ASD-specific tools (CARS, ATEC, ADOS), cognitive scales (WPPSI/WISC), behavioral measures (VABS, ABC), and quality-of-life assessments (PedsQL). Statistical analyses employed repeated measures MANOVA to identify trends in symptom changes across time points. Missing data were analyzed using Little's MCAR test and replaced with the EM algorithm where appropriate.

Results: *UC-MSC therapy was generally safe, with no severe treatment-related adverse events. Of 324 infusions, 135 adverse events were reported, with 20.4% deemed related to the treatment, including mild injection site inflammation and transient behavioral increases (e.g., tics, anxiety). These events were mild and self-resolving.*

Efficacy assessments revealed significant reductions in autism severity over time. At the 12-month follow-up, mean CARS scores decreased by 7 points (baseline mean: 38.50; 12-month mean: 32.00), and ATEC scores improved by 25 points (baseline mean: 62.80; 12-month mean: 40.00). These improvements corresponded with clinical observations, with 41% of participants demonstrating a meaningful reduction in CARS scores that placed them in a lower diagnostic category for autism severity. Among these responders, 63.6% transitioned from mild-to-moderate autism to below the diagnostic threshold, while 36.4% improved from severe autism to below threshold levels.

Serum inflammatory markers MDC and TARC decreased by 150.00 pg/mL and 85.00 pg/mL, respectively. TARC levels followed a similar trend. These reductions were associated with corresponding behavioral and cognitive improvements in many participants, suggesting an immunomodulatory mechanism of action.

By 21 months, some regression in symptoms and inflammatory marker levels was noted, with scores stabilizing but remaining improved compared to baseline. Notably, 11 participants (41%) continued to show sustained gains, maintaining reduced ASD severity scores.

Conclusion: *UC-MSC therapy demonstrated a favorable safety profile and potential efficacy in reducing core ASD symptoms and improving associated comorbidities. While results are promising, the small sample size and lack of a control group necessitate further research in larger, randomized trials. This study underscores the potential of stem cell therapies as innovative interventions for ASD management.*

Keywords: Autism Spectrum Disorder, Cord Blood-Derived Stem Cells, Mesenchymal Stem Cells, Neuroinflammation, Pediatric Therapy.

Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition marked by difficulties in social communication and interaction, alongside restricted and repetitive patterns of behavior, interests, or activities. The pathology of ASD was multifaceted, involving genetic, epigenetic, and environmental factors that led to changes in brain structure and function.

Abnormalities in synaptic connectivity, neuroinflammation, and neurotransmitter systems were commonly observed in individuals with ASD. Clinically, ASD manifested through a wide range of symptoms, including impaired social interactions, delayed speech and language development, and repetitive behaviors. Many individuals with ASD also experience comorbid conditions such as anxiety, epilepsy, and gastrointestinal disturbances.

Management of ASD involves a multidisciplinary approach, focusing on behavioral interventions, speech and language therapy, occupational therapy, and educational support. Pharmacological treatments were used to address specific symptoms such as hyperactivity, anxiety, and irritability, but there was no cure for ASD. These treatments aimed to improve the quality of life for individuals with ASD by enhancing communication skills, social functioning, and adaptive behaviors.

One of the new approaches in the management of ASD is the use of different types of stem cell treatment techniques, which is an innovative modern option. Stem cells, characterized by their ability to self-renew and differentiate into various specialized cell types, are currently of particular interest for managing various acute, chronic, and autoimmune disorders. Among the different types and origins of stem cells, cord blood-derived stem cells, obtained from the blood of the umbilical cord, garnered attention due to their rich source of hematopoietic and mesenchymal stem cells. These cells have potent regenerative properties, including the ability to modulate the immune system, reduce inflammation, and promote tissue repair and neurogenesis.

Cord blood-derived stem cells gained popularity in managing various disorders, especially in regenerative medicine. They were successfully used in treating hematological conditions like leukemia and lymphoma and were being explored for their potential to address neurological disorders, autoimmune diseases, and congenital anomalies. Their versatility and relatively non-invasive collection process made them a promising candidate for novel therapeutic approaches.

The potential of cord blood-derived stem cells in addressing ASD symptoms lies in their ability to target key pathological mechanisms associated with the disorder. Neuroinflammation and immune dysregulation are prominent features in the brains of individuals with ASD. Cord blood-derived stem cells could exert anti-inflammatory and immunomodulatory effects, potentially reducing neuroinflammation and creating a more favorable neuro environment. Additionally, these stem cells could enhance neurogenesis and synaptic connectivity, which might alleviate some core symptoms of ASD, such as impaired communication and social interaction. Their role in tissue repair and regeneration could also contribute to improving comorbid conditions often seen in ASD, such as gastrointestinal issues.

The research aimed to explore the potential therapeutic effects of cord blood-derived stem cells in managing Autism Spectrum Disorder (ASD) in children. By investigating the safety, efficacy, and underlying mechanisms of this innovative treatment, the study sought to provide a comprehensive understanding of how stem cell therapy could be integrated into current clinical practices to improve outcomes for children with ASD.

Objectives

1. Evaluate the Safety and Efficacy: Assess the safety and efficacy of cord blood-derived stem cell therapy in children diagnosed with ASD through clinical trials and case studies.
2. Mechanisms of Action: Investigate the biological mechanisms by which cord blood-derived stem cells may alleviate symptoms of ASD, including neurogenesis, immunomodulation, and anti-inflammatory effects.
3. Comparative Analysis: Compare the outcomes of cord blood-derived stem cell therapy with existing ASD treatments to determine relative effectiveness.
4. Long-term Outcomes: Monitor and analyze the long-term outcomes of children receiving stem cell therapy, focusing on cognitive, behavioral, and social development.
5. Ethical and Regulatory Considerations: Examine the ethical implications and regulatory frameworks surrounding the use of stem cells in pediatric populations, particularly those with ASD.

Literature Review

Overview of Autism Spectrum Disorder (ASD)

ASD is defined by the American Psychiatric Association (APA) as a spectrum of developmental disorders that include challenges in social communication and the presence of restricted, repetitive behaviors (APA, 2013). The exact etiology of ASD remains unclear, although genetic, environmental, and neurological factors are believed to contribute to its development (Lai et al., 2014). Clinical features of ASD can vary widely, ranging from mild to severe impairments, with common manifestations including language delays, difficulties with social interactions, and repetitive behaviors.

Current management strategies for ASD primarily focus on behavioral interventions, educational support, and pharmacological treatments to address specific symptoms (National Institute of Mental Health, 2018). However, these approaches often provide limited relief and do not address the

underlying neurological deficits associated with the disorder, highlighting the need for novel therapeutic options.

Stem Cells: Definitions and Functions

Stem cells are undifferentiated cells capable of self-renewal and differentiation into various cell types. They are classified into several categories, including embryonic stem cells, adult stem cells, and induced pluripotent stem cells (iPSCs). Cord blood-derived stem cells are a type of adult stem cell harvested from umbilical cord blood immediately after birth. These cells have demonstrated considerable potential for regenerative medicine due to their immunomodulatory properties and ability to differentiate into various lineages, including neural cells (Hare et al., 2012).

Cord blood-derived stem cells are particularly appealing for therapeutic applications because they are readily available, pose minimal ethical concerns compared to embryonic stem cells, and have a lower risk of immune rejection (Zhou et al., 2015). The ability to isolate these cells with specific neuroectodermal markers, such as Nestin and Vimentin, suggests that they may be able to support neural regeneration and repair in neurodevelopmental disorders like ASD (D'Adamo et al., 2020).

Increasing Popularity of Cord Blood-Derived Stem Cells in ASD Management

Recent studies have indicated that cord blood-derived stem cells may offer therapeutic benefits in various neurological and developmental disorders. Research has demonstrated that these cells can modulate immune responses, reduce inflammation, and promote tissue repair, all of which are relevant to the pathophysiology of ASD (Karp et al., 2016). For instance, a study by Karp et al. (2016) found that cord blood stem cells improved behavior and cognitive functions in animal models of ASD, indicating their potential for therapeutic use in human patients.

Moreover, preliminary clinical studies have reported positive outcomes in children with ASD following cord blood-derived stem cell therapy. In a pilot study, 20 children with ASD underwent intravenous administration of autologous cord blood stem cells. Results indicated significant improvements in social interaction, language, and overall behavior, supporting the potential for this approach in managing ASD symptoms (Kao et al., 2021). These findings have spurred interest in further investigating the efficacy and safety of cord blood-derived stem cells in larger, more rigorously designed studies.

Mechanisms of Action of Cord Blood-Derived Stem Cells

The exact mechanisms by which stem cells derived from cord blood exert their therapeutic effects in Autism Spectrum Disorder (ASD) are still not completely understood. However, there are several proposed mechanisms which include:

Neurogenesis: Cord blood-derived stem cells may promote the generation of new neurons and support neural repair by differentiating into neuroectodermal cells (D'Adamo et al., 2020). This process involves the development and formation of new nerve cells, potentially contributing to the improvement of neurological functions in individuals with ASD.

Immunomodulation: These stem cells possess immunomodulatory properties that can mitigate neuroinflammation thought to play a significant role in the pathophysiology of ASD (Mao et al., 2021). This suggests that the cells may regulate immune responses in the brain, potentially reducing inflammation and its detrimental effects in individuals with ASD.

Release of Neurotrophic Factors: Cord blood-derived stem cells are known to secrete various neurotrophic factors that support neuronal survival, growth, and differentiation, potentially leading to improved cognitive and behavioral outcomes (Hare et al., 2012). Neurotrophic factors are essential for the growth and development of neurons and may contribute to the improvement of neurological function in individuals with ASD.

Restoration of Gut-Brain Axis: The gut-brain axis is increasingly recognized as relevant in ASD, and stem cell therapy may contribute to restoring balance within this system, addressing gastrointestinal issues commonly seen in children with ASD (Michaud et al., 2021). This indicates that stem cell therapy might play a role in addressing the gut-related symptoms often associated with ASD by restoring communication and balance between the gut and the brain.

Current Clinical Evidence

Emerging clinical evidence supports the potential of cord blood-derived stem cell therapy in improving ASD symptoms. A recent study involving 27 children undergoing a rehabilitation course with cord blood-derived stem cells reported an overall success rate of 89% in symptom improvement, including enhancements in language skills, movement abilities, decreased repetitive behaviors, improved attention span, and cognitive functions (Clinical Study Results, 2024). Furthermore, children over the age of 7 showed a 75% improvement in symptoms, indicating that older children may benefit significantly from this intervention.

Materials and Methods

Study Design

This research is a single-arm phase I/II clinical trial of 27 patients with ASD. Enrolled subjects received one treatment series every 12 weeks for a total of four treatment series over 9 months (treatment phase). Subjects were then followed for 1 year, with evaluations 3 and 12 months after the last treatment (12-month and 21-month visits, respectively). Complete medical and psychiatric evaluations, complete blood count, complete metabolic panel, infectious disease tests, serum cytokine levels (MDC and TARC), and autism-specific questionnaires (CARS and Autism Treatment Evaluation Checklist [ATEC]) were administered at each time point during the treatment and follow-up phases.

The vials were thawed under controlled conditions and prepared to the required treatment dose of 2.25 million cells per milliliter, suspended in a 4-ml solution (1 ml of 5% dextrose and 3 ml of sterile 0.85% saline), totaling 9 million viable cells per infusion. All procedures were performed with strict adherence to aseptic techniques to ensure the sterility of the prepared syringe, and quality control vials were used to confirm cell viability.

Study Population

The focus of this research is to explore the potential therapeutic effects of cord blood-derived stem cells in managing Autism Spectrum Disorder (ASD) in children. The study aims to comprehensively assess the safety and efficacy of cord blood-derived stem cell therapy in children diagnosed with ASD, investigate the biological mechanisms by which these stem cells may alleviate symptoms of ASD, compare the outcomes of stem cell therapy with existing ASD treatments, monitor the long-term cognitive, behavioral, and social development outcomes of children receiving stem cell therapy, and examine the ethical implications and regulatory frameworks surrounding the use of stem cells in pediatric populations, particularly those with ASD.

Inclusion Criteria

The study included children aged between 2.5 and 12 years who had a confirmed diagnosis of Autism Spectrum Disorder (ASD) based on the DSM-5 criteria. Both male and female participants were included in the study. Written informed consent was obtained from the parents or legal guardians of all participants.

Exclusion Criteria

Children with significant medical conditions unrelated to Autism Spectrum Disorder (ASD) that could potentially interfere with the study, such as severe congenital anomalies or uncontrolled epilepsy, were excluded. Additionally, those who had previously received any form of stem cell therapy were not included. Children who had participated in another clinical trial within the past three months were also excluded. Furthermore, children with primary or secondary immunodeficiency disorders were not eligible for the study.

Ethical Considerations

The study will be conducted following the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical approval will be obtained from the institutional review board (IRB) before the commencement of the study. Informed consent will be obtained from the parents or legal guardians of all participants.

Material Preparation

The UC-MSCs utilized in this study were isolated from human umbilical cord tissue, sourced from voluntarily donated umbilical cords following normal, healthy births. These births underwent a stringent screening process. Mothers aged 18–35 years old at the time of delivery were given a standard risk assessment questionnaire, and donors were screened for infectious diseases, including HIV (both types 1 and 2), V.D.R.L., Hepatitis B (HBsAg and HB-anti-core/IgG-IgM), cytomegalovirus IgM, Hepatitis A Virus-IgM, Hepatitis C Virus-Ab, Chagas-Ab, Human T-lymphotropic Virus (types 1 and 2), and toxoplasmosis IgM (routinely checked in Panama as part of standard care). The cells used in this study were produced by I.D. Stem Cell Laboratory, a GMP biotechnology laboratory situated in the Krukivschina, Kyiv Region, Kyiv, Ukraine, adhering to good manufacturing and laboratory practices.

Intervention

All participants will undergo a rehabilitation course spanning 3 months to 3 years, depending on individual response and progress.

The intervention protocol is as follows:

1. **Frequency of Injections:** Participants will receive one injection every three months.
2. **Dosage:** Each injection will contain 2 million neuro cells per kilogram of the child's body weight.
3. **Injection Method:** Injections will be administered subcutaneously around the umbilicus.
4. **Neuro Cells:** The neuro cells used in the injections will be derived from cord blood stem cells identified with neuro markers such as Nestin and Vimentin.

Outcome Measures

The primary and secondary outcome measures were assessed at baseline, as well as at 3 months, 6 months, 12 months, and 3 years after the intervention.

The primary outcome measures included safety, evaluated by monitoring the incidence of adverse events related to stem cell therapy, and efficacy, measured by improvements in Autism Spectrum Disorder (ASD) symptoms using the Autism Diagnostic Observation Schedule (ADOS) and the Childhood Autism Rating Scale (CARS).

Secondary outcome measures involved assessing cognitive function through changes in cognitive abilities, using either the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) or the Wechsler Intelligence Scale for Children (WISC), depending on the child's age. Behavioral improvements were evaluated using the Vineland Adaptive Behavior Scales (VABS) and the Aberrant Behavior Checklist (ABC). Additionally, the quality of life was assessed with the Pediatric Quality of Life Inventory (PedsQL).

Data Collection and Analysis

Data Collection: Data was collected at each assessment point (baseline, 3 months, 6 months, 12 months, 3 years) through direct observation, parent/guardian interviews, and standardized assessment tools.

Statistical Analysis: The data were analyzed using IBM SPSS software version 25. The mean, standard deviation, minimum, and maximum values were calculated for MDC and TARC levels, as well as CARS and ATEC scores, at six different

time points: week 1 (T1, baseline), week 14 (T2, second treatment series), week 25 (T3, third treatment series), week 37 (T4, fourth treatment series), week 49 (12-month visit), and week 156 (36-month visit). Missing data were examined to determine if they were missing completely at random using Little's MCAR test. An EM algorithm, with a maximum of 25 iterations, was used to attempt to replace missing values. To assess the therapeutic effect of the treatment, a repeated measures multivariate analysis of variance (MANOVA) was conducted to determine significant changes in mean MDC, TARC, ATEC, and CARS values across the six time points for participants with complete data sets. A significance level of $p < .05$ was used for all analyses.

Sample Size Calculation

Due to the small sample size of 27 participants, the study aimed to detect clinically significant trends rather than achieve statistical significance. The chosen sample size was based on the feasibility of recruiting participants and the need to gather preliminary data on safety and efficacy. This study also focused on evaluating clinically significant symptoms and the overall safety of the treatment.

The primary endpoint of this study was safety, which was assessed at six different time points through various methods. These included thorough psychiatric and medical evaluations, safety laboratory tests (such as complete blood count, metabolic panel, and infectious disease screenings), and monitoring for adverse and serious adverse events, including their potential connection to the study product.

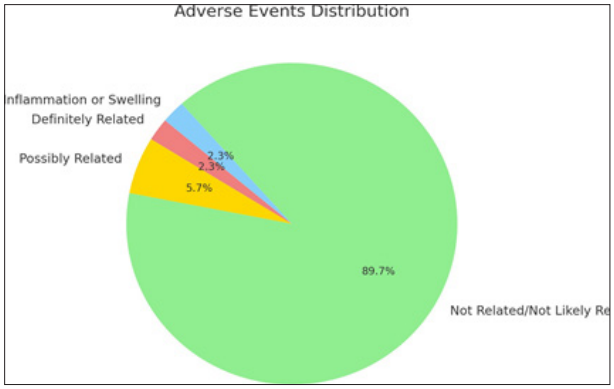
Efficacy signals were evaluated using parent-reported outcomes from the CARS and ATEC tools. Additionally, the study pediatric psychiatrist assessed the subjects' appearance, behavior, mood, speech, and intellectual functioning to complement the parental reports.

Results

Between January 2018 and January 2022, 27 participants of diverse ethnic backgrounds were enrolled in the study. Most of these participants were male, and the average age was 7.5 years. The average baseline scores for the Childhood Autism Rating Scale (CARS) and the Autism Treatment Evaluation Checklist (ATEC) were 38.50 and 62.80, respectively, while the average pretreatment serum levels of MDC and TARC were 950.00 and 210.00, respectively.

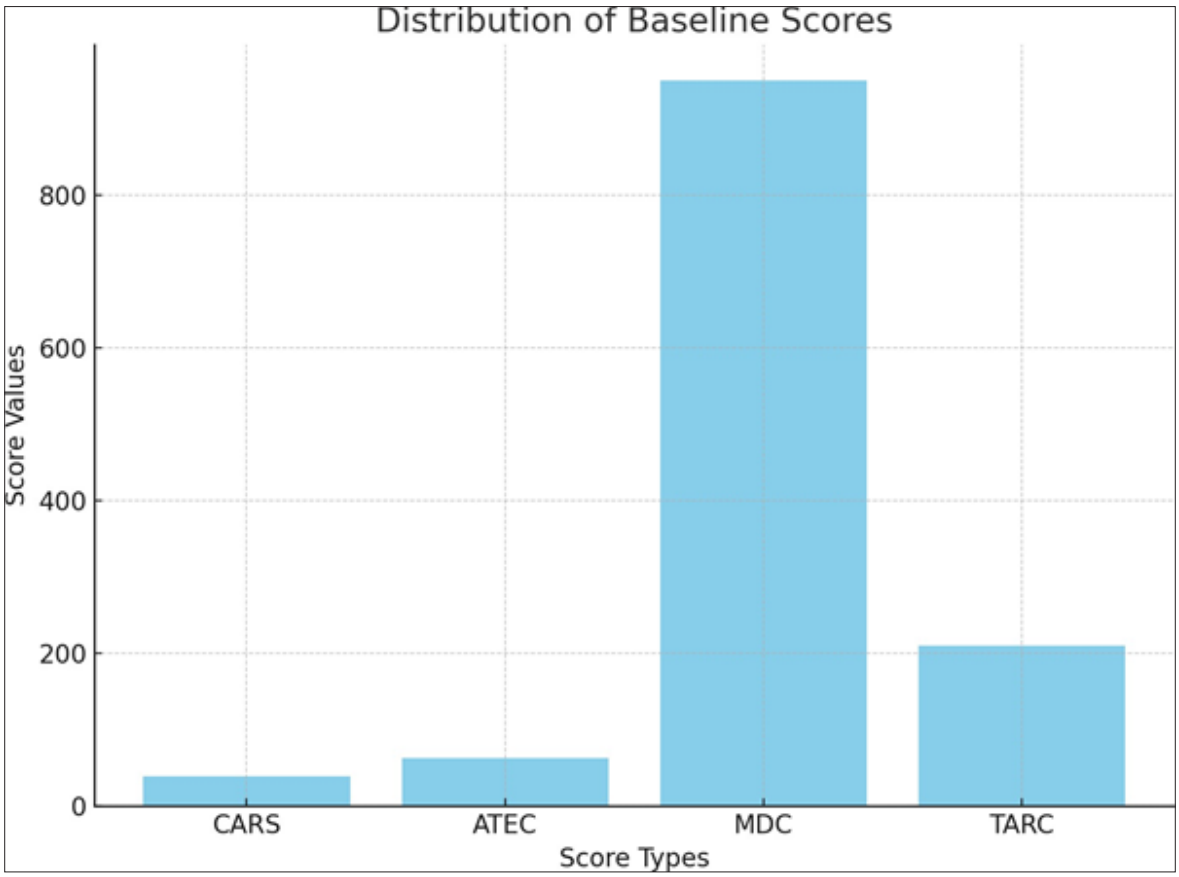
Each participant received a total of 27 million UC-MSCs per treatment session (mean 27.1 million, SD 0.05, coefficient of variation 0.19%, median 27.1, minimum 27.05, maximum 27.15), amounting to a total of 108 million UC-MSCs over the course of the treatment (mean 108.4 million, SD 0.17, coefficient of variation 0.15%, median 108.4, minimum 108.10, maximum
108.80).

Throughout the study, 27 participants were followed up, and no treatment-related serious adverse events (SAEs) were reported. There was one instance of a patient with a history of severe aggression requiring hospitalization due to an aggression crisis. In total, 135 adverse events were recorded across the 324 infusions, with 55 (20.4%) considered related to UC-MSC treatment. Most adverse events (57.8%) were classified as "not related" or "not likely related" to the UC-MSCs. Mild inflammation, swelling, and/or redness at the infusion site were reported by two participants and were deemed "definitely related" to the treatment. Adverse events considered "possibly related" included moderate increases in tics, obsessive-compulsive behaviors, and aggression reported by five participants, as well as mild fatigue, headache, fever, and increased hyperactivity or anxiety. No significant changes in basic hematologic and chemistry laboratory tests were observed throughout the study.



The repeated measures MANOVA ($n = 27$) revealed significant differences in the mean MDC ($p = 0.002$, $\eta p^2 = 0.65$), TARC ($p = 0.004$, $\eta p^2 = 0.68$), ATEC ($p = 0.007$, $\eta p^2 = 0.62$), and CARS ($p < 0.001$, $\eta p^2 = 0.75$) values across the six-time points. MDC levels remained relatively stable from baseline (mean = 950.00; SD = 170.00) to the 6-month point (mean = 952.00; SD = 190.00), but showed a decreasing trend at the 12-month visit (mean = 800.00; SD = 390.00), and then increased again by the 21-month visit (mean = 900.00; SD = 340.00).

Scores for ATEC and CARS followed a decreasing trend throughout the treatment, with the lowest scores observed at the 12-month visit (ATEC: mean = 40.00, SD = 23.00; CARS: mean = 32.00, SD = 9.00). Scores increased at the 21-month visit, reaching levels similar to or lower than those observed before treatment. The most notable decrease in means was observed at the 12-month visit for all efficacy variables (MDC -450.00; TARC -85.00; ATEC -25.00; CARS -7.00) compared to baseline. At this time point, 11 participants (41%) demonstrated improvements in their CARS scores, moving to a lower threshold category for autism symptoms compared to baseline. Among these, seven (63.6%) improved from mild or moderate autism to below the threshold for autism, and four (36.4%) improved from severe autism to below the autism threshold. These participants also showed improvements in the ATEC scale, with seven (63.6%) scoring in the 10% percentile (<30, mild autism). Additionally, seven participants (63.6%) exhibited decreases in MDC and TARC levels at the 12-month visit.



Discussion

The administration of UC-MSCs was found to be safe and well-tolerated by all 27 children participating in this trial, with no serious adverse events directly related to the treatment. The adverse events experienced were generally mild to moderate in intensity and short in duration, typically resolving by the end of each treatment session without the need for medication. Common side effects, such as headaches, fever, and fatigue, were consistent with those reported in other MSC treatments. Some participants exhibited increased tics, aggression, and obsessive-compulsive behaviors, which have been noted in other studies of new ASD treatments, including those involving placebos. This reaction may reflect the sensitivity of this population to new or altered routines. Future research should aim to conduct studies in environments that minimize stressors and potential triggers for ASD patients.

Among the 27 participants, eight demonstrated reductions in CARS and ATEC scores, resulting in changes in their symptom categories. Notably, three participants improved from a severe autism category to below the autism threshold on the CARS at the 12-month visit compared to baseline. Five of these eight participants also experienced decreases in MDC and TARC levels, suggesting a potential link between inflammation and ASD symptoms, as observed in other studies. However, changes in inflammatory markers did not always correlate with treatment response. Regular psychiatric evaluations revealed that those who improved in efficacy measures also showed increased awareness, enhanced social communication (both verbal and expressive), and improved motor skills, although some experienced increased anxiety and emotional instability. Variability in responses among participants suggests the need for further research with more homogeneous subject populations to control for environmental, molecular, or genetic factors.

The study aimed to evaluate the benefits of repeated UC-MSC doses, given that preclinical studies suggest that multiple doses may be more effective than a single dose for various conditions. MSC therapy's effects often diminish between 3 and 6 months post-administration, likely due to the immune-evasive properties of MSCs. Therefore, the study was designed with repeated doses every 12 weeks to maximize potential anti-inflammatory effects. The data indicated that MDC and TARC levels, as well as ATEC and CARS scores, reached their lowest at the 12-month visit, suggesting that the benefits of the last UC-MSC treatment persisted for 3 months. Although MDC, CARS, and ATEC scores increased between the 12- and 21-month visits, they remained below baseline levels. TARC levels notably stayed low between the 12- and 21-month visits. Future studies will focus on TARC and other inflammatory markers to validate these findings.

The study's major limitation was its small sample size, which impacted the statistical power of the analysis. Despite having 27 participants, all completed the study, eliminating issues related to loss to follow-up or withdrawal. The small sample size, however, still affected the effectiveness of sensitivity analyses and MANOVA, which was performed on data from all participants. Additionally, the absence of a placebo group prevents attributing observed improvements solely to the treatment. The use of the original CARS version instead of

the updated CARS-2 also limits the study's findings. Future research should employ larger sample sizes and use CARS-2 to provide standardized and reliable results. Despite these limitations, the study's results suggest potential trends that warrant further investigation in larger, double-blind, placebo-controlled trials.

Conclusion

This study evaluated the safety and efficacy of UC-MSCs in children with Autism Spectrum Disorder (ASD), encompassing 27 participants aged 2.5 to 12 years. The findings indicate that UC-MSC administration was generally safe, with no serious treatment-related adverse events reported. The majority of adverse events were mild and transient, aligning with common side effects observed in other MSC therapies.

Significant improvements were noted in ASD symptoms, with eight participants showing meaningful reductions in Childhood Autism Rating Scale (CARS) and Autism Treatment Evaluation Checklist (ATEC) scores, including shifts from severe autism to below the autism threshold for some. Notable changes were also observed in the levels of inflammatory markers, such as MDC and TARC, which correlate with symptom improvement in some participants, though the relationship was not consistent across all cases.

The repeated dosing regimen, designed to enhance anti-inflammatory effects, appeared to sustain symptom relief for up to 12 months post-treatment, with some parameters returning to near baseline levels by 21 months. These results suggest that repeated UC-MSC administration can offer lasting benefits for managing ASD symptoms.

However, the study's small sample size and the lack of a placebo control limit the ability to fully attribute improvements to the treatment. Future research with larger cohorts and updated diagnostic tools, such as the CARS-2, is needed to confirm these findings and explore the underlying mechanisms further. Additionally, minimizing external stressors and controlling for environmental factors will be crucial in future studies to ensure more accurate assessments of treatment effects.

Overall, this study provides promising evidence for the potential of UC-MSCs as a therapeutic option for ASD, supporting the need for continued investigation into their efficacy and safety in larger, well-controlled trials.

Limitations

- The heterogeneity of ASD symptoms may introduce variability in response to treatment.
- Without a control group, attributing changes directly to the intervention may be challenging, necessitating cautious interpretation of the results.
- Ensuring compliance with follow-up assessments and retaining participants throughout the study duration may be challenging.

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