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Safety and Feasibility of Intravenous Administration of Autologous Stem Cells from Human Exfoliated Deciduous Teeth (SHED) in Children with Cerebral Palsy: A First-in-Human Phase I Clinical Trial

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Additional Declarations: Competing interest reported. The authors declare the following potential conflicts of interest. YS, TK, and SS are named as inventors on a pending patent application related to the stem cell therapy described in this study. The authors have entered into a collaborative research agreement with Kidswell Bio Corporation (currently S-Quatre Corporation). In addition, SN and TI received consulting fees from Kidswell Bio Corporation (currently S-Quatre Corporation). Aside from these disclosures and the funding noted above, the authors declare no other conflicts of interest relevant to this study.

Title Page

Safety and Feasibility of Intravenous Administration of Autologous Stem Cells from Human Exfoliated Deciduous Teeth (SHED) in Children with Cerebral Palsy: A First-in-Human Phase I Clinical Trial

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Abstract

Background

Cerebral palsy (CP), often resulting from perinatal hypoxic-ischemic encephalopathy (HIE), is a lifelong neurological disorder with no curative treatment. Stem cells from human exfoliated deciduous teeth (SHED), derived from the neural crest, have demonstrated therapeutic potential in preclinical CP models, improving motor function even in the chronic phase. We conducted a first-in-human Phase I clinical trial to evaluate the safety and feasibility of autologous SHED therapy in children with CP.

Methods

This single-arm, open-label Phase I trial was conducted at Nagoya University Hospital. Eligible participants were children aged 6–11 years with CP (Gross Motor Function Classification System level II or III) associated with perinatal HIE. Three patients received a single intravenous infusion of autologous SHED at a target dose of 3×10^6 cells/kg. Safety was assessed as the primary outcome (up to 4 weeks) and as a secondary outcome (up to 52 weeks). Exploratory efficacy (motor, neuroimaging, and developmental scales) was evaluated up to 52 weeks.

Results

SHED infusion was well tolerated with no acute reactions or treatment-related adverse

events, and routine laboratory and physiological assessments showed no clinical abnormalities. Exploratory efficacy demonstrated consistent improvements in motor function, with Gross Motor Function Measure-66 scores increasing by a mean of 3.2 points at 12 weeks and showing a sustained upward trajectory across all patients through 52 weeks. The mean Gross Motor Function Measure Evolution Ratio of the enrolled patients during the observation period was 19.73. Brain diffusion MRI revealed localized quantitative anisotropy gains in major white matter tracts. All participants demonstrated gains in raw developmental age and developmental quotient across all the Kyoto Scale of Psychological Development domains. Vineland-II scores also showed modest, consistent improvements aligned with expected developmental trajectories in CP.

Conclusions

This study demonstrated that intravenous autologous SHED administration is safe and feasible in children with chronic CP. The preliminary clinical and structural improvements support further investigation in controlled phase II/III trials.

Trial registration

Japan Registry of Clinical Trials (jRCTb040230042; date of registration: 22nd June 2023))

Keywords

Cerebral Palsy; Stem Cells from Human Exfoliated Deciduous Teeth (SHED); Stem Cell Therapy; Safety; Feasibility; Hypoxic-Ischemic Encephalopathy (HIE)

Background

Over the past few decades, advances in perinatal medicine have led to a remarkable reduction in neonatal mortality worldwide. However, for surviving infants, cerebral palsy (CP) remains a major lifelong challenge, with the birth prevalence at 1 to 3 per 1,000 live births[1-3]. CP is a lifelong neurological disorder with no curative treatment, placing a considerable burden on affected individuals, their families, and healthcare resources[4]. This highlights the urgent need for new therapeutic strategies. One of the main causes of CP is hypoxic-ischemic encephalopathy (HIE), a brain injury resulting from insufficient oxygen and blood flow during the perinatal period[5]. Currently, therapeutic hypothermia is the only established neuroprotective treatment for moderate-to-severe HIE[6]. However, its efficacy is limited, and many affected children still develop neurological sequelae[7].

Stem cell-based therapies have been shown to be feasible and safe in early clinical trials for HIE, including studies of cord blood, cord tissue-derived mesenchymal stromal cells, and multi-lineage differentiating stress enduring cells, with encouraging developmental outcomes[8-10] . However, several important challenges remain to be addressed in stem cell

1 therapy for HIE in the acute/subacute phase. Clinical symptoms of CP often become
2 apparent only in the chronic phase[11], making it difficult to identify appropriate candidates for
3 early intervention. In addition, several recent reports indicate that even infants diagnosed
4 with mild HIE—who are not eligible for early interventions—develop neurological
5 impairments[12, 13]. Therefore, it is necessary to devise novel therapeutic strategies for which
6 efficacy can be demonstrated even after neurological symptoms have become apparent
7 following HIE injury.

8 Although several clinical trials in the chronic stages of perinatal brain injuries have
9 evaluated stem cells derived from bone marrow or umbilical cord and have reported modest
10 improvements[14-17], phase III trials are yet to demonstrate compelling efficacy. This lack of
11 success is presumed to reflect insufficient therapeutic effects and ambiguous mechanisms
12 of action. Consequently, there remains a high medical need for stem-cell products with
13 distinctive neurogenerative properties—differentiated from other existing stem-cell
14 modalities—that can deliver robust efficacy.

15 In this context, we focused on stem cells from human exfoliated deciduous teeth
16 (SHED) as a potential therapeutic option for CP. SHED are mesenchymal stromal cells
17 isolated from the dental pulp of deciduous (primary) teeth and originate from the neural
18 crest[18]. They exert their therapeutic effects predominantly through paracrine mechanisms,

including the release of cytokines, chemokines, growth factors, and extracellular vesicles into the local microenvironment[19]. Through these actions, SHED promote neuroprotection[20], anti-inflammatory effects[21], angiogenesis[22], and endogenous stem cell proliferation and differentiation, with particular relevance to neural tissue repair and regeneration[23-28]. Their therapeutic potential has been demonstrated in several neurological disease models[29-32]. In our previous study using a neonatal HIE model, we demonstrated that early SHED treatment reduces apoptosis, oxidative stress, and microglial activation, leading to improved histological and behavioral outcomes[33]. SHED also inhibit neuronal apoptosis and improve cognitive function in models of chronic cerebral ischemia[34]. Furthermore, our subsequent study showed that SHED treatment improved motor and cognitive function even in the chronic phase after motor symptoms had become apparent in a CP model, promoting neurogenesis via hepatocyte growth factor-mediated phosphoinositide 3-kinase/protein kinase B signaling and exhibiting stronger neurogenic effects than bone marrow-derived mesenchymal stromal cells and dermal fibroblasts[35]. From a translational perspective, SHED has several advantages. Ethical concerns are minimal, as the cells are obtained from naturally discarded deciduous teeth[36], and both autologous and allogeneic transplantation are feasible due to their low immunogenicity and immunomodulatory properties[37]. Taken together, the biological properties, accessibility, and safety profile of SHED underscore their

strong potential as a stem cell source for the treatment of neurological conditions, particularly chronic sequelae of neonatal brain injury such as CP.

Based on the evidence, we conducted an open-label phase I clinical trial to evaluate the safety and efficacy of SHED therapy in children with CP secondary to perinatal HIE. As the first-in-human phase I trial, the aim was to translate the therapeutic potential of SHED into clinical practice. The development of such therapies may improve the quality of life for affected children and their families while also contributing meaningfully to broader societal needs.

Here, we present the results of this phase I clinical trial, including safety, tolerability and exploratory efficacy outcomes assessed up to 52 weeks following SHED therapy in children with CP secondary to perinatal HIE.

Methods

Study Design and Ethics

This single-arm, open-label phase I clinical trial was conducted at Nagoya University Hospital and Mikawa Aoitori Medical and Rehabilitation Center for Developmental Disabilities. The primary aim of this study was to evaluate the safety and feasibility of a single intravenous infusion of autologous SHED in children with CP associated with perinatal HIE. Exploratory

evaluations of long-term efficacy were also conducted. The protocol was approved by the Certified Special Committee for Regenerative Medicine of Nagoya University (Approval No. NA8150011) and registered in the Japan Registry of Clinical Trials (jRCTb040230042). Written informed consent was obtained from the legal guardians of all participants.

Participants

Eligible participants were children aged 6–11 years with a diagnosis of CP classified as level II or III according to the Gross Motor Function Classification System (GMFCS)[38], with a documented history of perinatal HIE. Exclusion criteria included chromosomal abnormalities or major congenital anomalies, severe comorbidities, botulinum toxin treatment within the preceding 6 months, tendon-release surgery within the preceding 12 months, serious active infections or suspected serious active infections; positive serology for HBs antigen, HCV antibody, HIV antibody, HTLV-1 antibody, or syphilis serology; diabetes mellitus; a history of severe allergy or anaphylaxis; significant hepatic or renal dysfunction; and any other condition that, in the judgement of the investigators, would make inclusion in the trial inappropriate.

SHED Collection and Processing

Deciduous teeth were extracted under local anesthesia at an appropriate developmental stage, confirmed via dental radiography at Nagoya University Hospital. SHED were isolated from the pulp tissue and maintained as primary cultures at the Eil Regenerative Medicine Research Center (FA3150012*, Tokyo, Japan). Briefly, the dental pulp was extracted from deciduous teeth using dental files, minced, and then treated with a tissue processing enzyme. Cells were collected by centrifugation and cultured until colonies were confirmed, and then subcultured and cryopreserved as intermediate cell products. The cells were subsequently expanded through two passages and processed to obtain an intravenous formulation at the Rohto Stem Cell Processing Center (FA3190001*, Tokyo, Japan). (*Approval Number for the Specified Cell Processing Facility under the Act on the Safety of Regenerative Medicine in Japan)

SHED identity was confirmed by short tandem repeat analysis. Cells were cultured and expanded according to established mesenchymal stromal cell criteria, including adherence to plastic, expression of characteristic surface markers (positive for CD73, CD90, and CD105, and negative for CD34 and CD45), and multipotent differentiation capacity. A target dose of 3×10^6 cells/kg body weight was suspended in lactated ringer’s solution for intravenous infusion. The final product underwent sterility, endotoxin, and mycoplasma testing.

Intervention

A single intravenous infusion of SHED at a target dose of 3×10^6 cells/kg body weight was administered over approximately 1 hour, with a maximum flow rate of 3.0 mL/min. Heart rate, blood pressure, and oxygen saturation (SpO_2) were measured within 30 minutes before infusion, every 10 minutes (SpO_2: every 5 minutes) during infusion, within 10 minutes after completion, and at 1 hour post-infusion. Respiratory status and chest auscultation were assessed at the same time points, and electrocardiogram and SpO_2 were continuously monitored. Participants were admitted the day before infusion and were discharged on Day 3 following clinical evaluation.

Outcome Measures

The primary outcome was the occurrence of any adverse events within 4 weeks after infusion, assessed during hospitalization on Day 1 and Day 3, and at outpatient follow-up visits at Week 2 and Week 4. Secondary safety outcomes included extended evaluations up to 52 weeks, comprising clinical signs, twelve-lead electrocardiogram, chest X-ray, echocardiogram, and longitudinal laboratory tests. Exploratory efficacy outcomes were comprehensively evaluated at 12, 24, and 52 weeks post-administration. Assessments of motor function included GMFCS, Gross Motor Function Measure-66 (GMFM-66), Modified

Ashworth Scale (MAS), passive joint range of motion, and three-dimensional gait analysis. Additionally, brain MRI—comprising structural and diffusion tensor imaging —and neurodevelopmental assessments were conducted at 24 and 52 weeks post-administration. Due to the nature of the assessments, the evaluators were not blinded to the study conditions and throughout the 52-week observation period, the patient's routine rehabilitation programs and the use of assistive devices or orthoses remained stable without notable modifications.

Motor Function Assessments

Assessments of motor function included GMFCS, GMFM-66, MAS, passive joint range of motion were performed by experienced physical therapists.

Neuroimaging and differential tractography

To characterize longitudinal changes in white matter microstructure following SHED administration, diffusion MRI data were acquired at baseline and at, 24, and 52 weeks. Changes between time points were evaluated using differential tractography to identify relative gains and losses in quantitative anisotropy (QA) exceeding a predefined threshold of 20%. The identified tracts were mapped to a standard tractography atlas, and normalized streamline counts (ncount) were calculated for the corresponding pathways. Detailed acquisition parameters, preprocessing pipelines, and reconstruction settings are provided in the Supplementary Methods.

Cognitive, developmental, and adaptive behavior

Cognitive and developmental function was assessed using the Kyoto Scale of Psychological Development (KSPD)[39], which evaluates developmental age (DA) and provides a developmental quotient (DQ) for the overall domain and for three specific subscales: Postural-Motor (P-M), Cognitive-Adaptive (C-A), and Language-Social (L-S). DA was used as a direct indicator of developmental progress, while DQ provided an age-adjusted complementary measure. DQ was calculated as DA divided by chronological age and multiplied by 100 (DQ = DA/chronological age × 100), making it inherently age-dependent. Adaptive behavior was evaluated using the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II), administered through structured parental interviews to characterize daily functioning across four major domains: Communication, Daily Living Skills, Socialization, and Motor Skills. These assessments were administered by trained and experienced psychologists.

Three-dimensional gait analysis

To longitudinally evaluate gait function and patterns, three-dimensional gait analysis was performed at baseline and at 12, 24, and 52 weeks post-treatment at the Mikawa Aoitori Medical and Rehabilitation Center for Developmental Disabilities. Spatio-temporal parameters—including gait speed, cadence,and step width—were collected together with

kinematic metrics, specifically the Gait Deviation Index (GDI)[40, 41]. All evaluations were performed under standardized testing conditions across all observation time points. Hand grip strength (kg) was measured at baseline, 12, 24, and 52 weeks post-treatment to evaluate upper-limb motor function and overall physical strength in a standardized setting.

A schematic overview of the study design, including the timeline of SHED collection, infusion, and scheduled clinical/laboratory evaluations, is summarized in Figure 1.

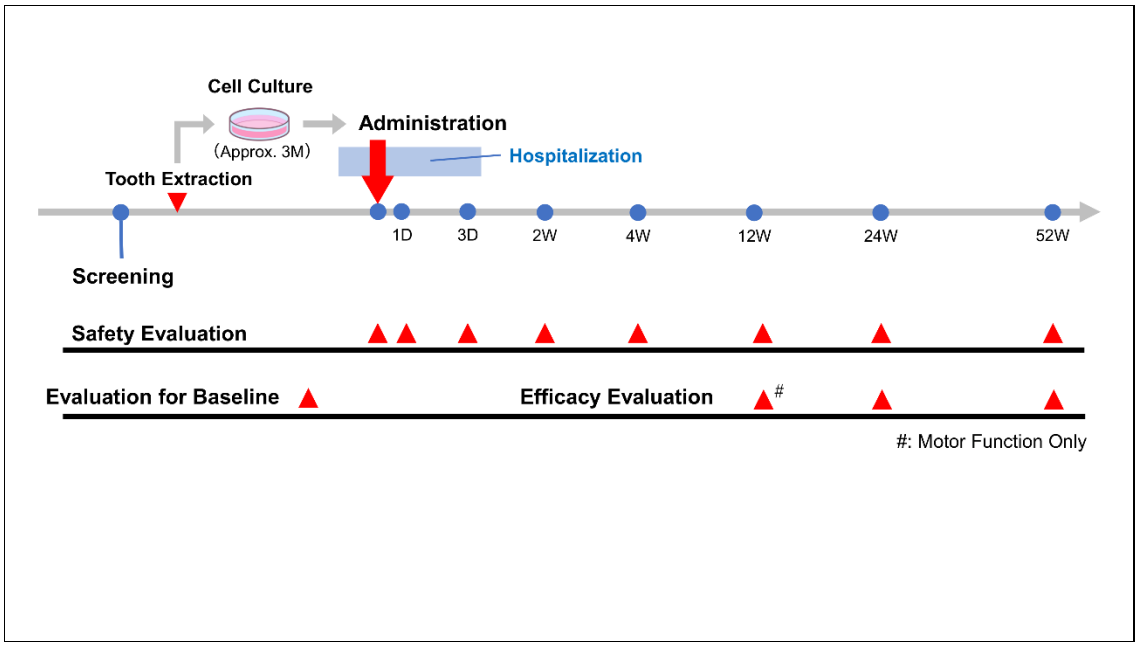


Figure 1. Study design

Schematic overview of the phase I clinical trial. Autologous SHED were obtained after tooth extraction, expanded in culture, and administered intravenously following screening. Safety was monitored continuously throughout the study, with systematic evaluations conducted at

predefined time points, and efficacy evaluations, including motor function assessments, were conducted at baseline, 12 weeks, and continued up to 24 and 52 weeks post-treatment.

Safety Considerations

Throughout the study, participants were closely monitored for infusion-related reactions, infection, embolism, and any other adverse events. All testing was performed in accordance with established protocols. Adverse events were graded according to CTCAE version 5.0, and their causal relationship to SHED administration was assessed by the investigators.

Statistical Analysis

Descriptive statistics were used to summarize demographic characteristics, safety findings, and outcome trends. For exploratory secondary efficacy endpoints, within-subject changes from baseline (pre-administration) to 52 weeks post-administration—including GMFM-66 scores—were evaluated using paired t-tests. In addition, the Gross Motor Function Measure Evolution Ratio (GMFMER) was calculated to contextualize the observed motor-function changes relative to expected natural progression[42]. All data analyses were performed according to the pre-approved statistical analysis plan using SAS version 9.4

(SAS Institute Inc., Cary, NC, USA). Safety outcomes and exploratory secondary efficacy endpoints were evaluated across the entire 52-week follow-up period.

Results

Patient characteristics

Baseline characteristics of the three enrolled patients are summarized in **Table 1**. All three patients had a history of perinatal asphyxia leading to HIE and met the inclusion criteria. Therapeutic hypothermia had been applied in one case. At enrollment, all patients were classified as GMFCS level III.

Table1. Patient Characteristics

	Case 1	Case 2	Case 3
Age (cell administration)	8y1m	6y10m	8y1m
Sex	Male	Female	Male
Gestational Age (w d)	40w6d	38w4d	35w6d
Birth weight (g)	2900	2958	2540
Apgar score 1min	8	0	2
Apgar score 5min	9	0	6
Umbilical cord blood gas pH	7.319	6.897	6.966
Umbilical cord blood gas BE (mmol/L)	-4.0	-20.6	-13.7

Sarnat staging	Unclassified	III	II
Therapeutic hypothermia	Not received	Received	Not received
MRI findings	BGT	W	W
CP subtype	Spastic-dyskinetic	Spastic	Spastic-dyskinetic
GMFCS Level	III	III	III
Epilepsy	+	+	-

BGT, Basal ganglia and thalamic injury; W, Watershed injury; CP subtype, Cerebral palsy subtype; GMFCS, Gross Motor Function Classification System; BE, Base Excess

Safety outcomes

All three patients completed the scheduled SHED infusions. Physiological parameters were monitored during and immediately after the infusion as defined in the protocol. Vital signs, including heart rate, blood pressure, SpO_2, and body temperature, remained stable in all three patients throughout the observation period (Figure 2). No clinically significant changes or acute interventions related to vital signs were required. Throughout the entire 52-week observation period, no serious adverse events or adverse events related to SHED administration were observed. All reported adverse events were Grade 1 or 2 in severity, transient, considered unrelated to SHED administration by the investigators, and resolved without sequelae. Moreover, for the secondary safety outcomes extending from Week 4 up

to Week 52, no delayed cell-related adverse events, chronic toxicities, or no delayed infections considered related to SHED administration occurred. Notably, although urticaria was observed in Case 3 at the end of the study, it was completely resolved within one month thereafter. A comprehensive summary of all adverse events observed over the 52-week study period, regardless of causality, is provided in Table 2.

Representative laboratory parameters, including hematology (WBC, Hb, platelets), renal function (creatinine), inflammatory markers (CRP), coagulation profiles (PT-INR, APTT, fibrinogen), and acid–base balance (pH, $PaCO_2$, base excess [BE]), are summarized in Figure 3. Temporal changes in these parameters remained within the clinically acceptable range during both the acute phase (up to 4 weeks) and the long-term follow-up period (up to 52 weeks), with no consistent abnormal trends. In addition, chest radiographs, twelve-lead electrocardiograms, and echocardiograms performed at predefined time points up to 52 weeks showed no findings suggestive of pulmonary embolism, systemic thrombosis, or cardiac dysfunction. Expanded laboratory data, including LDH, CK, electrolytes, bilirubin, and other coagulation factors, are provided in Supplementary Table 1 [see Additional file]. These data also indicated the absence of any significant abnormalities before or after SHED infusion.

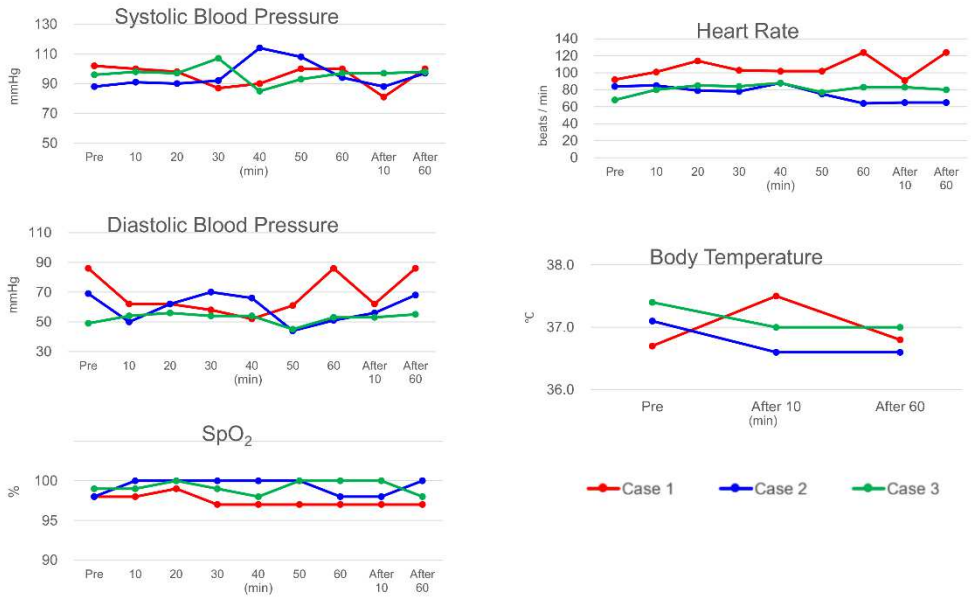


Figure 2. Vital signs during and after SHED infusion

Changes in systolic blood pressure, diastolic blood pressure, heart rate, oxygen saturation (SpO_2), and body temperature are shown for all three patients. The horizontal axis shows time relative to cell administration. Measurements were taken before (Pre), at 10-minute intervals during, and at 10 and 60 minutes after the infusion.

Table 2. Summary of Adverse Events

Case	Adverse Event	Onset Day[1)]	Severity[2)]	Outcome
1	Acute gastroenteritis	Day 17	Grade 1	Recovered
1	Influenza	Day 216	Grade 2	Recovered
1	Nasopharyngitis	Day 241	Grade 2	Recovered

2	Nasopharyngitis	Day 58	Grade 1	Recovered
2	Vomiting	Day 155	Grade 1	Recovered
2	Pyrexia	Day 270<	Grade 1	Recovered
3	Pyrexia	Day 84	Grade 1	Recovered
3	Urticaria	Day 151	Grade 1	Recovered
3	Urticaria	Day 303	Grade 2	Not resolved[3)]

1) Onset day: counted from the day of cell infusion, designated as Day 0

2) Severity was assessed according to the Common Terminology Criteria for Adverse

Events [43]

3) At the completion of the study

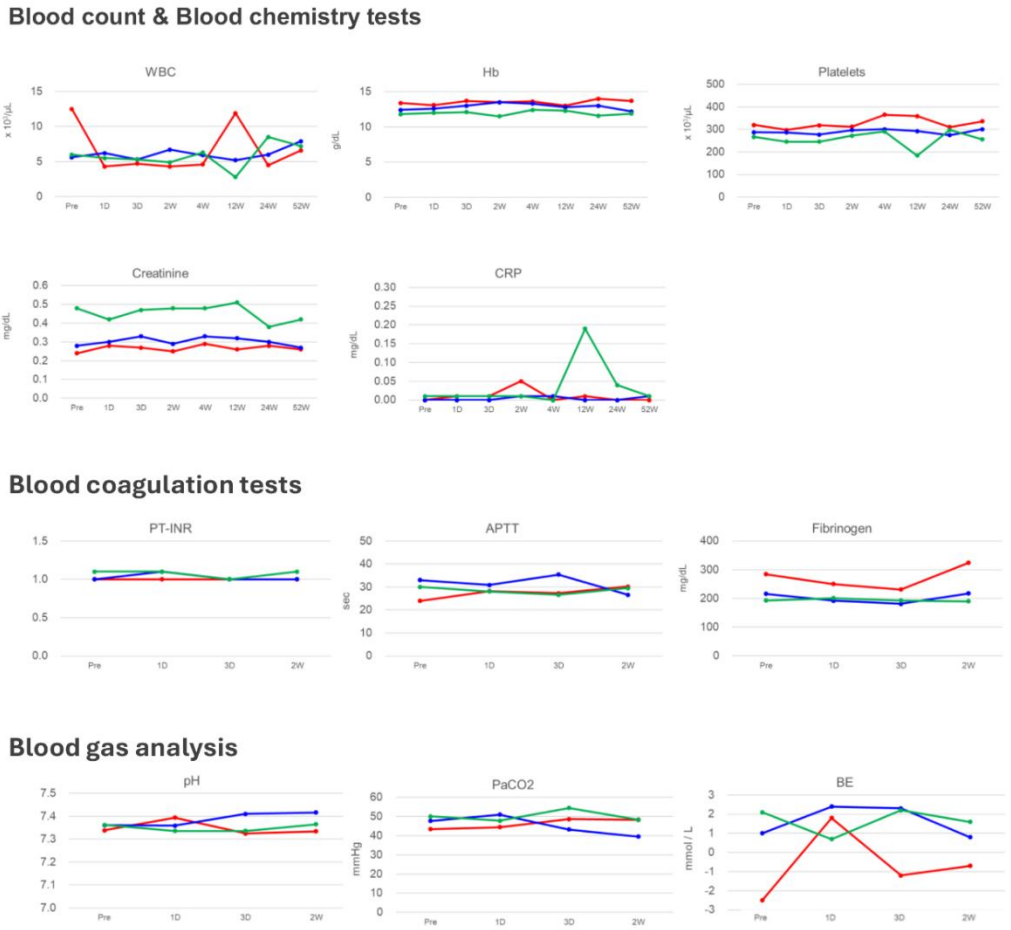


Figure 3. Changes in blood test results before and after SHED infusion

Hematology, biochemistry, coagulation, and blood gas parameters between baseline and post-treatment assessments.

Pre, pre-dose baseline; D, day; W, weeks; BE, Base Excess; WBC, White blood cell; Hb, Hemoglobin; CRP, C-reactive protein; PT-INR, international normalized ratio of prothrombin time; APTT, activated partial thromboplastin time; $PaCO_2$, partial pressure of arterial carbon

dioxide; BE, Base excess

Efficacy outcomes

Motor function and muscle tone

Changes in motor function from baseline up to 52 weeks post-treatment are illustrated in Figure 4. The mean GMFM-66 score improved from 44.7 ± 2.9 [mean ± S.D.] at baseline to 47.9 ± 3.9 at 12 weeks, and this improvement was sustained or further advanced, reaching 48.9 ± 2.6 at 24 weeks and 49.2 ± 2.9 at 52 weeks, demonstrating a statistically significant improvement compared with baseline (paired t-test, $p = 0.017$). Individual GMFM-66 scores from baseline to 12, 24, and 52 weeks changed as follows: Case 1: 45.3, 50.3, 50.3, and 50.9, Case 2: 41.6, 43.4, 45.9, and 45.9, Case 3: 47.3, 50.1, 50.6, and 50.9. During the observation period, the mean GMFMER of the enrolled patients was 19.73. Notably, all three patients demonstrated a consistent upward trajectory in motor function after cell infusion, with no decline observed in any patient from the 12-week assessment through 52 weeks. MAS scores showed joint- and patient-specific changes over 52 weeks, with decreases in muscle tone observed in several assessed movements, particularly knee extension and ankle dorsiflexion, whereas other movements remained unchanged or showed variable changes.

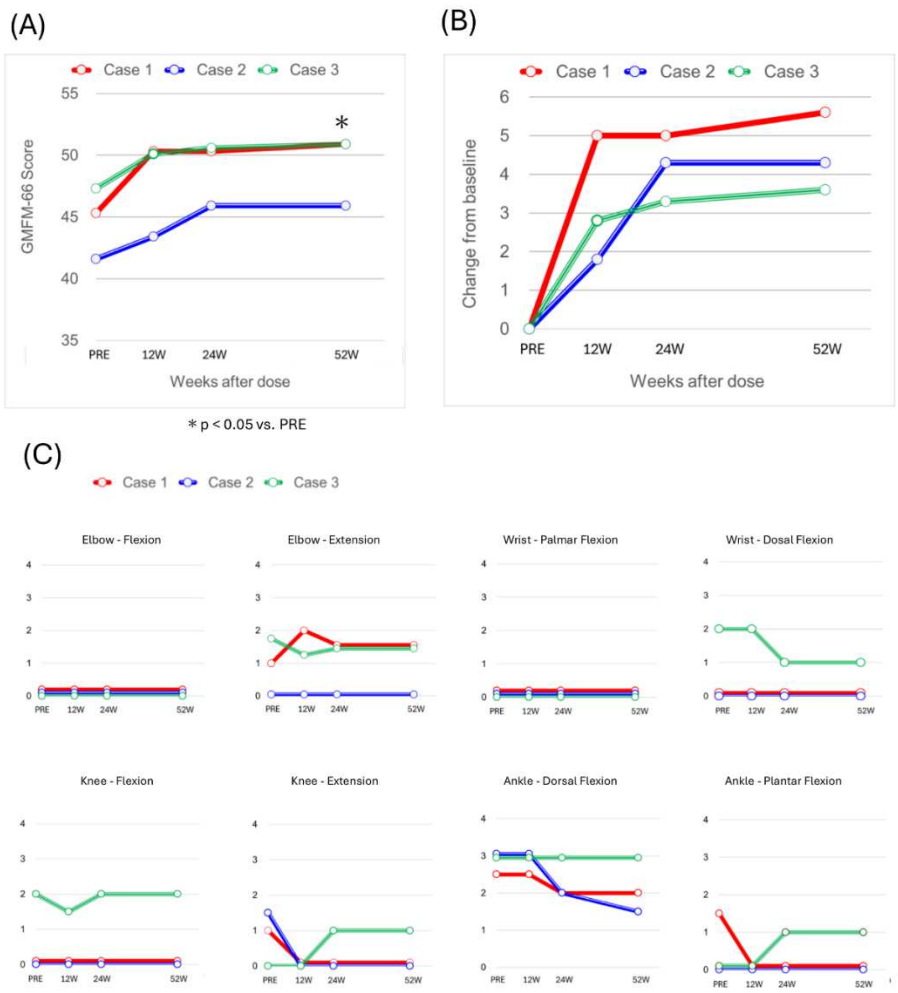


Figure 4. Changes in motor function and muscle tone after SHED infusion

(A) Trajectory of Gross Motor Function Measure-66 scores over time.

(B) Change from baseline in GMFM-66 scores at 12, 24, and 52 weeks post-dose.

Red, blue, and green lines represent Case 1, Case 2, and Case 3, respectively.

(C) Trajectory of Modified Ashworth Scale scores across upper and lower limb joint motions, including Elbow (Flexion/Extension), Wrist (Palmar/Dorsal Flexion), Knee (Flexion/Extension), and Ankle (Dorsal/Plantar Flexion). The X-axis represents follow-up time (weeks), and the Y-axis indicates score values. Modified Ashworth Scale scores were converted to numerical values for calculation (with '1+' treated as 1.5), and the averaged values of the left and right sides are presented.

PRE, pre-dose baseline; W, weeks.

Longitudinal white matter analysis using differential tractography

In Case 1, the 52-week diffusion MRI data were excluded from quantitative differential tractography analysis due to global artifactual elevations in QA values, likely reflecting algorithmic incompatibility during Q-space diffeomorphic reconstruction rather than poor raw image quality. At 24 weeks, only subtle, localized QA increases relative to baseline were observed within cerebellar tracts.

Case 2 demonstrated a mild QA decrease from baseline to 24 weeks in localized frontal white matter tracts. However, from 24 to 52 weeks, this pattern reversed, with net QA gains emerging across multiple regions. When comparing baseline to 52 weeks, substantial net QA gains were identified in major long-range tracts, primarily localized to the body and splenium of the corpus callosum, the right arcuate fasciculus, and the right cingulum (Figure 5a, b).

Additional minor or fragmented tracts exhibited partial QA variations across other regions (Supplementary Table 2). In Case 3, QA changes were minimal from baseline to 24 weeks. From 24 to 52 weeks, QA values demonstrated a steady increase, ultimately resulting in the distinct QA gains from baseline to 52 weeks centered on the genu and anterior body of the corpus callosum and the right cingulum (Figure 5c, d). As in Case 2, several minor tracts exhibited localized partial QA alterations (Supplementary Table 2).

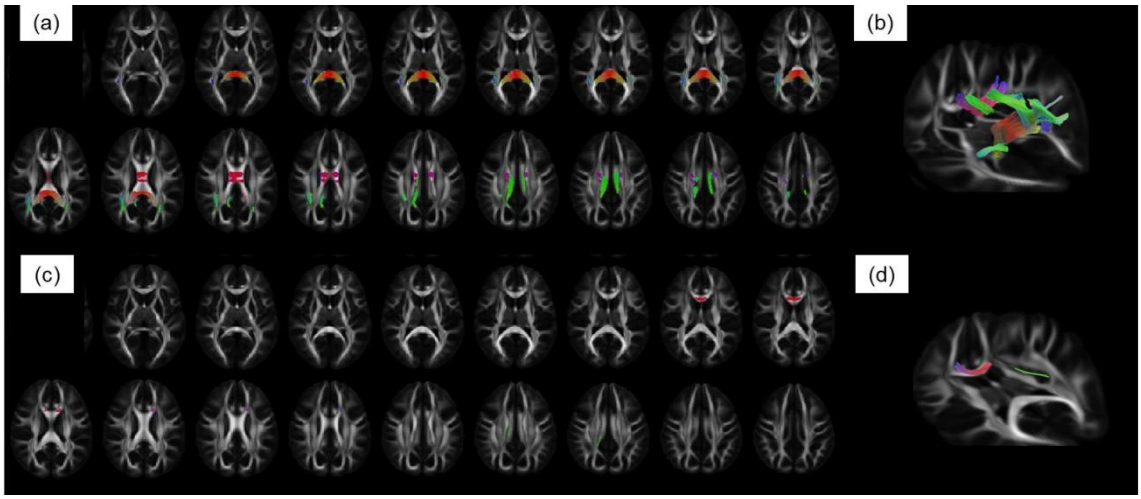


Figure 5. Quantitative anisotropy gains detected by differential tractography from baseline to 52 weeks in Cases 2 and 3

(a, b) Case 2: Axial slices (a) and 3D tractography rendering (b) demonstrating substantial net QA gains localized predominantly to the body and splenium of the corpus callosum (red/orange), the right arcuate fasciculus (blue/cyan), and the right cingulum (green/purple).

(c, d) Case 3: Axial slices (c) and 3D tractography rendering (d) demonstrating localized QA gains centered on the genu and anterior body of the corpus callosum (red/pink) and the right cingulum (green).

QA, quantitative anisotropy; 3D, three-dimensional.

Neurodevelopmental and Adaptive Behavioral Scales

Both raw DA and DQ from the KSPD increased across all three participants over the 52 week observation period. DA increased across postural-motor, cognitive-adaptive, and language-social domains in all three cases. Case 1 demonstrated the most robust improvement, with DA increases across all domains accompanied by an increase in overall DQ from 22 to 25. Case 2 showed DA gains in postural-motor and cognitive-adaptive domains, with a modest increase in overall DQ (7 to 8). Case 3 exhibited DA increases in postural-motor and cognitive-adaptive domains, while language-social DA remained stable; overall DQ increased from 11 to 13 (Table 3)

Vineland-II Adaptive Behavior Composite (ABC) scores also improved in all participants. Case 1 increased from 37 to 42 (+5 points), Case 2 from 24 to 25 (+1 point), and Case 3 from 22 to 26 (+4 points) (Table 3).

Table 3. Longitudinal Developmental and Adaptive Behavior Assessment Scores

	Case 1			Case 2			Case 3		
	Pre	**Post 24W**	**Post 52W**	**Pre**	**Post 24W**	**Post 52W**	**Pre**	**Post 24W**	**Post 52W**
Kyoto Scale of Psychological Development DA (months) [DQ]									
Overall	21 [22]	23 [23]	27 [25]	6 [7]	8 [9]	8 [8]	11 [11]	13 [13]	14 [13]
Postural-Motor	9 [9]	9 [9]	11 [10]	7 [9]	10 [11]	11 [12]	10 [11]	13 [13]	14 [12]
Cognitive-Adaptive	18 [19]	18 [18]	21 [19]	4 [5]	7 [8]	6 [7]	11 [11]	13 [13]	15 [13]
Language-Social	31 [33]	37 [36]	40 [37]	7 [9]	8 [9]	8 [8]	11 [12]	11 [11]	11 [10]
Vineland Adaptive Behavior Scales, Second Edition (Vineland-II)									
Adaptive Behavior Composite	37	38	42	24	25	25	22	26	26

Pre, pre-dose baseline; W, weeks; DA, Developmental Age (months); DQ, Development Quotient.

Three-dimensional gait analysis and physical function

Three-dimensional gait analysis was performed to evaluate longitudinal changes in gait function and patterns at baseline, 12 weeks, 24 weeks, and 52 weeks post-treatment. Quantitative evaluation was not feasible for Case 1 and Case 2 because of generalized athetosis and variability in testing conditions prevented acquisition of standardized, reproducible gait-cycle data. In Case 3, the GDI remained largely stable throughout the

observation period, showing no major fluctuations. Regarding spatio-temporal parameters, a markedly elevated cadence observed at baseline (approximately 162 steps/min) decreased to approximately 142 steps/min at 52 weeks, demonstrating a shift toward a near-normal gait pattern. Detailed quantitative data for all spatio-temporal parameters across all time points, including GDI, gait speed, cadence, and stride length, are provided in Supplementary Table 3.

Grip strength

Hand grip strength increased from baseline to 52 weeks in all three cases, although transient decreases were observed at 12 weeks in Cases 1 and 2. From baseline to 52 weeks, grip strength increased from 1.50 kg to 3.00 kg in Case 1, from 0.25 kg to 0.75 kg in Case 2, and from 1.25 kg to 3.50 kg in Case 3 (Figure 6).

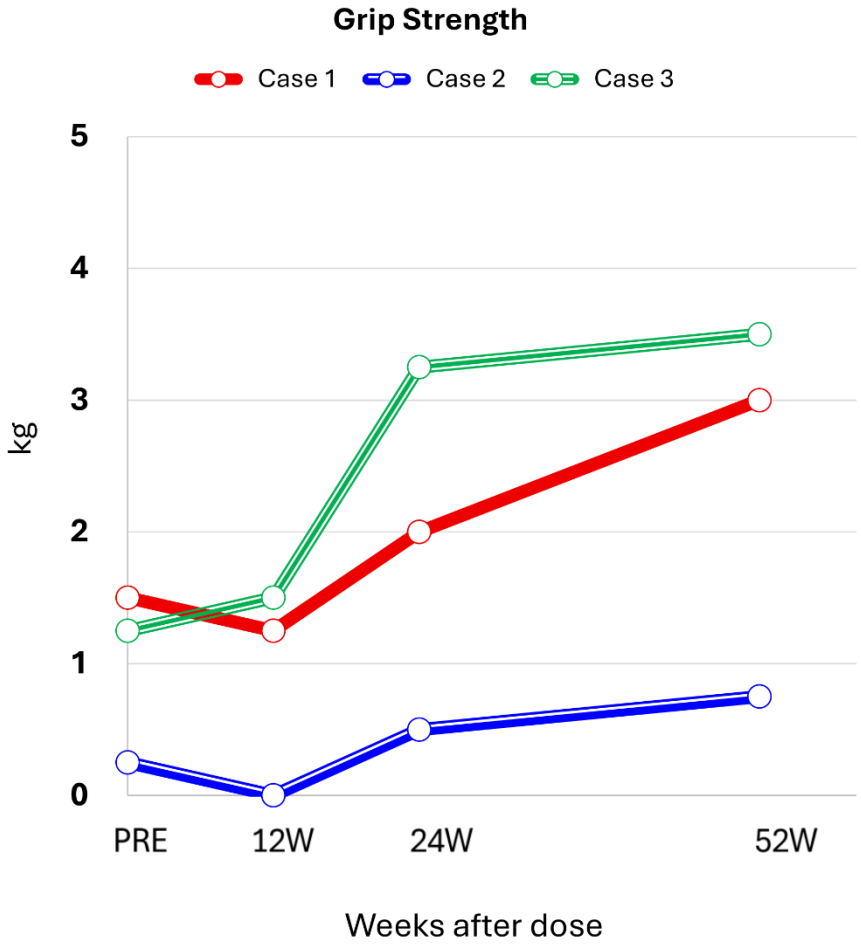


Figure 6. Longitudinal change from baseline in hand grip strength

Changes in hand grip strength (kg) over time at 12, 24, and 52 weeks post-dose

Red, blue, and green lines represent Case 1, Case 2, and Case 3, respectively.

PRE, pre-dose baseline; W, weeks.

Discussion

This first-in-human phase I trial investigated the long-term safety and clinical feasibility of intravenous autologous SHED administration in children with CP secondary to perinatal HIE, with exploratory efficacy outcomes, including motor function, assessed over a 52-week period.

All three patients completed the scheduled SHED infusion, and no adverse events considered related to SHED administration were observed throughout the 52-week follow-up period. Exploratory assessments demonstrated increases in GMFM-66 scores and changes in selected neuroimaging parameters, whereas neurodevelopmental scores were maintained or increased. Overall, these findings support the long-term safety and clinical feasibility of intravenous autologous SHED administration and warrant further investigation of its potential efficacy.

The primary aim of this phase I study was to evaluate the safety and feasibility of intravenous administration of autologous SHED in children with CP caused by perinatal HIE. No acute infusion reactions or serious adverse events such as embolism were observed. Laboratory tests, electrocardiography, and chest X-ray studies revealed no clinically significant abnormalities, and no changes in physiological parameters were detected either during or immediately after infusion. These results are consistent with prior stem-cells trials in neonatal brain injury and CP, in which autologous umbilical cord blood or

bone-marrow-derived mesenchymal stromal cells demonstrated favorable safety profiles. For example, Cotten et al. reported no infusion-related serious adverse events following intravenous autologous cord-blood infusion in neonates with HIE[8], and Sun et al. similarly observed no significant safety concerns with umbilical cord blood stem cells in infants with CP[17]. These studies collectively suggest that cell-based therapies for brain injury are under appropriate protocol. Moreover, adverse events previously reported with approved mesenchymal stromal cell products were not observed in our study. For example, Temcell® HS Inj. (allogeneic bone marrow–derived mesenchymal stem cells) for acute graft-versus-host disease has been associated with hematologic and hepatic disorders (e.g., thrombocytopenia, liver dysfunction, leukopenia), as well as serious adverse events such as anaphylaxis and severe infections[44]. Importantly, none of these adverse events emerged following SHED administration in this trial.

Preliminary but clinically meaningful improvements in gross motor function were observed during the 52-week follow-up period. The minimum clinically important difference for GMFM-66 has been reported to be approximately 1–2 points[45], and all three patients exceeded this threshold with an average increase of 4.5 points. Their mean GMFMER was 19.73, substantially surpassing values reported for recognized treatments, including stem cell therapy (6.0 ± 5.9), selective dorsal rhizotomy (6.5 ± 2.0), hippotherapy (13.3 ± 0.6),

and botulinum toxin treatment (5.0 ± 2.9)[46]. The findings in our cohort suggest a potentially greater magnitude of improvement in GMFMER than previously documented. Importantly, these clinically meaningful improvements in GMFM-66 scores were sustained or progressively enhanced up to 52 weeks post-infusion, diverging from the natural plateau typically observed in the chronic phase of CP[47].

The longitudinal changes in the single evaluable case (Case 3) suggest a stabilization of the gait pattern, primarily characterized by the normalization of cadence, rather than a marked improvement in overall kinematic deviation. At 52 weeks, although the GDI remained largely unchanged bilaterally without significant improvement, the abnormally high cadence observed pre-treatment decreased toward the normal range. This shift may reflect adaptation toward a calmer, dynamically stable gait pattern without excessive effort. However, these findings must be interpreted with extreme caution. Because quantitative data were obtained from only a single patient, it is difficult to definitively distinguish the potential effects of the intervention from natural developmental adaptations, habituation to the testing environment, or spontaneous variability.

Exploratory neuroimaging findings revealed localized increases in QA values along major white-matter pathways, specifically the body and splenium of the corpus callosum, cingulum, and arcuate fasciculus. Because these pathways are involved in motor control,

sensorimotor integration, and cognitive networks, their reinforced structural connectivity suggests that intravenous SHED administration may facilitate neural tissue repair and structural remodeling. Although these neuroimaging findings do not definitively prove causality, they offer valuable structural insights that align with observed clinical improvements. These exploratory findings are consistent with preclinical evidence showing that SHED administration ameliorates motor, memory, and learning impairments in animal models of CP[35]. Mechanistically, SHED exert paracrine effects through neurotrophic factors such as hepatocyte growth factor, activating endogenous neural stem cells and promoting neurogenesis. Furthermore, in vitro studies demonstrate that SHED possess stronger neurogenic potential than other stem cells, suggesting potential therapeutic advantages for CP[35]. By using QA values to minimize the confounding effects of crossing fibers, this analysis suggests a potential correlation between reinforced structural connectivity in the brain and clinical motor improvements.

In addition to motor and neuroimaging changes, all three participants demonstrated increases in raw DA, indicating consistent multi domain developmental gains. Although numerical changes in DQ were modest, this is expected in school-aged children, where increases in DA produce only small shifts in DQ because the chronological-age denominator is large; nevertheless, DQ remained stable or increased in parallel with DA

across all cases, might indicating meaningful developmental progression. Vineland-II Composite scores also maintained or showed modest numerical increases. These gains were small but consistent and broadly comparable to the gradual year-on-year developmental trajectories typically observed in children with CP and intellectual disability[48, 49]. Taken together, these findings suggest maintenance of functional abilities with possible modest enhancement following SHED administration.

From a translational perspective, SHED were administered to preclinical models using rats at 5 weeks of age, which corresponds to the preadolescent stage in humans[50] and aligns with the age of the participants in this study. In addition, SHED were obtained from deciduous teeth collected at an appropriate developmental stage, offering a practical and ethically acceptable source of autologous cells for pediatric patients.

Previous clinical studies in CP using umbilical cord blood or bone marrow-derived mesenchymal stromal cells have been limited by heterogeneous stem cell sources and diverse delivery routes[51], making it difficult to draw definitive conclusions regarding the therapeutic effects of each specific cell type. To the best of our knowledge, this study represents the first clinical application of stem cell therapy in children with CP that is directly guided by preclinical evidence demonstrating both therapeutic efficacy and

underlying mechanisms. This approach may help establish a foundation for future Phase II/III trials and ultimately support regulatory approval of this form of treatment.

This study has several limitations, including the small sample size, single-arm open-label design, absence of a control group, and the inability to distinguish potential treatment effects from natural development, ongoing rehabilitation, and repeated assessment effects. In addition, the neuroimaging analyses were exploratory and technically limited in one participant. Therefore, all efficacy findings should be interpreted as preliminary and hypothesis-generating.

Conclusion

In conclusion, this analysis demonstrated that a single intravenous infusion of autologous SHED was safe, clinically feasible, and associated with long-term improvements in motor function, and white matter microstructural integrity in children with established CP. These phase I find a robust clinical and structural foundation for proceeding to larger, controlled phase II/III clinical trials.

List of abbreviations

CP: Cerebral palsy; DQ: Developmental quotient; DWI: Diffusion-weighted imaging; GDI: Gait Deviation Index; GMFCS: Gross Motor Function Classification System; GMFM-66: Gross Motor Function Measure-66; GMFMER: Gross Motor Function Measure Evolution Ratio; HIE: Hypoxic-ischemic encephalopathy; KSPD: Kyoto Scale of Psychological Development; MAS: Modified Ashworth Scale; ncount: Normalized streamline counts; QA: Quantitative anisotropy; SHED: Stem cells from human exfoliated deciduous teeth; Vineland-II: Vineland Adaptive Behavior Scales, Second Edition

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and received approval for the protocol titled “A clinical trial to evaluate the safety and tolerability of stem cells from human exfoliated deciduous teeth in children with cerebral palsy” (date of approval: 15th June 2023) from the Certified Special Committee for Regenerative Medicine of Nagoya University (Approval No. NA8150011). The study was registered in the Japan Registry of Clinical Trials (jRCTb040230042). Written informed consent was obtained from the legal guardians of all participants prior to enrollment.

Consent for publication

Written informed consent for publication of study data was obtained from all participants.

Availability of data and materials

All data supporting the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare the following potential conflicts of interest. YS, TK, and SS are named as inventors on a pending patent application related to the stem cell therapy described in this study. The authors have entered into a collaborative research agreement with Kidswell Bio Corporation (currently S-Quatre Corporation). In addition, SN and TI received consulting fees from Kidswell Bio Corporation (currently S-Quatre Corporation). Aside from these disclosures and the funding noted above, the authors declare no other conflicts of interest relevant to this study.

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corporate reorganization on April 1, 2024, the Cell Therapy Division was transferred to S-Quatre Corporation, which has served as the funding source since that time. The sponsor provided protocols of SHED processing and oversaw product manufacturing but had no role in the design, conduct, analysis, or reporting of the study.

Authors' contributions

T.K., S.S., and Y.S. conceptualized and designed the study, and T.K. and Y.S. were responsible for patient recruitment. M.K., H.K., J.N., T.S., R.M., R.T., A.T., K.U., Y.T. and Y.M. were involved in data collection and critically revised the manuscript for important intellectual content. KS and HH performed the dental procedures, including tooth extraction and SHED collection. T.Mo., Y.F., S.N., T.I., and S.K. contributed to the physical therapy evaluations and 3D gait analysis. F.K. and S.S. were responsible for study monitoring, statistical analysis, and data validation. T.Ma. and T.K. performed the final data analysis and drafted the manuscript. Y.S. supervised the entire project, secured funding, and gave the manuscript final approval. All authors read and approved the final manuscript.

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References

1. Touyama M, Touyama J, Toyokawa S, Kobayashi Y. Trends in the prevalence of cerebral palsy in children born between 1988 and 2007 in Okinawa, Japan. Brain Dev. 2016;38:792-799.

2. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum Dev. 2010;86:329-338.

3. McIntyre S, Goldsmith S, Webb A, Ehlinger V, Hollung SJ, McConnell K, et al. Global prevalence of cerebral palsy: A systematic analysis. Developmental medicine and child neurology. 2022;64:1494-1506.

4. Liu F, Shen Q, Huang M, Zhou H. Factors associated with caregiver burden among family caregivers of children with cerebral palsy: a systematic review. BMJ Open. 2023;13:e065215.

5. Reid SM, Meehan E, McIntyre S, Goldsmith S, Badawi N, Reddihough DS. Temporal trends in cerebral palsy by impairment severity and birth gestation. Developmental medicine and child neurology. 2016;58 Suppl 2:25-35.

6. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. The New England journal of medicine. 2005;353:1574-1584.

7. Gunn AJ, Thoresen M. Hypothermic neuroprotection. NeuroRx. 2006;3:154-169.

8. Cotten CM, Murtha AP, Goldberg RN, Grotegut CA, Smith PB, Goldstein RF, et al. Feasibility of autologous cord blood cells for infants with hypoxic-ischemic encephalopathy. J Pediatr. 2014;164:973-979 e971.

9. Tsuji M, Sawada M, Watabe S, Sano H, Kanai M, Tanaka E, et al. Autologous cord blood cell therapy for neonatal hypoxic-ischaemic encephalopathy: a pilot study for feasibility and safety. Sci Rep. 2020;10:4603.

10. Sato Y, Shimizu S, Ueda K, Suzuki T, Suzuki S, Miura R, et al. Safety and tolerability of a Muse cell-based product in neonatal hypoxic-ischemic encephalopathy with therapeutic hypothermia (SHIELD trial). Stem Cells Transl Med. 2024;13:1053-1066.

11. Novak I, Morgan C, Adde L, Blackman J, Boyd RN, Brunstrom-Hernandez J, et al. Early, Accurate Diagnosis and Early Intervention in Cerebral Palsy: Advances in Diagnosis and Treatment. JAMA Pediatr. 2017;171:897-907.

12. Reiss J, Sinha M, Gold J, Bykowski J, Lawrence SM. Outcomes of Infants with Mild Hypoxic Ischemic Encephalopathy Who Did Not Receive Therapeutic Hypothermia. Biomedicine hub. 2019;4:1-9.

13. Falsaperla R, Sciuto S, Gioè D, Sciuto L, Pisani F, Pavone P, et al. Mild Hypoxic-Ischemic Encephalopathy: Can Neurophysiological Monitoring Predict Unfavorable Neurological Outcome? A Systematic Review and Meta-analysis. Am J Perinatol. 2023;40:833-838.

14. Bennet L, Tan S, Van den Heuij L, Derrick M, Groenendaal F, van Bel F, et al. Cell therapy for neonatal hypoxia-ischemia and cerebral palsy. Ann Neurol. 2012;71:589-600.

15. Kiasatdolatabadi A, Lotfibakhshaiesh N, Yazdankhah M, Ebrahimi-Barough S, Jafarabadi M, Ai A, et al. The Role of Stem Cells in the Treatment of Cerebral Palsy: a Review. Mol Neurobiol. 2017;54:4963-4972.

16. Xiao QX, Geng MJ, Sun YF, Pi Y, Xiong LL. Stem Cell Therapy in Neonatal Hypoxic-Ischemic Encephalopathy and Cerebral Palsy: a Bibliometric Analysis and New Strategy. Mol Neurobiol. 2023.

17. Sun JM, Song AW, Case LE, Mikati MA, Gustafson KE, Simmons R, et al. Effect of Autologous Cord Blood Infusion on Motor Function and Brain Connectivity in Young Children with Cerebral Palsy: A Randomized, Placebo-Controlled Trial. Stem Cells Transl Med. 2017;6:2071-2078.

18. Miura M, Gronthos S, Zhao M, Lu B, Fisher LW, Robey PG, et al. SHED: stem cells from human exfoliated deciduous teeth. Proc Natl Acad Sci U S A. 2003;100:5807-5812.

19. Mohd Nor NH, Mansor NI, Mohd Kashim MIA, Mokhtar MH, Mohd Hatta FA. From Teeth to Therapy: A Review of Therapeutic Potential within the Secretome of Stem Cells from Human Exfoliated Deciduous Teeth. Int J Mol Sci. 2023;24.

20. Ueda T, Ito T, Inden M, Kurita H, Yamamoto A, Hozumi I. Stem Cells From Human

Exfoliated Deciduous Teeth-Conditioned Medium (SHED-CM) is a Promising Treatment for Amyotrophic Lateral Sclerosis. Frontiers in pharmacology. 2022;13:805379.

21. Fallah A, Hosseinzadeh Colagar A, Khosravi A, Mohammad-Hasani A, Saeidi M. The role of natural exosomes from SHED-MSC in immunoregulation of M0/M1 polarized macrophage cells. Front Immunol. 2025;16:1550280.

22. Rikitake K, Kunimatsu R, Yoshimi Y, Tanimoto K. Investigation of Angiogenic Potential in CD146-Positive Stem Cells Derived from Human Exfoliated Deciduous Teeth. Int J Mol Sci. 2025;26.

23. Bar JK, Lis-Nawara A, Grelewski PG. Dental Pulp Stem Cell-Derived Secretome and Its Regenerative Potential. Int J Mol Sci. 2021;22.

24. Shu Y, Otake M, Seta Y, Hori K, Kuramochi A, Ohba Y, et al. Activation of cellular antioxidative stress and migration activities by purified components from immortalized stem cells from human exfoliated deciduous teeth. Sci Rep. 2024;14:15340.

25. Vu HT, Han MR, Lee JH, Kim JS, Shin JS, Yoon JY, et al. Investigating the Effects of Conditioned Media from Stem Cells of Human Exfoliated Deciduous Teeth on Dental Pulp Stem Cells. Biomedicines. 2022;10.

26. Soheilifar MH, Nobari S, Hakimi M, Adel B, Masoudi-Khoram N, Reyhani E, et al. Current concepts of microRNA-mediated regulatory mechanisms in human pulp tissue-derived

stem cells: a snapshot in the regenerative dentistry. Cell Tissue Res. 2023;393:229-251.

27. Candelise N, Santilli F, Fabrizi J, Caissutti D, Spinello Z, Moliterni C, et al. The Importance of Stem Cells Isolated from Human Dental Pulp and Exfoliated Deciduous Teeth as Therapeutic Approach in Nervous System Pathologies. Cells. 2023;12.

28. Shi X, Mao J, Liu Y. Pulp stem cells derived from human permanent and deciduous teeth: Biological characteristics and therapeutic applications. Stem Cells Transl Med. 2020;9:445-464.

29. Chen YR, Lai PL, Chien Y, Lee PH, Lai YH, Ma HI, et al. Improvement of Impaired Motor Functions by Human Dental Exfoliated Deciduous Teeth Stem Cell-Derived Factors in a Rat Model of Parkinson's Disease. International journal of molecular sciences. 2020;21.

30. Guo W, Zeng Z, Xing C, Zhang J, Bi W, Yang J, et al. Stem cells from human exfoliated deciduous teeth affect mitochondria and reverse cognitive decline in a senescence-accelerated mouse prone 8 model. Cytotherapy. 2022;24:59-71.

31. Zhang X, Lei T, Wang D, Cai S, Hang Z, Yang Y, et al. Stem cells from human exfoliated deciduous teeth relieves Alzheimer's disease symptoms in SAMP8 mice by up-regulating the PPARγ pathway. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2022;152:113169.

32. Xiao Z, Lei T, Liu Y, Yang Y, Bi W, Du H. The potential therapy with dental tissue-derived

mesenchymal stem cells in Parkinson's disease. Stem cell research & therapy. 2021;12:5.

33. Kitase Y, Sato Y, Ueda K, Suzuki T, Mikrogeorgiou A, Sugiyama Y, et al. A Novel Treatment with Stem Cells from Human Exfoliated Deciduous Teeth for Hypoxic-Ischemic Encephalopathy in Neonatal Rats. Stem Cells Dev. 2020;29:63-74.

34. Zhu S, Min D, Zeng J, Ju Y, Liu Y, Chen X. Transplantation of Stem Cells from Human Exfoliated Deciduous Teeth Decreases Cognitive Impairment from Chronic Cerebral Ischemia by Reducing Neuronal Apoptosis in Rats. Stem Cells Int. 2020;2020:6393075.

35. Kanzawa T, Onoda A, Okamoto A, Yue X, Shimode R, Takamoto Y, et al. Novel stem cell therapy for cerebral palsy using stem cells from human exfoliated deciduous teeth. Stem cell research & therapy. 2026;17:44.

36. Martinez Saez D, Sasaki RT, Neves AD, da Silva MC. Stem Cells from Human Exfoliated Deciduous Teeth: A Growing Literature. Cells Tissues Organs. 2016;202:269-280.

37. Li Z, Jiang CM, An S, Cheng Q, Huang YF, Wang YT, et al. Immunomodulatory properties of dental tissue-derived mesenchymal stem cells. Oral Dis. 2014;20:25-34.

38. Piscitelli D, Ferrarello F, Ugolini A, Verola S, Pellicciari L. Measurement properties of the Gross Motor Function Classification System, Gross Motor Function Classification System-Expanded & Revised, Manual Ability Classification System, and Communication Function Classification System in cerebral palsy: a systematic review with meta-analysis. Developmental

medicine and child neurology. 2021;63:1251-1261.

39. Society for the Kyoto Scale of Psychological Development Test. Shinpan K Shiki Hattatsu Kensahou 2001 Nenban.[The Kyoto Scale of Psychological Development Test 2001]. . Nakanishiya Shuppan. 2008.

40. Schwartz MH, Rozumalski A. The Gait Deviation Index: a new comprehensive index of gait pathology. Gait & posture. 2008;28:351-357.

41. Ito T, Noritake K, Ito Y, Tomita H, Mizusawa J, Sugiura H, et al. Three-dimensional gait analysis of lower extremity gait parameters in Japanese children aged 6 to 12 years. Scientific reports. 2022;12:7822.

42. Marois P, Marois M, Pouliot-Laforte A, Vanasse M, Lambert J, Ballaz L. Gross Motor Function Measure Evolution Ratio: Use as a Control for Natural Progression in Cerebral Palsy. Archives of physical medicine and rehabilitation. 2016;97:807-814.e802.

43. Institute NC. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 2017.

44. (PMDA) PaMDA. Report on the Deliberation Results. PMDA, Medical Device and Regenerative Medicine Product Evaluation Division; 2015.

45. Oeffinger D, Bagley A, Rogers S, Gorton G, Kryscio R, Abel M, et al. Outcome tools used for ambulatory children with cerebral palsy: responsiveness and minimum clinically

important differences. Developmental medicine and child neurology. 2008;50:918-925.

46. Marois P, Letellier G, Marois M, Ballaz L. Using the gross motor function measure evolution ratio to compare different dosage of hyperbaric treatment with conventional therapies in children with cerebral palsy - could it end the controversy? Frontiers in neurology. 2024;15:1347361.

47. Rosenbaum PL, Walter SD, Hanna SE, Palisano RJ, Russell DJ, Raina P, et al. Prognosis for gross motor function in cerebral palsy: creation of motor development curves. Jama. 2002;288:1357-1363.

48. Vos RC, Becher JG, Ketelaar M, Smits DW, Voorman JM, Tan SS, et al. Developmental trajectories of daily activities in children and adolescents with cerebral palsy. Pediatrics. 2013;132:e915-923.

49. Tan SS, van Gorp M, Voorman JM, Geytenbeek JJ, Reinders-Messelink HA, Ketelaar M, et al. Development curves of communication and social interaction in individuals with cerebral palsy. Developmental medicine and child neurology. 2020;62:132-139.

50. Sengupta P. The Laboratory Rat: Relating Its Age With Human's. International Journal of Preventive Medicine. 2013;4:624–630.

51. Qu J, Zhou L, Zhang H, Han D, Luo Y, Chen J, et al. Efficacy and safety of stem cell therapy in cerebral palsy: A systematic review and meta-analysis. Front Bioeng Biotechnol.

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