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Interventions and Management

1. Evaluation of a Customized 3D Printed ORGAN-Hand Orthotic Device for Unilateral Cerebral Palsy: a Pilot Study Priyanka Madaan, Nirmal Raj Gopinathan, Lokesh Saini, Aarti Chauhan, Harpreet Singh, Neelesh Kumar, Jitendra Kumar Sahu

Indian J Pediatr. 2021 Jul 5;1-3. doi: 10.1007/s12098-021-03859-6. Online ahead of print.

To achieve intensive activity-based and goal-directed rehabilitation for unilateral cerebral palsy (UCP), several static and functional upper limb orthoses have been used but with limited robust evidence-base. The current pilot study evaluated the feasibility and efficacy of a customized 3D-printed orthotic device in children with UCP. The attainment of a prespecified goal and Shriners Hospital Upper Extremity Evaluation (SHUEE) at 3 and 6 mo were the efficacy measures. Of the 14 screened children, 5 (median age: 7.9 y; 3 boys) were included. The 3-mo follow-up could be completed for 3 children while 6-mo follow-up could be completed for 1 child. Rest could not be assessed due to pandemic restrictions. Although none attained set goals till the last follow-up, all 3 children (at 3-mo follow-up) showed improvement in SHUEE scores without any significant safety concerns. Further studies on 3D-printed orthosis in UCP are the need of the hour.

PMID: [34227047](https://pubmed.ncbi.nlm.nih.gov/34227047/)

2. Interrater and test-retest reliability of the Hand Assessment for Infants Anna Ullenhag, Linda Ek, Ann-Christin Eliasson, Lena Krumlinde-Sundholm

Dev Med Child Neurol. 2021 Jul 5. doi: 10.1111/dmcn.14967. Online ahead of print.

Aim: To evaluate the interrater and test-retest reliability, standard error of measurement (SEM), and the smallest detectable difference (SDD) of the Hand Assessment for Infants (HAI). **Method:** HAI assessments of 55 infants (26 females, 29 males), 25 with clinical signs of unilateral cerebral palsy (CP) and 30 typically developing (mean [SD] age 6.8mo [2.4], range 3-11 mo), were scored individually by three therapists. Three clinically experienced occupational therapists (OT 1-OT 3) with extensive experience in using the HAI, independently scored the video recorded HAI play sessions. Analysis of the combined group of infants and just the infants with clinical signs of unilateral CP (12 females, 13 males; mean age 7.6mo [2.1]) were conducted. Intraclass correlation coefficients (ICC, 2.1), Bland-Altman plots, SEM, and SDD were calculated. **Results:** Interrater and test-retest reliability were excellent for the Both Hands Measure (BoHM) and the Each Hand Sum score (EaHS), with ICCs of 0.96 to 0.99. For individual items, the interrater and test-retest reliability was good to excellent (ICC 0.81-0.99). The SDD for the EaHS was 2 points, and for the BoHM the SDD it was 3 HAI units for infants with signs of unilateral CP. **Interpretation:** The HAI results showed good to excellent reliability. The SDDs were low, indicating that results beyond these levels exceed the measurement error and, thus, can be considered true changes.

PMID: [34224136](#)

3. Torsion Tool: An automated tool for personalising femoral and tibial geometries in OpenSim musculoskeletal models Kirsten Veerkamp, Hans Kainz, Bryce A Killen, Hulda Jónasdóttir, Marjolein M van der Krogt

J Biomech. 2021 Jun 26;125:110589. doi: 10.1016/j.jbiomech.2021.110589. Online ahead of print.

Common practice in musculoskeletal modelling is to use scaled musculoskeletal models based on a healthy adult, but this does not consider subject-specific geometry, such as tibial torsion and femoral neck-shaft and anteversion angles (NSA and AVA). The aims of this study were to (1) develop an automated tool for creating OpenSim models with subject-specific tibial torsion and femoral NSA and AVA, (2) evaluate the femoral component, and (3) release the tool open-source. The Torsion Tool (<https://simtk.org/projects/torsiontool>) is a MATLAB-based tool that requires an individual's tibial torsion, NSA and AVA estimates as input and rotates corresponding bones and associated muscle points of a generic musculoskeletal model. Performance of the Torsion Tool was evaluated comparing femur bones as personalised with the Torsion Tool and scaled generic femurs with manually segmented bones as golden standard for six typically developing children and thirteen children with cerebral palsy. The tool generated femur geometries closer to the segmentations, with lower maximum (-19%) and root mean square (-18%) errors and higher Jaccard indices (+9%) compared to generic femurs. Furthermore, the tool resulted in larger improvements for participants with higher NSA and AVA deviations. The Torsion Tool allows an automatic, fast, and user-friendly way of personalising femoral and tibial geometry in an OpenSim musculoskeletal model. Personalisation is expected to be particularly relevant in pathological populations, as will be further investigated by evaluating the effects on simulation outcomes.

PMID: [34218040](#)

4. A Pediatric Knee Exoskeleton With Real-Time Adaptive Control for Overground Walking in Ambulatory Individuals With Cerebral Palsy

Ji Chen, Jon Hochstein, Christina Kim, Luke Tucker, Lauren E Hammel, Diane L Damiano, Thomas C Bulea

Front Robot AI. 2021 Jun 18;8:702137. doi: 10.3389/frobt.2021.702137. eCollection 2021.

Gait training via a wearable device in children with cerebral palsy (CP) offers the potential to increase therapy dosage and intensity compared to current approaches. Here, we report the design and characterization of a pediatric knee exoskeleton (P.REX) with a microcontroller based multi-layered closed loop control system to provide individualized control capability. Exoskeleton performance was evaluated through benchtop and human subject testing. Step response tests show the averaged 90% rise was 26 ± 0.2 ms for 5 Nm, 22 ± 0.2 ms for 10 Nm, 32 ± 0.4 ms for 15 Nm. Torque bandwidth of P.REX was 12 Hz and output impedance was less than 1.8 Nm with control on (Zero mode). Three different control strategies can be deployed to apply assistance to knee extension: state-based assistance, impedance-based trajectory tracking, and real-time adaptive control. One participant with typical development (TD) and one participant with crouch gait from CP were recruited to evaluate P.REX in overground walking tests. Data from the participant with TD were used to validate control system performance. Kinematic and kinetic data were collected by motion capture and compared to exoskeleton on-board sensors to evaluate control system performance with results demonstrating that the control system functioned as intended. The data from the participant with CP are part of a larger ongoing study. Results for this participant compare walking with P.REX in two control modes: a state-based approach that provided constant knee extension assistance during early stance, mid-stance and late swing (Est+Mst+Lsw mode) and an Adaptive mode providing knee extension assistance proportional to estimated knee moment during stance. Both were well tolerated and significantly improved knee extension compared to walking without extension assistance (Zero mode). There was less reduction in gait speed during use of the adaptive controller, suggesting that it may be more intuitive than state-based constant assistance for this individual. Future work will investigate the effects of exoskeleton assistance during overground gait training in children with neurological disorders and will aim to identify the optimal individualized control strategy for exoskeleton prescription.

PMID: [34222356](#)

5. Clinical effects of assisted robotic gait training in walking distance, speed, and functionality are maintained over the long term in individuals with cerebral palsy: a systematic review and meta-analysis

Mariana Volpini, Mariana Aquino, Ana Carolina Holanda, Elizabeth Emygdio, Janaine Polese

Disabil Rehabil. 2021 Jul 7;1-11. doi: 10.1080/09638288.2021.1942242. Online ahead of print.

Purpose: To identify the short-term effects of robotic-assisted gait training (RAGT) on walking distance, gait speed and functionality of cerebral palsy (CP) patients, and to verify if the effects of RAGT are maintained in the long term. **Methods:** A systematic literature review was performed in PubMed, PEDro, CINAHL, and LILACS databases. Studies were included considering: (1) population (CP individuals); (2) study design (experimental studies); (3) type of intervention (RAGT); (4) outcome (gait parameters and function); and (5) period (short and long term). **Results:** This systematic review included seven articles in meta-analysis. Only walking distance, thru six minutes walking test, increased statistically after RAGT. However, RAGT demonstrated large clinical effects differences (minimal clinically important difference - MCID) in gait speed and Gross Motor Function Measure score (dimensions D and E), for CP population. After RAGT intervention, differences in short term (comparison 1) were maintained in long term (comparison 2) for all outcomes. Gait speed results were not significant. **Conclusions:** Evidence from the present study demonstrated that RAGT can be an important intervention to improve gait parameters and functionality, in children with CP, that are maintained over long-term. **Implications for Rehabilitation:** Robotic-assisted gait training (RAGT) is a beneficial treatment for children with cerebral palsy (CP). RAGT improvements in walking distance are maintained over the long-term in children with CP. RAGT demonstrated large clinical effect differences in gait speed and functionality in CP population.

PMID: [34232847](#)

6. Gait-assisted exoskeletons for children with cerebral palsy or spinal muscular atrophy: A systematic review

Carlos Cumplido, Elena Delgado, Jaime Ramos, Gonzalo Puyuelo, Elena Garcés, Marie André Destarac, Alberto Plaza, Mar Hernández, Alba Gutiérrez, Elena García

Review NeuroRehabilitation. 2021 Jun 24. doi: 10.3233/NRE-210135. Online ahead of print.

Background: Cerebral Palsy (CP) and Spinal Muscular Atrophy (SMA) are common causes of motor disability in childhood. Gait exoskeletons are currently being used as part of rehabilitation for children with walking difficulties. **Objective:** To assess the safety and efficacy and describe the main characteristics of the clinical articles using robot-assisted gait training (RAGT) with exoskeleton for children with CP or SMA. **Methods:** A computer search was conducted in five bibliographic databases regarding clinical studies published in the last ten years. In order to be included in this review for further analysis, the studies had to meet the following criteria: (1) assess efficacy or safety of interventions; (2) population had to be children with CP or SMA aged between 3 and 14; (3) exoskeleton must be bilateral and assist lower limbs during walking. **Results:** Twenty-one articles were selected, of which only five were clinical trials. 108 participants met the inclusion criteria for this study, all with a diagnosis of CP. The evidence level of the selected papers was commonly low. **Conclusions:** RAGT therapy seems to be safe for children with CP. However, further investigation is needed to confirm the results related to efficacy. There is no evidence of RAGT therapy for SMA children.

PMID: [34219676](#)

7. Effects of cane use on walking parameters and lower limb muscle activity in adults with spastic cerebral palsy: a cross-sectional study

Takahito Inoue, Yui Sato, Kotaro Shimizu, Hideyuki Tashiro, Yuichiro Yokoi, Naoki Kozuka

J Phys Ther Sci. 2021 Jul;33(7):544-548. doi: 10.1589/jpts.33.544. Epub 2021 Jul 1.

[Purpose] Adults with cerebral palsy often use a cane as a walking aid because of their decreased gait ability. However, it is unclear whether this affects lower limb muscle activity during walking. The purpose of this study was to clarify the influence of using a cane during walking on the spatio-temporal parameters of walking, lower limb muscle activity, and lower limb muscle coactivation in adults with spastic cerebral palsy. [Participants and Methods] Eleven participants with cerebral palsy were included. The spatio-temporal parameters of walking, lower limb muscle activity, and coactivation of lower limb muscle

were measured during a 10 m trial with no cane, one cane, and two canes. [Results] Walking speed was lower and the stride time longer when using two canes than when using no cane. All muscle activities significantly reduced when using two canes. No significant difference was observed between using no cane and one cane, except for walking speed. In addition, there was no significant difference in coactivation between the conditions. [Conclusion] This study revealed that when two canes were used, the walking speed was reduced, and lower limb muscle activity was reduced, reducing the burden. In contrast, the movement pattern was not suggested to have changed.

PMID: [34219962](#)

8. The muscle shortening manoeuvre: Applicability and preliminary evaluation in children with hemiplegic cerebral palsy – A retrospective analysis

Diego Longo, Marco Lombardi, Paolo Lippi, Daniela Melchiorre, Maria Angela Bagni, Francesco Ferrarello

J Rehabil Med Clin Commun. 2021 Jun 17;4:1000062. doi: 10.2340/20030711-1000062. eCollection 2021.

Introduction: Physiotherapy plays a key role in cerebral palsy rehabilitation, through addressing body function/structure deficits, minimizing activity limitations, and encouraging participation. The muscle shortening manoeuvre is an innovative therapeutic technique, characterized by the ability to induce changes in muscle strength in a short time. Objective: To describe the applicability and estimate the effect of the muscle shortening manoeuvre applied to improve motor weakness and joint excursion of the ankle in children with hemiplegic cerebral palsy. Methods: Nine children with hemiplegic cerebral palsy received 3 intervention sessions in one week. Muscle strength, passive and active range of motion were assessed before, during and after the training, and at 1-week follow-up. Results: The children experienced an immediate increase in muscle strength and joint excursion of the ankle; the improvements were still present at follow-up after 7 days. Conclusion: The muscle shortening manoeuvre may be an effective intervention to induce an immediate increase in muscle strength and range of motion of the ankle in children affected by hemiplegia due to cerebral palsy, thus promoting better physical functioning.

PMID: [34239706](#)

9. Associations Between Subclass Profile of IgG Response to Gluten and the Gastrointestinal and Motor Symptoms in Children with Cerebral Palsy

Reidun Stenberg, Melanie Uhde, Mary Ajamian, Peter H Green, Anna Myleus, Armin Alaedini

J Pediatr Gastroenterol Nutr. 2021 May 25. doi: 10.1097/MPG.0000000000003181. Online ahead of print.

Objective: Gastrointestinal problems are often seen in children with cerebral palsy, although the etiology and underlying mechanisms are not fully understood. Recent data point to significantly elevated levels of IgG antibody to dietary gluten in cerebral palsy independent of celiac disease, a gluten-mediated autoimmune enteropathy. We aimed to further characterize this antibody response by examining its subclass distribution and target reactivity in the context of relevant patient symptom profile. Methods: Study participants included children with cerebral palsy (n = 70) and celiac disease (n = 85), as well as unaffected controls (n = 30). Serum IgG antibody to gluten was investigated for subclass distribution, pattern of reactivity towards target proteins, and relationship with gastrointestinal symptoms and motor function. Results: The anti-gluten IgG antibody response in the cerebral palsy cohort was comprised of all four subclasses. However, in comparison with celiac disease, IgG1, IgG2, and IgG3 subclasses were significantly lower, whereas the IgG4 response was significantly higher in cerebral palsy. Within the cohort of cerebral palsy patients, levels of anti-gluten IgG1, IgG3, and IgG4 were greater in those with gastrointestinal symptoms, and the IgG3 subclass antibody correlated inversely with gross motor function. The anti-gluten IgG antibodies targeted a broad range of gliadin and glutenin proteins. Conclusion: These findings reveal an anti-gluten IgG subclass distribution in cerebral palsy that is significantly different from that in celiac disease. Furthermore, the observed association between IgG subclass and symptom profile is suggestive of a relationship between the immune response and disease pathophysiology that may indicate a role for defects in gut immune and barrier function in cerebral palsy.

PMID: [34231978](#)

10. Association of Chronic Pain With Participation in Motor Skill Activities in Children With Cerebral Palsy

Haresh D Rochani, Christopher M Modlesky, Li Li, Barbara Weissman, Joshua Vova, Gavin Colquitt

JAMA Netw Open. 2021 Jul 1;4(7):e2115970. doi: 10.1001/jamanetworkopen.2021.15970.

This cross-sectional study examines the association between pain and activities requiring motor skill performance among a nationally representative sample of US children with cerebral palsy.

PMID: [34232305](#)**11. The cerebral palsy panorama study in western Sweden: More associated impairments in cerebral palsy observed**

Kate Himmelmann

Acta Paediatr. 2021 Jul;110 Suppl 472:25-26. doi: 10.1111/apa.15926.

PMID: [34240766](#)**12. Vibration therapy role in neurological diseases rehabilitation: an umbrella review of systematic reviews**

Lucrezia Moggi, Alessandro de Sire, Nicola Marotta, Andrea Demeco, Antonio Ammendolia

Disabil Rehabil. 2021 Jul 5;1-9. doi: 10.1080/09638288.2021.1946175. Online ahead of print.

Purpose: To summarize the findings and evaluate the role of vibratory therapy in the rehabilitation of neurological diseases. **Methods:** We systematically research PubMed, Scopus, Embase, Physiotherapy Evidence Database (PEDro), Web of Science, and Cochrane library databases from the inception until November 2020. We included studies that compared whole-body vibration (WBV) or focal muscle vibration (FMV) with placebo, sham, or another form of exercise in neurological disease rehabilitation in children and adults that result in motor impairments and disability. **Results:** We included 16 systematic reviews with good methodological quality evaluated using the Joanna Briggs Institute Umbrella Review Assessment and Review of Information appraisal tool. In stroke patients, WBV appears to play a role in improving gait and balance, while FMV is more effective in reducing spasticity. In multiple sclerosis and cerebral palsy, no evidence suggested that vibration therapy increases some patient outcomes. **Conclusion:** WBV and FMV appear to play a considerable role in reducing spasticity and improving gait, balance, and motor function in stroke patients. By contrast, vibration therapy seems to be unable to reduce spasticity in multiple sclerosis and cerebral palsy. Also, correct use parameters for this therapy could not be defined. **IMPLICATIONS FOR REHABILITATION:** Based on the growing number of systematic reviews, this umbrella review aimed to summarize the findings and evaluate the role of vibration therapy in the rehabilitation of neurological diseases. Whole-body vibration and focal muscle vibration appear to play a considerable role in reducing spasticity and improving gait, balance, and motor function in patients affected by stroke. Focal muscle vibration appears to be more useful if applied to non-spastic antagonist muscles with reciprocal inhibitory action on spastic muscles in subjects affected by stroke. Vibration therapy seems not to be able to reduce spasticity in multiple sclerosis and cerebral palsy.

PMID: [34225557](#)**13. Epidemiology and pathogenesis of stroke in preterm infants: A systematic review**

B Roy, K Walker, C Morgan, M Finch-Edmondson, C Galea, M Epi, N Badawi, I Novak

J Neonatal Perinatal Med. 2021 Jun 29. doi: 10.3233/NPM-200597. Online ahead of print.

Background: Perinatal stroke is one of the principal causes of cerebral palsy (CP) in preterm infants. Stroke in preterm infants is different from stroke in term infants, given the differences in brain maturation and the mechanisms of injury exclusive to the immature brain. We conducted a systematic review to explore the epidemiology and pathogenesis of periventricular hemorrhagic infarction (PVHI), perinatal arterial ischemic stroke (PAIS) and cerebral sinovenous thrombosis (CSVT) in preterm infants. **Methods:** Studies were identified based on predefined study criteria from MEDLINE, EMBASE, SCOPUS and

WEB OF SCIENCE electronic databases from 2000 -2019. Results were combined using descriptive statistics. Results: Fourteen studies encompassed 546 stroke cases in preterm infants between 23 -36 weeks gestational ages and birth weights between 450 -3500 grams. Eighty percent (436/546) of the stroke cases were PVHI, 17%(93/546) were PAIS and 3%(17/546) were CSVT. Parietal PVHI was more common than temporal and frontal lobe PVHI. For PAIS, left middle cerebral artery (MCA) was more common than right MCA or cerebellar stroke. For CSVT partial or complete thrombosis in the transverse sinus was universal. All cases included multiple possible risk factors, but the data were discordant precluding aggregation within a meta-analysis. Conclusion: This systematic review confirms paucity of data regarding the etiology and the precise causal pathway of stroke in preterm infants. Moreover, the preterm infants unlike the term infants do not typically present with seizures. Hence high index of clinical suspicion and routine cUS will assist in the timely diagnosis and understanding of stroke in this population.

PMID: [34219672](#)

14. Risk and Prognostic Factors in Perinatal Hemorrhagic Stroke

Hüseyin Çaksen, Fatma Tuba Köseoğlu, Ahmet Sami Güven, Hüseyin Altunhan, Mehmet Sinan İyisooy, Saim Açıkgozoğlu

Ann Indian Acad Neurol. Mar-Apr 2021;24(2):227-233. doi: 10.4103/aian.AIAN_580_20. Epub 2021 Apr 5.

Background: Perinatal stroke encompasses a heterogeneous group of focal neurological injuries early in brain development. In this study, we aimed to compare risk and prognostic factors in preterm and term infants with perinatal hemorrhagic stroke (PHS). Patients and methods: The study includes 66 infants with PHS. The infants were evaluated for demographic characteristics, fetal and maternal risk factors, perinatal events, clinical and neuroimaging findings, complications, and sequales. Results: Of 66 infants with PHS, 44 (66.70%) were preterm and 22 (33.30%) were term infants. Primiparity, mucosal bleeding, and multiple lobes involvement were more common in term infants than preterm infants ($P < 0.05$); however, respiratory insufficiency, neonatal sepsis, perinatal asphyxia, respiratory distress syndrome, use of invasive mechanical ventilation, use of noninvasive mechanical ventilation, and prolonged hospitalization were more common in preterm infants than term infants ($P < 0.05$). Eight (12.12%) infants died during infancy period. Small for gestational age and mucosal bleeding were more common in infants who are dead than those alive ($P < 0.05$). Forty-two (63.63%) infants were followed. Cerebral palsy and/or epilepsy and/or hydrocephalus were diagnosed in 36 (85.72%) infants during follow-up. Conclusion: Our findings showed that PHS was much more common in preterm infants. Mucosal bleeding and multiple lobes involvement were more common in term infants. PHS has high morbidity and mortality rates. Small for gestational age and mucosal bleeding were more common in infants who are dead.

PMID: [34220067](#)

15. Extra-uterine growth restriction in preterm infants: Neurodevelopmental outcomes according to different definitions

Domenico Umberto De Rose, Francesco Cota, Francesca Gallini, Anthea Bottoni, Giovanna Carmela Fabrizio, Daniela Ricci, Domenico Marco Romeo, Eugenio Mercuri, Giovanni Vento, Luca Maggio

Eur J Paediatr Neurol. 2021 Jun 24;33:135-145. doi: 10.1016/j.ejpn.2021.06.004. Online ahead of print.

Aim: Extra-uterine Growth Restriction (EUGR) is common among preterm infants. Two types of EUGR definitions are still now available: cross-sectional definitions and longitudinal ones. In a cohort of very preterm infants, we aimed to evaluate which definition could better predict neurodevelopmental outcomes at 2 years of corrected age. We used Italian Neonatal Study Charts (INeS) growth charts and INTERGROWTH-21st (IG-21) standard charts and compared results. Method: We retrospectively collected data from clinical charts of 324 preterm newborns with a gestational age ≤ 30 weeks born from 2012 to 2017. Then we compared forty-eight definitions (24 cross-sectional and 24 longitudinal) of EUGR, in term of neurodevelopmental outcomes at 2 years of corrected age. Results: We included in the study 254 preterm infants, whose clinical information met the enrolment criteria. Nineteen out of 48 definitions of EUGR were significantly predictive both for Griffith's Development Quotient (GDQ) and Neurodevelopment Impairment (NDI). Among these, longitudinal definitions appeared to have a higher negative predictive value for NDI than cross-sectional ones. Furthermore, infants with EUGR appeared to have a lower cognitive score than their peers without EUGR. Interpretation: A loss of Zs > 1 SDS in weight and head circumference, calculated from when physiological weight loss is over and identified as soon as possible rather than at discharge, better predicts neurodevelopmental outcomes of preterm infants.

PMID: [34243041](#)

16. Clinical utilisation of the Infant Monitor of vocal Production (IMP) for early identification of communication impairment in young infants at-risk of cerebral palsy: a prospective cohort study

R Ward, N Hennessey, E Barty, C Elliott, J Valentine, R Cattle Moore

Dev Neurorehabil. 2021 Jul 9;1-14. doi: 10.1080/17518423.2021.1942280. Online ahead of print.

Aim: To report prospective longitudinal data of early vocalizations of infants identified "at-risk" of cerebral palsy (CP) for early identification of communication impairment. **Method:** This case-control longitudinal prospective cohort study reports on the assessment of 36 infants, 18 identified as at-risk of CP at the time of enrolment and 18 typically developing (TD) children, at three time points: 6 months, 9 months and 12 months of age. Data were obtained through criterion and norm referenced assessments of vocalization behaviors. **Results:** Early vocal behaviors of infants identified as at-risk of CP did not differ from their age matched peers at 6 months of age, however, significant group differences emerged at 9 and 12 months when pre-canonical and canonical babble typically emerge. Generalized linear mixed models analysis showed that the rate of development of early language ability and more complex speech-related vocal behaviors was slower for infants at risk of CP when compared to TD infants, with over 75% of infants with CP showing below normal vocal production and impaired language by 12 months of age. **Interpretation:** Our data suggest characteristics of infant vocalizations associated with pre-canonical and canonical babbling provide a strong evidence base for predicting communication outcomes in infants at risk of CP.

PMID: [34241555](#)

17. COpenhagen Neuroplastic TRaining Against Contractures in Toddlers (CONTRACT): protocol of an open-label randomised clinical trial with blinded assessment for prevention of contractures in infants with high risk of cerebral palsy

Maria Willerslev-Olsen, Jakob Lorentzen, Katrine Røhder, Anina Ritterband-Rosenbaum, Mikkel Justiniano, Andrea Guzzetta, Ane Vibeke Lando, Anne-Mette Bæk Jensen, Gorm Greisen, Sofie Ejlersen, Line Zacho Pedersen, Britta Andersen, Patricia Liphthay Behrend, Jens Bo Nielsen

BMJ Open. 2021 Jul 6;11(7):e044674. doi: 10.1136/bmjopen-2020-044674.

Introduction: Contractures are frequent causes of reduced mobility in children with cerebral palsy (CP) already at the age of 2-3 years. Reduced muscle use and muscle growth have been suggested as key factors in the development of contractures, suggesting that effective early prevention may have to involve stimuli that can facilitate muscle growth before the age of 1 year. The present study protocol was developed to assess the effectiveness of an early multicomponent intervention, CONTRACT, involving family-oriented and supervised home-based training, diet and electrical muscle stimulation directed at facilitating muscle growth and thus reduce the risk of contractures in children at high risk of CP compared with standard care. **Methods and analysis:** A two-group, parallel, open-label randomised clinical trial with blinded assessment (n=50) will be conducted. Infants diagnosed with CP or designated at high risk of CP based on abnormal neuroimaging or absent fidgety movement determined as part of General Movement Assessment, age 9-17 weeks corrected age (CA) will be recruited. A balanced 1:1 randomisation will be made by a computer. The intervention will last for 6 months aiming to support parents in providing daily individualised, goal-directed activities and primarily in lower legs that may stimulate their child to move more and increase muscle growth. Guidance and education of the parents regarding the nutritional benefits of docosahexaenic acid (DHA) and vitamin D for the developing brain and muscle growth will be provided. Infants will receive DHA drops as nutritional supplements and neuromuscular stimulation to facilitate muscle growth. The control group will receive standard care as offered by their local hospital or community. Outcome measures will be taken at 9, 12, 18, 24, 36 and 48 months CA. Primary and secondary outcome measure will be lower leg muscle volume and stiffness of the triceps surae musculotendinous unit together with infant motor profile, respectively. **Ethics and dissemination:** Full approval from the local ethics committee, Danish Committee System on Health Research Ethics, Region H (H-19041562). Experimental procedures conform with the Declaration of Helsinki. Trial registration number: NCT04250454. Expected recruitment period: 1 January 2021-1 January 2025.

PMID: [34230015](#)

18. Correlation between CT scan Findings of the Head and Motor Disturbances in Children with Cerebral Palsy

K Rahman, M M Rahman, K Fatema

Mymensingh Med J. 2021 Jul;30(3):678-683.

Cerebral palsy (CP) is the commonest movement disorder in childhood. Clinical spectrum of CP is variable and CT scan of brain is an important mode of diagnosis and prognosis in resource limited set up. This study was done to categorize the CT scan findings and correlate them with the type of motor disturbances of CP patients. This was a cross sectional study done in 100 children diagnosed as CP carried out in Pediatric Neurology unit, BSMMU from July 2009 to July 2010. The patients were randomly selected and CT scan was done in all the patients. Detailed history and clinical examination was done to find out the baseline characteristics, risk factors and topographic type of CP patients. Among 100 patients 92% had abnormal CT scan finding. Most common abnormality was cerebral atrophy. Maximum number of abnormal CT scan was found in quadriplegic CP (92%). Highest number of children was in 13-24 months (29%) and a slight male predominance was found. Commonest risk factor was perinatal asphyxia (75%). The brain lesions are often associated with a clinical phenotype where specific needs may be anticipated and addressed. This is important for the planning of intervention in the child with CP.

PMID: [34226455](#)

19. Bisphosphonate use in children with cerebral palsy

Tim Hurley, Zunera Zareen, Philip Stewart, Ciara McDonnell, Denise McDonald, Eleanor Molloy

Review Cochrane Database Syst Rev. 2021 Jul 5;7(7):CD012756. doi: 10.1002/14651858.CD012756.pub2.

Background: Cerebral palsy (CP) is a heterogeneous group of non-progressive disorders of posture or movement, caused by a lesion of the developing brain. Osteoporosis is common in children with cerebral palsy, particularly in children with reduced gross motor function, and leads to an increased risk of fractures. Gross motor function in children with CP can be categorised using a tool called the Gross Motor Function Classification System (GMFCS). Bisphosphonate increases bone mineral density (BMD) and reduces fracture rates. Bisphosphonate is used widely in the treatment of adult osteoporosis. However, the use of bisphosphonate in children with CP remains controversial, due to a paucity of evidence and a lack of recent trials examining the efficacy and safety of bisphosphonate use in this population. **Objectives:** To examine the efficacy and safety of bisphosphonate therapy in the treatment of low BMD or secondary osteoporosis (or both) in children with cerebral palsy (GMFCS Levels III to V) who are under 18 years of age. **Search methods:** In September 2020, we searched CENTRAL, MEDLINE, Embase, six other databases, and two trial registers for relevant studies. We also searched the reference lists of relevant systematic reviews, trials, and case studies identified by the search, and contacted the authors of relevant studies in an attempt to identify unpublished literature. **Selection criteria:** All relevant randomised controlled trials (RCTs), and quasi-RCTs, comparing at least one bisphosphonate (given at any dose, orally or intravenously) with placebo or no drug, for the treatment of low BMD or osteoporosis in children up to 18 years old, with cerebral palsy (GMFCS Levels III to V). **Data collection and analysis:** We used standard methodological procedures expected by Cochrane. We were unable to conduct any meta-analyses due to insufficient data, and therefore provide a narrative assessment of the results. **Main results:** We found two relevant RCTs (34 participants). Both studies included participants with non-ambulatory CP or CP and osteoporosis. Participants in both studies were similar in severity of CP, age distribution, and sex distribution. The two trials used different bisphosphonate medications and different intervention durations, but further comparison of the interventions was not possible due to a lack of published data from one trial. One trial received funding and support from research, academic, and hospital foundations, with pharmaceutical companies providing components of the calcium and vitamin supplement; the other trial did not report sources of funding. We judged one study at an overall high risk of bias; the other as overall unclear risk of bias. **Primary outcome:** Compared to placebo or no treatment, both studies provided very low certainty evidence of improved BMD at least four months post-intervention in children treated with bisphosphonate. Only one study (12 participants) provided sufficient detail to assess a measure of the effect, and reported an improvement at six months post-intervention in lumbar spine z-score (mean difference (MD) 18%, 95% confidence interval (CI) 6.57 to 29.43; very low certainty evidence). **Secondary outcomes:** Very low certainty evidence from one study found that bisphosphonate reduced serum N-telopeptides (NTX) more than placebo; the other study reported that both bisphosphonate plus alfacalcidol and alfacalcidol alone reduced NTX, but did not compare groups. One study reported inconclusive results between groups for serum bone-specific alkaline phosphatase (BAP). The other study reported that both bisphosphonate plus alfacalcidol and alfacalcidol alone reduced BAP, but did not compare groups. Neither study reported data for the effect of bisphosphonate treatment on changes in volumetric BMD in the distal radius or tibia, changes in fracture frequency, bone pain, or quality of life. One study reported that two participants had febrile events noted during their first dosing schedule, but no further adverse events were reported in either relevant study. **Authors' conclusions:** Based on the available evidence, there is very low certainty evidence that bisphosphonate treatment may improve bone health in children with cerebral palsy. We could only include one study with 14 participants in the assessment of the effect size; therefore, the precision of the effect estimate is low. We could only evaluate one planned primary outcome, as there

was insufficient detail reported in the relevant studies. Further research from RCTs on the effect and safety of bisphosphonate to improve bone health in children with cerebral palsy is required. These studies should clarify the optimal standard treatment regarding weight-bearing exercises, vitamin D and calcium supplementation, and should include fracture frequency as a primary outcome.

PMID: [34224134](#)

20. Postoperative complications in pediatric patients with cerebral palsy

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Background/purpose: To assess surgical outcomes of patients with cerebral palsy (CP) and if they differ from patients without CP. **Methods:** The NSQIP-Pediatric database from 2012 to 2019 was used to compare differences in presenting characteristics and outcomes between patients with and without CP. Chi-square tests and multivariable logistic regression analysis were used to determine significance. **Results:** 119,712 patients, 433 (0.4%) with CP, 119,279 (99.6%) without, were identified. Patients with CP had more postoperative complications (19.4% vs. 6.9%, $p < 0.001$) with an OR of 3.2, (95%CI 2.5-4.1, $p < 0.001$) on univariable analysis. They underwent fewer laparoscopic procedures (79.1% vs. 90.8%, $p < 0.001$), had more readmissions (10.2% vs. 3.8%, $p < 0.001$), reoperations (5.1% vs. 1.2%, $p < 0.001$), and longer length of stays (LOS) (median 3 versus 1 day, $p < 0.001$). On multivariable analysis, having CP did not increase the odds of postoperative morbidity (OR 0.99, 95% CI 0.7-1.3), but higher ASA class, congenital lung malformation, gastrointestinal disease, coagulopathy, preoperative inotropic support, oxygen use, nutritional support, and steroid use significantly increase the odds of morbidity, all of which were more common in patients with CP. **Conclusion:** Patients with CP have more postoperative complications, open procedures, and longer LOS. Patient complexity may account for these differences and risk-directed perioperative planning may improve outcomes.

PMID: [34218929](#)

21. Breast Health Experiences in Women with Cerebral Palsy: A Qualitative Approach

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Womens Health Rep (New Rochelle). 2021 Jun 28;2(1):195-200. doi: 10.1089/whr.2020.0115. eCollection 2021.

Background: All women, regardless of disability status, should receive screening for breast cancer. In 2010, only 61.4% of women with disabilities (WWD) received a mammogram in the past 2 years compared to 75% of women without disabilities. The purpose of this study is to explore breast cancer screening experiences of women with cerebral palsy (CP) with the aim of identifying factors that could improve screening rates for WWD. **Methods:** Thirty women with CP, 22-72 years of age, residing in New York, Chicago, or Los Angeles areas participated in individual or group interviews about breast health. Twenty-five of the participants identified themselves as white, and one self-identified as Hispanic or Latina. Facilitators used a semistructured guide across the three sites. Qualitative analysis utilized an iterative coding process to generate themes related to breast health. **Results:** We identified six predominant themes in these interviews, which revolved around physical, environmental, and emotional barriers and facilitators. Within each theme, we identified subthemes. Physical barriers included the most highly identified subthemes of age, pain, holding breath, holding still, spasticity, standing, fatigue, and positioning. Self-advocacy and communication between the health care professional and the patient were the most common subthemes identified among the emotional facilitators. **Conclusion:** Women with CP perceive a variety of issues impacting breast health. These findings are multifaceted and suggest that improving screening rates for women with CP should address these barriers and facilitators.

PMID: [34235506](#)

Prevention and Cure

22. Antenatal magnesium sulfate to prevent cerebral palsy

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Magnesium sulfate given to women before birth at <30 weeks' gestation reduces the risk of cerebral palsy in their children. Our study aimed to assess the impact of a local quality improvement programme, primarily using plan-do-study-act cycles, to increase the use of antenatal magnesium sulfate. After implementing our quality improvement programme, an average of 86% of babies delivered at <30 weeks' gestation were exposed to antenatal magnesium sulfate compared with a historical baseline rate of 63%. Our study strengthens the case for embedding quality improvement programmes in maternal perinatal care to reduce the impact of cerebral palsy on families and society.

PMID: [34233908](#)

23. Mesenchymal Stem Cell (MSC)-Derived Extracellular Vesicles Protect from Neonatal Stroke by Interacting with Microglial Cells

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Mesenchymal stem cell (MSC)-based therapies are beneficial in models of perinatal stroke and hypoxia-ischemia. Mounting evidence suggests that in adult injury models, including stroke, MSC-derived small extracellular vesicles (MSC-sEV) contribute to the neuroprotective and regenerative effects of MSCs. Herein, we examined if MSC-sEV protect neonatal brain from stroke and if this effect is mediated via communication with microglia. MSC-sEV derived from bone marrow MSCs were characterized by size distribution (NanoSight™) and identity (protein markers). Studies in microglial cells isolated from the injured or contralateral cortex of postnatal day 9 (P9) mice subjected to a 3-h middle cerebral artery occlusion (tMCAO) and cultured (in vitro) revealed that uptake of fluorescently labeled MSC-sEV was significantly greater by microglia from the injured cortex vs. contralateral cortex. The cell-type-specific spatiotemporal distribution of MSC-sEV was also determined in vivo after tMCAO at P9. MSC-sEV administered at reperfusion, either by intracerebroventricular (ICV) or by intranasal (IN) routes, accumulated in the hemisphere ipsilateral to the occlusion, with differing spatial distribution 2 h, 18 h, and 72 h regardless of the administration route. By 72 h, MSC-sEV in the IN group was predominantly observed in Iba1+ cells with retracted processes and in GLUT1+ blood vessels in ischemic-reperfused regions. MSC-sEV presence in Iba1+ cells was sustained. MSC-sEV administration also significantly reduced injury volume 72 h after tMCAO in part via modulatory effects on microglial cells. Together, these data establish feasibility for MSC-sEV delivery to injured neonatal brain via a clinically relevant IN route, which affords protection during sub-acute injury phase.

PMID: [34235636](#)