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NEWS
Cerebral Palsy Research

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Interventions and Management

1. Dexterity and Finger Sense: A Possible Dissociation in Children With Cerebral Palsy.

Guedin N, Fluss J, Thevenot C.

Percept Mot Skills. 2018 Jan 1:31512518779473. doi: 10.1177/0031512518779473. [Epub ahead of print]

Both hand and finger sensory perception and motor abilities are essential for the development of skilled gestures and efficient bimanual coordination. While finger dexterity and finger sensory perception can be impaired in children with cerebral palsy (CP), the relationship between these two functions in this population is not clearly established. The common assumption that CP children with better sensory function also demonstrate better motor outcomes has been recently challenged. To study these questions further, we assessed both finger dexterity and finger gnosia, the ability to perceive one's own fingers by touch, in groups of 11 children with unilateral (i.e., hemiplegic CP) and 11 children with bilateral spastic CP (i.e., diplegic CP) and compared them with typical children. In our sample, children with hemiplegia exhibited finger dexterity deficit in both hands and finger gnosia deficit only in their paretic hand. In contrast, children with diplegia exhibited finger gnosia deficits in both hands and finger dexterity deficit only in their dominant hand. Thus, our results indicated that children with spastic hemiplegia and diplegia present different sensory and motor profiles and suggest that these two subgroups of CP should be considered separately in future experimental and clinical research. We discuss the implications of our results for rehabilitation.
PMID: 29860919

2. Pronator teres selective neurectomy in children with cerebral palsy.

Helin M, Bachy M, Stanchina C, Fitoussi F.

J Hand Surg Eur Vol. 2018 Jan 1:1753193418780590. doi: 10.1177/1753193418780590. [Epub ahead of print]

The objective of this study was to evaluate the results after selective pronator teres (PT) neurectomy in children with spastic hemiplegia. Patients with PT spasticity without contracture and an active supination improvement after PT botulinum toxin injection were included. Hand function and deformities were evaluated with the House score, Gschwind and Tonkin pronation deformity classification and Zancolli's classification. Twenty-two patients (mean age 11.6 years) were included in this study. The average follow-up was 32.6 months. All but one patient improved their supination with a preoperative mean active supination of 5° (range -80-70°) and postoperative of 48° (range 10-90°). Active pronation was always maintained at the last follow-up. PT selective neurectomy appears to improve active and passive forearm supination and should be included in a global strategy of treatments to improve upper limb function in children with cerebral palsy.
PMID: 29871566

3. Responsiveness of the ACTIVLIM-CP questionnaire measuring global activity performance in children with cerebral palsy.

Paradis J, Arnould C, Thonnard JL, Houx L, Pons-Becmeur C, Renders A, Brochard S, Bleyenheuft Y.

Dev Med Child Neurol. 2018 Jun 4. doi: 10.1111/dmcn.13927. [Epub ahead of print]

To investigate the responsiveness of the ACTIVLIM-CP questionnaire after two evidence-based interventions for children with cerebral palsy (CP). Seventy-five children with CP either participated in an intensive motor-skill learning intervention (hand-arm bimanual intensive therapy including lower extremities [HABIT-ILE], n=47) or received botulinum neurotoxin-A (BoNT-A) injection(s) into lower extremities combined with conventional physical therapy (n=28). All children were assessed three times: at baseline (T0 ; before HABIT-ILE/the day of BoNT-A injection), at T1 (last day of HABIT-ILE/6wks after BoNT-A injection), and at follow-up (T2 ; 3-4mo after the beginning of intervention). Parents completed ACTIVLIM-CP and three other activity questionnaires. Responsiveness was analysed using group (based on intervention), subgroup (based on gross motor function level), and individual approaches. For the HABIT-ILE group, significant improvements in ACTIVLIM-CP were observed for the T0 -T1 period ($p<0.001$) but not for the T1 -T2 period. No significant changes were found in the BoNT-A group during assessments ($p=0.84$). In the subgroup analysis for the HABIT-ILE group (T0 -T1), greater changes were demonstrated for children in Gross Motor Function Classification System levels III and IV ($p<0.001$, effect size=1.36). The individual approach was congruent with the group approach. ACTIVLIM-CP demonstrated high responsiveness after HABIT-ILE, showing that this scale may be used to investigate global activity performance in clinical trials focusing on improving daily life activities. Good responsiveness of ACTIVLIM-CP questionnaire during intensive motor-skill learning intervention. Higher responsiveness for children in Gross Motor Function Classification System (GMFCS) levels III and IV versus I and II after intensive intervention. ACTIVLIM-CP is useful to identify children improving their performance after botulinum neurotoxin-A injection.
PMID: 29869417

4. Management of Neuromuscular Hip Dysplasia in Children With Cerebral Palsy: Lessons and Challenges.

Davids JR.

J Pediatr Orthop. 2018 Jul;38 Suppl 1:S21-S27. doi: 10.1097/BPO.0000000000001159.

Optimal clinical decision making and surgical management of hip dysplasia in children with cerebral palsy (CP) requires an understanding of the underlying pathophysiology (pathomechanics and pathoanatomy), incidence, and natural history. The incidence of hip dysplasia in children with CP is directly related to the degree of motor impairment. A subluxated or dislocated hip in a child with CP can compromise the quality of life for both the child and their caregivers. The goal of this article is to highlight the events over the last 25 years that have had the greatest impact on the management of hip dysplasia in children with CP. It is my opinion that the 2 most significant advances during this time have been the development of a classification system based upon motor impairment (the Gross Motor Function Classification System), and the development of surveillance programs for hip dysplasia in children with CP. This article will contrast neuromuscular hip dysplasia with developmental dysplasia of the hip. It will be shown how the development and utilization of the Gross Motor Function Classification System has contributed to our understanding of the epidemiology and natural history of hip dysplasia in children with CP, and to the assessment of outcomes following surgical management. The impact of hip surveillance programs on early soft tissue surgeries, skeletal hip reconstructions, and the incidence of hip dislocations and salvage surgeries will be reviewed. Challenges in the implementation of hip surveillance programs in resource poor and decentralized health care delivery systems will be considered, and innovative approaches identified.
PMID: 29877942

5. A novel sensor-based assessment of lower limb spasticity in children with cerebral palsy.

Choi S, Shin YB, Kim SY, Kim J.

J Neuroeng Rehabil. 2018 Jun 4;15(1):45. doi: 10.1186/s12984-018-0388-5.

To provide effective interventions for spasticity, accurate and reliable spasticity assessment is essential. For the assessment, the Modified Tardieu Scale (MTS) has been widely used owing to its simplicity and convenience. However, it has poor or moderate accuracy and reliability. We proposed a novel inertial measurement unit (IMU)-based MTS assessment system to improve the accuracy and reliability of the MTS itself. The proposed system consists of a joint angle calculation algorithm, a function to detect abnormal muscle reaction (a catch and clonus), and a visual biofeedback mechanism. Through spastic knee and ankle joint assessment, the proposed IMU-based MTS assessment system was compared with the conventional MTS assessment system in 28 children with cerebral palsy by two raters. The results showed that the proposed system has good

accuracy (root mean square error < 3.2°) and test-retest and inter-rater reliabilities (ICC > 0.8), while the conventional MTS system has poor or moderate reliability. Moreover, we found that the deteriorated reliability of the conventional MTS system comes from its goniometric measurement as well as from irregular passive stretch velocity. The proposed system, which is clinically relevant, can significantly improve the accuracy and reliability of the MTS in lower limbs for children with cerebral palsy.
PMID: 29866177

6. Effect of mindfulness yoga programme MiYoga on attention, behaviour, and physical outcomes in cerebral palsy: a randomized controlled trial.

Mak C, Whittingham K, Cunnington R, Boyd RN.

Dev Med Child Neurol. 2018 Jun 4. doi: 10.1111/dmcn.13923. [Epub ahead of print]

To investigate the efficacy of an embodied mindfulness-based movement programme (MiYoga), targeting attention in children with cerebral palsy (CP). Total number of participants 42, with 24 boys (57.1%) and 18 girls (42.9%); mean age 9y 1mo, SD 3y; Gross Motor Function Classification System levels I=22, II=12, III=8) and their parents were randomized to either MiYoga (n=21) or waitlist comparison (n=21) groups. The primary outcome was attention postintervention measured by the Conners' Continuous Performance Test, Second Edition (CCPT). Secondary outcomes included parent and child mindfulness, child quality of life, parental well-being, child executive function, child behaviour, child physical measures, and the parent-child relationship. Children in the MiYoga group demonstrated significantly better attention postintervention than the waitlist comparison group, with lower inattention scores on the hit reaction time standard error (F1,33 =4.59, p=0.04, partial eta-squared [ηp2]=0.13) variable and fewer perseveration errors (F1,33 =4.60, p=0.04, ηp2=0.13) on the CCPT. Intention-to-treat analysis also revealed that sustained attention in the MiYoga group was significantly better than in the waitlist comparison group postintervention (F1,37 =5.97, p=0.02, ηp2=0.14). Parents in the MiYoga group demonstrated significantly decreased mindfulness (Mindfulness Attention Awareness Scale; F1,33 =10.130, p=0.003, ηp2=0.246). MiYoga offers a lifestyle intervention that improves attention in children with CP. MiYoga can be considered as an additional option to standard rehabilitation to enhance attention for children with CP. MiYoga, an embodied mindfulness-based movement programme, can enhance attention (more attentive and consistent performance) in children with cerebral palsy. MiYoga had no significant effect on physical functioning.
PMID: 29869333

7. Effect of Risperidone on the Motor and Functional Disability in Children With Choreoathetoid Cerebral Palsy.

Kamate M, Mittal N, Metgud D.

Pediatr Neurol. 2018 Apr 20. pii: S0887-8994(17)31304-8. doi: 10.1016/j.pediatrneurol.2018.04.002. [Epub ahead of print]

Therapeutic options for management of choreoathetoid cerebral palsy, which is a permanent disorder, are very limited. Available medications either have significant side effects or are unsuitable for long-term use. Risperidone has shown promise in the management of chorea and has been found to be safe in children less than five years. Children with choreoathetoid cerebral palsy were enrolled after parental consent and given risperidone for six-month period along with standard care. The choreoathetoid movements were assessed using Abnormal Involuntary Movement Scale, the upper-limb functions were assessed using Quality of upper extremity skill tests, and the quality of life using Cerebral palsy-Quality of life. Side effects were monitored clinically, by biochemical tests and electrocardiogram. Of 42 children with choreoathetoid cerebral palsy who were screened over a period of one year, 35 subjects meeting the study criteria were enrolled. Thirty children completed six months of risperidone therapy, the remaining five subjects were excluded because of time missed due to intercurrent unrelated illnesses. Data of these 30 children were analyzed as per per-protocol analysis. Their mean age was 6.35 ± 3.17 years. Abnormal movements showed statistically significant decline after risperidone (19.7 vs 14.7, P < 0.0001). Functional ability of upper limbs and quality of life also showed improvement (37.0 vs 43.8, P < 0.0001 and 64.3 vs 70.0, P < 0.0001, respectively) after six months of risperidone therapy. Positive change in the behavior was also noted. It was well tolerated without significant side effects. Risperidone is a promising drug to manage children with choreoathetoid cerebral palsy and is well tolerated in children.
PMID: 29859722

8. How do adolescents with cerebral palsy participate? Learning from their personal experiences.

Wintels SC, Smits DW, van Wesel F, Verheijden J, Ketelaar M; PERRIN PiP Study Group.

Health Expect. 2018 Jun 1. doi: 10.1111/hex.12796. [Epub ahead of print]

Participation in society can be difficult for adolescents with cerebral palsy (CP). Information is often based on quantitative studies, and little is known about their personal participation experiences. The aim of this study was to examine the participation experiences of adolescents (aged 12-17 years) with CP. A qualitative participatory research method was used. Twenty-three semi-structured open interviews were conducted with 13 male and 10 female adolescents (mean age 15 years) with CP. An interview checklist was developed jointly with adolescents with CP. This checklist ensured that the adolescents reflected on various participation areas, that is school, sports, health care and work. The analysis was based on principles of grounded theory. From the adolescents' experiences, 4 key categories were identified. One concerned participation, as such, expressed as "My participation experiences," including experiences, thoughts and feelings while participating in daily life. Three other categories concerned factors that influence participation experiences, expressed as "My disability," "Me as a person" and "My environment." These 4 categories together formed a model showing the interactions and dynamics of participation according to adolescents with CP. Adolescents with CP expressed their participation experiences, including various important influencing factors. This study conceptualized these experiences into a dynamic model. This experience-based participation model may provide new, personalized perspectives for practice, for instance in rehabilitation, but also for schools and sports (or sports clubs) attended by adolescents. Focusing on personal and environmental factors might be the key to successful participation.
PMID: 29858544

9. Functional Communication Profiles in Children with Cerebral Palsy in Relation to Gross Motor Function and Manual and Intellectual Ability.

Choi JY, Park J, Choi YS, Goh YR, Park ES.

Yonsei Med J. 2018 Jul;59(5):677-685. doi: 10.3349/ymj.2018.59.5.677.

The aim of the present study was to investigate communication function using classification systems and its association with other functional profiles, including gross motor function, manual ability, intellectual functioning, and brain magnetic resonance imaging (MRI) characteristics in children with cerebral palsy (CP). This study recruited 117 individuals with CP aged from 4 to 16 years. The Communication Function Classification System (CFCS), Viking Speech Scale (VSS), Speech Language Profile Groups (SLPG), Gross Motor Function Classification System (GMFCS), Manual Ability Classification System (MACS), and intellectual functioning were assessed in the children along with brain MRI categorization. Very strong relationships were noted among the VSS, CFCS, and SLPG, although these three communication systems provide complementary information, especially for children with mid-range communication impairment. These three communication classification systems were strongly related with the MACS, but moderately related with the GMFCS. Multiple logistic regression analysis indicated that manual ability and intellectual functioning were significantly related with VSS and CFCS function, whereas only intellectual functioning was significantly related with SLPG functioning in children with CP. Communication function in children with a periventricular white matter lesion (PVWL) varied widely. In the cases with a PVWL, poor functioning was more common on the SLPG, compared to the VSS and CFCS. Very strong relationships were noted among three communication classification systems that are closely related with intellectual ability. Compared to gross motor function, manual ability seemed more closely related with communication function in these children.
PMID: 29869466

10. Screening and assessment of chronic pain among children with cerebral palsy: a process evaluation of a pain toolbox.

Orava T, Provvidenza C, Townley A, Kingsnorth S.

Disabil Rehabil. 2018 Jun 8;1-9. [Epub ahead of print]

Though high numbers of children with cerebral palsy experience chronic pain, it remains under-recognized. This paper describes an evaluation of implementation supports and adoption of the Chronic Pain Assessment Toolbox for Children with Disabilities (the Toolbox) to enhance pain screening and assessment practices within a pediatric rehabilitation and complex continuing care hospital. A multicomponent knowledge translation strategy facilitated Toolbox adoption, inclusive of a clinical practice guideline, cerebral palsy practice points and assessment tools. Across the hospital, seven ambulatory care clinics with cerebral palsy caseloads participated in a staggered roll-out (Group 1: exclusive CP caseloads, March-December; Group 2: mixed diagnostic caseloads, August-December). Evaluation measures included client electronic medical record audit, document review and healthcare provider survey and interviews. A significant change in documentation of pain screening and

assessment practice from pre-Toolbox (<2%) to post-Toolbox adoption (53%) was found. Uptake in Group 2 clinics lagged behind Group 1. Opportunities to use the Toolbox consistently (based on diagnostic caseload) and frequently (based on client appointments) were noted among contextual factors identified. Overall, the Toolbox was positively received and clinically useful. Findings affirm that the Toolbox, in conjunction with the application of integrated knowledge translation principles and an established knowledge translation framework, has potential to be a useful resource to enrich and standardize chronic pain screening and assessment practices among children with cerebral palsy. Implications for Rehabilitation It is important to engage healthcare providers in the conceptualization, development, implementation and evaluation of a knowledge-to-action best practice product. The Chronic Pain Toolbox for Children with Disabilities provides rehabilitation staff with guidance on pain screening and assessment best practice and offers a range of validated tools that can be incorporated in ambulatory clinic settings to meet varied client needs. Considering unique clinical contexts (i.e., opportunities for use, provider engagement, staffing absences/turnover) is required to optimize and sustain chronic pain screening and assessment practices in rehabilitation outpatient settings. Evaluation studies; cerebral palsy; chronic pain; disabled children; implementation; knowledge translation; pain measurement
PMID: 29882678

11. Pathophysiology of chronic pain in cerebral palsy: implications for pharmacological treatment and research.

Blackman JA, Svensson CI, Marchand S.

Dev Med Child Neurol. 2018 Jun 7. doi: 10.1111/dmcn.13930. [Epub ahead of print]

The high prevalence of chronic pain in individuals with cerebral palsy (CP) across the lifespan has been well documented, as has its negative impact on quality of life. However, without an understanding of the underlying (possibly unique) pathophysiology of pain in CP, identification of more effective management options, such as innovative and individualized pharmacological approaches to non-opioid pain treatment, will be significantly hindered. We review, briefly, what is known about chronic pain in CP and present what we need to know with respect to the neurobiology of pain and new developments in pain treatment research that might be applied to CP. WHAT THIS PAPER ADDS: Pain conditions in cerebral palsy have differing mechanisms and will not respond to the same treatments. Novel analgesics under development include inhibitors of ion channels, nerve growth factor, and calcitonin gene-related peptide.
PMID: 29882358

12. The effect of spinal bracing on sitting function in children with neuromuscular scoliosis.

Blomkvist A, Olsson K, Eek MN.

Prosthet Orthot Int. 2018 Jun 1;:309364618774063. [Epub ahead of print]

Scoliosis is common in children with neuromuscular deficits. It is often associated with an asymmetric sitting position and with poor balance. Many children with neuromuscular scoliosis spend most of their day sitting. To describe how sitting function is affected by treatment with a modified custom-moulded Boston brace in children with neuromuscular scoliosis. Retrospective review of medical records. A review of medical records from children fitted with scoliosis braces, including analysis of sitting, using a pressure-mapping system. A total of 106 children with a median age of 11.3 (1.7-17.7) years were included. The most frequent diagnoses were cerebral palsy (n = 33) and myelomeningocele (n = 17). Around 56 children could sit without support and 24 children were independent walkers. The Cobb angle was between 19° and 126°. Sitting function as noted in medical records improved in 73/105 children and deteriorated in five. The pressure mapping showed that symmetry was improved in 44/86 children, while three deteriorated. Stability improved in 20/40 children and seven decreased. Bracing had a positive effect on sitting function in children with neuromuscular scoliosis. Clinical relevance Bracing can reduce the need for support in sitting. Children with severe scoliosis can get a better sitting function with a brace. Sitting analysis with pressure mapping can identify sitting problems needing correction of the brace and adaptations of the chair.
PMID: 29871529

Prevention and Cure

13. Treatment targets for M2 microglia polarization in ischemic stroke.

Wang J, Xing H, Wan L, Jiang X, Wang C, Wu Y.

Biomed Pharmacother. 2018 Jun 5;105:518-525. doi: 10.1016/j.biopha.2018.05.143. [Epub ahead of print]

As the first line of defense in the nervous system, resident microglia are the predominant immune cells in the brain. In diseases of the central nervous system such as stroke, Alzheimer's disease, and Parkinson's disease, they often cause inflammation or phagocytosis; however, some studies have found that despite the current controversy over M1, M2 polarization could be beneficial. Ischemic stroke is the third most common cause of death in humans. Patients who survive an ischemic stroke might experience a clear decline in their quality of life, owing to conditions such as hemiplegic paralysis and aphasia. After stroke, the activated microglia become a double-edged sword, with distinct phenotypic changes to the deleterious M1 and neuroprotective M2 types. Therefore, methods for promoting the differentiation of microglia into the M2 polarized form to alleviate harmful reactions after stroke have become a topic of interest in recent years. Subsequently, the discovery of new drugs related to M2 polarization has enabled the realization of targeted therapies. In the present review, we discussed the neuroprotective effects of microglia M2 polarization and the potential mechanisms and drugs by which microglia can be transformed into the M2 polarized type after stroke.
PMID: 29883947

14. Effect of mannose targeting of hydroxyl PAMAM dendrimers on cellular and organ biodistribution in a neonatal brain injury model.

Sharma A, Porterfield JE, Smith E, Sharma R, Kannan S, Kannan RM.

J Control Release. 2018 Jun 5;283:175-189. doi: 10.1016/j.jconrel.2018.06.003. [Epub ahead of print]

Neurotherapeutics for the treatment of central nervous system (CNS) disorders must overcome challenges relating to the blood-brain barrier (BBB), brain tissue penetration, and the targeting of specific cells. Neuroinflammation mediated by activated microglia is a major hallmark of several neurological disorders, making these cells a desirable therapeutic target. Building on the promise of hydroxyl-terminated generation four polyamidoamine (PAMAM) dendrimers (D4-OH) for penetrating the injured BBB and targeting activated glia, we explored if conjugation of targeting ligands would enhance and modify brain and organ uptake. Since mannose receptors [cluster of differentiation (CD) 206] are typically over-expressed on injured microglia, we conjugated mannose to the surface of multifunctional D4-OH using highly efficient, atom-economical, and orthogonal Cu (I)-catalyzed alkyne-azide cycloaddition (CuAAC) click chemistry and evaluated the effect of mannose conjugation on the specific cell uptake of targeted and non-targeted dendrimers both in vitro and in vivo. In vitro results indicate that the conjugation of mannose as a targeting ligand significantly changes the mechanism of dendrimer internalization, giving mannosylated dendrimer a preference for mannose receptor-mediated endocytosis as opposed to non-specific fluid phase endocytosis. We further investigated the brain uptake and biodistribution of targeted and non-targeted fluorescently labeled dendrimers in a maternal intrauterine inflammation-induced cerebral palsy (CP) rabbit model using quantification methods based on fluorescence spectroscopy and confocal microscopy. We found that the conjugation of mannose modified the distribution of D4-OH throughout the body in this neonatal rabbit CP model without lowering the amount of dendrimer delivered to injured glia in the brain, even though significantly higher glial uptake was not observed in this model. Mannose conjugation to the dendrimer modifies the dendrimer's interaction with cells, but does not minimize its inherent inflammation-targeting abilities.
PMID: 29883694

15. Extracellular Signal-Related Kinase (ERK) 2 has duality in function between neuronal and astrocyte expression following neonatal hypoxia-ischemic cerebral injury.

Thei L, Rocha-Ferreira E, Peebles D, Raivich G, Hristova M.

J Physiol. 2018 Jun 6. doi: 10.1113/JP275649. [Epub ahead of print]

Hypoxia-ischemia (HI) is a major cause of neonatal brain injury resulting in cerebral palsy, epilepsy, cognitive impairment and other neurological disabilities. The role of Extracellular signal-Regulated Kinase (ERK) isoforms and their MEK-dependent phosphorylation in HI has previously been explored but remains unresolved at cellular level. This is pertinent given the

growing awareness of the role of non-neuronal cells in neuroprotection. Using a modified Rice-Vannuccci model of HI in the neonatal mouse we observed time and cell-dependent ERK phosphorylation (pERK), with strongly up-regulated pERK immunoreactivity first in periventricular white matter axons within 15-45 min of HI, followed by forebrain astrocytes and neurons (1-4 h post HI), and return to baseline by 16 h. We explored the effects of pharmacological ERK-blockade through the MEK inhibitor SL327 on neonatal HI-brain damage following HI alone (30 or 60 min) or LPS-sensitized HI insult (30 min). Global inhibition of ERK phosphorylation with systemically applied SL327 abolished forebrain pERK immunoreactivity, significantly reduced cell death and associated microglial activation at 48h post HI. We then explored the effects of cell specific ERK2 deletion alone or in combination with global ERK1 knockout under the same conditions of HI insult. Neuronal ERK2 deletion strongly decreased infarct size, neuronal cell death and microglial activation in grey matter following both HI alone or LPS-sensitised HI. ERK1 deletion attenuated the protective effect of neuronal ERK2 deletion. Removal of astroglial ERK2 produced a reverse response, with 3-4 fold increase in microglial activation and cell death. Our data suggests cell-specific and time-dependent role of ERK in neonatal HI, with a predominant, neurotoxic effect of neuronal ERK2, which is counteracted by neuroprotection by ERK1 and astrocytic ERK2. Overall, global pharmacological inhibition of ERK phosphorylation is strongly neuroprotective.
PMID: 29873394

16. Association Between Oxygen Saturation Targeting and Death or Disability in Extremely Preterm Infants in the Neonatal Oxygenation Prospective Meta-analysis Collaboration.

Askie LM, Darlow BA, Finer N, Schmidt B, Stenson B, Tarnow-Mordi W, Davis PG, Carlo WA, Brocklehurst P, Davies LC, Das A, Rich W, Gantz MG, Roberts RS, Whyte RK, Costantini L, Poets C, Asztalos E, Battin M, Halliday HL, Marlow N, Tin W, King A, Juszczak E, Morley CJ, Doyle LW, Gebski V, Hunter KE, Simes RJ; Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration.

JAMA. 2018 Jun 5;319(21):2190-2201. doi: 10.1001/jama.2018.5725.

There are potential benefits and harms of hyperoxemia and hypoxemia for extremely preterm infants receiving more vs less supplemental oxygen. To compare the effects of different target ranges for oxygen saturation as measured by pulse oximetry (Spo2) on death or major morbidity. Prospectively planned meta-analysis of individual participant data from 5 randomized clinical trials (conducted from 2005-2014) enrolling infants born before 28 weeks' gestation. Spo2 target range that was lower (85%-89%) vs higher (91%-95%). The primary outcome was a composite of death or major disability (bilateral blindness, deafness, cerebral palsy diagnosed as ≥2 level on the Gross Motor Function Classification System, or Bayley-III cognitive or language score <85) at a corrected age of 18 to 24 months. There were 16 secondary outcomes including the components of the primary outcome and other major morbidities. A total of 4965 infants were randomized (2480 to the lower Spo2 target range and 2485 to the higher Spo2 range) and had a median gestational age of 26 weeks (interquartile range, 25-27 weeks) and a mean birth weight of 832 g (SD, 190 g). The primary outcome occurred in 1191 of 2228 infants (53.5%) in the lower Spo2 target group and 1150 of 2229 infants (51.6%) in the higher Spo2 target group (risk difference, 1.7% [95% CI, -1.3% to 4.6%]; relative risk [RR], 1.04 [95% CI, 0.98 to 1.09], P = .21). Of the 16 secondary outcomes, 11 were null, 2 significantly favored the lower Spo2 target group, and 3 significantly favored the higher Spo2 target group. Death occurred in 484 of 2433 infants (19.9%) in the lower Spo2 target group and 418 of 2440 infants (17.1%) in the higher Spo2 target group (risk difference, 2.8% [95% CI, 0.6% to 5.0%]; RR, 1.17 [95% CI, 1.04 to 1.31], P = .01). Treatment for retinopathy of prematurity was administered to 220 of 2020 infants (10.9%) in the lower Spo2 target group and 308 of 2065 infants (14.9%) in the higher Spo2 target group (risk difference, -4.0% [95% CI, -6.1% to -2.0%]; RR, 0.74 [95% CI, 0.63 to 0.86], P < .001). Severe necrotizing enterocolitis occurred in 227 of 2464 infants (9.2%) in the lower Spo2 target group and 170 of 2465 infants (6.9%) in the higher Spo2 target group (risk difference, 2.3% [95% CI, 0.8% to 3.8%]; RR, 1.33 [95% CI, 1.10 to 1.61], P = .003). In this prospectively planned meta-analysis of individual participant data from extremely preterm infants, there was no significant difference between a lower Spo2 target range compared with a higher Spo2 target range on the primary composite outcome of death or major disability at a corrected age of 18 to 24 months. The lower Spo2 target range was associated with a higher risk of death and necrotizing enterocolitis, but a lower risk of retinopathy of prematurity treatment.
PMID: 29872859

17. Fixel-based analysis reveals alterations is brain microstructure and macrostructure of preterm-born infants at term equivalent age.

Pannek K, Fripp J, George JM, Fiori S, Colditz PB, Boyd RN, Rose SE.

Neuroimage Clin. 2018 Jan 11;18:51-59. doi: 10.1016/j.nicl.2018.01.003. eCollection 2018.

Preterm birth causes significant disruption in ongoing brain development, frequently resulting in adverse neurodevelopmental outcomes. Brain imaging using diffusion MRI may provide valuable insight into microstructural properties of the developing brain. The aim of this study was to establish whether the recently introduced fixel-based analysis method, with its associated measures of fibre density (FD), fibre bundle cross-section (FC), and fibre density and bundle cross-section (FDC), is suitable

for the investigation of the preterm infant brain at term equivalent age. High-angular resolution diffusion weighted images (HARDI) of 55 preterm-born infants and 20 term-born infants, scanned around term-equivalent age, were included in this study (3 T, 64 directions, b = 2000 s/mm2). Postmenstrual age at the time of MRI, and intracranial volume (FC and FDC only), were identified as confounding variables. Gestational age at birth was correlated with all fixel measures in the splenium of the corpus callosum. Compared to term-born infants, preterm infants showed reduced FD, FC, and FDC in a number of regions, including the corpus callosum, anterior commissure, cortico-spinal tract, optic radiations, and cingulum. Preterm infants with minimal macroscopic brain abnormality showed more extensive reductions than preterm infants without any macroscopic brain abnormality; however, little differences were observed between preterm infants with no and with minimal brain abnormality. FC showed significant reductions in preterm versus term infants outside regions identified with FD and FDC, highlighting the complementary role of these measures. Fixel-based analysis identified both microstructural and macrostructural abnormalities in preterm born infants, providing a more complete picture of early brain development than previous diffusion tensor imaging (DTI) based approaches.
Diffusion; Fixel-based analysis; Neonate; Prematurity
PMID: 29868441

18. Early Detection of Hypothermic Neuroprotection Using T2-Weighted Magnetic Resonance Imaging in a Mouse Model of Hypoxic Ischemic Encephalopathy.

Doman SE, Girish A, Nemeth CL, Drummond GT, Carr P, Garcia MS, Johnston MV, Kannan S, Fatemi A, Zhang J, Wilson MA.

Front Neurol. 2018 May 8;9:304. doi: 10.3389/fneur.2018.00304. eCollection 2018.

Perinatal hypoxic-ischemic encephalopathy (HIE) can lead to neurodevelopmental disorders, including cerebral palsy. Standard care for neonatal HIE includes therapeutic hypothermia, which provides partial neuroprotection; magnetic resonance imaging (MRI) is often used to assess injury and predict outcome after HIE. Immature rodent models of HIE are used to evaluate mechanisms of injury and to examine the efficacy and mechanisms of neuroprotective interventions such as hypothermia. In this study, we first confirmed that, in the CD1 mouse model of perinatal HIE used for our research, MRI obtained 3 h after hypoxic ischemia (HI) could reliably assess initial brain injury and predict histopathological outcome. Mice were subjected to HI (unilateral carotid ligation followed by exposure to hypoxia) on postnatal day 7 and were imaged with T2-weighted MRI and diffusion-weighted MRI (DWI), 3 h after HI. Clearly defined regions of increased signal were comparable in T2 MRI and DWI, and we found a strong correlation between T2 MRI injury scores 3 h after HI and histopathological brain injury 7 days after HI, validating this method for evaluating initial injury in this model of HIE. The more efficient, higher resolution T2 MRI was used to score initial brain injury in subsequent studies. In mice treated with hypothermia, we found a significant reduction in T2 MRI injury scores 3 h after HI, compared to normothermic littermates. Early hypothermic neuroprotection was maintained 7 days after HI, in both T2 MRI injury scores and histopathology. In the normothermic group, T2 MRI injury scores 3 h after HI were comparable to those obtained 7 days after HI. However, in the hypothermic group, brain injury was significantly less 7 days after HI than at 3 h. Thus, early neuroprotective effects of hypothermia were enhanced by 7 days, which may reflect the additional 3 h of hypothermia after imaging or effects on later mechanisms of injury, such as delayed cell death and inflammation. Our results demonstrate that hypothermia has early neuroprotective effects in this model. These findings suggest that hypothermia has an impact on early mechanisms of excitotoxic injury and support initiation of hypothermic intervention as soon as possible after diagnosis of HIE.
hypothermia; hypoxic-ischemic; magnetic resonance imaging; neonatal encephalopathy; neuroprotection
PMID: 29867720

19. Relationship Between Short Term Variability (STV) and Onset of Cerebral Hemorrhage at Ischemia-Reperfusion Load in Fetal Growth Restricted (FGR) Mice.

Minato T, Ito T, Kasahara Y, Ooshio S, Fushima T, Sekimoto A, Takahashi N, Yaegashi N, Kimura Y.

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Fetal growth restriction (FGR) is a risk factor exacerbating a poor neurological prognosis at birth. A disease exacerbating a poor neurological prognosis is cerebral palsy. One of the causes of this disease is cerebral hemorrhage including intraventricular hemorrhage. It is believed to be caused by an inability to autoregulate cerebral blood flow as well as immaturity of cerebral vessels. Therefore, if we can evaluate the function of autonomic nerve, cerebral hemorrhage risk can be predicted beforehand and appropriate delivery management may be possible. Here dysfunction of autonomic nerve in mouse FGR fetuses was evaluated and the relationship with cerebral hemorrhage incidence when applying hypoxic load to resemble

To compare autonomic nerve function in FGR mice with that in control mice, fetal short term variability (STV) was measured from electrocardiograms. In the FGR group, a significant decrease in the STV was observed and dysfunction of cardiac autonomic control was confirmed. Among genes related to nerve development and differentiation, Ntrk and Neuregulin 1, which are necessary for neural differentiation and plasticity, were expressed at reduced levels in FGR fetuses. Under normal conditions, Neurogenin 1 and Neurogenin 2 are expressed mid-embryogenesis and are related to neural differentiation, but they are not expressed during late embryonic development. The expression of these two genes increased in FGR fetuses, suggesting that neural differentiation is delayed with FGR. Uterine and ovarian arteries were clipped and periodically opened to give a hypoxic load mimicking the time of labor, and the bleeding rate significantly increased in the FGR group. This suggests that FGR deteriorates cardiac autonomic control, which becomes a risk factor for cerebral hemorrhage onset at birth. This study demonstrated that cerebral hemorrhage risk may be evaluated before parturition for FGR management by evaluating the STV. Further, this study suggests that choosing an appropriate delivery timing and delivery method contributes to neurological prognosis improvement.
PMID: 29867536

20. Short- and long-term neonatal outcomes according to differential exposure to antenatal corticosteroid therapy in preterm births prior to 24 weeks of gestation.

Kim SM, Sung JH, Kuk JY, Cha HH, Choi SJ, Oh SY, Roh CR.

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To assess the effects of differential exposure to antenatal corticosteroid (ACS) on short- and long-term outcomes of infants born before 24 weeks of gestation.This is a retrospective cohort study of 147 infants delivered by 116 women at 21-23 weeks of gestation between January 2001 and December 2016 at a tertiary referral hospital in Seoul, Korea. Eligible subjects were categorized into the following three groups according to ACS exposure: non-user (n = 53), partial-course (n = 44), and complete-course (n = 50). Univariable and multivariable analyses were used to compare neonatal mortality, neonatal morbidities including intraventricular hemorrhage (IVH), and neurodevelopmental impairment including cerebral palsy among the three groups. Neonatal mortality rate was significantly lower in the ACS-user groups (non-user, 52.8%; partial-course, 27.3%; complete-course, 28.0%; P = 0.01), but complete-course of ACS therapy had no advantages over partial-course. A lower incidence of IVH was observed in the complete-course group (non-users, 54.8%; partial-course, 48.6%; complete-course, 20.5%; P = 0.003). Multiple logistic regression analysis showed that ACS therapy, either partial- or complete-course, was associated with a lower rate of neonatal mortality (adjusted odds ratio (aOR) 0.375; 95% confidence interval (CI) 0.141-0.996 in partial-course; aOR 0.173; 95% CI 0.052-0.574) in complete-course). IVH (aOR 0.191; 95% CI 0.071-0.516) was less likely to occur in the complete-course group than in the non-user group. Neurodevelopmental impairment of survivors at 18-22 month after birth was not significantly different among the three groups. ACS therapy in preterm births at 21-23 weeks of gestation was associated with significantly reduced rates of neonatal mortality and IVH, especially with complete administration.
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