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Single blind randomised controlled trial of GAME (Goals - Activity - Motor Enrichment) in infants at high risk of cerebral palsy

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ABSTRACT

Background: Cerebral palsy (CP) is caused by a lesion in the developing infant brain. Recent neuroplasticity literature suggests that intensive, task-specific intervention ought to commence early, during the critical period of neural development.
Aims: To determine whether "GAME" (Goals - Activity - Motor Enrichment), a motor learning, environmental enrichment intervention, is effective for improving motor skills in infants at high risk of CP.
Methods and procedures: Single blind randomised controlled trial of GAME versus standard care. Primary outcome was motor skills on the Peabody Developmental Motor Scales-2 (PDMS-2). Secondary outcomes included Canadian Occupational Performance Measure (COPM), Bayley Scales of Infant and Toddler Development (BSID-III) and Gross Motor Function Measure-66 (GMFM-66). Outcome assessors were masked to group allocation and data analyzed with multiple regression.
Outcomes and results: All n = 30 infants enrolled received the assigned intervention until 16 weeks post enrolment. At 12 months of age, n = 26 completed assessments. Significant between group differences were found in raw scores on the PDMS-2 in favour of GAME (B = 20.71, 95%CI 1.66-39.76, p = 0.03) and at 12 months on the total motor quotient (B = 8.29, 95%CI 0.13-16.45, p = 0.05). Significant between group differences favored GAME participants at 12 months on the cognitive scale of the BSID-III and satisfaction scores on the COPM.
Conclusion: GAME intervention resulted in advanced motor and cognitive outcomes when compared with standard care.

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1. Introduction

Cerebral palsy (CP), the most common physical disability of childhood, occurs because of a lesion in the developing brain (Bax, Goldstein, & Rosenbaum, 2005). The lesions associated with an eventual diagnosis of CP usually occur during the prenatal or perinatal period. A small percentage acquires their injury after the neonatal period and account for approximately 5.6% of CP (ACPR Group, 2013). Since the brain injury of CP occurs early it is important to develop evidence based rehabilitation protocols that enhance the neuroplasticity mechanisms at work in the developing brain (Ulrich, 2010). Many effective rehabilitation interventions for older children with CP exist (Novak, McIntyre, & Morgan, 2013), but most have not been trialled early with infants because recruitment is difficult, since the diagnosis typically occurs after 18 months of age. Infants regarded as "high-risk" because of prematurity or other neonatal medical problems are known to have higher rates of adverse neuro-motor and cognitive problems (Spittle, Orton, Anderson, Boyd, & Doyle, 2012). Consequently although early intervention is endorsed for high-risk infants, the efficacy for infants with CP is not yet firmly established (Blauw-Hospers & Hadders-Algra, 2005). A number of early intervention clinical trials are now registered and open to recruitment and therefore new outcome data is expected in the coming years (Eliasson, Sjöstrand, Ek, Krumlinde-Sundholm, & Tedroff, 2014; Guzzetta, Boyd, & Perez, 2013; Prosser, Ohlrich, Curatalo, Alter, & Damiano, 2012).

We developed an early intervention programme based on best available evidence of interventions that work in older children and that aim to harness the neuroplasticity mechanisms at work in the developing brain (Johnston, 2004). This intervention, GAME (Goals Activity Motor Enrichment) (Morgan, Novak, Dale, Guzzetta, & Badawi, 2014),was first tested in a small pilot study (n = 6 GAME; n = 7 Standard Care) (Morgan, Novak, Dale, & Badawi, 2015) with promising results in improving motor outcomes of GAME participants when compared to standard care (SC). Our earlier pilot also established feasibility of procedures for recruitment and randomisation. The aim of this phase 2 study was to determine whether GAME intervention improved motor outcomes and parent perception and satisfaction with motor performance after 16 weeks of intervention, and then again at 12 months when compared with SC. The term "phase 2" is used to describe a study testing the effectiveness of a treatment (https://www.nlm.nih.gov/services/ctphases.html). We hypothesized that infants randomised to GAME would have superior motor skills at both time points.

2. Methods

2.1. Participants

Infants were included if they were corrected age (CA) 3-4 months and: scored as "absent fidgety" on General Movements Assessment (GMA); OR were aged 5-6 months with a CP diagnosis provided by a pediatrician after clinical examination OR had abnormal neuroimaging including either Magnetic Resonance Imaging (MRI) or Cranial Ultrasound (CUS), such that a CP diagnosis was considered extremely likely. Infants were excluded if they were inpatients, had medical conditions that precluded active involvement in therapy (such as oxygen dependency) or lived in a remote location not accessible for home visits by the research team. Infant characteristics can be found in Table 1 and Appendix A.

2.2. Study timeline and protocol

Infants were recruited from 6 participating Sydney hospitals with Neonatal Intensive Care Units (NICUs) and the Cerebral Palsy Alliance between February 2013 and June 2014. The study received ethical approval by the Sydney Children's Hospital Network, the University of Notre Dame Australia and the Cerebral Palsy Alliance human research ethics committees. Once eligibility was determined, parental consent was obtained and all baseline assessments and demographic data were collected.

2.3. Covariate

Motor severity is a known predictor of responsiveness to intervention. Due to the young age of the participants, the Gross Motor Function Classification Scale (GMFCS) could not to be used to reliably rate the severity of motor impairment (Rosenbaum et al., 2002). We therefore needed to use the best clinically available severity predictor which is neuroimaging blind-scored by a paediatric neurologist and paediatric radiologist to estimate severity of the brain injury. The variable we developed was based on published neuroimaging severity and outcome prediction data (de Vries, van Haastert, Benders, & Groenendaal, 2011). Neuroimaging was not available for n = 2 and only cranial ultrasound was available for n = 3. A score form was created from best available literature (Ferrari, Todeschini, & Guidotti, 2011; Krageloh-Mann & Horber, 2007; Kidokoro, Neil, & Inder, 2013). When multiple images were available, the series closest to term equivalent age was used for preterm infants and closest to day 7 for infants with hypoxic ischaemic encephalopathy. Severity results were ordinally coded as: 0 = normal OR unlikely to have CP; 1 = likely to have ambulant CP (e.g. focal vascular insults); and 2 = likely to have non-ambulant CP, (e.g. significant basal ganglia/thalamus lesions or diffuse brain injury). When neuroimaging data was not available it was coded as "missing".