Research in Developmental Disabilities 55 (2016) 256–267

Contents lists available at ScienceDirect

Research in Developmental Disabilities

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

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ARTICLE INFO

Article history:
Received 7 August 2015
Received in revised form 9 April 2016
Accepted 13 April 2016

Keywords:
Cerebral palsy
Motor learning
Early intervention
Environmental enrichment

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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http://dx.doi.org/10.1016/j.ridd.2016.04.005
0891-4222/

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".

Table 1
Characteristics of participants.

Infant characteristics		GAME n = 15	SC n = 15
AGE	Enrolment corrected age (weeks) mean (SD)	15.73 (4.76)	20.07 (5.08)*
SEX	Male, n (%)	8 (53)	9 (60)
CP RISK FACTORS	Birth weight (kg), mean(SD)	2.31 (1.02)	2.65 (1.12)
	Multiple births, n (%)	2 (13)	2 (13)
	Hypoxic Ischaemic Encephalopathy, n (%)	4 (27)	2 (13)
	Birth gestational age (weeks), mean (SD)	34.27(5.27)	35.27 (5.09)
	• 28 weeks, n (%)	1(6)	1(6)
	• 28-31 weeks, n (%)	4(27)	3(20)
	• 32-36 weeks,n (%)	2(13)	2(13)
	• >36 weeks,n (%)	8(53)	9(60)
CP DETECTION	GMs Absent fidgety, n (%)	15 (100)	13(87)
	GMs not assessed, n (%)	0	2 (13)
	Neuroimaging available, n (%)		
	• MRI	13 (87)	12 (80)
	• CUS only	1 (6)	2 (13)
	• No imaging	1 (6)	1 (6)
	Neuroimaging results, n (%) (MRI or CUS - term equivalent age)		
	• Normal	0	1 (6)
	• Unilateral injury	1(6)	3(20)
	• Bilateral injury	13(87)	10(67)
CP SEVERITY SCORES (predicted by blind scoring of imaging)	• 3 = predict non-ambulant CP + VI	4(27)	2(13)
	• 2 = predict non-ambulant CP no VI OR ambulant CP + VI	4 (27)	1 (6)
	• 1 = predict ambulant CP no VI OR VI alone	4 (27)	7 (47)
	• 0 = predict no CP and no VI	2 (13)	4 (27)
	• Missing (ie no imaging available)	1 (6)	1 (6)
Associated impairments n (%)	• Severe cerebral vision impairment (CVI)	4(27)	3(20)
	• Severe ROP (Grade 3)	0	1(6)
	• Epilepsy (uncontrolled)	1(6)	1(6)
	• Hearing Impairment	0	1(6)
	• Microcephaly (>3 SD below mean)	5 (33)	3 (20)
FAMILY CHARACTERISTICS			
SOCIAL RISK	Maternal age; mean (SD)	33.73 (4.73)	31.07 (7.11)
	Mother's education beyond secondary school, n (%)	10 (67)	6 (40)
	Primary language not English, n (%)	7 (47)	3 (20)
	High social risk, n (%)	9 (60)	11 (73)

*$p < 0.05$; CP severity score based on neonatal imaging and visual function; VI = vision impairment (either severe ROP or diagnosed severe cerebral vision impairment [CVI]).

2.4. Randomisation

An officer not connected with the study randomised participants at a separate location. The Primary Investigator was informed of group allocation and then informed parents. The allocation sequence was computer generated and assignments concealed using sequentially numbered opaque envelopes. No stratification was used in terms of gestational age, or type or severity of brain injury.

2.5. Intervention

Participants received their assigned intervention from enrollment until 12 months corrected age. As a result, the length of the total intervention period varied depending on the child's age at enrolment. Infants randomised to standard care either continued with pre-existing therapy arrangements or were referred to a local intervention site by their referring institution. Appendix B contains a checklist of intervention content for both GAME and standard care as recommended by the Tidier Guidelines (Hoffmann et al., 2014).

2.5.1. GAME intervention

GAME is an acronym for Goals, Activity and Motor Enrichment (Morgan et al., 2014). The intervention is based on the principles of active motor learning, family centred care, parent coaching and environmental enrichment. Intervention was customised to parent goals and enrichment style and the child's motor ability. To increase the dose of motor practice families were provided with a home program containing suggested activities according to identified goals. The intervention was offered via home visits at least fortnightly until the infants first birthday (CA).

2.5.2. Standard care intervention

"Standard care" (SC) describes the current follow-up and/or therapeutic interventions used when an infant at high risk of CP is discharged from hospital. It is not possible to standardise the frequency, intensity or type of interventions received in the

SC group. Therapeutic approaches used and modes and intensity of delivery are varied. All SC providers used a combination of centre based visits and home programs. Some infants in SC received home visits as well as clinic based appointments. Intervention approaches varied and was typically "eclectic" borrowing from a variety of therapy intervention paradigms including neurodevelopmental therapy and sensory integration. Appendix B contains information about the key differences between GAME and SC in this study, using the TIDIER guidelines.

2.6. Outcome measures

2.6.1. Motor

The primary outcome was motor skills as measured by the Peabody Developmental Motor Scales - Second edition (PDMS-2), a norm referenced assessment of gross and fine motor skills in children 0-6 years. Results are expressed as raw scores, standard scores and total motor quotient (TMQ), which is regarded as the best estimator of motor ability. The manual describes TMQs of 90-110 as "average", 80-89 as "below average", 70-79 as "poor" and 35-69 as "very poor". The PDMS-2 has been validated as a discriminative measure and two studies have demonstrated its' responsivity to change in infants and toddlers with CP (Kolobe, Palisano, & Stratford, 1998; Wang, Liao, & Hsieh, 2006). PDMS-2 assessments were obtained at baseline, 16 weeks after therapy had commenced and at the end of the intervention period when infants were 12 months CA. Two highly experienced assessors (one physiotherapist and one occupational therapist) who were blinded to group allocation scored the PDMS-2 assessments from video. High inter-rater reliability has previously been established for this tool, giving confidence that these two independent raters rated children the same way (Folio & Fewell, 2000).

2.6.2. Function

Secondary outcomes included the Canadian Occupational Performance Measure (COPM) (Carswell et al., 2004), an individualised criterion-referenced measure of performance and satisfaction with performance of a parent-selected range of activities. The COPM has previously been used in studies of infants and toddlers to identify problem areas and goals (Law et al., 2011). In this study COPM was used at baseline to prioritise parent goals for their baby's development and assess parent's perception of their infants' performance on identified goals and their own satisfaction with the infant's current ability. After 16 weeks of intervention the COPM was rescored and new priority areas identified. At 12 months the second COPM was rescored. Two occupational therapists with more than 10 years' experience and blinded to group allocation scored all COPMs post enrolment via telephone call.

2.6.3. Cognitive

Cognitive skills were assessed using the Bayley Scales of Infant and Toddler Development - Third Edition (BSID-III) and motor function using the Gross Motor Function Measure (GMFM-66) (Russell, Rosenbaum, Avery, & Lane, 2002). These measures were taken at 12 months only and scored by blinded assessors. Two physiotherapists each with more than 10 years experience scored all GMFMs and experienced assessors from NICU follow-up clinics scored BSID-III assessments.

2.6.4. Environment

Enrichment of the home environment was assessed with the Affordances in the Home Environment for Motor Development - Infant Scale (AHEMD-IS) (Caçola, Gabbard, Santos, & Batistela, 2011). AHEMD-IS identifies opportunities available within the home to promote motor development, including characteristics of the indoor and outdoor environment and the presence of a range of toys and equipment. This tool is a validated, parent self-report however sensitivity to change has not been established (Caçola, Gabbard, Montebelo, & Santos, 2014). Total score possible for infants younger than 11 months is 66 while from 12 months possible total score is 93, to account for the expected increase in available learning materials. To compare change from baseline to follow-up at 12 months we compared percentages of total score, as per test developer recommendations (personal communication).

2.6.5. Parent mental health

The Depression, Anxiety and Stress Scales - 21 (DASS-21) (Lovibond & Lovibond, 1995) is an adult self-report designed to measure the emotional states of depression, anxiety and stress. It is a 21-item questionnaire and was used to measure parent mental health at baseline, 16 weeks after randomization and at the 12-month time point. Lower scores are associated with more normal levels of depression, stress and anxiety. The DASS-21 manual supplies "normal", "mild", "moderate", "severe" and "extremely severe" values for each subscale. We used the DASS to monitor parent mental health during the study.

2.6.6. Dose of intervention

The intensity of time spent on therapy is known to affect outcomes and therefore a logbook was provided to each participant, to capture the amount of time in minutes spent on: (a) parent led practice of home program activities and (b) therapist led face-to-face intervention sessions.

2.7. Sample size estimation

The study sample size was estimated from a power calculation based on our earlier published pilot data (Morgan et al., 2015) using motor composite scores of the PDMS-2. We considered a clinical meaningful difference between the groups to be at least 5 standard score points (0.5 of a standard deviation). With an alpha value of 5% and power of 80%, using a minimal clinically important difference of 10% and accounting for a 20% dropout rate, we estimated the sample size required to be n = 30; 15 per group.

2.8. Statistical analysis

Analysis was carried out using SPSS and reported according to the CONSORT statement. Descriptive statistics (frequencies, means and 95% CIs) were used to describe the sample at baseline. Independent *t*-tests were used to compare baseline measure mean scores and parent and infant characteristics, where data were normally distributed. Random missing data was imputed as last observation carried forward. Where there were no results available due to dropouts, only the data available were analysed so as not to introduce new biases. Between-group differences for child outcomes were analysed using multiple regression to determine whether group allocation predicted outcome. As infants were too young to accurately use GMFCS as a motor severity variable, a neuroimaging +/− vision impairment severity variable was used as a covariate within the regression analysis. The severity variable was the aforementioned imaging ordinal score, plus a weighting point of +1 if the infant had severe vision impairment (i.e. consistently visually unresponsive to a moving toy stimulus; but motorically responsive to the same stimulus if an auditory cue was paired to the stimulus), since vision impairment is a known confounder of motor development. Outcomes on the COPM and AHEMD-IS were analysed using linear regression without the severity covariate. Parent mental health scores, home environment scores and dose of intervention were compared with independent *t*-tests.

3. Results

3.1. Participants

Thirty infants from twenty-nine families were recruited and randomised to GAME (n = 15) or SC (n = 15). Mean age at enrolment was 17.9 weeks (SD 5.31). There was one set of twins randomised to SC and two infants who were twins randomised to GAME. The flow of participants is summarised in Fig. 1. Adherence to study protocols was excellent until the 16-week time point with no dropouts and all participants receiving intervention as per protocol.

Between the 16-week time point and the final 12 month time point, 4 infants dropped out of the study, all from the GAME group. Reasons for drop out included: relocation overseas or interstate for increased family support (n = 3 of 4) and experimental stem cell treatment (n = 1 of 4). Data were analysed for all infants remaining in the study at 12 months, n = 11 in GAME and n = 15 in SC.

3.2. Baseline equivalence

Participant characteristics are summarised in Table 1. Groups were equivalent at baseline on infant characteristics, except for age at enrolment where the GAME infants were about 4 weeks younger by chance. Social risk was classified as “high” or “low” based on previously used criteria (Roberts et al., 2008). There were no significant between group differences on child motor function (Table 2) at baseline. The baseline (when available) and follow-up data for PDMS-2 (raw and TMQ), GMFM, Bayley Cognition and COPM (performance and satisfaction) were normally distributed and therefore we used parametric statistics as planned. Parent mental health scores were different at baseline with GAME parents having higher rates of depression, but no between group differences on the other sub-scales or total score (Table 3).

3.3. Data normality

Baseline DASS scores were normally distributed for depression and stress but not anxiety. Follow-up DASS scores on all subscales at both time-points (with the exception of depression at 16-weeks and 12-months) were all abnormally distributed and therefore we used non-parametric statistics for analyses of DASS. The AHEMD-IS was normally distributed at both time-points and therefore we used parametric statistics. Total dose was of therapy was normally distributed as was therapist time and we used parametric statistics, but home program time was abnormally distributed and therefore we used non-parametric statistics. We also analysed the relationship between: (a) total therapy dose and motor outcomes on the primary measure; and (b) a) total therapist delivered therapy dose and motor outcomes on the primary measure by calculating Pearson correlations coefficients.

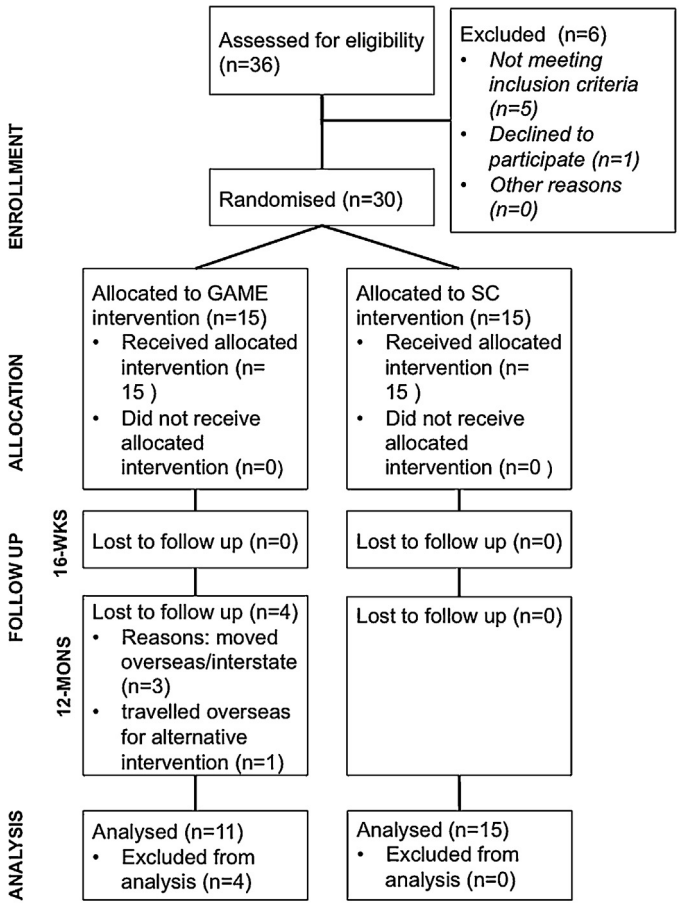

Fig. 1. Flow of participants through trial.

3.4. Child outcomes

Primary and secondary outcomes for GAME and SC infants are presented in Table 2.

3.4.1. Primary motor outcome 16 weeks after enrolment

After 16 weeks of intervention, no statistically significant between-group differences were found on the TMQ. Significant between group differences were found in change in raw scores in favour of GAME.

3.4.2. Primary motor outcome 12 months corrected age

Statistically significant between-group differences were found at 12 months on both the PDMS-2 TMQ and raw scores favouring GAME. To confirm these findings we conducted a mixed model analyses, which accounted for the baseline age difference and group allocation. The effect of GAME intervention over time was large (Partial Eta Squared = 0.201, where any effect over 0.14 is considered large) (Cohen, 1988). Confirmatory, significant between-group differences were evident on the GMFM-66 favouring GAME. In addition, mean BSID-III cognition scores were significantly higher for GAME at 12 months.

3.4.3. Functional outcomes

Significant between-group differences on COPM performance at 16-weeks were found in favour of GAME; mean change 3.55 (1.92) compared to 2.58 (2.21) for SC. There were no statistically significant differences between the groups in change scores on the satisfaction scale (GAME: 1.62 [SD 3.22] and SC: 2.00 [SD 1.78]). At 12 months, parent perception of their infant's movement skills did not significantly differ between the groups: GAME 2.57 [2.44]; and SC 1.09 [1.06]. Parents of infants in GAME did however have higher rates of satisfaction with their child's improvements (satisfaction change scores: GAME 2.66 [2.68] and SC 0.39 [1.17]).

Table 2
Outcomes at baseline, after 16 weeks and at 12 months.

Outcome		Group		Estimate of Effect (95% CI)	p-value
Time Point	Measure	GAME (n=15) Mean (SD)	SC (n=15) Mean (SD)		
INFANT MOTOR DEVELOPMENT					
Baseline	PDMS-2				
	Raw	33.60(13.71)	41.93 (16.49)	-	0.14
16-weeks	PDMS-2				
	Raw	73.20(36.40)	77.20 (44.25)	20.71 (1.66,39.76)	0.03*
12-months	PDMS-2				
	Raw	124.64(55.98)	107.93 (51.11)	51.58 (26.64,76.52)	0.01*
Baseline	PDMS-2				
	TMQ	84.87 (7.89)	82.93 (7.92)	-	0.51
16-weeks	PDMS-2				
	TMQ	79.13(16.11)	71.93 (16.02)	7.58 (−1.37, 16.52)	0.09
12 -months	PDMS-2				
	TMQ	72.64(17.75)	67.34(16.12)	8.29 (0.13, 16.45)	0.05*
PARENT PERCEPTION OF INFANT MOTOR PERFORMANCE					
Baseline	COPM Performance	3.05 (1.09)	3.19 (0.58)	-	0.41
16-weeks	COPM Performance	6.53 (2.08)	5.94 (2.56)	1.86 (0.58, 3.14)	0.01*
16-week new	COPM Performance	3.75 (1.48)	3.45 (1.15)	-	0.53
	COPM performance				
12-months		6.64 (2.55)	4.54 (2.82)	1.61 (−0.11, 3.34)	0.07
Baseline	COPM Satisfaction	5.18 (2.24)	4.40 (1.64)	-	0.28
16-weeks	COPM Satisfaction	6.80 (2.37)	6.19 (2.80)	0.35 (−1.35, 2.13)	0.08
16-week new	COPM Satisfaction	4.05 (1.89)	4.78 (2.51)	-	0.53
12-months	COPM Satisfaction	7.00 (2.45)	5.18 (2.82)	2.14 (0.40, 3.89)	0.02*
INFANT MOTOR FUNCTION					
12-months	GMFM-66	34.97 (13.42)	32.51 (9.99)	7.96 (0.00, 15.96)	0.05*
INFANT COGNITIVE DEVELOPMENT					
12-months	BSID-III				
	Cognition	6.27 (4.69)	4.40 (4.09)	3.85 (0.39,7.31)	0.03*
HOME ENRICHMENT					
Baseline	AHEMD-IS	50.40 (14.08)	55.00 (11.83)	-	0.34
12-months	AHEMD-IS	55.09 (13.90)	53.60 (10.66)	2.30 (−10.88, 6.30)	0.59

PDMS-2 = Peabody Developmental Motor Scales - Second edition; TMQ = total motor quotient; COPM = Canadian Occupational Performance Measure; GMFM-66 = Gross Motor Function Measure; BSID-III = Bayley Scales of Infant and Toddler Development (expressed as standard scores); AHEMD-IS = Affordances in the Home Environment for Motor Development Infant Scale (expressed as percentage of total possible score).
* Statistically significant.

3.4.4. Child diagnostic outcomes

Appendix A contains diagnostic outcome data for all 30 infants. At 12 months of age n = 24 (83%) had received a diagnosis of CP from a medical practitioner including 3 of the 4 who had dropped out of the study. A further two infants were globally delayed, three were undiagnosed but displaying neurological abnormalities such as motor asymmetry or mild spasticity and the developmental outcome of one infant was unknown. Of the 3 children with either no imaging or normal imaging, n = 1 had mild diplegia and a cognitive delay, n = 1 had bilateral lower limb spasticity but no diagnosis and n = 1 had monoplegia and cognitive delay at 12 months.

3.4.5. Parent and environment outcomes

Between-group differences on the AHEMD-IS scores at 12 months were non-significant. DASS 21 scores were compared at 12 months and no statistically significant differences existed between the groups in total DASS 21 score or in any of the subscales (Table 3). A wide distribution of scores occurred, but not with isolated extreme values. For anxiety ratings, at baseline and 16-weeks n = 20/30 (66%) had normal DASS scores and n = 10/30 (33%) had abnormal DASS scores; and at 12-months n = 19/26 (73%) had normal DASS scores and n = 7/26 (27%) had abnormal DASS scores. For stress ratings: at baseline n = 19/30 (63%) had normal DASS scores and n = 11/30 (37%) had abnormal DASS scores; at 16-weeks: n = 24/30 (80%) had normal DASS scores and n = 6/30 (20%) had abnormal DASS scores; and at 12-months n = 20/26 (77%) had normal DASS scores and n = 6/26 (23%) had abnormal DASS scores.

Table 3
Parent mental health at Baseline, after 16 weeks and at 12 months.

Measure	GAME Mean (SD)	SC Mean (SD)	p-value
DASS-21 Total Score			
Baseline	29.60(21.26)	21.47(10.62)	0.2
16 weeks[+]	30.80 (24.92)	21.20 (17.95)	0.29
12 months[+]	22.73 (21.06)	19.20 (17.38)	0.65
Depression Sub-Scale			
Baseline	10.67 (7.55)	4.53 (3.89)	0.01[*]
16 weeks	10.00 (7.67)	6.27 (5.70)	0.14
12 months	8.18 (7.13)	6.00 (7.13)	0.45
Stress Sub-Scale			
Baseline	13.33 (9.58)	13.07 (5.60)	0.93
16 weeks[+]	14.27 (10.28)	9.87 (6.65)	0.23
12 months[+]	10.00 (10.51)	9.07 (6.50)	0.88
Anxiety Sub-Scale			
Baseline[+]	5.60 (6.29)	3.87 (4.69)	0.62
16 weeks[+]	6.53 (8.57)	5.07 (7.32)	0.74
12 months[+]	4.55 (5.52)	4.13 (6.07)	0.65

DASS-21 = Depression Anxiety and Stress Scale short-form.
[*] Statistically significant.
[+] Non-parametric test used.

3.4.6. *Dose of intervention*

Complete logbooks were kept by 10 GAME families and 7 SC families and were collected at 12 months. Hours of face-to-face therapy could be ascertained for all families, however total dose (therapy delivered by therapist plus therapy delivered by parents) could only be calculated for those with completed logbooks. Infants in GAME received a mean of 21.91 (SD 4.25) hours of therapy (median 22 h) over the study period and SC 14.82 (SD 12.89) hours (median 13 h). There was no statistically significant difference between groups ($p = 0.09$). Parents in GAME reported they spent a mean of 47.70 (23.30) minutes per day (median 54 mins) carrying out the home programme while SC parents spent 42.29 (35.87) minutes (median 30 mins). There was no statistically significant difference between groups ($p = 0.36$). The total dose of therapy for GAME infants from enrolment until 12 months was 216.00 (87.26) hours and for SC infants 164.29 (98.79) hours. There were no statistically significant differences in dose of therapy over the entire study period ($p = 0.27$). There were low and non-significant correlations between motor outcomes and dose (total dose $R = 0.08$ and or therapist delivered therapy $R = 0.28$).

4. Discussion

GAME intervention appears to lead to improved short and medium term motor outcomes when compared with a similar dose of SC. This is evidenced both in the norm referenced measure (PDMS-2) as well as the criterion referenced GMFM-66.

The PDMS-2 TMQ scores were not statistically significant after 16 weeks, despite an estimate of effect of 7.5 favouring GAME, probably with the effect washed out due to large variances in both groups. At baseline, the TMQ variance was 0.5 of a SD for both groups, but increased to >1.0 SD by 16-weeks, indicating: (a) infants were of heterogeneous severities with varying capacities to respond to intervention; and (b) that norm referenced assessments might overestimate ability at younger ages, when infants have a more limited motor repertoire. At baseline, mean PDMS-2 TMQ scores for both groups were "below average" (described by test developers as a score between 80 and 89), but after 16 weeks had dropped further into the "poor" range (described by test developers as a TMQ between 70 and 79) for both groups, despite receiving intervention. At 12 months the TMQ had dropped further again, into the "very poor" range (TMQ below 69) for SC participants. This finding was not unexpected. Infants with CP continue to develop and "gain" raw score points over time, but are not expected to perform within the "normal range" but rather fall further behind peers over time. On average GAME participants, did not fall as far behind as those in SC in this study implying that characteristics of GAME intervention could be "protective".

The great majority of our sample had bilateral brain injuries albeit of varying severities, whereas in the CP population one third typically have unilateral injuries with milder motor disabilities (Novak et al., 2012). In addition during the study period it became clear that 8 of 30 (27%) had severe vision impairments identified by formal testing (4 per group), which exceeds the CP population norm of 10% (ACPR Group, 2013). Vision impairment is a known contributor to delayed motor development (Tröster & Brambring, 1993) and in children with CP is a predictor of non-ambulation (Wu, Day, Strauss, & Shavelle, 2004). These sampling errors meant that our study sample was "more severely affected" than a representative CP "population sample". In practice this may have meant our recruited sample might have been lower responders than a more representative CP population sample. Nevertheless, by controlling for severity of brain injury in the analysis, we observed that children with milder brain injury responded better to GAME intervention than those with severe brain injury. This finding fits with current thinking about the impact of brain injury on outcome (de Vries et al., 2011).

Given the unexpectedly high number of infants with severe vision impairments that were recruited to this study we would recommend formal visual function assessments be completed early to allow appropriate supports and intervention to be put in place. The assessment of visual function by Ricci et al. is one potentially useful test (Ricci et al., 2011).

After intervention, cognitive scores as measured by the BSID-III were superior for GAME infants, which we hypothesise could be a result of the environmental enrichment component built into GAME intervention. A recent meta-analysis demonstrated that in vulnerable families home visiting had a small positive mean effect on child cognitive outcomes (Filene, Kaminski, Valle, & Cachat, 2013). The consistency of home visiting in GAME allowed specific exchanges and information sharing to take place concerning customisation of play space, toys and play routines to enrich the infant's learning environment. Measuring cognitive outcomes by motor manipulation of cognitive test items in infants with CP is complex and may have dampened our ability to detect cognitive change. Many items are dependent on age appropriate hand motor function and most widely used tools are not validated or sensitive to change in children with CP (Yin Foo, Guppy, & Johnston, 2013). A recent study of 4-5 year olds with CP showed that almost 40% of participants were unable to complete enough items to score a complete IQ test due to difficulties with items requiring verbal ability and accurate fine motor performance (for example, pointing) (Sherwell et al., 2014). It is likely that infants in this study with poor hand function may have scored lower than their actual ability. Measuring cognition accurately in children with severe forms of CP is an area requiring urgent research.

The high number of infants diagnosed with CP by 12 months (n = 24; 83%) demonstrated the feasibility and accuracy of recruiting young infants with CP to clinical trials using Prechtl's General Movements Assessment (GMA) (Einspieler, Prechtl, Bos, Ferrari, & Cioni, 2004). To our knowledge this is the first study published in literature to recruit a sample of young infants (—6 months) where over 80% had CP. The 2 infants not diagnosed with CP but whom had severe global delay (all domains —2 SDs below the mean) had absent fidgety movements at 12-16 weeks but non-specific changes on neuroimaging. The combination of term equivalent MRI and GMA at fidgety age is recommended to most accurately identify infants with the highest risk of CP, as neuroimaging alone is less sensitive (Bosanquet, Copeland, Ware, & Boyd, 2013). Three infants in this study were performing within the normal range on the PDMS-2 at 12 months although two had persisting mild asymmetries and two had spastic catches bilaterally at the ankle. Another infant who had also scored in the normal range on the norm referenced tests, was predicted from imaging not to have CP was nevertheless diagnosed with mild spastic diplegia at 12 months. Defining clinical diagnostic criteria for this group of mildly affected infants is difficult and, in the absence of obvious activity limitations that are required for a diagnosis of CP (Bax et al., 2005), clinicians are understandably reluctant to use the CP label. It is also a possibility that early motor intervention may have optimised the outcomes of these infants.

In the GAME group, COPM parent satisfaction scores reached statistical and clinical significance (as per literature conventions) at 12-months, whereas SC did not. Perhaps parent education about CP in the GAME group led to parents being more realistic and therefore satisfied about their child's motor skills at 12 months.

Measuring home enrichment is complex and we attempted to do this by using a new scale, the AHEMD-IS. Although not statistically significant, mean scores in the GAME group increased as a percentage of total possible score over the study period. This may indicate that parents in this group were more likely to provide a wider variety of learning materials to match motor challenge as their child developed. A limitation of the AHEMD-IS is the focus on the physical home environment and variety of motor stimulation; it does not account for opportunities in other environments that the infant is exposed to. In addition, the scale does not capture parental responsiveness, a known contributor to child developmental outcomes (Warren & Brady, 2007). Future studies of GAME should include measures of parental responsiveness as well as more responsive measures of the physical environment.

Professional mental health support was offered to all mothers with abnormal DASS-21 anxiety or depression scores at any time point. Pleasingly parent mental health did not worsen but remained stable over the course of the study. This finding is important because GAME intervention did not seek to specifically target improvements in parent mental health, rather we sought to confirm that early detection and intervention did not adversely affect parent mental health. Parents in this sample experienced more anxiety and stress at most time points when compared to the typical population. This finding confirms previous literature about stress being a common experience when parenting a child with a disability (Schuengel et al., 2009). Although by 12 months mean scores for all subscales were in the normal range, approximately 20% of mothers were scoring in the moderate to severe DASS range for depression and/or anxiety. This finding highlights the importance of the availability of evidence based parent support programmes for parents of infants newly diagnosed with disabilities (Schuengel et al., 2009). In addition, two thirds of the sample was considered to be at high social risk plus one third were from families where English was not the first language spoken at home. The combination of high social risk and higher than average levels of depression and anxiety amongst these mothers, highlights the vulnerability of families with young infants at high risk of CP and other disabilities. EI programmes should include family support options that assist parents in their role and provide strategies to support their mental health and enhance their well-being.

Previous CP trials (Gordon, 2011; Sakzewski, Ziviani, & Boyd, 2013) in older children have shown that high-dose motor-learning based therapy leads to better results than low-dose motor-learning therapy, causing experts to hypothesise that many therapy interventions studied to date might be under-dosed. Interestingly, in older children, when two effective motor-learning interventions are compared head-to-head at the same high-dose, similar patient outcomes result. Recent systematic reviews have therefore identified that in addition to type of therapy mattering (effective versus ineffective) also the intensity of the therapy is important for treatment success (Myrhaug, Østensjø, Larun, Odgaard-Jensen, & Jahnsen, 2014). In our GAME study, the difference in dose of intervention was not statistically significant between the groups, due to the large variation within each group, however the median values clearly demonstrate that most GAME participants received a

higher number of therapy sessions and most GAME parents engaged in more home practice. Correlations between dose and PDMS-2 scores at the primary end-point were low, but this may also be an artefact of small sample sizes, which was further exacerbated by the volume of missing logbook data. It is therefore still possible that both the higher dose of intervention as well as characteristics of GAME contributed to the gains achieved in the GAME group but more research is needed.

4.1. Limitations

We recruited the intended sample size and as hypothesised observed between-group differences. However, our estimated sample size, based on earlier pilot data included no infants with visual impairments who are known to be less responsive to intervention. In addition, in this study the spread of severity was considerably wider as evidenced by the confidence intervals in the primary outcome at follow up. Plus n = 4 (13%) dropped out, although the a priori power calculation accounted for an even larger dropout rate of 20%. When we consider all of these trial factors together it is conceivable that this might have dissolved some of the effect size of the final results. However, in the 12-month analysis, missing data could not have substantially biased the secondary results because there was only after treatment BSID-III and GMFM-66 data, plus baseline and severity covariates were available for all individuals and included in all analyses (Sterne et al., 2009).

The variation of brain injury in CP remains a limitation in applying and measuring interventions. In this study, the brain injuries of enrolled infants ranged from mild white matter injury to BGT with diffuse cortical injury. Clearly this variability led to a variety in response to treatment. We used a novel severity variable to account for the variation in brain injury in our sample. This has not been previously tested and is thus a study limitation, however it predicted outcome accurately 75% of the time which proved more accurate than the most recognised severity tool, GMFCS, which is 58% in this age group (Gorter, Ketelaar, Rosenbaum, Helders, & Palisano, 2009). A further limitation is the incomplete information about the intervention content of the SC group. As expected there was substantial variety in intensity, mode and type of therapy offered. Motor task practice and the provision of a home program were common elements across both groups. Due to the great variability within SC we cannot be certain how differences in parameters such as dose, duration of intervention and specific aspects of each intervention may have contributed to the overall results of the study, Future studies should endeavour to identify the specific elements of GAME that led to the demonstrated benefits.

Finally, by chance infants in GAME were a month younger on average at enrolment raising the possibility that these infants might have had an advantage by having more intervention, however a within-subject analysis confirmed that enrolment age did not explain the between-group GAME and SC differences.

5. Conclusion

Our study suggests that 6-9 months of GAME, a clinically feasible intervention, is more effective than SC to advance the motor function of infants at high risk of CP. As expected, infants with milder brain injury responded better to intervention than those with severe brain injury. Furthermore using the GMA to recruit very young infants with CP to clinical trials is possible. GAME is a promising new early intervention for infants.

Funding source

Ms. Morgan is personally supported by an NHMRC/Cerebral Palsy Foundation Doctoral Scholarship1018027.

Financial disclosure

The authors have no financial relationships relevant to this article to disclose.

Conflict of interest

The authors have no conflicts of interest to disclose.

Acknowledgements

We thank the children and their families who participated in this study and the Sydney Children's Hospital Network for assistance with recruitment. We acknowledge and sincerely thank Dr Kristina Prelog, Ms. Jane Berry, Ms. Prue Golland, Dr. Petra Karlsson, Dr. Karen Walker and Mrs. Salli-Ann Wilson for their assistance with blind scoring of infant and family assessments and neuroimaging data. We also thank Claire Galea for her invaluable assistance with data analysis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ridd.2016.04.005.

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