LEARN2MOVE 0-2 YEARS: A RANDOMIZED CONTROLLED TRIAL ON EARLY INTERVENTION IN INFANTS AT VERY HIGH RISK OF CEREBRAL PALSY

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ABSTRACT

Aim: Evidence for early intervention in infants at very high risk (VHR) of cerebral palsy is limited. Therefore, we performed a randomized controlled trial in VHR-infants, comparing effects of COPCA (COPing with and CAring for infants with special needs) and Typical Infant Physiotherapy (TIP).

Method: Forty-three VHR-infants (median gestational age 32 weeks, 26 boys) were included before 9 months corrected age, based on a severe brain lesion or clear neurological dysfunction. They were randomly assigned to one year of COPCA (n=23) or TIP (n=20). Infants were assessed during and after the intervention with a battery of neuromotor, cognitive, functional and family tests, with the Infant Motor Profile (IMP) as primary outcome. Physiotherapeutic intervention sessions were video-taped, quantitatively analyzed and used for process analyses. Outcome was evaluated with non-parametric tests and linear mixed effect models.

Results: Infant outcome was comparable after receiving COPCA or TIP and not associated with specific physiotherapeutic actions. Age and brain lesion influenced infant outcome most. However, concerning the family, COPCA-related intervention elements were associated with better family empowerment.

Interpretation: One year of COPCA and one year of TIP in VHR-infants have similar effects on child and family outcome. Yet, specific COPCA-elements are associated with better family outcome.

What this paper adds

- One year of COPCA- or TIP-intervention resulted in similar VHR-infant outcome
- Age and type of brain lesion influenced infant's developmental outcome mostly
- COPCA-related intervention elements were positively associated with family empowerment
- Knowledge about contents of intervention assists in understanding active ingredients

Worldwide, infants at risk for neurodevelopmental disorders such as cerebral palsy receive early intervention. Many different intervention programs exist. Gradually our knowledge on the effect of early intervention increases. Reviewed post-discharge intervention programs for premature infants affect cognition until preschool, but effects on motor development are less and limited to infancy.[1] However, most preterm infants do not develop cerebral palsy (CP), as they do not have a serious brain lesion, such as periventricular leukomalacia (PVL) or cerebral infarctions.[2] Currently, little is known about the effects of early intervention in such very high risk (VHR) infants.

Recently, two systematic reviews[3,4] addressed the effect of early intervention in VHR-infants. They concluded that limited evidence for the effect of early intervention in VHR-infants is available, as only a few studies have been performed that applied various interventions and usually suffered from a lack of power and other methodological shortcomings. Both reviews suggested that a combination of interventional ingredients might be most promising for a beneficial effect, but opinions on the nature of the ingredients varied. This means that additional information on the effect of early intervention in VHR-infants is urgently needed.

In a previous study on the effect of three months of intervention in young VHR-infants, the VIP-project,[5,6] we combined the standard design of a randomized controlled trial (RCT) with a detailed process analysis of the interventions: COPing with and CAring for infants with special needs – a family centred program (COPCA) and the control intervention Typical Infant Physiotherapy (TIP). At RCT-level, both intervention groups developed similarly. Process analysis revealed that contents of intervention was associated with outcome, especially in the subgroup of infants diagnosed with CP. Challenging the infant and coaching the family were positively associated with motor outcome, whereas sensory experience was negatively associated with motor outcome. However, only about a quarter of the groups was diagnosed with CP. Therefore, we embarked on another intervention study in infants at even higher risk for CP, the LEARN2MOVE 0-2 years (L2M0-2) study,[7] using a similar double approach of RCT design and process analysis of the COPCA- and TIP-interventions. COPCA and TIP were now applied for a longer period: one year. Outcome was evaluated in a broad way, including child (neuromotor and cognitive), functional (daily life) and family outcome. We focused on the following questions: 1) do VHR-infants receiving COPCA or TIP differ in neuromotor, cognitive or functional outcome 2) do families receiving COPCA or TIP differ in outcome; 3) are specific physiotherapeutic actions related to child and family outcome; 4) is dosage of intervention expressed in daily activity of infant bathing as a measure of the implementation of intervention in daily life[8] associated with outcome; and 5) does the nature of the brain lesion, and especially the most severe brain lesion cystic periventricular leukomalacia (cPVL), affect the effect of intervention? We hypothesized that no or minor differences between COCPA and TIP are present at RCT-level on infant outcome measures, due to heterogeneity in interventions and knowledge from other intervention trials. We expected a more positive family outcome for COPCA, as COPCA is a family centred

approach. We hypothesized on the basis of our previous trial[5,6] that specific PT-actions - such as coaching and challenging - will be positively related to motor and functional outcome. Moreover, we hypothesized a better functional outcome in infants in whom the intervention was best implemented, measured by bathing activities. This hypothesis was based on the assumption that a higher exposure to intervention elements is associated with a better outcome. Finally, we expected that early intervention has least effect in infants with more severe brain lesions, as we assumed that a more affected brain will have less capability to reorganize or compensate.

METHOD

Participants

Infants were eligible for the study when they presented between 0 and 9 months corrected age (CA) with a VHR for CP. The latter[2] meant the fulfilment of one of the following criteria: 1) cystic PVL; 2) severe asphyxia with brain lesions on magnetic resonance imaging (MRI); 3) parenchymal lesions as result of infarction or haemorrhage; or 4) clinical dysfunction suspect for development of CP. Infants were recruited between November 2008 and November 2013 by paediatricians, child neurologists and physiotherapists from 12 hospitals in the northern half of the Netherlands. Seventy-seven infants fulfilled the inclusion criteria and caregivers of 43 infants gave informed consent to participate (Figure 1). The 43 infants in the study were randomly assigned to receive one year COPCA (n=23) or TIP (n=20). Randomization was stratified according to the four above mentioned inclusion criteria, with random sequence generating and concealment of groups by one of the authors (TD). After inclusion, imaging data were reclassified in order to obtain a uniform classification of brain lesions. Reclassification was performed by an experienced child neurologist (RJV) into the following categories: a) PVL, divided into non-cystic and cystic; b) cortical infarction; c) posthaemorrhagic porencephaly; d) basal ganglia or thalamic lesions; e) no or non-specific brain lesions. The study was approved by the Medical Ethical Committee of the University Medical Center of Groningen and registered in the Dutch trial register under NTR1428.

Interventions

COPCA consists of two main components: 1) a family and educational component and 2) a neurodevelopmental component. The first stresses family autonomy and coaches families to cope with their situation and make their own decisions. The neurodevelopmental component is based on the Neuronal Group Selection Theory. It aims to increase the size of the motor repertoire (variation) and to enhance adaptability in an active learning process with trial and error experiences.[9] TIP in the Netherlands is an eclectic mix of different approaches and theories, traditionally based on NeuroDevelopmental Treatment (NDT).

However, over time, a more functional approach with more family involvement, has been integrated resulting in a heterogeneous mix of physiotherapeutic ingredients.[9]

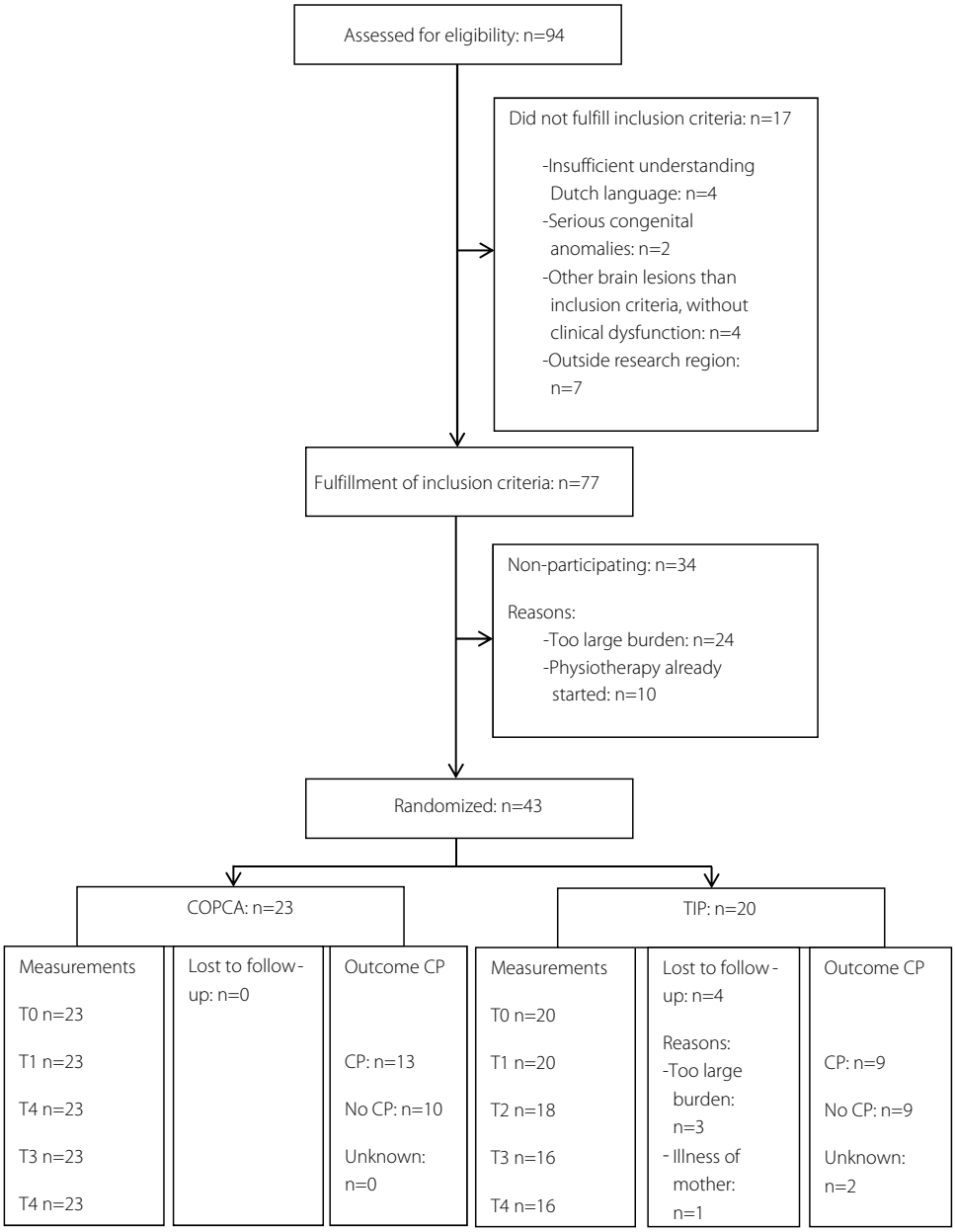

Figure 1: Flow diagram participants

The randomized parallel intervention started after inclusion and lasted one year. COPCA was provided at home once a week; TIP was in general also provided once a week at home, but occasionally it was delivered in an outpatient setting or in another frequency.

Supplementary Table 1: Neuromotor, cognitive, functional and family outcome measures at the different measurements during and after the intervention period

Measures	T0	T1	T1	T3	T4
IMP	+	+	+	+	+
TINE	+	+	+	+	+
GMFCS					+
AIMS	+	+	+	+	+
BSID-II PDI	+	+	+	+	+
BSID-II MDI	+	+	+	+	+
GMFM-88	+	+	+	+	+
GMFM-66	+	+	+	+	+
GMFM-adapted	+	+	+	+	+
PEDI	+		+	+	
FES	+		+	+	

Measurement: T0 = baseline (before the intervention period); T1 = after 3 months of intervention; T2 = after 6 months of intervention; T3 = after 12 months of intervention; T4 = at 21 months corrected age (after the intervention period). IMP = Infant Motor Profile; TINE = Touwen's Infant Neurological Examination; GMFCS = Gross Motor Function Classification system; AIMS = Alberta Infant Motor Profile; BSID-II – Bayley Scales of Infant Development, PDI = Psychomotor Developmental Index, MDI = Mental Developmental Index; GMFM = Gross Motor Function Measure; CA = corrected age, the additional assessment at 21 months corrected age is scheduled for infants who enter the study before the corrected age of 8 months; PEDI = Pediatric Evaluation of Disability Index; FES = Family Empowerment Scale. The GMFM is developed for children with CP, but infrequently used below age 2, because infants are usually not yet diagnosed with CP at that age. We used total scores of the original GMFM-88 and the shortened version GMFM-66. In addition, we applied the infant adaptation of the GMFM (Hielkema et al. 2013), which we called 'GMFM-adapted'.

Infant and family measurements

In the time period between November 2008 and September 2015, in each infant an extensive battery of tests was performed at baseline (T0, i.e., immediately after inclusion, before start of the intervention), after 3 months (T1), after 6 months (T2) and after 12 months of intervention (T3, i.e., at the end of the study's intervention period) and at 21 months CA (T4; only if the infant had an age below 8 months CA at inclusion, as in the other infants T3 and T4 coincided; n=3). Supplementary table 1 shows which measurements were used at the various measurement moments (see also Hielkema et al 2010).[7] Assessors were blinded for type of intervention, caregivers were asked not to inform them.

Our primary outcome was the Infant Motor Profile (IMP),[10] a video-based measurement to assess motor behaviour. The IMP does not only assess motor performance, but also the

quality of motor behaviour in the domains of variation (i.e., the size of the motor repertoire), adaptability (i.e., the ability to select adaptive motor strategies), fluency and symmetry. IMP-scores are expressed in percentages of the maximum score and are based only on the abilities of the infant at the time of the assessment.

Secondary neuromotor outcome measures consisted of the Touwen Infant Neurological Examination (TINE),[11] Gross Motor Function Classification System (GMFCS),[12] the Albert Infant Motor Scale (AIMS),[13] the Gross Motor Function Measure (GMFM)[14] and the Bayley Scales of Infants Development - Psychomotor Developmental Index, second edition (BSID-II PDI).[15] The TINE was used to document neurological condition and provided information on the absence or presence of CP at the last measurement (21 months CA). In case of CP, severity was classified according to the GMFCS. Realizing that our primary outcome measure was relatively new and that evaluation of motor development of VHR infants is difficult we also documented motor development with other instruments. The AIMS and GMFM were used to document gross motor function, the BSID-II PDI to assess gross and fine motor capacity. Of the AIMS and BSID-II PDI raw scores were used as percentiles and developmental indices of many infants were below the 5th percentile or at the lowest level (below 55) and therefore lacked discriminatory sensitivity in our groups. Cognitive development was assessed with BSID-II's Mental Developmental Index (BSID-II MDI);[15] again total raw scores were used in the analyses.

For functional outcome, i.e. functioning in daily life, we interviewed parents with the Dutch version of the Pediatric Evaluation of Disability Index (PEDI).[16] The PEDI results in a total score and three subscores: self-care, mobility and social function.

Family functioning was measured with the Family Empowerment Scale (FES),[17] an instrument that measures empowerment in families with children with developmental problems. The original questionnaire consists of three subscales: 1) empowerment in the family system, 2) empowerment in the service system and 3) parents' involvement in the community. The first two subscales were translated into Dutch for the L2M-study.[18] Both the two subscales and their total score were used as measures of family empowerment.

All above described measurements have shown to be sufficiently valid and reliable,[7] except the Dutch version of the FES, as the psychometric properties of the Dutch version had not been evaluated. The psychometric properties of the original FES are adequate.[17]

Quantification of intervention sessions

We aimed to video-record physiotherapy sessions three times: 1 month, 6 months and 12 months after the onset of intervention. As video-recording after 12 months was only moderately successful (31 videos (72% of participants) obtained), we only used video-recordings obtained after 1 month (n=41) and after 6 months (n=37). Comparable with the VIP-study, contents of the 1 and 6 months videos was largely similar (cf. Dirks et al. 2011[9]).

Supplementary Table 2: Percentages of time spent on physiotherapy actions for COPCA and TIP

Physiotherapy actions	**COPCA** (n=23) Median % (range)	**TIP** (n=20) Median % (range)	**ICC's** (n=10)
Neuromotor actions			
Facilitation techniques**	0 (0-6)	10 (1-29)	0.788
Sensory experience*	1 (0-17)	5 (0-15)	0.928
Passive motor experience**	0 (0-3)	1 (0-11)	0.782
SPMB, no interference	43 (19-74)	33 (21-54)	0.786
CSPMB, infant continues activity*	38 (0-68)	27 (6-56)	0.947
CSPMB, activity flow over into hands-on techniques**	0 (0-6)	10 (0-28)	0.983
Not specified neuromotor actions	6 (1-75)	6 (1-11)	0.702
Educational actions			
Caregiver training**	0 (0-11)	13 (0-65)	0.921
Caregiver coaching**	82 (4-98)	0 (0-40)	0.945
Not specified educational actions**	6 (1-75)	83 (13-100)	0.933
Communication			
Information exchange	5 (0-23)	7 (1-17)	0.819
- About COPCA	0 (0-1)	0 (0-3)	-
- About NDT**	0 (0-1)	1 (0-6)	-
- About family issues	5 (0-21)	5 (0-11)	0.696
Instruction	7 (1-20)	5 (1-17)	0.942
- Giving hints	2 (0-8)	1 (0-15)	-
- Multiple options	0 (0-8)	1 (0-8)	-
- Strict instruction	3 (0-7)	1 (0-16)	0.551
Provide feedback	15 (2-37)	22 (5-31)	0.908
- Ask & listen	1 (0-13)	0 (0-5)	0.620
- Share information	4 (0-12)	6 (1-22)	0.837
- Evaluate procedure	10 (0-26)	8 (2-25)	0.683
- What went right/wrong	0 (0-0)	0 (0-1)	-
Not specified communication	57 (24-89)	60 (44-78)	0.866
Position			
Supine	29 (0-58)	29 (1-55)	0.998
Prone	17 (5-52)	19 (4-41)	0.984
Side	2 (0-15)	2 (0-9)	0.976
Sitting	30 (0-70)	26 (10-60)	0.977
Standing	0 (0-14)	1 (0-32)	0.998
Walking	0 (0-4)	0 (0-4)	0.984
Transition**	2 (1-7)	5 (1-15)	0.920
Not specified position	2 (0-67)	2 (0-13)	0.831

Supplementary Table 2: Percentages of time spent on physiotherapy actions for COPCA and TIP (Continued)

Physiotherapy actions	**COPCA** (n=23) Median % (range)	**TIP** (n=20) Median % (range)	**ICC's** (n=10)
Situation			
Motor activity and play	96 (46-100)	95 (66-100)	0.969
Feeding	0 (0-42)	0 (0-32)	0.998
Dressing	0 (0-14)	0 (0-17)	0.965
Carrying	1 (0-15)	1 (0-10)	0.953

% = median percentage of time spent on physiotherapy actions during physiotherapy sessions 1 and 6 months after the start of intervention; differences between groups tested with Mann Whitney U-tests, *p<0.05; **p<0.01; ICC = Intraclass Correlation Coefficient. ICC's were calculated on the basis of 10 videos by two independent observers. ICC's were calculated if more than 2% of time was spent on a PT-action

Therefore, we decided to use the mean scores of these two intervention sessions for further analyses. This implies that in infants in whom only one of these intervention videos was available, single video information was used (filmed after 1 or 6 months of intervention).

Video-recordings were analysed with the Groningen Observer Protocol 2.0 (GOP 2.0)[19] with the computer program The Observer (version 11.5, Noldus, Wageningen). Total percentage of time spent on specific physiotherapeutic actions was scored within five main categories: neuromotor actions, educational actions, communication, position, and situation. Within each category, specific behaviours could be specified in subcategories (so-called modifiers). Two persons from the L2M0-2 study group, (RT and SJH), scored the videos independently and had overall a good to excellent interobserver reliability (details in supplementary table 2).

Quantification of infant positioning during bathing

We had scheduled to videotape bathing sessions at T0, T2 and T3. We aimed to analyse the bathing sessions to measure implementation of intervention into daily life activities (cf. Dirks et al. 2016[8]). Unfortunately, we were not very successful in collecting these video-data (missing videos: T0: n=2, T2: n=17, T3: n=14). Major reasons for missing videos were; 1) infants were showered with their parent (n=13 videos), 2) parents did not allow videotaping of bathing (n=8 videos), infants who were lost to follow-up before completion of the trial (n=6 videos) and logistical problems (n=6 videos). Due to the large proportion of missing data we decided not to use the bathing videos as a measure of implementation of the interventions in the analyses.

Data analyses

Power calculation was based on the IMP, our primary outcome measure. A sample size of 19 infants in both intervention groups, resulted in a power of 80% (α=0.05) to detect a clinically relevant change of 7.5 points in the total IMP score (SD = 8.2).

To achieve data reduction in the process analysis on the role of specific physiotherapeutic actions, we used factor analysis by applying principal axis factoring with an Oblimin rotation (as we dealt with interrelated physiotherapeutic actions; SPSS version 21). The factor analysis resulted in three components: 1) NDT versus COPCA factor, a dimension reflecting the diametrically opposed core elements of NDT (hands-on techniques and training) and COPCA (coaching and challenging self- generated motor activities), with a high score reflecting NDT-like actions and a low score COPCA-like actions; 2) non-directive communication and self-produced motor behaviour (SPMB), i.e., physiotherapeutic actions incorporated in the COPCA-approach ; and 3) directive communication and training, i.e., physiotherapeutic actions that are discouraged in COPCA (Table 1). Total variance explained with these three factors was 45% (factor 1: 21%; factor 2: 15%; factor 3: 9%), with a Kaiser-Mayer-Olkin Measure of 0.681. Factor loadings per infant were used as indicators of contents of intervention and we considered a minimal factor loading's value of 0.45 as significantly contributing to the factor.

Our study design was based on the RCT, comparing the infant and family outcomes at different measurement times. At the RCT-level we used univariate statistics only to compare baseline characteristics and outcome at 21 months CA. For this purpose, we used SPSS version 21. As the data were not normally distributed, we used non-parametrical statistics. Differences in baseline characteristics and outcome between the two intervention groups were tested with Mann Whitney U and Chi-square tests. Estimates of differences of the median outcome values at 21 months CA were expressed by Hodges Lehmann.

Multilevel analyses were performed with nlme (linear and non-linear mixed effect models) library in R version 3.3.1[20] to study longitudinal potential differential effects of COPCA and TIP on the main motor (IMP), cognitive (BSID-II MDI), functional (PEDI) and family (FES) outcome parameters, taking into account the age in corrected months and possibly confounding factors. We used linear mixed effects models to describe the subject-specific time profiles per infant, as this type of analysis takes into account correlation between observations from the same infant. We first tested possible effects over time of intervention (COPCA versus TIP), taking into account possible interaction effects of intervention with age. In these analyses we did not use measurement moment as indicator of time but corrected age in months (and its square), to get the best model fit and avoid introducing error by neglecting the unstructured nature of the data. In the analyses, we adjusted a priori for the following background variables: gestational age, level of parental education, and presence of cystic PVL (a major predictor of CP[21]), as these factors are known to influence motor and

cognitive outcome.[1,2,21] We repeated these analyses for each of the outcome variables in a similar way for the three factors describing physiotherapy (1= NDT versus COPCA; 2=non-directive communication; 3=directive communication), using similar models for each outcome and again, a priori adjusted for the selected covariates. We considered p-values below 0.01 as statistically significant.

Table 1: Factor analysis physiotherapeutic actions

	Factors		
PT-actions	1: NDT versus COPCA	2: Non-directive communication	3: Directive communication
Facilitation techniques	0.796		
Passive motor experience	0.763		
Challenged to SPMB, activity flows over into hands-on techniques	0.738		
Feedback: share information	0.609		
Caregiver training	0.519		-0.604
Information about NDT	0.467		
Caregiver coaching	-0.785		
Challenged to SPMB, infant is allowed to continue activity	-0.534		
Feedback: ask & listen to caregivers		0.778	
Self Produced Motor Behaviour (SPMB), no interference		0.615	
Information about family issues		0.610	
Information about COPCA		0.461	
Instruct: giving hints		0.459	
Instruct: strict instruction			-0.600
Feedback: evaluate procedure			-0.660
Feedback: what went right & wrong			-0.456

The table shows results of factor-analysis, applying principal axis factoring with Oblimin rotation. Numbers shown in the table are factor loadings, i.e. to which extent the different physiotherapeutic actions (PT-actions) contribute to the different factors. Factor loadings above 0.45 were regarded as contributing sufficiently to the factor. Only factor loadings above 0.45 are shown in the table. Positive factor loadings contribute positively to the factor, negative factor loadings contribute negative to the factor (i.e. are oppositely related to the concerning factor. For example: In case of factor 1, NDT versus COPCA, it means: facilitation techniques (positive loading) contribute to the factor's NDT-component whereas caregiver coaching (negative loading) contributes to factor's COPCA-component).

RESULTS

Participation

Of the 43 included infants (n=23 COPCA, n=20 TIP), four infants were lost to follow-up, all from the TIP-group (Figure 1). Reasons for withdrawal from the study were maternal illness (n=1), and study burden (n=3). Of two 'lost' infants we did obtain information on outcome in terms of CP and GMFCS-level around 21 months CA, based on information from medical records, obtained with caregivers' permission.

Baseline characteristics of caregivers and infants, of both intervention groups were comparable (Table 2). In both groups frequency of intervention was somewhat lower than the intended once a week, amongst others due to holidays and logistic factors. At 21 months CA 22 out of 41 infants (54%) were diagnosed with CP, without significant differences between COPCA and TIP. Also, no significant differences in severity of CP expressed by GMFCS-levels were present (Table 2).

Neuromotor, functional and family outcome

At RCT-level neuromotor, functional and family outcome of the two intervention groups at the various measurement moments was similar (supplementary table 3).

Also the multilevel analyses showed that the effect of COPCA and TIP intervention on the various outcome measures was comparable (Table 3a). Outcome was especially affected by age (IMP, BSID-MDI and PEDI) and the presence of cystic PVL (BSID-MDI). No interaction effects of intervention with age and cystic PVL were found. The FES was independent of infant's age and brain lesion.

We repeated the multilevel analyses with the three factors describing interventional elements with physiotherapeutic actions (Table 3b). None of the factors were significantly associated with infant outcome, although the association between factor 2 and IMP approached significance; it suggested that more time spent with non-directive communication might have been associated with worse IMP-scores. Also in these analyses infant outcomes were mainly associated with age and cystic PVL. Family outcome was associated with one of the physiotherapeutic factors: factor 1 was associated with total FES score, indicating that less time spent with the NDT-approach and more time spent with the COPCA-approach was associated with better FES scores.

Table 3 shows the results of the linear mixed effects models with random intercept (all models) and random slope (random linear time effect, IMP models only). In table 3a, effects of intervention on outcome are shown. In table 3b, effects of interventional elements, measured by factors 1, 2 and 3, are shown. Besides the effects of intervention (3a) and interventional elements (3b) on outcome, covariates statistically significant contributing to

outcome are shown. No significant effects of caregivers' educational level, gestational age or interaction effects for intervention with both age and cystic periventricular leukomalacia were found (data not shown in the table).

Table 2: Baseline characteristics and outcome CP

	COPCA (n=23)	TIP (n=20)	p-value
Gestational age (weeks): median (range)	32 (26-41)	29 (26-41)	0.10
Preterm/term# (n)	15/8	13/7	0.99
Birth weight (grams): median (range)	1915 (770-4410)	1375 (720-5400)	0.07
Gender# (n): female/male	8/15	9/11	0.50
Twins# (n)	6	4	0.64
Maternal age at infant's birth (years): median (range)	29 (19-45)	31 (17-41)	0.34
Educational level mother (n)			
Low/medium/high	5/13/5	6/6/8	0.64
Unknown	0	0	
Educational level father (n)			
Low/medium/high	8/10/5	5/5/9	0.17
Unknown	0	1	
Age at baseline (months): median (range)	1.4 (0.1-8.6)	2.5 (0.9-9.0)	0.07
Brain lesions# (n)			
- PVL	7 (cystic: 5)	6 (cystic: 5)	
- Cortical infarction	2	1	0.93
- Posthaemorrhagic porencephaly	5	7	
- Basal ganglia/thalamus	5	3	
- No/non-specific lesion	4	3	
Frequency of interventions per month: median (range)	3.0 (1.8-4.0)	2.5 (1.3-4.3)	0.09
Diagnosis at 21 months CA#			
- CP	13 (57%)	9 (45%)	0.17
- No CP	10 (43%)	9 (45%)	
- Unknown	0 (0%)	2 (10%)	
GMFCS of infants with CP			
- Level 1	3 (23%)	0 (0%)	
- Level 2	4 (31%)	3 (33%)	0.25
- Level 3	1 (8%)	4 (44%)	
- Level 4	2 (15%)	1 (11%)	
- Level 5	3 (23%)	1 (11%)	
Type of CP#			
- Unilateral spastic	4 (31%)	1 (11%)	0.18
- Bilateral spastic	9 (69%)	8 (89%)	

CP = cerebral palsy; COPCA = COPing with and CAring for infants with special needs – a family centered programme); TIP = typical infant physiotherapy; CA= corrected age; PVL = periventricular leukomalacia; GMFCS = Gross Motor Classification System; # = nominal variable

p-values based on non-parametric tests; for ordinal, interval and ratio variables tested with Mann Whitney U; for nominal variables# tested with chi square, linear by linear association.

Supplementary table 3: Outcome in both intervention groups at the various measurement moments

	T0 median age 2m (0.1-9)		T1 median age 5m (3-12)		T2 median age 8m (6-15)		T3 median age 14m (12-21)		T4 median age 21 m (20-22)		
	COPCA (n=23) median (range)	TIP (n=20) median (range)	COPCA (n=23) median (range)	TIP (n=20) median (range)	COPCA (n=23) median (range)	TIP (n=18) median (range)	COPCA (n=23) median (range)	TIP (n=16) median (range)	COPCA (n=23) median (range)	TIP (n=16) median (range)	HL estim (95% CI)
IMP Total score	66 (58-75)	70 (56-75)	72 (60-77)	73 (62-83)	73 (58-84)	76 (62-84)	76 (59-88)	79 (67-89)	82 (69-94)	81 (69-89)	0 (-5;4)
• **Variation**	71 (65-79)	69 (61-81)	69 (60-83)	72 (54-88)	72 (59-89)	73 (59-95)	71 (59-91)	71 (62-90)	72 (60-96)	72 (60-90)	0 (-6;5)
• **Adaptability**	76 (71-86)	67 (64-69)	86 (83-92)	85 (71-93)	75 (50-100)	80 (50-90)	80 (50-100)	85 (63-100)	92 (75-100)	87 (67-96)	4 (-2;9)
• **Performance**	36 (30-61)	39 (29-63)	50 (32-68)	55 (37-74)	58 (32-84)	60 (39-81)	75 (33-88)	75 (57-89)	83 (33-92)	84 (49-90)	-1 (-7;5)
• **Fluency**	67 (50-75)	70 (50-100)	75 (67-75)	75 (67-75)	75 (67-75)	75 (63-75)	75 (70-88)	75 (70-80)	75 (67-90)	73 (60-80)	0 (0;5)
• **Symmetry**	87 (67-100)	89 (50-100)	90 (67-100)	94 (63-100)	92 (50-100)	95 (75-100)	89 (56-100)	93 (61-100)	89 (61-100)	88 (67-100)	0 (-11;6)
AIMS	5 (2-21)	7 (2-19)	11 (2-22)	12 (4-46)	20 (3-39)	16 (6-45)	37 (6-57)	32 (12-57)	50 (5-56)	45 (10-56)	3 (-6;1)
BSID-MDI	11 (6-67)	18 (4-67)	41 (11-75)	49 (7-74)	63 (20-91)	62 (10-89)	84 (51-105)	85 (66-110)	104 (55-125)	104 (13-126)	0 (-13;12)
BSID-PDI	12 (5-36)	13 (7-36)	25 (8-46)	28 (7-54)	35 (6-59)	35 (4-61)	56 (19-70)	47 (32-70)	67 (10-90)	64 (22-76)	1 (-8;13)
GMFM-88	6 (2-19)	6 (3-21)	10 (3-20)	13 (4-24)	16 (4-31)	17 (5-29)	23 (7-39)	19 (8-42)	28 (4-48)	36 (15-66)	-4 (-14;5)
GMFM-66	16 (8-27)	17 (8-24)	23 (10-29)	23 (17-43)	27 (14-44)	25 (10-47)	43 (16-63)	37 (18-56)	49 (10-67)	53 (27-62)	-2 (-11;8)
GMFM-adapted	6 (2-21)	7 (3-22)	12 (3-24)	14 (5-44)	19 (3-44)	19 (5-50)	37 (7-64)	32 (7-65)	51 (5-71)	58 (19-70)	-7 (-18;6)

Supplementary table 3: Outcome in both intervention groups at the various measurement moments (Continued)

	T0 median age 2m (0.1-9)		T1 median age 5m (3-12)		T2 median age 8m (6-15)		T3 median age 14m (12-21)		T4 median age 21 m (20-22)		
	COPCA (n=23) median (range)	TIP (n=20) median (range)	COPCA (n=23) median (range)	TIP (n=20) median (range)	COPCA (n=23) median (range)	TIP (n=18) median (range)	COPCA (n=23) median (range)	TIP (n=16) median (range)	COPCA (n=23) median (range)	TIP (n=16) median (range)	HL estim (95% CI)
FES Total score	94 (73-120)	94 (80-104)	NT	NT	98 (82-120)	92 (70-108)	99 (80-120)	96 (75-107)	NT	NT	NT
• **Family**	50 (33-60)	47 (38-55)	NT	NT	51 (41-60)	51 (41-60)	50 (39-60)	48 (40-59)	NT	NT	NT
• **Service system**	45 (33-60)	45 (35-53)	NT	NT	48 (41-60)	46 (28-52)	48 (31-60)	46 (27-53)	NT	NT	NT
PEDI Total score	1 (0-23)	2 (0-24)	NT	NT	17 (3-52)	19 (3-56)	45 (5-81)	38 (25-98)	NT	NT	NT
• **Self care**	0 (0-10)	0 (0-11)	NT	NT	7 (1-17)	9 (1-17)	13 (4-25)	15 (9-25)	NT	NT	NT
• **Social functioning**	1 (0-11)	2 (0-11)	NT	NT	7 (1-52)	7 (2-12)	17 (1-28)	15 (9-28)	NT	NT	NT
• **Ambulation**	0 (0-3)	0 (0-2)	NT	NT	3 (0-13)	3 (0-28)	14 (0-39)	11 (2-45)	NT	NT	NT

Note: Because we continued with the statistically more appropriate longitudinal multilevel analyses, we only show median data during the intervention period and statistical analyses only at 21 months corrected age. AIMS=Alberta Infant Motor Scale; COPCA = COPing with and CAring for infants with special needs; FES=Family Empowerment Scale; GMFM=Gross Motor Function Measure; HL estim = Hodges Lehmann estimate of the median difference; IMP=Infant Motor Profile; m=months; MWU = Mann Whitney U; PEDI=Pediatric Evaluation of Disability Index; TIP=typical infant physiotherapy; T0=baseline; T1=after 3 months, T2=after 6 month, T3=after 12 months intervention; T4=around 21 months corrected age; 95%CI = 95% Confidence Interval; NT=not tested

Table 3: Longitudinal analyses, using linear mixed effect models.

3a: Model with interventions COPCA (=0) and TIP (=1)

	IMP – total score		BSID II MDI – raw score		PEDI – total score		FES – total score	
	regression coefficient	p-value	regression coefficient	p-value	regression coefficient	p-value	regression coefficient	p-value
Intervention	0.69	0.632	-4.1	0.322	-3.7	0.368	-4.8	0.356
Age	1.39	**0.001**	7.6	**<0.001**	1.1	0.090	0.31	0.156
Quadratic age	-0.031	**0.001**	-0.15	**<0.001**	0.13	**0.001**	NA	NA
Cystic PVL	-2.8	0.144	-15.8	**0.004**	-9.7	0.015	6.6	0.243

3b: Model with factors 1) NDT versus COPCA; 2) non-directive communication; 3) directive communication

	IMP – total score		BSID II MDI – raw score		PEDI – total score		FES – total score	
	regression coefficient	p-value	regression coefficient	p-value	regression coefficient	p-value	regression coefficient	p-value
Factor 1	0.13	0.823	-1.8	0.285	0.24	0.845	-5.5	**0.009**
Factor 2	-1.4	0.018	-2.3	0.165	-1.6	0.181	-0.47	0.644
Factor 3	-0.77	0.240	1.5	0.402	2.5	0.057	0.76	0.456
Age	1.4	**<0.001**	7.7	**<0.001**	1.1	0.060	1.2	0.22
Quadratic age	-0.03	**<0.001**	-0.15	**<0.001**	0.13	**<0.001**	NA	NA
Cystic PVL	-2.8	0.031	-10.5	**0.005**	-8.8	**0.002**	0.22	0.83

p-value <0.01 considered as statistically significant, bold numbers show statistically significant p-values; PVL = periventricular leukomalacia; NA = no added value

Table 3 shows the results of the linear mixed effects models with random intercept (all models) and random slope (random linear time effect, IMP models only). In table 3a, effects of intervention on outcome are shown. In table 3b, effects of interventional elements, measured by factors 1, 2 and 3, are shown. Besides the effects of intervention (3a) and interventional elements (3b) on outcome, covariates statistically significant contributing to outcome are shown. No significant effects of caregivers' educational level, gestational age or interaction effects for intervention with both age and cystic periventricular leukomalacia were found (data not shown in the table).

DISCUSSION

In our study, infant outcome was not influenced by type of intervention or associated with interventional elements. Age and type of brain lesion, in the form of cPVL, determined infant's developmental outcome most; they did not interact with type of intervention. At RCT-level COPCA was not associated with better family outcome, but COPCA-related actions were associated with better family empowerment.

Being aware of overlap between interventions and having knowledge of previous studies, the similar outcome in the randomized intervention groups was not unexpected. It raises the question whether the RCT is always the gold standard for measuring

effectiveness of interventions, especially if heterogeneity within interventions is present.[5,22] Knowing about RCT's pitfalls, we did a detailed process analysis of physiotherapy contents, independent from group randomization, to retrieve distinguishing interventional elements. After analysing contents of intervention, a clear contrast was found between NDT-related actions (hands-on techniques, caregiver training) and COPCA-related actions (challenging the infants to self- produced motor behaviour, caregiver coaching). Despite the clearly discriminating interventional elements, we did not find any significant association between the elements and infant outcome. This finding differs from our previous study,[5,6] in which multiple associations between contents of intervention and infant outcome were present. The current absence of associations may be related to differences in study design. First, in the L2M-study, most infants had severe brain lesions; in the VIP-study, most infants had no or non-significant brain lesions. It could be surmised that the presence of serious brain lesions alters the effect of early physiotherapy. Recent reviews and intervention studies suggest that multifaceted interventions may be most effective for VHR-infants.[3,4] Where we did find comparable infant outcome in our study, the GAME-study (Goals-Activity-Motor-Enrichment)[23] noted an advantage for the GAME-intervention on infant's motor and cognitive outcome. The difference in outcome may be related to differences in neuromotor approach: COPCA uses a 'hands-off' strategy to stimulate infants to develop own strategies, whereas the GAME-study uses combined principles of motor learning and dynamic systems theory, in which manual guidance is provided when needed and withdrawn when the infant shows the ability to begin to demonstrate the motor action. Differences in outcome for infants with severe brain lesions (L2M0-2 and GAME-study) compared with infants with no or non-significant brain lesions (VIP-project), may suggest that severely affected infants may benefit from some hands-on assistance, whereas infants with less severely affected neuromotor development may profit more from trial and error to develop their own motor strategies. Also, the intervention's duration and dosage may have affected outcome. The VIP-project provided a three months intervention twice a week, the L2M-study a one year intervention once a week. Literature suggests positive effects of short and intensive interventions.[24] Unfortunately, we did not succeed in gathering sufficient data about implementation of the intervention, i.e. dosage of interventional elements in daily life activities. Our findings emphasize the need for good measurement tools for implementation of interventions into daily life.

We did find an association between interventional elements and family outcome: family empowerment was negatively associated with NDT-related actions and positively with COPCA-related actions. One of COPCA's key components is coaching, aiming to empower caregivers in making their own decisions, both within their own family system and in the health care system.[9] The positive relation between COCPA-related actions and family empowerment may be the result of an effect of coaching over time. Empowering

caregivers aims to promote a sense of mastery over situations, which is positively related to psychological health of caregivers[25] and may influence caregivers' health and well-being on the longer term.

Strengths of our study are the longitudinal evaluation of VHR-infants from early age onwards, knowledge about infants' brain lesions, the detailed process analysis of intervention contents and the broad evaluation of child and family with a range of different outcome measurements. The longitudinal design allowed for a mixed-effect model analysis, allowing for the adjustment for potential confounders, taking into account the correlation structure in the data. Our study is one of the few early intervention studies that had brain imaging data for all infants[1], and therefore, we were able to study relations between severe brain lesions and outcome and possible interaction effects. The detailed process analysis made it possible to study real contents of the intervention programs, and allowed to uncover potential working elements within the intervention programs. It is a strategy to cope with the large heterogeneity within interventions. Knowledge about contents of intervention is needed, because information of active ingredients is the basis for establishing evidence-based interventions. Development is known to be influenced by many factors that are interrelated[25], and therefore we used a broad spectrum of outcome measurements, both for infant's and family outcome, to gain insight in the complex infant and family system.

A limitation of our study is the small sample size, which resulted in underpowering after drop outs. This may have occluded possible effects of intervention at RCT-level. Another limitation is the selective attrition in the TIP group, which may be explained by caregivers' perceptions that the study offered no gains, as the infant would anyway receive TIP. Caregivers in the COPCA-group were aware that they received a novel intervention and this may have contributed to the absence of drop outs in the COPCA-group. The inclusion of a few infants who presented with clinical signs suggestive of CP but without a severe lesion of the brain is another limitation, as none of them was diagnosed with CP. Looking back, it would have been better to include only infants with severe brain lesions. The absence of information on dosages of intervention in daily life certainly is also a limitation.

In conclusion, our study shows that COPCA and TIP as performed in the Netherlands have a similar effect on child and family outcome. In addition, the study demonstrated positive associations between COPCA-elements and family outcome, but not between interventional elements and infant outcome. Based on our findings and previous studies, we suggest to combine different ingredients as possibly effective elements in early intervention for VHR-infants: aiming to empower families by coaching and providing them with sufficient information, stimulating infant's neuromotor development by trying to elicit self-produced motor behaviour, with some assistance if the infant is not able to perform by him- or herself, in a challenging environment with adaptations when needed, and sufficient dosing and implementation of the interventional elements into daily life.[3,4] We

recommend for future studies collaboration of networks nationally and internationally, to have a longitudinal follow-up of VHR-infants in larger study groups, in which contents and implementation of intervention is further investigated.

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MEASURING GROSS MOTOR FUNCTION IN YOUNG INFANTS WITH OR AT VERY HIGH RISK OF CEREBRAL PALSY

PART III