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Research paper

The effectiveness of Baby-CIMT in infants younger than 12 months with clinical signs of unilateral-cerebral palsy; an explorative study with randomized design

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ABSTRACT

Aim: To explore the effectiveness of baby-CIMT (constraint-induced movement therapy) and baby-massage for improving the manual ability of infants younger than 12 months with unilateral cerebral palsy (CP).

Method: Infants eligible for inclusion were 3–8 months old with asymmetric hand function and at high risk of developing unilateral CP. Thirty-seven infants were assigned randomly to receive baby-CIMT or baby-massage. At one year of age 31 children were diagnosed with unilateral CP, 18 (8 boys, 6.1 ± 1.7 months) of these had received baby-CIMT and 13 (8 boys, 5.0 ± 1.6 months) baby-massage. There were two 6-week training periods separated by a 6-week pause. The Hand Assessment for Infants (HAI), Assisting Hand Assessment (AHA), the Parenting Sense of Competence Scale (PSCS) and a questionnaire concerning feasibility were applied.

Results: There was improvement in the "Affected hand score" of HAI from median 10 (6;13 IQR) to 13 (7;17 IQR) raw score in the baby-CIMT group and from 5 (4;11 IQR) to 6 (3;12 IQR) for baby-massage with a significant between group difference ($p = 0.041$). At 18-month of age, the median AHA score were 51 (38;72 IQR) after baby-CIMT ($n = 18$) compared to 24 (19;43 IQR) baby-massage ($n = 9$). The PSCS revealed an enhanced sense of competence of being a parent among fathers in the baby-CIMT group compared to fathers in the baby-massage ($p = 0.002$). Parents considered both interventions to be feasible.

Conclusion: Baby-CIMT appears to improve the unimanual ability of young children with unilateral CP more than massage.

What this paper adds?

Baby-CIMT performed during the first year of life in children diagnosed with unilateral CP at one year of age appears to positively influence the early development of hand function. Parents found both programs feasible.

Abbreviations: AIMS, Alberta Infant Motor Scale; Baby-CIMT, baby constraint-induced movement therapy; CP, cerebral palsy; CIMT, Constraint-induced movement therapy; HAI, Hand Assessment for Infants; MRI, Magnetic resonance imaging; PSCS, Parenting Sense of Competence scale; RCT, randomized controlled trial; WMDI, white matter damage of immaturity

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1. Introduction

Infants with unilateral brain lesions are at high risk of developing unilateral cerebral palsy (CP) and in the light of the considerable plasticity of the young brain, possible early interventions deserve exploration (Basu, Pearse, Kelly, Wisher, & Kisler, 2014; Martin, Chakrabarty, & Friel, 2011). Most early interventions to date have targeted the general motor and cognitive development of infants with CP but none have focused on improving hand function in infants at risk of developing unilateral CP (Orton, Spittle, Doyle, Anderson, & Boyd, 2009; Morgan, Darrah et al., 2016). However, constraint-induced movement therapy (CIMT), developed specially to improve the function of the affected hand of individuals with unilateral CP has proven effective for older children (Chiu & Ada, 2016) and shown promise for infants in a retrospective study (Nordstrand, Holmefur, Kits, & Eliasson, 2015) but has not yet been systematically used with infants. An obstacle to conducting early intervention studies with infants is the unclear diagnosis and lack of tools for measuring and evaluating the development of hand function at an early age (Krumlinde-Sundholm, Ek, & Eliasson, 2015). Now, baby-CIMT (Eliasson, Sjostrand, Ek, Krumlinde-Sundholm, & Tedroff, 2014), together with the new Hand Assessment for Infants (HAI) developed to measure how infants use their hands (Krumlinde-Sundholm et al., 2017) will make it possible to explore the effectiveness of early interventions with infants below 12 months with high risk of unilateral CP.

It is a challenge to perform an early intervention with infants with CP since this diagnosis is most often made at a later age. CP registers indicate the average age for a diagnosis of CP is 19 months, but the age range is wide (see McIntyre, Morgan, Walker, & Novak, 2011). Unilateral lesions do not necessarily lead to unilateral CP and indeed only approximately 30% of all children who suffer a neonatal stroke eventually develop unilateral CP (Husson et al., 2010). Hand asymmetries, the usual clinical signs of unilateral CP typically do not appear until 4–6 months of age. Furthermore, the available tools for assessment cannot detect or quantify potential asymmetries between the two hands (Greaves, Imms, Dodd, & Krumlinde-Sundholm, 2010; Krumlinde-Sundholm et al., 2015). The new assessment tool, HAI, which is designed for infants 3–12 months, makes it possible to measure hand function in infants at risk of unilateral CP (Krumlinde-Sundholm et al., 2017). HAI has been developed to measure how the infant uses their hands both separately and together during play.

The primary objective of this exploratory study was to compare the effectiveness of baby-CIMT and baby-massage provided by parents in the home environment on the development of manual ability of infants with unilateral CP during the first year of life. Our first hypothesis was that baby-CIMT develops manual ability more rapidly even though baby-massage does promote general development (Bennett, Underdown, & Barlow, 2013). Our second hypothesis was that manual ability develops more rapidly during the training periods than during the pause between these periods. Moreover, we asked whether the effect was maintained at the follow-up at 18 months of age, if the intervention was feasible, and if the treatment protocols influenced self-rated parental competence.

2. Methods and design

2.1. Trial design

In this exploratory study, a randomised design was employed to allocate participants to different groups for the evaluator-blinded prospective parallel-group trial, conducted from 2009 to 2015 at the Astrid Lindgren Children's Hospital, a tertiary hospital in Stockholm, Sweden. The participants were assigned randomly to receive either baby-CIMT or baby-massage (Fig. 1) during two 6-week periods separated by 6-weeks with follow up at 18 months of age. There were five different time points for data collection (Fig. 1). Physiotherapy (about 1or 2 times each month) and other planned interventions continued as usual for both groups. The study was approved by the Stockholm Regional Ethical Review Board (no. 2009/1100-32). The trial registration number is SFO-V4072/2012, 05/22/2013 and further details are presented in the study protocol (Eliasson, Sjostrand et al., 2014).

2.2. Participants

The infants were recruited from various follow-up programs and other clinics at Astrid Lindgren Children's Hospital. Infants between 3 and 8 months of corrected age and a ≥15% difference between the two hands assessed by the HAI (Krumlinde-Sundholm et al., 2017) were eligible to participate. Infants also needed to be considered at high risk of developing unilateral CP, that is, had a known neonatal event that affected the brain, and/or clinical signs that had been identified by a child neurologist or physiotherapist using assessments such as the Alberta Infant Motor Scale (AIMS) or Hammersmith Infant Neurological Examination (HINE) (Novak et al., 2017, Darrah, Piper, & Watt, 1998; Dubowitz & Dubowitz 1981). The exclusion criteria were 1) severe visual impairment, 2) seizures that could not be controlled by antiepileptic drugs and 3) families who were not able to communicate in either English or Swedish. Infants were withdrawn from the study at one year of age if assessed by a paediatric neurologist as having no unilateral CP (see procedure). All parents received oral and written information concerning the study before providing the written informed consent.

2.3. Randomisation and blinding

Eligible children were randomized to the interventions. Randomisation was stratified by age (3–4, 5–6, and 7–8 months, corrected for prematurity) and neonatal event (neonatal arterial stroke at a gestational age ≥week 37, preterm birth at < week 37, and unknown/other) and performed after the first assessment when the consent form was completed. A list of random numbers associated with these stratification factors was generated before initiation of the intervention and was known only to the first author (ACE), who

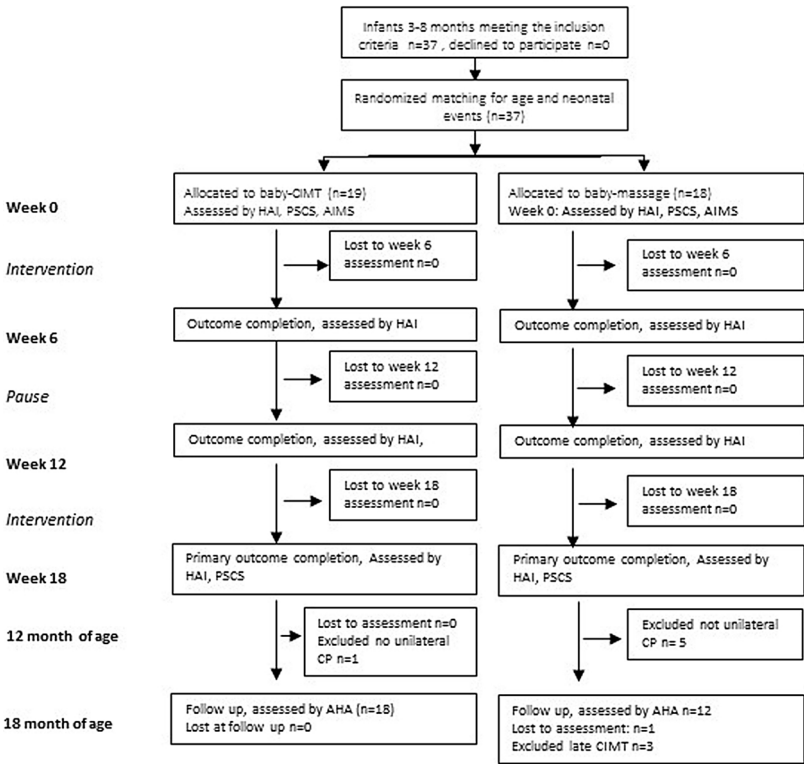

Fig. 1. Flow chart of participant and outcome assessment through the trial.

assigned the families to the different interventions. The parents were not informed of the study hypotheses. Only the assessors of the video recordings of HAI and Assisting Hand Assessment (AHA) (LE) and the brain scans (FL) were blinded to group allocation.

2.4. Intervention

2.4.1. Baby-CIMT

Baby-CIMT was carried out for 30 min each day, 6 days each week for 12 weeks (in total, 36 h) (Eliasson, Sjostrand et al., 2014). During this training, the non-affected hand was restrained by a mitten or something similar, which was comfortable and accepted well by the infant. The training was provided in the home environment by the parents who received coaching and supervision during weekly home visits by an occupational therapist (LS). The infant seated as upright and as stable as possible with the parent seated in front of them to facilitate the infant's eye contact, interaction with parents and self-initiated actions.

The training included several components in which grasping action and toy exploration was the main focus, described further in the study protocol (Eliasson, Sjostrand et al., 2014). The choice of toys depended on the infant's individual ability to perform motor actions in combination with their cognitive ability. The specific focus for each week were specified depending on the infant's ability and progress. The actual duration of training was noted in a diary.

2.4.2. Baby-massage

The infant received full-body massage once each day, 6 days each week, for 12 weeks (72 occasions), the sessions could be 5–30 min depending on the infant's mood (Eliasson, Sjostrand et al., 2014). The parents were instructed to choose a time of day when their infant was usually calm and they felt relaxed. The actual number of massages was noted in a diary. Before starting, the parents received three sessions of individualised instruction from a certified instructor in baby-massage.

2.5. Procedure for assessment

The primary measures of outcome were the HAI, administered once every 6 weeks for a total of four times during the 18-week study period (at the hospital). The Parenting Sense of Competence Scale (PSCS) was completed before and after the study period by both mothers and fathers (Johnston & Mash, 1989). The questionnaire regarding the feasibility and perceived effectiveness of the intervention was completed by the parents after the study period. For clinical purposes neuroimaging was performed at different time points during the first years. The child was examined clinically and diagnosed by a paediatric neurologist (KT) at one year of age corrected for prematurity. The result of this examination was used for further inclusion or exclusion of infants (Fig. 1). The follow-up assessment at 18 months of age was performed with the AHA.

2.6. Assessments of outcome

The HAI is a newly developed standardized observation-based test for infants 3–12 months of age who are at risk of developing CP (Krumlinde-Sundholm et al., 2017). It assesses the degree and quality of goal-directed manual actions performed with each hand separately as well as both hands together. The test procedure comprises a semi-structured, video-recorded 10–15-min play session. A test kit of carefully selected toys is presented to the infant so as to encourage and elicit toy exploration, making a wide range of motor actions observable. During the HAI assessments, the child was seated in a baby seat/bouncer or highchair depending on sitting ability.

The HAI is a criterion-referenced test with established construct validity evaluated by Rasch measurement model analysis (Bond & Fox 2015). It contains 17 items (12 unimanual and 5 bimanual) scored on a 3-point rating scale. The sum of raw scores is transformed in the Rasch analysis into an interval level, logit based "Both hand measure" on a 0–100 HAI-unit scale, where a higher score indicates better performance. For the unimanual items each hand is scored separately with a raw score range from 0 to 24. In this study such scores are reported as the "Non-affected hand score" and the "Affected hand score". Additionally, from the unimanual scores an asymmetry index is calculated as the percentage difference between hands (Krumlinde-Sundholm et al., 2017). This index ($\geq$15%) was used only as an inclusion criteria.

The AHA examines how effectively children with unilateral CP from 18 months of age use their affected hand in bimanual activities. A 15-min play session is video-recorded and 20 items are then scored on a 4-point rating scale (AHA version 5.0) (Holmefur & Krumlinde-Sundholm, 2016). The measure is reported as AHA-units ranging from 0 to 100 with a higher score indicating better performance.

The PSCS is a self-reported questionnaire that measures parents' sense of confidence and satisfaction of the parenting (Johnston & Mash, 1989). It contains 16 statements to which parents respond on a six-level Likert-type scale ranging from agreement to disagreement (maximally 96 points). A higher score indicates a greater sense of competence.

A 5-item questionnaire explored parents' perceptions of the feasibility and effectiveness of the intervention (see Table 4).

2.7. Baseline measurement

The Alberta Infant Motor Scale (AIMS), administered at baseline, describes gross motor development relative to a norm-referenced sample (Darrah et al., 1998).

A paediatric neurologist (KT) performed a clinical examination at one year of age (corrected for prematurity) and collected information from neuroimaging and previous clinical examinations such as AIMS (Darrah et al., 1998) and Hammersmith Infant Neurological Examination (HINE) (Dubowitz & Dubowitz 1981) on all children. CP was diagnosed employing the criteria of the Surveillance for Cerebral Palsy in Europe (a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE)," 2000).

Brain lesions were characterized on the basis of available neuroimaging, collected for clinical purposes at various time points and with various protocols. All images were visually reassessed by experienced neuroradiologists (FL) unaware of the clinical diagnosis and functional outcome. The basic patterns of damage were classified as normal, white-matter damage of immaturity (WMDI), focal ischaemic or haemorrhagic lesions, brain malformations, and miscellaneous or unclassifiable lesions (Ashwal et al., 2004).

2.8. Size of the study population

Since no study of this nature has been reported previously, the necessary sample size was estimated from a power calculation based on the AHA observed in connection with a previous study in older children (Eliasson, Shaw, Berg, & Krumlinde-Sundholm, 2011). As with the AHA, we considered a mean difference of six HAI-units to be clinically relevant difference. To achieve a significance level of 5%, a power of 80% and an assumed standard deviation of six HAI-units, 32 children were required.

2.8.1. Statistical analysis

All analyses were carried out using the SPSS 22.0 software (MedCalc) and are reported in accordance with the CONSORT statement. The data of infants with a confirmed diagnosis of unilateral CP at one year of corrected age were analysed based on their group allocation at randomisation. Demographic and baseline information was examined for differences between the intervention groups (Table 1). Data were tested for normality and were found to violate the assumption of normal distribution. Therefore, non-parametric statistics were applied in this exploratory study. Possible differences of results between intervention groups were measured with Mann-Withney U. The Wilcoxon signed rank test was used to compare change over time within the groups for each corresponding data point for both groups. The Spearman rank correlation was used to explore correlations between selected demographic variables (age at inclusion and HAI-units at inclusion) and treatment effect (Both hand measure changes). In all cases, the level of significance was set at $p < 0.05$. For the effect of an intervention, Cohen's d was interpreted as indicating a small ($d < 0.2$), medium ($d = 0{,}2 - 0.5$), or large ($d > 0.8$) effect (Cohen, 1988).

Table 1
Baseline demographic characteristics of the infants who were diagnosed with unilateral CP at 12 month CA (n = 31).

	Baby-CIMT (n = 18)	Massage (n = 13)
Gestational age, weeks, mean (SD)	34 (6.5)	34 (6.5)
Age, CA, months, mean (SD)	6 (1.7)	5 (1.6)
Gender, M/F	8/10	8/5
Preterm/Term	8/10	7/6
Both hands HAI-units (0–100), mean (SD)	52 (8)	49 (10)
Affected hand		
Left/Right, N (%),	7 (39%)/11 (61%)	8 (61%)/5 (39%)
AIMS (percentile)		
< 5	3 (20%)	6 (55%)
5–10	3 (20%)	2 (18%)
10–25	6 (40%)	0 (0%)
> 25	3 (20%)	3 (27%)
Missing	3	2
Neuroimaging[a]		
No sign of lesion	0	1
Focal infarct	4	4
WMDI	7	5
Miscellaneous	3	0
Malformation	1	1
No imaging	3	2
Affected hemisphere		
None/unclear	0	1
Right = Left	0	0
Left	3	1
Left > Right	7	3
Right	2	5
Right > Left	3	1
Associated lesions		
Normal/unclear	0	1
TH	2	0
TH + BG	6	2
TH + PLIC	2	0
TH + BG + PLIC/CeP	2	3
TH + BG + PLIC + CeP	1	3
PSCS (0–96 raw score), median (IQR)[b]		
Mothers	72 (64:77)	76 (72:83)
Fathers*	70 (66:73)	79 (68:88)
Education of parent beyond upper secondary school (≥12 year)	11	10

Abbreviations;: CA = Corrected age for children born before week 37.[a] HAI = Hand Assessment for Infants, AIMS = Alberta Infant Motor Scale, BG = basal ganglia, CeP = cerebral peduncle, PLIC = posterior limb of internal capsule, TH = thalamus, WMDI = White Matter Damage of Imaturity, Imaging[a] (Magnetic Resonance Imaging (n = 26), ultrasound (n = 1) and Computed tomography (n = 3)) was performed close to term, or at term equivalent age in preterms. 6 scans were also performed at an age of more than 9 months of age. PSCS = Parenting Sence of Competence scale [b] completed by 16 parents for baby-CIMT and 11 for baby-massage, * p < 0,05

3. Results

3.1. Characteristics of the study population

The 37 infants eligible to participate were all enrolled and 19 assigned in randomized fashion to receive baby-CIMT and 18 to baby-massage. The steps performed are summarised in Fig. 1. Adherence to the study protocol was excellent, all families fulfilled the interventions and there were no dropouts. However, six infants did not fulfil the diagnostic criteria at 12 months of age and were therefore excluded, since the baby-CIMT is currently considered appropriate for infants with unilateral CP. The children excluded had bilateral CP (n = 2) or exhibited no sign of CP (n = 4) at 12 months of age, for further information see Table 2. The final group of 31 infants were further analyzed. There were no significant differences between groups on the children's baseline characteristics, the fathers in the baby-CIMT group scored lower on sense of competence (Table 1). Neuroimaging showed signs of lesions that could explain the CP in all but one infant who was extremely preterm (no radiology n = 5). Bilateral involvement of brain structure was found in 14 infants. In almost all infants with brain lesion, imaging showed associated lesions in which the thalamus was the most commonly involved structure followed by the basal ganglia. For further information, see Table 1.

Baby-CIMT was conducted for a mean of 35 (SD 10) of the expected 36 h; 52 (SD 26) of the expected 72 sessions of baby-massage were completed. No adverse effects were reported for either group. Further baseline characteristics can be found in Table 1.

Table 2
Descriptive information of the excluded children (n = 6).

Child	GA	Inclusion age, month	Ass index, Both hands HAI, start	Unilateral CP, 1 year	Neuroimaging	Group
1	42	4	23	No	Focal infarct, TH BG (MRI at 2 days)	Baby-massage
2	40	7	21	No	No radiology	Baby-massage
3	31	6	35	No	WMDI, BG, TH, R > L (MRI at TEA)	Baby-Massage
4	30	5	25	No	No radiology	Baby-massage
5	39	7	47	Bilateral-CP	Maldevelopment, L (MRI at TEA)	Baby-massage
6	39	8	80	Bilateral-CP	Bilateral WMDI, R = L, PLIC, TH (MRI at 2yr)	Baby-CIMT

HAI = Hand assessment for Infants, Ass-index = Asymmetry index, Both hands = Both hand measure, is different scorings of HAI. GA = gestational age, WMDI: white matter damage of immaturity, TH = thalamus, BG = basal ganglia, TEA = term equivalent age, R = right, L = left, PLIC = Posterior limb of internal capsule. MRI = Magnetic Resonance Imaging.

3.2. The primary outcome of HAI after 18 weeks of enrolment

For detailed information see Table 3. The Affected hand score showed improvement in both groups (baby-CIMT $p = 0.0001$, baby-massage $p = 0.0001$) but more for baby-CIMT than baby-massage ($p = 0.041$). The effect size for baby-CIMT was high (Cohen's $d = 0.64$). The Non-affected hand score showed improvement in both groups (baby-CIMT $p = 0.004$, baby-massage $p = 0.002$) with no difference between interventions ($p = 0.636$) (Table 3, Fig. 2A).

Although the Both hand measure improved by 10 HAI-units (median) in the baby-CIMT group ($p = 0.001$) and not at all in the baby-massage group, this difference was not statistically significant ($p = 0.141$) (Table 3, Fig. 2B). The effect size for baby-CIMT was medium (Cohen's $d = 0.57$).

3.2.1. Variation and correlations

To explore the data for Both hand measure in greater detail, individual differences in development were examined. There were 46% (6/13) who did not change or demonstrated decreased ability (Both hand measure change; ≤1 HAI-unit) after baby-massage, but just one infant (5%) in the baby-CIMT group. For both groups, the change on the Both hands measure over the 18 weeks showed no correlation with the baseline value (baby-CIMT: r = 0.320 and baby-massage r: = −0.374, both p > 0.05). Likewise, for both group the change on the Both hands measure over the 18 weeks showed no correlation with inclusion age (baby-CIMT: r = –0.127, and baby-massage: r = 0.120, both p > 0,05).

3.2.2. Changes in hand use during the 18-week intervention

The data are presented for the various time-periods in Table 3 and Fig. 2. For baby-CIMT, both the Affected hand score and Both hand measure increased after the first training period (week 0–6, $p = 0.009$ and $p = 0.001$ respectively), but not during the pause in between treatments. After the second training period (week 12–18), only the Both hand measure was elevated ($p = 0.048$). Baby-massage was associated with only minor changes in either Both hand measure or Affected hand score at any time point (statistically significant for first period although the median Both hand measure did not change) (Table 3).

3.3. The parentś sense of competence

At baseline, there were no group differences between the mothers, whereas the fathers in the baby-massage group felt somewhat more competent as parents (Table 1). During the study period the mothers' feeling of competence did not change, median change in the PSCS score of 1.00 for baby-CIMT, and 0 for baby-massage revealed no difference between interventions ($p = 0.610$). The baby-massage fatherś median score was reduced by 1 point while this score increased 3.5 points for the fathers in the baby-CIMT group, showing increased sense of competence of being a parent for fathers in the baby-CIMT group ($p = 0.002$).

3.4. Parents' perception of the experience and feasibly of the treatment

The parents in both groups perceived the experience and feasibility of the treatment in a similar manner (1st question) (Table 4). All parents in the baby-CIMT group reported that the intervention was 'good' for or had "some effect" on the development of hand function (2nd question), but only 42% of the parents in the baby-massage were that positive. In terms of the effect on the child's general development (3rd question), 63% of the parents in the baby-CIMT and 27% in the baby-massage rated this as "good". All parents in the baby-CIMT group said they will recommend such treatment to other families, while most in the baby-massage group were unsure (4th question).

3.5. The 18-month follow-up

At the time of follow-up, data were missing for one child in the baby-massage group. Three children in the baby-massage group had received CIMT during the follow-up period and were therefore excluded (Fig. 1). The median AHA measure was 51 (IQR 38:72) for the baby-CIMT group (n = 18) and 24 (IQR 19:43) for baby-massage (n = 9).

Table 3
The results of HAI scores for the 31 infants were diagnosed with unilateral CP at 12 month CA. Median (md) and interquartile range (IQR) of HAI scores at baseline, after the first period of intervention (week 6), after pause (week 12), and after the second period of the intervention (week 18).

Outcome	Groups								Difference within groups[a]		Difference between groups[b]
	baseline		week 6		week 12		week 18		week 0–18		week 0–18
HAI	B-CIMT n = 18	B-mass n = 13	B-CIMT n = 18	B-mass n = 13	B-CIMT n = 18	B-mass n = 13	B-CIMT n = 18	B-mass n = 13	B-CIMT n = 18	B-mass n = 13	B-CIMT–B-mass
Both Hand measure (0–100) md (IQR)	50 (*48:60*)	49 (*45:52*)	57 (*50:65*)	48 (*47:57*)	60 (*50:69*)	49 (*46:59*)	60 (*51:72*)	49 (*45:53*)	p = 0.0003	p = 0.136	p = 0.145
Affected hand raw score (0–24) md IQR	10 (*6:13*)	5 (*4:11*)	13 (8:*15*)	5 (*4:13*)	12 (6–17)	6 (*4:14*)	13 (*7:17*)	6 (*3:12*)	p = 0.0001	p = 0.0001	p = 0.041
Non-affected hand raw score (0–24) and IQR	22 20:23	22 19–23					24 23–24	24 24:24	p = 0.004	p = 0.002	p = 0.636

B-CIMT = Baby CIMT, B-mass = Baby-massage.
[a] Calculated using the Wilcoxon signed rank test.
[b] Calculated with the Mann–Whitney *U* test.

Table 4
The parent's experience of the treatment and feeling about their child's development.

Question	B-CIMT, n (%)	B-Massage, n (%)
1. What was your experience of the treatment? (baby-CIMT n = 17, baby-massage n = 12)		
Very easy	1 (6)	2 (16)
Easy	10 (59)	4 (34)
Difficult	6 (35)	5 (42)
Very difficult	0	1 (8)
2. What was your feeling about the effect of the treatment on your child's development of hand function? (baby-CIMT n = 17, baby-massage n = 12)		
Good effect	10 (59)	5 (42)
Some effect	7 (41)	0
Minimal effect	0	0
No effect	0	3 (25)
No opinion	0	4 (33)
3. What was your feeling about the effect of the treatment on your child's general development? (baby-CIMT n = 16, baby-massage n = 11)		
Good effect	10 (63)	3 (27)
No effect	4 (25)	6 (54)
Delayed the development	0	0
No opinion	2 (12)	2 (19)
4. Would you recommend the treatment to other families? (baby-CIMT n = 17, baby-massage n = 11)		
Yes, it has given us a lot	17 (100)	5 (45)
Maybe, it has been of some importance	0	5 (45)
Doubtful, it has been of minimal value	0	1 (10)
No, it was a burden	0	0
5. How important was the support at home? (baby-CIMT n = 16)		
Of great importance	12 (75)	NA
Of some importance	4 (25)	NA
Less important	0	NA
Not needed	0	NA

NA = Not applicable.

4. Discussion

In this first explorative study, infants who received baby-CIMT exhibited a better development in the affected hand over the 18-week study period than those receiving baby-massage, supporting the first hypothesis. The variation in individual outcome was extensive but the treatment effect of baby-CIMT was of moderate effect size. The improvement seen in this study as well as in a previous retrospective study (Nordstrand et al., 2015) appear to support the benefits of an intensive activity-dependent intervention. Moreover, our study design with a pause in between the two intervention periods, indicated that improvement is more related to the active training periods by the baby-CIMT group, supporting the second hypothesis but both hypothesis needs further exploration.

The extensive activity-dependent plasticity of the developing brain has been demonstrated in animal models by the development and organisation of the cortico-spinal tract that occurs at an early age (Eyre, 2007; Friel, Williams, Serradj, Chakrabarty, & Martin, 2014). Whether the baby-CIMT was provided early enough to influence the organisation of the cortico-spinal tract is not presently known. A high 18-month functioning level predicts favourable future longitudinal development of hand function (Nordstrand, Eliasson, & Holmefur, 2016).

HAI is a measure that is influenced by the infant's impairment as well as the expected typical development during the first year (Krumlinde-Sundholm et al., 2017). The effect of intervention on the Affected hand score was significant but not for the Both hand measure. A possible explanation is that the training was directed towards the affected hand and the infants had not yet learned to transfer their new skills to bimanual performance. Furthermore these infants might be somewhat late in their overall manual development. Perhaps bimanual training should be explored for the older infants. Differentiated hand roles typically develop from about eight months of age when children start to do more advanced activities (Greaves, Imms, Krumlinde-Sundholm, Dodd, & Eliasson, 2012).

Although the variation in treatment effect was large for both groups there was no relation to functioning at baseline (severity of impairment), or age of treatment (starting at 4–8 month). This low relationship is in agreement with findings in older children (Eliasson et al., 2011; Gordon, Charles, & Wolf, 2006). Interestingly, some infants in both groups demonstrated minor or negative development during these 18 weeks while others exhibited good development independent of the type of intervention. However, it was only one child (5%) in the baby-CIMT compared to 46% in the baby-massage who had no improvement or decreased ability (Both hand measure change; ≤ 1 HAI-unit) during the study period. This lack of development and response to treatment already at this early age is of course discouraging information but is known from children at later ages (Sakzewski et al., 2011). Concerns about possible adverse effects of CIMT has been expressed (Basu et al., 2014), thus, it was important to investigate the effects on the non-affected hand. Nevertheless, a clear and important conclusion here is that baby-CIMT does not affect the development of the non-affected hand negatively, there were significant improvements in both groups with no between group differences.

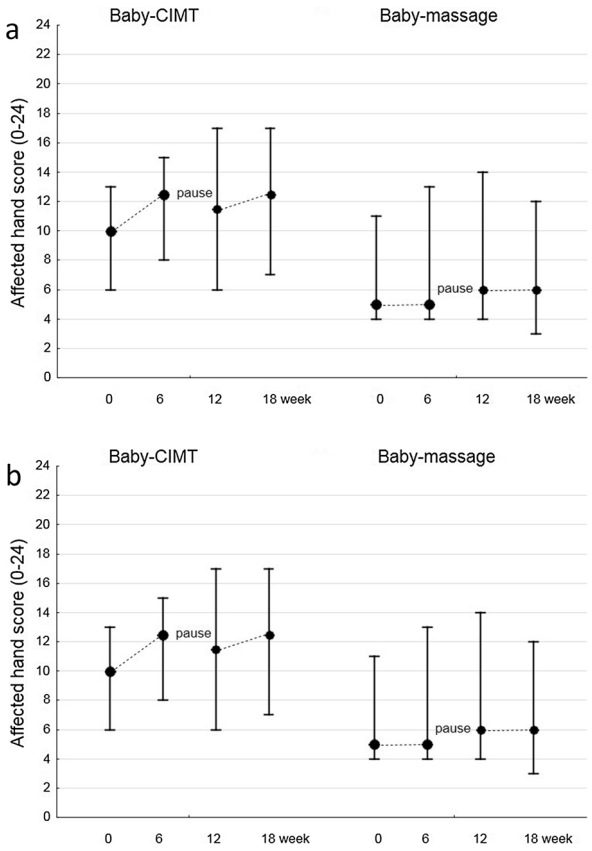

Fig. 2. Median and interquartile range (IQR) of HAI at baseline (0 week), after the first period of intervention (week 6), after pause (week 12), and after the second period of the intervention (week 18) for both the baby-CIMT and baby-massage group in A) for the Affected hand score (0–24) and in B) for Both hands measure in HAI- units (0–100).

4.1. The parents' perspective

The parents considered both intervention programs to be feasible. Parents involved in baby-CIMT were more satisfied, thought that the training improved the development of their infanťs hand function, and even felt that it was beneficial for their child's general development. This overall positive feedback indicates satisfaction with being the training provider, even during this vulnerable period in their lives. The unstructured feedback revealed that these parents appreciated clear goals and coaching strategies used during the weekly home visits in the baby-CIMT program (Eliasson, Sjostrand et al., 2014). The mothers' sense of competence of parenting, as assessed on the PSCS scale, was maintained in both groups and this sense even seemed to increase somewhat for the fathers in the baby-CIMT group. This requires further investigation since the diagnosis or emergence of a disability is known to affect the entire family (Schuengel et al., 2009).

4.2. Strengths and limitations

The infants recruited had asymmetric hand function together with other neurological signs of unilateral CP. The asymmetry involved reduced hand use and a lack of various hand actions as described by the HAI assessment. The 15% difference between hands cut-off value is well exceeding the side difference seen in the HAI for infants with typical development (personal communication, Krumlinde-Sundholm). Although all our infants met the inclusion criteria, six children were withdrawn as they were diagnosed with bilateral CP or without CP at one year of age and hence they were not the target group for this intervention. No research has yet evaluated the effect of CIMT in older children with bilateral CP, and children without CP are expected to develop normally. The prognostic value of early asymmetric hand use as an indicator of unilateral CP needs to be further investigated. Difficulties with early diagnosis and the fact that the diagnostic subtype may change during the first years of life (Surveillance of cerebral palsy in Europe (SCPE), 2000) are known from previous early intervention studies (Blauw-Hospers, Dirks, Hulshof, Bos, & Hadders-Algra, 2011; Morgan, Novak, Dale, Guzzetta, & Badawi, 2016). In the present cases, neuroimaging was not used for inclusion, but was used to describe the sample. The neuroimaging revealed the expected variation including the presence of associated lesions and minor involvement of the other hemisphere (Holmstrom et al., 2010). Detailed analysis of the brain scans was somewhat limited since many of the infants were scanned at an early age, when the endpoint of the lesions had not fully developed. There were also too few infants

with each type of lesion to allow statistical analysis of subgroups.

When choosing a control intervention, different theoretical assumptions concerning development were taken into consideration. Baby-CIMT involves active training, while with baby-massage the infant is passive. Thus, with baby-massage, we could control for the placebo effect of an additional treatment to some extent. The parents participated in a special course and the baby-massage involved increased attention and parent-infant interaction and was satisfactory for the family when provided on a daily basis. However, the two different interventions were not fully comparable with respect to dosage of interventions. The dosage of baby-CIMT (36 h, distributed over 30 min daily practice) is also less than the 60–90 h usually recommended for older children (Eliasson, Krumlinde-Sundholm et al., 2014). However, when planning this project, we were especially concerned with the feasibility, whether parents could provide the training and what kind of support they would need as well as the short duration of alertness in young infants. Although the dosage as well as the distribution were suitable for the families it calls for further exploration.

A further limitation was the relatively small sample size, especially since we unexpectedly obtained unequal numbers of children with unilateral CP in the two groups. There were limitations in the ability to estimate the sample size since there were no available studies for similar ages and assessment and we could not control for the natural history in this age group. The study would probably have benefited from larger sample size. At the time of the 18-month follow up, some children in the baby-massage group were excluded since they had received CIMT during the follow up period leaving a very small group for analysis. We considered it unethical to ask families to refrain from further interventions until the time of this 18-month follow up. Another weakness is the repeated statistical analysis, but any random changes would probably only exert a minor impact on the findings. The reported data points vary from the study protocol (Eliasson, Sjostrand et al., 2014). The end-point of the intervention was after 18 weeks for consistency (rather than 12 month of age). Follow up was somewhat earlier (18 month) than the planned (2 years of age) investigation due to the fact that several parents in the baby-massage group wanted to have a period of CIMT.

By this first explorative study we have obtained some evidence that baby-CIMT is effective However more research is needed. First, research should explore whether baby-CIMT is better than low intensity of usual care. Further research should address the impact of different starting points, reflecting different ages of diagnosis as well as the dosages delivered. As a consequence and to be able to conduct such studies we need to know more about early signs of unilateral CP and its development during the first year, and the impact of different types of brain lesions. Further evaluations of HAI are also needed including investigation of agreement within and between raters, and defining the smallest detectable change.

4.3. Conclusion and clinical implications

In agreement with the results of CIMT studies in older children (Chiu & Ada, 2016), baby-CIMT appears to have a positive influence on the early development of hand function and might even be beneficial for later development of hand function. The baby-CIMT program was also considered to be feasible by the parents and no adverse effects were found. Further research is required to identify whether baby-CIMT can be adopted as standard clinical practice. However, if the program is conducted by experienced therapists following the manual used in this study, baby-CIMT seems to be safe without adverse effects.

Founding

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Declaration of conflicting interests

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