Cognitive outcome of early intervention in preterms at 7 and 9 years of age: a randomised controlled trial

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ABSTRACT

Objective Examine the effect of an early intervention programme on cognitive outcome at 7 and 9 years in children with birth weight (BW) <2000 g.
Design A randomised controlled trial of a modified version of the Mother–Infant Transaction Program.
Setting A single tertiary neonatal unit.
Patients 146 infants were randomised into a preterm control group (74) or a preterm intervention group (72).
Interventions The intervention consisted of eight sessions shortly before discharge and four home visits by specially trained nurses focusing on the infants' unique characteristics, temperament, developmental potential and the interaction between infants and parents.
Main outcome measures Outcomes were assessed with the Wechsler Intelligence Scale for Children (WISC-III).
Results Mean BWs were 1396 (429) g in the intervention group and 1381(436) g in the control group. After adjusting for the possible clustering effects of twin pairs and maternal education, there were no significant differences in WISC-III scores at age 7 or 9. The mean difference was 4.1 points (95% CI −1.5 to 9.8 points) in favour of the intervention group at 7 years and 2.2 points (95% CI −3.4 to 7.6 points) at 9 years. At 7 years, a 6.8 points difference in the Verbal Comprehension Index (95% CI 0.5 to 13.0 points) was found in favour of the intervention group. Loss to follow-up at age 7 and 9 was 11% and 14%, respectively.
Conclusions This intervention programme did not have a sustained significant effect on overall cognitive outcomes in preterm children at age 7 and 9.
Trial registration number The trial has been registered at http://www.clinicaltrials.gov (identifier NCT00222456).

What is already known on this topic

The beneficial effects of early intervention programmes to enhance cognitive development of preterm children remain unclear. There are few randomised controlled trials and research on long-term outcomes is sparse.

What this study adds

An early intervention programme does not seem to have a prolonged significant influence on cognitive scores (IQ) in preterm children at 7 and 9 years of age. The attenuation of intervention effect is consistent with findings of other long-term studies of preterm children at risk.

INTRODUCTION

Preterm infants are at increased risk of developing long-term cognitive and neurobehavioural problems.[1 2] Compared with term-born peers, preterm children have poorer academic achievements, and they often need special educational services in school.[3 4] Given the significant risk of neurodevelopmental problems, several early intervention (EI) programmes have been developed to enhance the child's cognitive and neurodevelopmental development.[5 6 7] A systematic review of EI programmes showed an overall beneficial effect from various strategies. Positive neurocognitive outcomes were found up to age 3, followed by a diminishing effect from age 5.[8] Furthermore, a meta-analysis of EI programmes found a significant effect on cognitive outcomes at 24 months corrected age. At school age however, there was no longer any effect of the intervention programme on cognitive outcomes.[9] These findings contrast those of a small study by Achenbach *et al*[10 11] based on the Mother–Infant Transaction Program (MITP). Achenbach's study found favourable long-term effects on preterm children's cognitive and behavioural development at age 7 and 9. Due to the conflicting results and particularly the limited research on long-term effects of EI programmes, we designed a randomised controlled trial (RCT) with long-term follow-up. The intervention was a modified version of the MITP and theoretically based on the transactional model of development, which emphasises the mutual interdependence between the child and the environment.[12] According to this model, different biological and environmental risk factors are expected to act in interactive relationships and implies that preterm children's adaptation is shaped by their ongoing daily transactions with the caregiver.[13] Thus, a more optimised interaction which enables the parents to interpret the infant and act more competently according to the infant's cues may result in a strengthened parent–infant relationship and stimulate the child's later neurocognitive development and competence.[12 13]

Measuring cognitive outcomes is important, as improved cognitive functioning may reduce the need for educational support and school failure in these children at risk. We have previously reported favourable effects of this EI programme on cognitive performance at age 5.[14] An extended follow-up at school age, when the children are introduced to increasing academic demands, may answer the question whether a brief intervention has effect on cognitive performance later on. Thus, the aim of the present study was to investigate whether an intervention in an early phase of development has beneficial effects on cognitive outcomes in prematurely born children at 7 and 9 years.

METHODS

Study design

Details of the study design have been described elsewhere[14 15] and are only briefly outlined here. Between March 1999 and September 2002, all surviving infants treated at the University Hospital of North Norway (UNN) with a birth weight (BW) <2000 g, with no congenital anomalies and whose mothers' first language was Norwegian, were eligible for this study. The infants were randomly assigned to either a preterm intervention (PI) (n=72) or a preterm control (PC) (n=74) group. Randomisation was arranged in random blocks of four and six, using computer-generated random numbers and stratified by gestational age (GA) (≤28 and >28). Because of the nature of the intervention, twins were allocated to the same group and triplets were excluded. The allocation was performed by using sealed opaque envelopes, identified by stratification group and opened after the completion of various questionnaires, and opened by the research nurse. Written informed consent was obtained if the parents agreed to participate. The study was approved by the regional committee for medical research ethics and the Norwegian Data Inspectorate.

Intervention programme

The intervention programme was a modified version of the MITP.[7] The modification consisted of an initial debriefing session, where the parents were allowed to share their experiences about the hospital stay and express difficult feelings. Active participation and involvement of both parents were encouraged. After the initial session, the intervention consisted of 1-h daily sessions with both parents and their infant the last 7 days before planned discharge from hospital, at a postmenstrual age of at least 34 weeks. The intervention was carried out by eight specially trained neonatal nurses. Each session addressed aspects of the infant's behaviour such as reflexes, self-regulation and interaction, signs of distress and behavioural states and how parents could bring the infant into a quiet alert state for mutual social interaction. The last two in-hospital sessions focused on the parents' sensitivity and responsiveness in daily caretaking routines.

The daily in-hospital sessions were followed by four home visits by the same intervention nurse at 3, 14, 30 and 90 days after discharge. The home visits explored the family's adjustment to the home environment, interaction between the infants and the parents, how to support and stimulate the infant and evaluation and discussions about the intervention programme. A complete overview of the intervention programme is summarised by Rauh *et al*.[7] A detailed log of every intervention visit was kept and was regularly reviewed and supervised by a senior child psychologist (JAR) to maintain the consistency of the intervention. The intervention families did not have access to the intervention nurses outside the scheduled intervention visits. The control group followed the department's standard routines for discharge of preterm infants, which consisted of a clinical examination, including visual and auditory screening, an offer of training in infant massage from the unit's physiotherapist and a discharge consultation with one of the clinicians on the ward. Both groups had access to standard follow-up after discharge.

Baseline data

Perinatal variables were collected from medical records. GA was determined by ultrasound examinations between 16 and 18 weeks of gestation. The Score for Neonatal Acute Physiology II[16] and the Clinical Risk Index for Babies[17] were calculated as a measure of the severity of initial illness. Small for gestational age was defined as BW more than 2 SDs below the mean for GA and gender, based on Norwegian data.[18] Intraventricular haemorrhage was graded according to Papile[19] and periventricular leukomalacia was defined by the presence of echolucensis by cerebral ultrasound. Social variables used in the analyses were collected from parents at discharge in a separate questionnaire.

Outcome measures

The primary outcome of this study was cognitive performance at 7 and 9 years of age and this was assessed by the Norwegian version of Wechsler Intelligence Scale for Children (WISC-III).[20] This test consists of 13 subtests that are combined into three IQ scores; full scale IQ (FSIQ), verbal IQ (VIQ) and performance IQ (PIQ). Based on the 13 subtests, the following IQ Index scores are summarised; verbal comprehension, perceptional organisation, freedom from distractibility and processing speed. The split-half reliability and test–retest reliability of the WISC-III scores are >0.93.[21] The cognitive testing was performed by four specially trained test technicians. All examinations were video-recorded and reviewed regularly to maintain consistent scoring. At 7 and 9 years, medical examination was performed on clinical indication only. All assessments were blinded to the children's group allocation.

Power calculations

The original power analysis in this study was based on having an 80% chance of detecting a clinically significant group difference of 7.5 IQ points at age 2, using the Bayley Scale of Infant Development II (power=0.80). This indicated that 64 infants were needed in each preterm group. Allowing for withdrawals, the target sample size was 70 infants in each group.

Statistical analyses

Linear mixed model (LMM) analysis was used to test for group differences in cognitive outcomes at 7 and 9 years controlling for maternal education.[22] This method accounts for the potential clustering effect of twin pairs when including family affiliation as a random effect. Differences in continuous variables are given as mean differences with 95% CIs. Pearson χ^2 tests and one-way analysis of variance were used to compare baseline demographic family variables. Group comparisons on demographic child variables were done by LMM analysis. p Values <0.05 were considered significant. All tests were 2-sided. All results are reported as intention to treat. Data were analysed by SPSS V.19.0.

RESULTS

During the study period, a total of 203 infants with a BW <2000 g were treated at UNN. This represented 96% of all infants with BWs <2000 g born in the two counties Troms and Finnmark. One hundred and sixty-eight infants fulfilled the inclusion criteria, and 146 infants (87%) from a total of 130 families were randomised. Sixteen families had both twins included in the study. The basic characteristics at the time of randomisation are shown in table 1. The groups were similar in sociodemographic and neonatal characteristics except for a slight difference in maternal education (mean difference 1.1 years (95% CI 0.03 to 2.2 years); p=0.04) in favour of the intervention group (table 1). All mothers in the intervention group participated in every intervention session, whereas the fathers participated in a median of 6 of 12 sessions (IQR: 4–9 sessions). The patient flow until 9 years is shown in figure 1. The follow-up rates at 7 and 9 years were 89% and 86%, respectively. Children unable to complete the assessment were withdrawn.

Cognitive outcomes

The results of cognitive outcomes at 7 and 9 years are presented in tables 2 and 3, respectively. When adjusting for maternal education and taking the dependency caused by twin pairs into account, there were no significant differences between the PI and PC groups in FSIQ, VIQ and PIQ scales. However, the observed means in the PI group were consistently higher than in the PC group for all measures on both occasions. A notable difference was found at 7 years, where the PI group scored significantly higher on the Verbal Comprehension Index; nevertheless, there were no significant differences on the other WISC-III Index scores at 7 and 9 years.

Table 1 Infant characteristics and social factors at randomisation

Infant characteristics	Intervention (N=72)	Control (N=74)
BW, mean (SD), g	1396 (429)	1381 (436)
400–1000 g, n (%)	20 (28)	20 (27)
1001–1500 g, n (%)	15 (21)	20 (27)
1501–2000 g, n (%)	37 (51)	34 (46)
GA, mean, (SD), weeks	30.2 (3.1)	29.9 (3.5)
<28 weeks, n (%)	17 (24)	19 (27)
28–32 weeks, n (%)	36 (50)	37 (50)
≥33 weeks, n (%)	19 (26)	18 (24)
SGA* (%)	11 (13)	10 (14)
Twins, n (%)	16 (22)	14 (19)
Prenatal steroids, n (%)	53 (74)	57 (77)
SNAP-II score, mean (SD)	8.3 (10.9)	10.4 (11.3)
CRIB score, mean (SD) (N=85)	3.2 (2.8)	2.7 (2.9)
Received ventilation, n (%)	29 (40)	37 (50)
Duration of ventilation, mean (SD), d (N=66)	7.0 (18.6)	7.1 (17.3)
Postnatal steroid use, n (%)	9 (13)	10 (14)
Oxygen therapy at 36 weeks of gestation, n (%)	11 (15)	14 (19)
Abnormal cerebral ultrasound, n (%)		
IVH grade 1 or 2	7 (10)	8 (11)
IVH grade 3 or 4	3 (4)	5 (7)
Periventricular leukomalacia	4 (6)	8 (11)
Maternal and social characteristics		
Mother's age, mean (SD), years	30.8 (6.1)	29.1 (6.4)
Firstborn children, n (%)	40 (56)	37 (54)
Mother's education, mean (SD), years (N=131)†	14.6 (2.8)	13.5 (3.2)
Father's education mean, (SD), years (N=131)†	13.8 (3.1)	13.5 (3.2)
Mother's monthly income‡	15.8 (7.7)	14.6 (6.7)
Father's monthly income‡	21.1 (8.7)	19.9 (8.1)

SNAP-II indicates the Score for Neonatal Acute Physiology II (includes mean blood pressure, lowest temperature, P02/fraction of inspired oxygen ratio, serum pH, multiple seizures and urine output); CRIB, Clinical Risk Index for Babies (includes BW, GA, congenital malformations, maximal base deficits in the first 12 h, minimal appropriate fraction of inspired oxygen in the first 12 h and maximal appropriate fractions of inspired oxygen in the first 12 h).
*SGA, defined as a BW >2 SD below the mean for GA.
†Calculated for 131 families due to 15 twin pairs.
‡Average monthly income (SD) in 1000 Norwegian kroner.
BW, birth weight; GA, gestational age; IVH, intraventricular haemorrhage; SGA, small for gestational age.

DISCUSSION

The main purpose of this study was to examine the effect of a parent- sensitising intervention in the hospital–home transition on preterm children's cognitive performance at 7 and 9 years. The results showed that the MITP did not have a sustained effect on preterm children's overall cognitive performance at 7 and 9 years of age. The PI group scored consistently higher than the PC group on the FSIQ, VIQ and PIQ. However, the only significant difference was found on the Verbal Comprehension Index at 7 years.

These results are not in line with our previous finding of significantly higher IQ scores at 5 years in favour of the intervention group.[14] At 5 years, this difference was within a clinically significant range, which was considered to be more than 5 points.[23] According to the transactional model, development is viewed to be cumulative, meaning that the effects of an intervention may emerge in the course of time.[12] Based on this theoretical model, a larger effect could have been expected in the present study.

Although we did not find any significant differences between the groups in the overall IQ scores, the PI group scored consistently higher than the PC group on all measurements. At 7 years, the differences in the IQ scores were in the range of 4–5 points with relatively large CIs. These differences might be clinically relevant and the lack of significance might be due to lack of power as this study was designed to detect a difference of 0.5 SD or about 7.5 points. As such, the analyses were slightly underpowered according to the original goals. Loss to follow-up and dependency in the data due to twin pairs have reduced power to detect such an effect to a minimum of 0.76. However, at 9 years the observed group differences were further reduced to only 1–2 IQ points, and this attenuation over time is in line with two meta-analyses[8 24] which could not find beneficial effects of intervention after 5 years. The Infant Health and Development Program found beneficial effects of their intervention on cognitive outcome at 3 years, but reported no significant difference at 5 and 8 years of age.[25] However, improved cognitive scores were found within the heavier preterm infants with a BW >2000 g at 8 years. A similar tendency was reported by the Avon Premature Infant Project. They reported that the small effect on cognitive scores at 2 years was no longer detected at 5 years.[26] The only study that has reported an increased effect on cognitive outcome over time is the Vermont study.[10 11] They reported an effect of the MITP on cognitive outcome at 7 and 9 years, and this was interpreted as an improved parent–child relationship resulting in a cumulative positive effect consistent with the transactional model.[12] However, the sample size was rather small and included relatively healthy moderately preterm infants born in the presurfactant period, which might limit the generalisation of their results. Interestingly, children in the PI group had significantly higher scores at the Verbal Comprehension Index measured at 7 years. VIQ is found to be more influenced by the children's background, knowledge learnt from the environment and cultural experiences,[27 28] whereas biological factors are more related to perceptual-performance

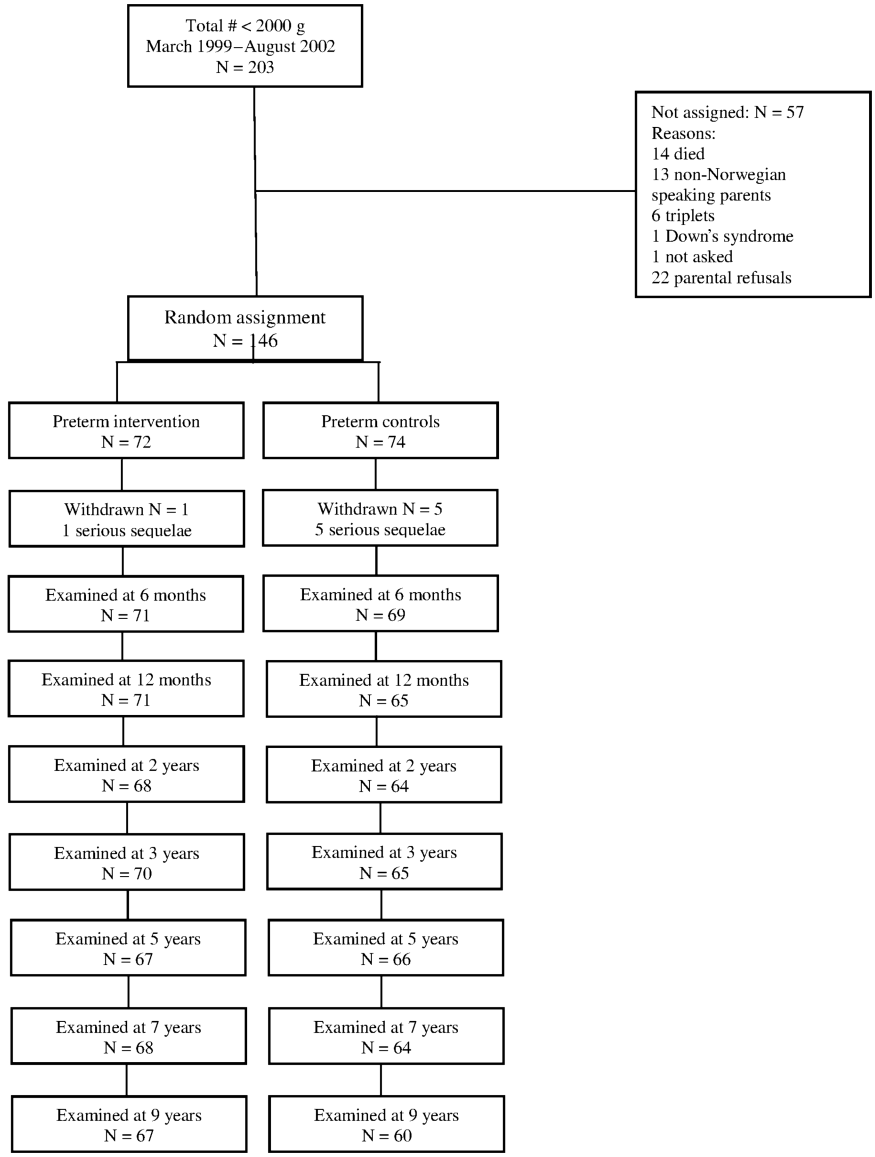

Figure 1 Study_flow_diagram.

outcomes.[29] In line with this knowledge, we adjusted the analyses for maternal education as the mothers in the PI group had slightly longer education than mothers in the PC group had. After controlling for this factor, the significant difference between the children's verbal abilities might suggest a more optimised parent–child relationship, which in turn has contributed to improved verbal comprehension abilities at 7 years. Verbal functions as reflected in the ability to form verbal concepts, listen to questions, reason and create thoughts are important skills in an academic setting. However, the practical implication of these test scores in terms of their actual academic functioning in school remains to be more studied.

Table 2 Cognitive outcomes at 7 years of age

	Intervention Mean (SD) (N=68)	Control Mean (SD) (N=62)	Adjusted mean difference (95% CI)*	p Value*
Full scale IQ score	96.3 (14.6)	91.5 (17.8)	4.1 (−1.5 to 9.8)	0.15
Total verbal IQ score	98.6 (15.8)	92.8 (18.8)	5.0 (−1.0 to 11.1)	0.10
Total performance IQ score	94.2 (15.8)	91.8 (15.9)	1.8 (−3.8 to 7.4)	0.52
Verbal Comprehension Index	100.1 (15.8)	92.6 (20.1)	6.8 (0.5 to 13.0)	0.035
Perceptual Organisational Index	94.6 (14.9)	92.8 (15.4)	1.0 (−4.3 to 6.3)	0.71
Freedom from distractibility	94.8 (16.5)	91.9 (20.4)	2.0 (−4.4 to 8.4)	0.54
Processing Speed Index	97.2 (14.5)	93.5 (17.2)	3.8 (−1.8 to 9.4)	0.18

The means presented are estimated marginal means from a linear mixed model that adjusts for mother education and the clustering effect of twins.
*Adjusted for clustering effects of twin pairs and maternal education.

Table 3 Cognitive outcomes at 9 years of age

	Intervention Mean (SD) (N=66)	Control Mean (SD) (N=59)	Adjusted mean difference (95% CI)	p Value*
Full scale IQ score	100.9 (14.3)	98.2 (16.6)	2.12 (−3.4 to 7.6)	0.45
Total verbal IQ score	102.7 (13.7)	99.69 (16.3)	2.4 (−2.9 to 7.8)	0.37
Total performance IQ score	98.7 (17.7)	97.2 (15.8)	1.1 (−4.9 to 7.2)	0.71
Verbal Comprehension Index	104.1 (13.8)	100.1 (15.6)	3.5 (−1.8 to 8.7)	0.19
Perceptual Organisational Index	99.8 (17.1)	98.4 (15.3)	0.8 (−5.0 to 6.6)	0.78
Freedom from distractibility	97.2 (14.5)	96.4 (15.1)	0.5 (−5.0 to 5.9)	0.86
Processing Speed Index	94.9 (16.2)	92.8 (20.0)	2.2 (−4.3 to 8.7)	0.51

The means presented are estimated marginal means from a linear mixed model that adjusts for mother education and the clustering effect of twins.
*Adjusted for clustering effects of twin pairs and maternal education.

Additionally, we think it is reasonable to assume that school plays an important role for children at these ages. We speculate whether being in a structured educational environment itself might have contributed to attenuate the differences between the preterm groups as they are exposed to multiple sources of stimuli, both intellectually and socially, and in fact spend more time outside their family environment.

Methodological strengths of this study were the recruitment from a geographically defined area, and that almost all preterm infants born in the area (96%) were eligible for inclusion making this study a population-based RCT. Our follow-up rate is high in a long-term follow-up study, which strengthens the validity and generalisability of the results. A possible weakness was that BW rather than GA was used as inclusion criterion. Consequently, this rendered more mature growth-restricted infants to be included in the study, making conclusions more difficult to generalise. However, the growth-restricted infants were evenly distributed among the groups, limiting the influence on group differences in the study.

CONCLUSION

Benefits of EIs on cognitive outcome are reported in various studies at infant and preschool age, but long-term improvements are not consistently found. Our results show diminishing effects of this EI as the preterm children develop and enter the school system. We conclude that this EI programme did not a have a sustained significant effect on cognitive outcomes at age 7 and 9.

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