Early Intervention Improves Cognitive Outcomes for Preterm Infants: Randomized Controlled Trial

WHAT'S KNOWN ON THIS SUBJECT: Knowledge regarding the beneficial effects of early intervention programs on cognitive outcomes for preterm infants and their families is limited. There are few randomized controlled trials, and long-term results are conflicting.

WHAT THIS STUDY ADDS: The authors demonstrate that a modified version of a sensitizing parental intervention program (the Mother-Infant Transaction Program) showed beneficial effects on cognitive outcomes for preterm infants with birth weights of <2000 g at corrected age of 5 years.

abstract

OBJECTIVE: The goal was to examine the effectiveness of an early intervention on cognitive and motor outcomes at corrected ages of 3 and 5 years for children with birth weights (BWs) of <2000 g.

METHODS: A randomized controlled trial of a modified version of the Mother-Infant Transaction Program was performed. Outcomes were assessed with the Bayley Scales of Infant Development II and the Wechsler Preschool and Primary Scale of Intelligence-Revised at 3 and 5 years, respectively. McCarthy Scales of Children's Abilities and the grooved pegboard test were used to test motor outcomes at 5 years.

RESULTS: A total of 146 infants were assigned randomly (intervention group: 72 infants; control group: 74 infants). The mean BWs were 1396 ± 429 g for the intervention group and 1381 ± 436 g for the control group. After adjustment for maternal education, a nonsignificant difference in Mental Developmental Index scores at 3 years of 4.5 points (95% confidence interval: −0.3 to 9.3 points) in favor of the intervention group was found, whereas the intervention effect on full-scale IQ scores at 5 years was 6.4 points (95% confidence interval: 0.6–12.2 points). Significantly more children in the intervention group had IQ scores of ≥85 at 3 and 5 years. There were no differences between the groups with respect to motor outcomes.

CONCLUSION: This modified version of the Mother-Infant Transaction Program improved cognitive outcomes at corrected age of 5 years for children with BWs of <2000 g. *Pediatrics* 2010;126:e1088–e1094

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KEY WORDS

cognitive and motor outcome, early intervention, premature infants, randomized controlled trial, Mother-Infant Transaction Program

ABBREVIATIONS

BW—birth weight
BSID-II—Bayley Scales of Infant Development II
CI—confidence interval
EI—early intervention
MITP—Mother-Infant Transaction Program
MDI—Mental Developmental Index
PDI—Psychomotor Developmental Index
OR—odds ratio
GA—gestational age
SGA—small for gestational age

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Preterm infants are at increased risk of neurobehavioral impairment.[1] In addition to biological risk, environmental factors, parents' adjustment to the preterm birth, and specific parenting behaviors are important for infants' neurobehavioral development.[2,3] Various early intervention (EI) strategies have been developed to improve long-term outcomes.[4–9] Earlier studies of the efficacy of these programs yielded conflicting results, and there are few studies with long-term follow-up data. These EI strategies differ considerably in design, intervention load, timing, and cost.[10] Meta-analyses of data on postdischarge intervention programs reported significant effects on cognitive outcomes at infant and preschool (<5 years) ages but not at school age or on motor outcomes.[10–12] More research is needed to identify the target population, the aspects of programs that are useful, and the families who might benefit from EI programs.[12]

One small study of the Mother-Infant Transaction Program (MITP),[13] a program based on the transactional model of development,[14] showed improved intelligence in the intervention group at 9 years.[7] The transactional model of development places equal emphasis on the infant and the parents and considers disturbed parent-child interactions to have a major influence on the child's neurodevelopment.[14] For example, infant temperament and responsiveness are thought to influence the experiences provided by the parents, and this mutual interaction affects the child's development in a positive or negative direction.[15] One important feature in the neurodevelopment of preterm infants is the parents' ability to respond contingently and to be interactively sensitive partners.[16,17]

Because of the conflicting results of the EI programs and the promising results of the MITP, a randomized controlled trial with long-term follow-up monitoring was designed. The intervention program, which was a modified version of MITP,[13] aimed at sensitizing parents to their infants' individual characteristics, to achieve mutually stimulating, positive, parent-infant interactions. We reported previously that this EI program led to sustained reduction of parenting stress,[18] improved joint attention performance,[19] and more-nurturing child-rearing attitudes in mothers.[20] However, there was no effect on cognitive and motor outcomes at corrected age of 24 months.[21]

The aim of this study was to examine the effects of a modified version of the MITP on cognitive and motor outcomes for preterm children. In this article, we report the effects of this EI program on cognitive and motor outcomes at corrected ages of 3 and 5 years.

METHODS

Study Groups and Randomization

The methods used in this study were described in detail previously.[18–21] Preterm infants with birth weights (BWs) of <2000 g who were treated at the University Hospital of North Norway between March 1999 and September 2002, who had no major congenital abnormalities, and whose mothers' first language was Norwegian were eligible for the study.

The parents were informed about the study by the study coordinating nurse ~2 weeks before planned discharge, and written informed consent was obtained if the parents agreed to participate. Within gestational age (GA) strata (<28 or ≥28 weeks), infants were assigned randomly to an intervention or control group. The randomization was arranged in random blocks of 4 and 6, by using computer-generated random numbers. Allocation was through sealed opaque envelopes (identified according to stratification group and numbered consecutively), which were opened by the coordinating study nurse after the parents had completed various questionnaires. Because of the nature of the intervention, twin pairs were allocated to the same group and triplets were excluded. The study was approved by the regional committee for medical research ethics and the Norwegian Data Inspectorate.

Intervention

The intervention program was a modified version of the MITP.[7] The modifications were to add an initial debriefing session, in which the parents could talk about their experiences of the hospital stay and express feelings such as grief, disappointment, or anger, and to encourage both parents to participate in the intervention sessions.[22] After the initial session, the intervention consisted of 1-hour daily sessions with both parents and their infant on 7 consecutive days, starting 1 week before planned discharge at postmenstrual age of ≥34 weeks.

Each session addressed aspects such as the infant's reflexes, self-regulation and interactions, signs of distress, and predominant states and how parents could bring the infant into a quiet alert state for mutual social interaction. The last 2 in-hospital sessions were devoted to the parents achieving sensitivity and responsiveness toward their infant through daily routines. The daily in-hospital sessions were followed by 4 home visits by the same intervention nurse, 3, 14, 30, and 90 days after discharge. The home visits addressed adjustment to the home environment, interactions between the parents and the infant, how to guide and to stimulate the infant, and discussion and evaluation of the intervention program. Additional details of the content in the intervention sessions were provided by Rauh et al.[13] The EI program was implemented by 8 neonatal nurse specialists trained especially for this intervention. Both parents were encouraged to participate in the intervention sessions. The timing of the intervention with respect to the hospital-home transition was chosen in an effort to reduce the risk of spillover effects in a small NICU. To maintain the consistency of the intervention, a detailed log of every intervention session was regularly reviewed and supervised by the coordinating nurse (Ms Tunby) and a clinical child psychologist (Dr Rønning). The participants in the intervention group did not have access to the intervention nurses outside the scheduled intervention dates.

The control group followed the department's standard protocol for the discharge of preterm infants; this included a physical examination and an offer of training in infant massage from the unit's physiotherapist, a clinical examination including visual and auditory screening, and a discharge consultation with 1 of the pediatricians from the ward. Both groups had access to standard follow-up care after discharge.

Baseline Data

Perinatal variables were collected from medical records. GA was determined through ultrasound examination at 16 to 18 weeks of gestation. The Score of Neonatal Acute Physiology[23] and the Clinical Risk Index for Babies[24] were calculated as measures of the initial severity of illness. Small for GA (SGA) was defined as BW >2 SD below the mean for GA; Norwegian BW data were used.[25] Intraventricular hemorrhage was graded as described by Papile et al,[26] and periventricular leukomalacia was defined by the presence of echolucensies on cerebral ultrasound scans. Social variables used in the analyses were collected from parents at discharge, with a separate questionnaire.

Main Outcomes

The primary outcomes for this study were differences in cognitive and motor performance at corrected ages of 3 and 5 years.

Outcome Measures

Cognitive and motor outcomes at 3 years were assessed by using the Norwegian version of the Bayley Scales of Infant Development II (BSID-II).[27] The BSID-II includes a mental score, which yields a Mental Developmental Index (MDI), and a motor score, which yields a Psychomotor Developmental Index (PDI). Both MDI and PDI are standardized to exhibit a mean score of 100 and a SD of 15. If an infant scored <50, then a nominal score of 40 was assigned, as suggested by others.[28] The Norwegian version of the Wechsler Preschool and Primary Scale of Intelligence-Revised[29] was used to measure cognitive outcomes at 5 years of age. This test consists of 11 subtests, which are divided into a full-scale IQ, verbal IQ, and performance IQ. Motor outcomes were measured with McCarthy Scales of Children's Abilities (parts 9 and 11),[30] which consists of 5 subtests for gross coordination. To measure fine motor function, the grooved pegboard test[31] was used. The cognitive and motor testing was performed by 4 specially trained test technicians. All examinations were video-recorded and reviewed regularly, to maintain consistent scoring. All children underwent a medical examination (performed by Dr Dahl) for possible neurologic sequelae at 2 years of age. At 3 and 5 years of age a medical examination was performed on clinical indication only. All assessors were blinded to the children's group allocation.

Power Calculations

The study size was calculated originally to detect a difference in BSID-II MDI scores at corrected age of 2 years of ~0.5 SD ($\alpha = .05$; $\beta = .80$). This analysis indicated that 63 infants were needed in each preterm group. To allow for withdrawals, the target size was 70 infants in each group.

Statistical Analyses

Differences in continuous variables between the preterm groups were tested by using linear mixed models, which make it possible to account for potential clustering effects by including twin pairs when family is included as a random effect. Differences in continuous variables are given as mean differences with 95% confidence intervals (CIs). Binary outcomes were analyzed through logistic regression, with robust SEs and differences given as odds ratios (ORs) with 95% CIs. *P* values of <.05 were considered significant. All tests were 2-sided. All results are reported on the basis of intention to treat. Stata 10 (Stata Corp, College Station, TX) was used for the analyses.

RESULTS

A total of 203 infants with BWs of <2000 g were born during the study period. This represented 96% of all infants with BWs of <2000 g who were born in the counties of Troms and Finnmark during the recruitment period. One hundred sixty-eight infants fulfilled the inclusion criteria, and 146 infants (87%) from a total of 131 families were assigned randomly. The basic characteristics at the time of randomization 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 year [95% CI: 0.03–2.2 years]; $P = .04$) in favor of the intervention group (Table 1). All mothers in the intervention group participated in every intervention session, whereas the fathers participated in a median 6 of 12 sessions (interquartile range: 4–9 sessions). The patient flow until 5 years is shown in Fig 1.

TABLE 1 Infant Characteristics and Social Factors at Randomization

	Intervention ($N = 72$)	Control ($N = 74$)
Infant characteristics		
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, wk	30.2 ± 3.1	29.9 ± 3.5
<28 wk, *n* (%)	17 (24)	19 (27)
28–32 wk, *n* (%)	36 (50)	37 (50)
≥33 wk, *n* (%)	19 (26)	18 (24)
Male, *n* (%)	38 (53)	39 (53)
Twin, *n* (%)	16 (22)	14 (19)
Prenatal steroid use, *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 ($N = 62$)	7.0 ± 18.6	7.1 ± 17.3
Postnatal steroid use, *n* (%)	9 (13)	10 (14)
Oxygen therapy at 36 wk of gestation, *n* (%)	11 (15)	14 (19)
Abnormal cerebral ultrasound findings, *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, y	30.8 ± 6.1	29.1 ± 6.4
Firstborn child, *n* (%)	40 (56)	37 (54)
Mother's education, mean ± SD, y ($N = 131$)[a]	14.6 ± 2.8	13.5 ± 3.2
Father's education, mean ± SD, y ($N = 131$)[a]	13.8 ± 3.1	13.5 ± 3.2
Mother's monthly income, mean ± SD, 1000 Norwegian kroner ($N = 131$)[a]	15.8 ± 7.7	14.6 ± 6.7
Father's monthly income, mean ± SD, 1000 Norwegian kroner ($N = 131$)[a]	21.1 ± 8.7	19.9 ± 8.1

SNAP-II indicates Score for Neonatal Acute Physiology II (includes mean blood pressure, lowest temperature, Po_2/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 deficit in the first 12 hours, minimal appropriate fraction of inspired oxygen in the first 12 hours, and maximal appropriate fraction of inspired oxygen in the first 12 hours); IVH, intraventricular hemorrhage.
[a] Calculated for 131 families due to 15 twin pairs.

Cognitive and motor outcomes at 3 years are presented in Table 2. Ninety-two percent of the randomly assigned children ($n = 134$) were assessed, and 1 child in the control group was assigned a nominal MDI score. In the primary analysis, there was a significant difference in mean MDI scores in favor of the intervention group. Seventeen (25%) of the children in the control group had MDI scores of <85, compared with 7 (10%) in the intervention group (OR: 0.34 [95% CI: 0.13–0.90]; $P = .03$). With adjustment for maternal education, the mean difference in MDI scores was reduced by 1.2 points (adjusted mean difference: 4.5 points [95% CI: −0.3 to 9.3 points]; $P = .06$). There was no significant group difference in motor outcomes (PDI scores) (Table 2).

Cognitive outcomes at 5 years are presented in Table 3. Ninety percent of the randomly assigned children ($n = 131$) were assessed. In the primary analysis, there were significant differences in full-scale IQ, verbal IQ, and performance IQ scores in favor of the intervention group. Seventeen (26%) of the children in the control group had full-scale IQ scores of <85, compared with 3 (5%) in the intervention group (OR: 0.14 [95% CI: 0.04–0.48]; $P = .002$). With adjustment for maternal education, the group differences were slightly decreased and the difference in verbal IQ scores was not statistically significant (Table 3).

There were no significant differences between the 2 groups in total motor skills at 5 years of age. In subscale analyses, children in the intervention group were significantly more skilled in standing on 1 foot ($P = .03$) and in placing the right keys in a box with the nondominant hand ($P = .03$).

DISCUSSION

The main finding of this study was that this modified version of the MITP led to a significant difference in mean IQ scores at 5 years in favor of the intervention group. This difference was within the clinically significant range, which is considered to be ≥5 points.[32] Furthermore, significantly more children in the intervention group scored within a normal range (scores of ≥85) at both 3 and 5 years. At 3 years, the primary analysis of MDI scores showed a significant difference in favor of the intervention group. However, because of the strong association between maternal education and intelligence, we adjusted for maternal education in a secondary analysis. After the adjustment, the group differences in MDI scores at 3 years and verbal IQ scores at 5 years were no longer significant, although the estimates still showed improvements in favor of the intervention group.

Only a few previous studies reported follow-up data on cognitive outcomes beyond 2 years.[7,33–36] The Infant Health and Development Program[35] reported significant differences in cognitive outcomes at corrected ages of 2 and 3 years in favor of the intervention group, but the effects were no longer detectable at 5 years of age. A more-recent study was the Avon Premature Infant Project,[36] which demonstrated a small advantage in cognitive outcomes at 2 years of age, but the effect was no longer present at 5 years of age. In con-

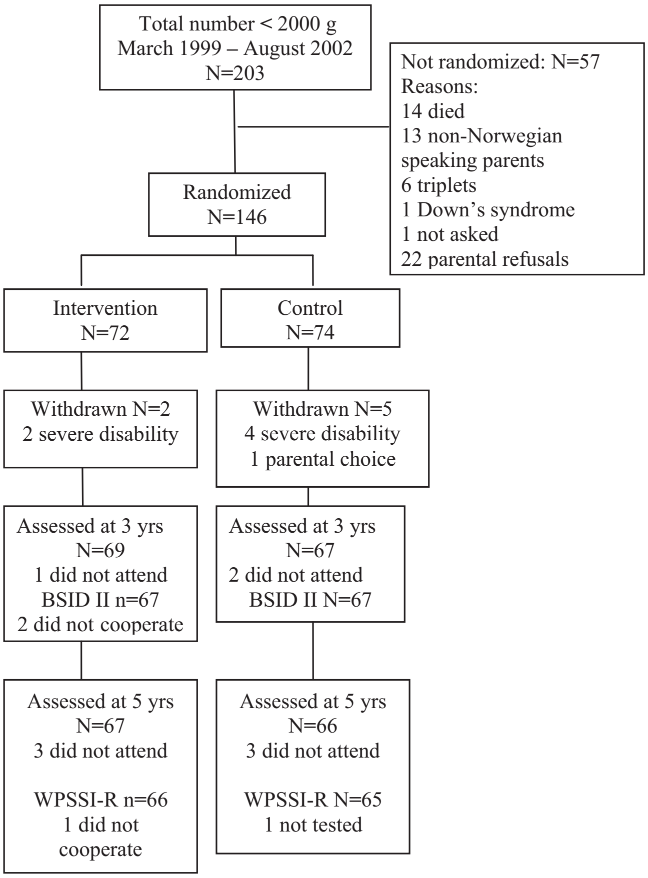

FIGURE 1
Study flow diagram. WPSSI-R indicates Wechsler Preschool and Primary Scale of Intelligence-Revised.

TABLE 2 Cognitive and Motor Outcomes at Corrected Age of 3 Years

	Intervention	Control	Difference, Mean (95% CI)[a]	P[a]
MDI score	$N = 67$	$N = 67$		
Mean ± SD	97.9 ± 11.1	92.3 ± 15.6	5.7 (0.9 to 10.5)	.02
≥100, n (%)	30 (44)	23 (34)		
85–99, n (%)	30 (44)	27 (40)		
84–70, n (%)	6 (9)	12 (18)		
<70, n (%)	1 (1.5)	5 (4)		
PDI score	$N = 66$	$N = 66$		
Mean ± SD	93.7 ± 13.6	92.8 ± 14.5	1.2 (−3.8 to 6.5)	.6
≥100, n (%)	23 (35)	23 (35)		
85–99, n (%)	34 (51)	31 (47)		
84–70, n (%)	6 (9)	7 (11)		
<70, n (%)	3 (5)	5 (7)		

[a] Adjusted for clustering effect of twin pairs.

trast, our study demonstrated a different pattern, which was similar to the results from the original MITP study reported by Achenbach et al.[7] The fact that this study demonstrated sustained effects on intelligence from 3 to 9 years of age in favor of the intervention group indicates that our results are promising.

We hypothesize that the modified MITP creates a positive feedback loop through enhanced interactions between less-stressed[18] and more-confident parents and their responsive infants,[19] according to the transactional model of development.[14] Other factors contributing to the delayed effects may be methodologic issues, because the BSID-II was shown to be a poor predictor of cognitive outcomes at school age for preterm infants,[37] or the "sleeper effect."[38] The apparently high cognitive scores in both preterm groups may be explained by the secular trend in IQ scores over time (the Flynn effect).[39]

In contrast to the cognitive outcomes, we did not detect any difference in motor outcomes at either 3 or 5 years, except in 2 subscale analyses. The differences in subscales should be interpreted with great care because of multiple comparisons. Furthermore, the motor outcome measures used are fairly crude and may not be able to detect subtle motor changes. We have no records of physiotherapy received after discharge. A recent study reported beneficial effects of the Infant Behavioral Assessment and Intervention Program on motor development at corrected age of 2 years,[40] which is in contrast to most other EI programs.[12] The authors hypothesized that the Infant Behavioral Assessment and Intervention Program contributes to improved motor development through improved self-regulatory competencies in the infant and thus increased abilities to explore and to process information.[40]

Published EI programs differ in content, timing, intervention load, and possible cost-benefit effects. Different EI studies are heterogeneous with respect to the introduction of the intervention, that is, soon after birth,[41,42] in the hospital-home transition,[7] or after discharge from the hospital.[6] Some reports showed that the Newborn Individualized Developmental Care and Assessment Program started soon after birth had beneficial effects on short-term morbidity and cognitive and motor outcomes,[43–45] but other studies did not document this.[46] Both the Newborn Individualized Developmental Care and Assessment Program and the

TABLE 3 Cognitive Outcomes at Corrected Age of 5 Years

	Intervention ($N = 66$)	Control ($N = 65$)	Crude Difference, Mean (95% CI)[a]	P^a	Adjusted Difference, Mean (95% CI)[b]	P^b
Full-scale IQ score						
Mean ± SD	102.3 ± 13.5	95.6 ± 19.2	7.2 (1.3 to 13.0)	.02	6.4 (0.6 to 12.2)	.03
<70, *n* (%)	1 (2)	6 (9)				
70–84, *n* (%)	2 (3)	11 (17)				
85–99, *n* (%)	29 (44)	17 (26)				
≥100, *n* (%)	34 (52)	31 (48)				
Verbal IQ score, mean ± SD	102.4 ± 14.0	96.3 ± 18.1	6.2 (0.4 to 11.9)	.04	5.5 (−0.3 to 11.3)	.06
Performance IQ score, mean ± SD	101.3 ± 15.8	95.3 ± 18.4	6.9 (0.8 to 13.0)	.03	6.3 (0.2 to 12.3)	.04

[a] Adjusted for clustering effect of twin pairs.
[b] Adjusted for clustering effect of twin pairs and maternal education.

MITP try to sensitize parents to their infants' individual characteristics and, given these similarities, we speculate that a combination of components from the Newborn Individualized Developmental Care and Assessment Program and the MITP approach might have additional beneficial effects. Future studies should attempt to identify the more-effective components of these sensitizing intervention programs.

There has been some controversy regarding the costs of various EI programs. The estimated costs of this program were approximately $1000 in training costs per intervention nurse, and we trained 3 nurses per 1000 live births. The intervention costs per child (12 sessions) were $640, and the travel costs per family were $1700; this is inexpensive, compared with other EI studies.[10] It is important to take into consideration the fact that travel costs are much higher in sparsely populated northern Norway than in most other parts of the world. Therefore, it should be possible to implement this EI program in more-densely populated areas.

A strength of this study is that it was a population-based, randomized, controlled trial, with blinded assessors and high follow-up rates at both 3 and 5 years of age. In addition, we managed to involve both parents in more sessions, compared with comparable studies.[41] However, there are potential weaknesses in the study. We used BW instead of GA as the inclusion criterion. This led to the inclusion of some more-mature, SGA infants, which makes it more difficult to generalize from the results. The SGA infants were distributed evenly between the preterm groups, however, and this should not bias the group differences. Another weakness was the lack of blinding of the parents, which might have biased the results. Although we found significant differences in favor of the intervention group, the CIs were wide, mainly because of the limited number of children included in this study.

CONCLUSION

This EI program demonstrated increased effects over time on cognitive outcomes for preterm infants with BWs of <2000 g. The observed differences at 5 years of age were of a magnitude commonly thought to be of clinical importance.

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