Developmental care and very preterm infants : neonatal, neurological, growth and developmental outcomes

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The Leiden Developmental Care Project

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Voor Eric,
Jim en Andrea
en mijn lieve Hailey en Zoë

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CHAPTER 1

Introduction

Incidence of preterm birth

The incidence of preterm birth is increasing in The Netherlands as well as in the United States. In 2004, 12.5% of all live births in the United States was a preterm birth, which is an increase of 18% since 1990. Although multiple births have contributed to this recent rise, preterm rates for singletons have also increased, up 11% since 1990[1]. The preterm birth rate continued to rise in 2005 (to 12.7% in 2005) as did the rate for LBW births (8.2%)[2].

In 2001 there were approximately 16,000 infants born preterm (less than 37 weeks pregnancy) in the Netherlands, which is 8% of all live births. There were 2,200 very preterm births (born less that 32 weeks pregnancy). The incidence of very preterm births has increased between 1983 and 1999 from 1,068 to 2,170 infants, which is a relative increase from 6.8 per 1000 to 10.8 per 1000 live births[3].

As some of the risk factors for a premature birth are also increasing, i.e. older average age that a woman has her first child as well as a higher maternal age in general, infertility treatments, multiple births, better prenatal care and improved diagnosis and treatment, it is expected that the rise in infants born prematurely will continue[4].

Risks associated with prematurity

Advanced technology in the treatment of preterm infants has resulted in decreasing mortality rates. However all preterm infants are at heightened risk of morbidity and mortality compared with infants born at higher gestational ages[2]. Some of the complications that may occur as the result of being born preterm are respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), patent ductus arteriousus (PDA), necrotizing enterocolitis (NEC), infections, bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP)[5]. Higher survival rates of very preterm infants have not necessarily led to lower morbidity rates, and has been associated with a higher incidence of intraventricular hemorrhage and BPD[6-8].

Follow-up outcomes of preterm infants

Follow-up studies show that preterm infants have an increased risk of developmental disorders[6,9-11]. Neuromotor abnormalities are the most frequent of the "hidden disabilities" among ex-preterm children and are frequently associated with poorer cognitive ability and attention deficit disorder[12]. A meta-analysis showed

increased risk of cognitive deficits and behavioral problems in preterm infants, with cognitive deficits greater and in direct proportion to the infant's gestational age and birthweight[13]. Studies report a higher risk of later disabilities or handicaps at school age as well as learning and behavioral disorders in preterm infants [14,15]. In addition, VLBW children have an increased risk of developing attention deficit hyperactivity disorders (ADHD), have generalized anxiety and more symptoms of depression[16].

The NICU environment

Research on the sensory development of the preterm infant have shown that many of the environmental factors and care practices in the NICU have a significant impact on infant sensory development. In addition, problems of sleep deprivation are related to care practices and NICU organization[17,18]. Current evidence suggests that the NICU environment has strong influences on physiological functioning (hypoxemia, apneas, etc.) and in turn influences the long-term development of the weak and vulnerable central nervous system[19,20]. Because premature infants cannot regulate incoming stimuli, they become easily overstimulated and stressed. Als and colleagues propose that there is a sensory mismatch of the premature infant's developing nervous system's expectations for environmental inputs and the actual sensory overload that is experienced in the neonatal intensive care. This in turn can lead to a greater chance for later developmental problems[21,22].

Parents of premature infants

In addition, many factors in the NICU environment may adversely affect parent-infant attachment and parent involvement essential for long-term development[23]. Family bonding in the NICU is often a very difficult process, due to the separation of parents and child at birth and the continued physical restraints of the complex critical care environment. Cronin et al report that parents of very low birth weight infants (< 1500 grams) continue to manifest stress even up to 5 years after the birth of the child[24]. Involving parents in the care of their infant and instructing them in premature behavior may facilitate bonding, increase parents' confidence in care-giving and possibly decrease the chance of later disturbances in the parent-child relationship.

The nature of the relationships that families develop with health care providers in the NICU may have a profound influence on how individuals and families respond to the experience of having a preterm infant[25].

Developmental Care

The challenge confronting healthcare professionals who care for preterm infants and their families is not only to assure the infants' survival, but to optimize their developmental course and outcome[26].

In order to address these problems, researchers have concentrated on ways to improve the care and environment of the NICU for infants and parents through the use of developmental care programs. In the last 15-20 years, interest has increased and programs have been implemented in various neonatal nurseries. The philosophy behind developmental care is to reduce stress and support development of premature infants as well as their parents. The NIDCAP (Newborn Individualized Developmental Care and Assessment Program) is a comprehensive program used as a framework for the implementation of individualized developmental care in the NICU[26].

NIDCAP

The NIDCAP program is an approach in which the infant's behavior provides the best information from which to design care[27]. Repeated, systematic behavioral observations of the infant are carried out and recommendations for caregiving are made based on these observations. These behavioral observations are based on the Synactive Theory of Development which states that there is a continuous interaction of five subsystems within the developing infant: the autonomic system, the motor system, the state organizational system, the attentional-interactive system, and the self-regulatory system [27,28]. The infant is in constant interaction with the environment and the infant's level of functioning can be observed via these subsystems.

The autonomic system's functioning is observable in the infant's breathing patterns, color fluctuations and visceral stability or instability such as bowel movements, gagging and hiccoughing. The motor system functioning is observable in the infant's body tone, postural repertoire and movement patterns, as reflected in facial and trunkal tone, tone of the extremities and in the extensor and flexor postures and movements of face, trunk and limbs. State organization is observable in the infant's range of available states (from sleeping, to alert, to aroused), their robustness and modulation and the patterns of transitions from state to state. Some infants show the full continuum of states, from deep sleep to light sleep, then to drowsy and quiet alert and to active awake and aroused and then to upset and crying[29]. Other infants during interactions move from sleep to aroused states and immediately back to sleep again, skipping the alert state. Thus state stability and the smooth transition from state to state would reflect intact state organization whereas the opposite would reflect disorganization[21]. The attention and interaction system is

seen in the infant's ability to come to an alert, attentive state and to use this state to take in information from the environment and in turn, elicit and modify these inputs from the world around him. The self-regulatory system is seen in the strategies the infant uses to maintain a balanced, relatively stable state of subsystem integration or to return to a more balanced and relaxed state[28] (Table 1).

The five subsystems are interdependent and interrelated. For example, physiological stability lays the foundation for motor and state system control. State organization, the management of sleep–wake cycles, creates a component of self-regulatory competence. The loss of integrity in one system influences the other systems, as they manage environmental demands [30].

The behavior of the infant and how the infant is coping with the environmental inputs can be observed via the subsystems and the balance of avoidance, stress behaviors and approaching, self-regulatory behaviors[21,27]. The infant uses these strategies and mechanisms to move away from and avoid inappropriate environmental demands or to seek out and move towards inputs currently appropri-

Table 1. Behavioral systems and channels of communication

Subsystems	**Channels of communication**
Autonomic/physiologic	- respiration pattern - color changes - heart rate - visceral stability
Motor	- posture - tone - movements
State[29] - Deep sleep - Light sleep - Drowsy - Quiet alert - Active awake, aroused - Upset, crying	- range of states - state transition patterns - robustness of states
Attention-Interaction	- ability of the infant to come to an alert, attentive state, take in input and interact with the environment
Self-regulatory	- strategies used to return to a calm balanced state - behaviors the infant uses to bring and keep the subsystems in balance

Based on the Synactive Theory of Development from Als[27]

ate for the infant's intake capacities. Avoidance behaviors are believed to reflect stress. Approach and self-regulatory behaviors are seen when the input does not exceed the capabilities of the infant. For example, extension behaviors primarily are thought to reflect stress and disorganization and flexion behaviors are thought to reflect self-regulatory competence. Diffuse behaviors are thought to reflect stress and well-defined robust behaviors reflect self-regulatory balance [21].

This model is based on the assumption that the infant actively and consistently, through his behavior, communicates his/her thresholds for sensitivity versus competence. The range of infant behaviors becomes evident as the infant matures[30].

If the input is too much for the infant and his own regulatory capacities are exceeded, a further parameter of functioning is seen in the kind and amount of facilitation that is needed to help the infant return to a more balanced subsystem functioning[28]. Sensitivity to these signs of organization or disorganization provides the caregiver with an understanding of each infant's threshold for activity and stimulation[30].

In the healthy full term newborn the five subsystems are mature, integrated, synchronized and managed smoothly. All five systems are managed easily and without stress. The less mature, healthy preterm or sick preterm may be unable or partially able to manage environmental inputs, demonstrating over-reactive responses and poor tolerance from even minimal input. Loss of control and stress responses become frequent unless the environment and caregivers work to read the infant's messages and thresholds for sensitivity and adjust care and handling and the environment based on the infant's behavioral communications[30].

A behavioral observation method is used based on the assumption that the behavior of the infant is the primary route for communicating thresholds to stress or relative functional stability. The observation is carried out for 20 minutes before caregiving or handling in order to have a baseline of the infant's behavior, during the caregiving and for at least 10 minutes after caregiving in order to assess the infant's ability to recover and what interventions may be needed to help facilitate the infant. The observation sheet is divided into 2-minute time segments in which specific behaviors observed can be checked. A narrative descriptive of the infant's behavior before, during and after caregiving is made based on the observation, with interpretation of behavioral signals as stress vs. self-regulatory behaviors. On the basis of this description, an individualized developmental care plan is made with suggestions for the reduction of stress behaviors and the increase of self-regula-

tory behaviors. These may include interventions in the physical environment of the infant, direct caregiving and discharge planning[28]. The emphasis of NIDCAP is on an individual approach in which the behavior of the infant is used to deliver caregiving.

Various components of a developmental care program may consist of:

a) Reducing environmental sources of stress by lowering noise, light and activity levels and the use of incubator covers. Nurseries should be quiet, soothing places with individual dimmed lighting.
b) Supporting motor development by positioning the infant in comfortable aligned, softly flexed positions during sleep and caregiving interaction and using various materials and buntings to provide soft boundaries.
c) Providing containment by gently swaddling the infant's body, arms and legs with your hands or with a soft blanket to reduce diffuse and jerky movements during caregiving interactions.
d) Reducing the physiological and behavioral destabilization associated with procedural handling by providing support or containment, allowing the infant a "time-out" when thresholds to stress are exceeded, and providing aids for self-regulation, such as pacifiers or objects to grasp.
e) Supporting organization of sleep-wake states through preserving undisturbed rest periods and providing light-dark cues for the development of circadian rhythms.
f) Attention to readiness for and the ability to take oral feedings, providing individual feeding support determined by the infant's individual needs and preferences. Feeding success is not only judged by the infant's intake but also by the infant's overall energy levels and autonomic, motor and state functioning.
g) Involving parents in the care of their infant and guiding parents in recognizing their infants behaviors and ways in which they can support their infant during caregiving interactions [21,31,32].

Developmental care studies carried out up to 2000

Studies evaluating the effect of individual developmental care were published from the mid 1980's. The first study published was a phase-lag study, after that various RCT's were carried out[31,33-37]. Many of the developmental care studies originate from the United States and Sweden where most infants remained in the same neonatal unit until discharged to home (Table 2).

Table 2. NIDCAP studies published before 2000

Author and year	Design	Participant's	N	Intervention	Main outcomes
Als 1986	Phase-lag	Birthweight < 1250 g GA < 28 weeks Ventilated ≥ 24 hours in first 48 hours of life and 60% FiO2 ≥ 2 hours in first 48 hours	E=8 C=8	Caregiving by NIDCAP trained personnel until discharge	Days ventilation Days O^2 Days before bottle feeding 2 APIB system scores at term age MDI and PDI at 3, 6 and 9 months
Als 1994	RCT	Birthweight < 1250 g GA < 30 weeks Ventilated within first 3 hours and > 24 hours of first 48 hours	E=20 C=18	Caregiving by NIDCAP trained personnel until discharge	Days ventilation (ns) Days O^2 (p=0.05) IVH Days before bottle feeding (p=0.05) Severity of BPD Days of hospitalization MDI and PDI at 9 months
Buehler 1995	RCT	Birthweight ≤ 2500 GA 30-34 weeks No ventilatory support Also 3rd C group of healthy full-term infants	E=12 C=12 FT=12	Individual developmental care by specially trained personnel until discharge	4 APIB system scores at term age 3 Prechtl summary scores and total Prechtl score at term age Outcomes comparable to full term infants in E group
Fleischer 1995	RCT	Birthweight < 1250 g GA ≤ 30 weeks No ventilation in first 3 hours or for > 24 hours of first 48 hours of life	E=17 C=18	Individual developmental care by specially trained personnel until discharge	Days ventilation and /or CPAP Duration of stay > 42 weeks PCA (p=0.05) 4 APIB system scores at term age
Ariagno 1997	RCT	Birthweight < 1250 g GA ≤ 30 weeks No ventilation in first 3 hours or for > 24 hours of first 48 hours of life	E=11 C=12	Follow-up of some of original participants of RCT by Fleischer, 1995	No significant difference in MDI and PDI at 4, 12 months and 24 months

All outcomes are significant in favor of the intervention group unless otherwise indicated
E: experimental group, C: control group, RCT: Randomized Controlled Trial, GA: gestational age, MDI: Mental Development Index, PDI: Psychomotor Development Index, IVH: intraventricular hemorrhage, PCA: postconceptional age

Developmental Care in NICU's in the Netherlands

Developmental care programs were relatively unknown in the Netherlands in 1999. Since then, the interest for developmental care and NIDCAP has increased. Studies that have been published to date are scarce. Before NICU's in the Netherlands implement developmental care programs, research is needed to evaluate the effectiveness of this program in our present neonatal system.

One of the criticisms of developmental care programs has been that it is difficult to ascertain which of the components are responsible for the improved outcomes[36,38-40]. It was suggested that research is needed in which the effectiveness of the various components of the developmental care program can be evaluated in addition to the comprehensive NIDCAP program.

In this thesis we have attempted to answer some of these questions as well as measure the effect of developmental care in a NICU in the Netherlands. The study consisted of a pilot study measuring the effect of a short-term, hospital based intervention with parents in which they were instructed in preterm infant behavior with the goal of increasing their responsiveness to their infant and therefore their confidence in caregiving. This was followed by two consecutive randomized controlled trials.

The phase one RCT evaluated the effect of basic elements of developmental care (standardized incubator covers and nests and positioning aids) designed to reduce stress and improve physiological stability in infants compared to standard care, which at that time consisted of no covers or nesting.

The phase two RCT studied the effect of the comprehensive NIDCAP (Newborn Individualized Developmental Care and Assessment Program), with the use of the behavioral observation and assessment tool with recommendations for caregiving as well as supporting the parents, as compared to the basic elements of developmental care.

Outline of this thesis

This thesis examines the effect of a developmental care program in a tertiary NICU at two locations in the Netherlands on preterm infants born < 32 weeks gestational age.

Chapter 2 describes a pilot study to evaluate the effect of a short-term, hospital based intervention with parents and their premature infants born < 32 weeks gestational age in the neonatal department of the Leiden University Medical Center, in which parents were instructed in understanding preterm infant behavioral cues.

In Chapter 3 we examine the effects of basic developmental care on short-term morbidity, growth and neurodevelopmental outcomes to term age.

Chapter 4 studies the effect of basic developmental care on 1 and 2 year growth and neurodevelopmental outcomes.

Chapter 5 describes the effect of the comprehensive NIDCAP developmental care program on short-term morbidity, growth and neurodevelopmental outcomes to term age.

Chapter 6 examines the effect of NIDCAP on 1 and 2 year growth and neurodevelopmental outcomes.

Chapter 7 contains the General Discussion on the results of this study.

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CHAPTER 2

Reading Preterm Infants' Behavioral Cues: An Intervention Study with Parents of Premature Infants Born < 32 weeks

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Abstract

The effect of a short-term intervention with parents in the Neonatal Intensive Care Unit (NICU) on their knowledge of infant behavioral cues and confidence in caregiving was examined. Ten sets of parents with a total of 22 premature infants born < 32 weeks gestational age admitted to a NICU were enrolled in a time-lag control trial over an 8 month period. The intervention group was given 4 sessions of instructions on preterm infant behavior for a period of 2 weeks. The control group did not receive the instructions. All parents completed two subscales of the Mother and Baby Scale (MABS) at weeks 1 and 3 and a short questionnaire concerning nursing support at week 3. Intervention parents completed a pre-and post-test on knowledge of preterm infant behavioral cues at weeks 1 and 3. There was a significant improvement in the post-test scores concerning knowledge of preterm infant behavioral cues and a higher nursing support score for mothers in the intervention group. Intervention mothers showed no significant improvement in confidence in caregiving. Only half of the intervention group fathers participated in the sessions and there were no significant differences in fathers' scores. While the intervention significantly increased maternal knowledge of infant behavioral cues, there was no significant effect on mothers' confidence in caregiving. Very few fathers participated in the entire intervention. A longer, more intensive program with a larger sample size and finding ways of incorporating more participation from fathers is recommended.

Introduction

The advances in recent years in neonatology have resulted in a marked improvement in the mortality of premature infants [1-3]. As more infants are surviving, the importance of finding ways to improve developmental outcomes and their quality of life becomes paramount. In addition to the increasing concern with the developmental support of the infant, there has been a heightened appreciation of the psychological strain and emotional stresses encountered by the family of the sick neonate [4].

In addition, many factors in the neonatal intensive care unit (NICU) environment may adversely affect parent-infant attachment and parent involvement essential for long-term development [5]. Family bonding in the NICU is often a very difficult process, due to the separation of parents and child at birth, uncertainty about their child's wellbeing and the continued physical restraints of the complex critical care environment. Cronin et al reported that parents of very low birth weight infants continue to manifest stress even up to 5 years after the birth of the child [6]. In addition, because of their poor motor stability and difficulty maintaining alertness, premature infants do not engage in the social interactions typical of term infants. Preterm infants' cues and interaction signals are often weak and disorganized and too often missed [7]. This in turn may make it more difficult for the parents to form a relationship with their infant.

Involving parents in the care of their infant and instructing them in premature behavior may facilitate bonding, increase parents' confidence in caregiving and possibly decrease the chance of later disturbances in the parent-child relationship [6]. Supporting parents to understand their infant's level of communication through his/her behavior may help them feel more comfortable with their baby and may promote bonding between parents and child.

Various interventions aimed at improving the contact between parents and their infant have been carried out, with some showing promising results [8-11]. The studies differed in type and length of intervention as well as study design. Some studies were only carried out with participation from the mothers and continued over a longer period of time with home-based follow-up instructions. A shorter hospital-based intervention may be more relevant to the Dutch situation where infants may be transferred to regional hospitals once they are stabilized.

The present study examined the effects of a short-term, hospital based intervention with parents and their premature infants in the neonatal department of a tertiary Dutch university hospital. The intervention program was based on aspects of developmental supportive care with the goal of positively influencing parental

knowledge and responsiveness to premature infant signals and behavioral cues. It was based on the assumption that once parents understand their infant's behavior, they will be in a better position to respond to and interact with their infant in an appropriate and developmentally supportive way and therefore be more confident and comfortable in their interaction with their infants.

Methods

Design

The study took place in a 17 - bed level III NICU and was a time-lag design. The study was approved by the review board and medical ethics committee of the hospital and written informed consent was obtained from parents. Inclusion criteria were: birth of a preterm infant < 32 weeks with no congenital malformation and requiring no major surgery. The duration of the study was 8 months.

Control group parents were first recruited consecutively over a 4-month period. Parents in the control group received the standard support normally given by the nurses. After questionnaires and data were collected from the control group, the recruitment of the intervention group of parents began and was carried out over a 4-month period.

Intervention

The researcher met with the parents in the intervention group four times over a two-week period during the infants' second and third week of life and the sessions lasted between 20 and 30 minutes. The teaching sessions were interactive in nature and were primarily carried out with parents and infant individually at the infant's bedside. Material with photos was used for explaining infant behavior and how to read premature infant's cues [7,10,12-14]. The goal was to support parents in becoming more knowledgeable in preterm behavior in order to better understand their own infant's behavior. Care was taken to present the information in an interactive manner that was easily understandable and supportive of the parents own observations of their child.

Measures

Demographic variables collected were parental age, educational level and country of birth (Netherlands/other). Infant characteristics at birth were the infant's gender, gestational age, birth weight, Apgar score at 5 minutes and twin (yes/no).

Neonatal behavior and parental confidence

Two subscales of the MABS (Mother and Baby Scales) were given to parents to complete. The MABS is a parent-report measure of neonatal behavior and parental caretaking confidence [15]. The subscale "Lack of Confidence in Caregiving" (LCC) assesses parental perception of their own caregiving confidence, contains 13 items and has a reliability of 0.93 as measured by Cronbach's alpha. The subscale "Global Confidence" (GC) is a short impressions measure from the overall impressions and experiences section, contains 3 items and has a reliability of 0.81. A higher score of the LCC scales indicates an increase in the lack of confidence in caregiving, whereas a higher score in the GC scales indicates a higher overall global confidence. The subscales of the MABS were translated from English into Dutch and two of the questions in the subscale "lack of confidence in caregiving" were altered slightly so that they would be more appropriate for the situation in the neonatal intensive care unit. Cronbach's alpha was then computed for each subscale. Alpha was reasonable to good.

Knowledge of premature infant behavior

In addition, parents of the intervention group were given a pre- and post-test on premature infant behavior developed specifically for this study, based on the material that would be presented in the instructions started when their infants were 1 and 3 weeks old. The questionnaire measures knowledge of infant behavior. Total possible score was 30. A high score indicated increased knowledge.

Parents' experience of nursing support in the NICU

Parents from both groups were asked at the end of week 3 to complete a short questionnaire concerning their experience in the neonatal intensive care unit. Four of the items were found via reliability analysis to form a scale concerning nursing support given to the parents in those first three weeks (Cronbach's alpha = .81).

The items were:

1. How did you find the support from the nursing staff the first week?
2. How was it the weeks thereafter?
3. Do you feel that you received sufficient information about your baby?
4. Do you feel that the nursing staff involved you enough in the caring for your baby?

Need for more knowledge

An open-ended question was asked at post-test if parents felt the need for more knowledge concerning premature infant behavior (yes or no).

Procedure

Parents in the control group and intervention group completed subscales from the Mother and Baby Scale (MABS) questionnaire when their infant was one week old and again two weeks later. The intervention group was given 4 sessions of instructions in preterm infant behavior for a period of 2 weeks. The control group did not receive the instructions. All parents received along with the 2 modified subscales of the Mother and Baby scale (MABS) at weeks 1 and 3 a short questionnaire concerning nursing support at week 3. In addition the intervention group completed a pre- and post-test on knowledge of preterm infant behavioral cues at weeks 1 and 3. At the end of the 3 weeks parents were interviewed concerning their experience in the NICU.

Statistics

Data was analyzed using SPSS 11 for Windows (SPSS Inc., Chicago, Illinois, USA). Demographic variables and questions concerning parents' experience in the neonatal department were compared between groups using Pearson's chi-square and t-tests. Differences between groups for the MABS scores were compared using independent group t-tests and differences between pre- and post-tests within each group were compared using the paired sample t-tests.

Results

Participants

Twenty-eight preterm infants of 13 sets of parents admitted to the neonatology department were enrolled after meeting the inclusion criteria. Three couples dropped out, one because their infant died after one week and two because their child was transferred to another hospital. There were five sets of twins; in two sets, one of the twins died and in one set, one twin had anomalies, so these three children were also excluded from the study. In addition the control group and intervention group each had one set of living healthy twins. In total 3 infants died, 2 were transferred and one was born with anomalies, leaving 22 infants with 10 sets of parents in the sample.

Intervention and Control Variables

There were no significant differences in age, educational level or country of birth between mothers and fathers in the control and intervention groups (Table 1). No parents from either group had ever had a premature infant before. There were no significant differences in gender, gestational age at birth, birth weight or Apgar score at 5 minutes between infants in the control and intervention groups (Table 2).

Table 1. Comparison of parent characteristics

	Control (n-=10)	**Intervention (n=10)**	***p* value**
Maternal age at infant's birth			
< 30 years	8	6	0.33
≥ 30 years	2	4	
Paternal age at infant's birth			
< 30 years	3	2	0.61
≥ 30 years	7	8	
Maternal education level (low/intermediate/high)*	4/5/1	1/9/0	0.14
Paternal education level (low/intermediate/high)*	9/1	9/1	1.00
Country of birth mother (Netherlands/other)	9/2	9/2	1.00
Country of birth father (Netherlands/other)	9/1	8/2	0.53

Comparisons were done using chi-square; *p* value significance = <.05
* Low = vocational training, intermediate = high school, high = college/university

Table 2. Comparison of infant characteristics

	Control (n-=11) Mean (sd)	**Intervention (n=11) Mean (sd)**	***p* value**
Gender (female/male)	5/6	6/5	0.67
Gestational age at birth (weeks)	29.0 (1.8)	28.5 (1.2)	0.47
Birth weight (grams)	1075.1 (208.7)	1215.4 (402.8)	0.32
Apgar score at 5 minutes	7.8 (1.3)	7.6 (1.9)	0.79
One of a twin (no/yes)	6/5	8/3	0.38

Comparisons were done using t-test or chi-square test as appropriate.

Outcome variables

Knowledge of preterm infant behavior

There was a significant improvement in the post-test scores concerning knowledge of preterm infant behavioral cues for mothers who underwent the training (pre-test score 15.5; post-test score 24.1 from a possible total score of 30, p= < 0.001). Since only 5 fathers in the intervention group participated in the teaching sessions and 2 of them did not complete the post-test on infant behavior they were not included in this analysis.

Confidence in caregiving (CCG) and global confidence (GC)

There was no significant difference in the baseline MABS scores of the control group and intervention group of mothers and fathers, indicating that both groups had comparable initial levels of confidence in caregiving at the start of the study (mothers: mean CCG score: C=20.9, I= 18.3, p=0.54; mean GC score: C=9.6, I=9.6, p=0.95; fathers: mean CCG score: C=16.7, I= 18.6, p=0.64; mean GC score: C=10.7, I= 11.1, p=0.76).

Scores were analyzed separately for mothers and fathers, since only 5 fathers in the intervention group actually participated completely in the training. Two fathers from the control group and three fathers from the intervention group did not complete all of the questionnaires.

The difference between the MABS scores pre- and post-test was calculated for each person and the mean difference scores of both groups were then compared. A negative mean score showed an improvement in confidence in caregiving, whereas a positive mean score showed a decrease in confidence in caregiving. There was no significant difference in the scores between mothers, although the intervention group mothers showed more improvement. When comparing the fathers, we found no significant differences in the mean scores; however the scores of the intervention fathers showed an improved confidence in caregiving, while the scores of the control fathers showed a decreased confidence in caregiving. There was no significant difference in the mean difference in global confidence between mothers or fathers (Table 3).

Experience of nursing support in the NICU

The mothers in the intervention group showed a significantly higher support score than the control group, meaning that they felt they received more support from the nursing staff. There was however no significant difference in the fathers' scores (Table 4).

Table 3. Mean score differences in pre- and posttest MABS

Variables	Group	N	Mean	Std. Dev.	*p* value
Mean score differences confidence in caregiving mothers*	control intervention	11 11	- 0.82 - 2.27	10.59 9.53	0.74
Mean score differences global confidence mothers	control intervention	11 11	1.91 0.36	2.39 2.42	0.15
Mean score differences confidence in caregiving fathers*	control intervention	9 8	3.33 - 3.50	8.4 8.6	0.12
Mean score differences global confidence fathers	control intervention	9 8	0.22 1.38	1.9 1.8	0.23

Paired samples t-test; *p* value significance = <.05
*Negative score indicates improvement

Table 4. Parents' experience of nursing support in the NICU

Variables	Group	N	Mean	Std. Dev.	*p* value
Support parents*	control	17	16.88	2.2	.049*
	intervention	17	18.29	1.8	
Support/mothers*	control	10	16.10	2.3	.017*
	intervention	10	18.40	1.6	
Support/fathers*	control	7	18.00	1.7	ns
	intervention	7	18.14	2.1	

Independent samples t-test; * *p* value significance = < .05
*Higher score indicates more support.

In total 14 of the control group parents felt the need for more knowledge as opposed to only 8 parents in the intervention group, which is a significant difference (p = .022). When the data was tested to see if there was a difference between the fathers and mothers, a higher number of mothers and fathers in the control group wanted more information; however the differences were not significant.

Discussion

The goal of this study was to investigate if a short-term intervention explaining infant behavioral cues with parents would increase parental knowledge of premature infant behavior and enhance parents' confidence in caregiving in interacting with their infant. The significant improvement in the parental knowledge of premature infant behavior suggests that the training was in itself effective. Also the fact that 14 of the control parents felt the need for more knowledge concerning premature infants as opposed to only 8 parents in the intervention group suggests that the training fulfilled a need that parents have during this period.

In addition, parents in the intervention group did feel that they had received more support. However, their feelings of confidence in caregiving did not improve significantly. The evaluation of the training during the interviews showed that parents enjoyed the instructions, felt it had been helpful in their interactions with their premature infant and recommended it be offered to all parents.

An issue to consider is whether the revised version of the MABS subscales is an appropriate tool sensitive enough to measure parents' feelings of confidence in dealing with their infants in the intensive care unit. This scale was originally developed for interventions with mothers of newborns and was used for the first time with parents of premature infants. The global confidence scores were reasonably high in the pre-test which made it difficult to show a difference after an intervention. Only more studies with larger samples using this instrument will tell us if it is an appropriate one. Since this study had a small sample size and large standard deviations in the scores, replication with a larger sample could give more insight in the effects of the intervention and for whom the intervention is most beneficial.

Finally, while fathers initially expressed interest in the intervention, less than half of them actually participated in the teaching sessions. As fathers in general are becoming more involved in the caregiving of their children it is important to find ways to include them in the care of their premature infants as well. This could in turn help support mothers through having their partner also understand the ways in which their infant may respond to interactions. Further studies are needed to find a way to incorporate more fathers, perhaps with less individual instruction and more written information that could be read at their leisure. Fathers often returned to work and did not visit as frequently as mothers and when they did come to the unit wanted to spend that time alone with their baby. Most of the mothers who received the training stated that they shared much of the information with the fathers; however this "transferring" of knowledge was not measurable.

Recommendations for future research include a study with a larger population, implementing the program within the first few days after the birth, creating a program with a longer period of instruction with follow-up if infants are transferred and finding ways of incorporating more participation from fathers.

Key guidelines

Based on the feedback from parents in the study, the following guidelines and recommendations have been made.

In order to have a developmental care program succeed, the entire team should be involved:

- Educate and train the nursing and medical team in infant behavioral cues so that they can support the parents and infants. A formalized training program such as NIDCAP (Newborn Individualized Developmental Care and Assessment Program) can provide training and guidance in the implementation of a developmental care program.
- Continuing in-service training and lessons for nursing and medical team.
- Have trained developmental specialists on staff who can implement and maintain the developmental care program. Parents often commented that they appreciated having someone to discuss their infant's behavior with instead of just the medical aspects.
- A developmental specialist should participate in the rounds to give feedback about the infant's behavior.

Parents felt the need for more information concerning premature infant behavior and how they could support their infant:

- Try not to overwhelm parents with information, instead begin the first week with basic information about the program and getting to know their infant and gradually increase this as parents are able to incorporate it. Be sensitive to where parents are in the process.
- Make booklets with photos and explanation of infant behavioral cues available for parents whose infant is admitted to the NICU. Create literature for parents that they can read at their leisure about development of premature infants from birth until term age.
- Make a library for parents of existing developmental care books and books with information of premature infants that they can read at their leisure.
- Make contact with mothers who are already admitted to the hospital if possible

to introduce the program. This gives parents time to get acquainted with the developmental specialist and what support is available.
- Regular infant observations with write-ups with key recommendations at the bedside for team and parents.

Increase parental participation and input and offer support to the fathers as well:
- To make the program more accessible to fathers, have developmental specialists available in the evening when fathers usually come to see their infant so that they also can be supported and included in the program. Fathers indicated that they would like to take part in understanding their infant's behavior more, but could not take time off from work during the day to do this.
- Encourage parents to participate together in the infant's care, for example, when one parent is doing caregiving, the other parent could support and comfort the infant.
- Create a multidisciplinary developmental team that also includes parents of ex-premature babies. It is important to get the input of parents because they are the experts and have an understanding of what parents go through. Fathers could also help to create a program that would be more accessible to other fathers.

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CHAPTER 3

Effects of Basic Developmental Care on Neonatal Morbidity, Neuromotor Development and Growth at Term Age of Infants Who Were Born at < 32 Weeks

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Abstract

Objective: The goal of this study was to investigate the effect of basic elements of developmental care (DC, incubator covers and positioning aids) on days of respiratory support and intensive care, growth and neuromotor development at term age in infants born < 32 weeks gestation.

Methods: Infants were randomly assigned within 48 hours of birth to the developmental care group or the standard care control group (no covers or nests). The intervention continued until the infant either was transferred to a regional hospital or was discharged from the hospital. Respiratory support was defined as days of mechanical ventilation and/or CPAP. Intensive care was defined as requiring mechanical ventilation and/or CPAP and/or weight <1000 grams. Length, weight and head circumference were measured (bi)weekly and at term age. Neuromotor development was defined as definitely abnormal (presence of a neonatal neurological syndrome, such as apathy or hyperexcitability, hypotonia or hypertonia, hyporeflexia or hyperreflexia, hypokinesia or hyperkinesia, or a hemi-syndrome), mildly abnormal (presence of only part of such a syndrome), or normal.

Results: A total of 192 infants were included (developmental care: 98; control: 94). Thirteen infants (developmental care: 7; control: 6) were excluded according to protocol (admitted for less than or died within the first 5 days: *n* =12; taken out at parents' request: *n* =1), which left a total of 179 infants who met inclusion criteria. In-hospital mortality was 12 (13.2%) of 91 in the developmental care group and 8 (9.1%) of 88 in the control group. There was no significant difference in the number of days of respiratory support, number of intensive care days, short-term growth, or neuromotor developmental outcome at term age between the developmental care and control groups. Duration of the intervention, whether only during the intensive care period or until hospital discharge, had no significant effect on outcome.

Conclusions: Providing basic developmental care in the NICU had no effect on short-term physical and neurological outcomes in infants who were born < 32 weeks gestation.

Introduction

Advanced technology in the treatment of premature infants has resulted in decreasing mortality rates[1,2] [3]. Follow-up studies, however, have shown either an unchanging or increased incidence of physical disabilities, developmental delays and learning or behavioral and/or attention deficit/hyperactivity disorders [1,2,4,5]. Because premature infants cannot regulate incoming stimuli, they become easily overstimulated and stressed, which can lead to hypoxemia, apnea and variations in blood pressure. Als et al propose a sensory mismatch of the premature infant's developing nervous system's expectations for environmental inputs and the actual sensory overload that is experienced in the NICU. This in turn can lead to a greater chance for later developmental problems[6-8]. To prevent these secondary consequences, several investigators have begun to focus on ways to improve the NICU environment for infants and parents through the use of developmental care (DC) programs.

Most research has been based on the NIDCAP (Newborn Individualized Developmental Care Program), which is a comprehensive approach in which caregiving is based on the individual behavior of the infant [8]. A meta-analysis by Jacobs et al concluded that the evidence showing a positive effect from the NIDCAP program is inconclusive, and they recommended additional studies with a larger sample size, long-term follow-up and the inclusion of cost-effectiveness evaluations [9]. A Cochrane review evaluated the effects of various elements of DC (positioning, clustering of nursery care activities and modification of external stimuli) as well as the NIDCAP individualized developmental care approach. Although there was evidence of limited benefits of developmental care interventions and no major harmful effects reported, there were a large number of outcomes with no or conflicting results. The single developmental care trials that did show a significant effect of an intervention on a major clinical outcome were based on small sample sizes, and the findings were often not supported in other small trials[10]. More randomized trials were recommended in which the effectiveness of developmental care programs can be evaluated. No studies have been carried out to examine a less intensive, more basic developmental care program.

The aim of this randomized controlled trial (RCT) was to explore the effectiveness of the implementation of elements of basic developmental care to reduce stress and improve physiological stability in preterm infants on neonatal morbidity, neuromotor development and growth at term age.

Methods

The study was carried out from April 2000 to May 2002 at a tertiary NICU at 2 locations in the Netherlands: Leiden University Medical Center in Leiden and Juliana Children's Hospital in The Hague. The inclusion criteria was birth at a gestational age of < 32 (31+6) weeks. Exclusion criteria were major congenital anomalies, need for major surgery and having a drug-addicted mother. After parental informed consent was obtained by the resident or staff member on call, infants were randomly assigned within 48 hours of birth to the DC group or the control group using sealed envelopes made in groups of 6 using a computer-generated randomization allocation. According to protocol, infants in both groups who were admitted for less then 5 days were excluded from follow-up, because the duration of the basic DC intervention was hypothesized not to be long enough to obtain an effect. A power analysis performed before the study showed that a total sample size of 140 infants was needed to show a significant difference ($p < .05$) with a power of 80%; based on a difference of half a standard deviation on the developmental test scores at 1 and 2 years of age, corrected for prematurity, and was deemed sufficient power for the short-term primary neonatal outcomes.

The intervention included the reduction of light and sound through the use of standardized incubator covers and supporting motor development and physiological stability by positioning the infant in ways that encourage flexion and containment through the use of standardized nests and positioning aids. Infants in the control group received standard care, which at that time consisted of no covers or nesting. The Ethical Committees of both locations approved the study.

Definitions

Severity of illness was analyzed using the CRIB (Clinical Risk Index for Babies) score which assesses initial neonatal risk. Scores are given for birth weight, gestational age, maximum and minimum fraction of inspired oxygen and maximum base excess during the first 12 hours, and the presence of congenital malformation[11]. Inborn infants were infants who were born in the participating tertiary neonatal center.

The primary medical outcome variables included duration of respiratory support, number of days in intensive care and short-term growth. Mechanical ventilation and/or continuous positive airway pressure (CPAP) were measured in days. When an infant received both mechanical ventilation and CPAP in 1 day, the method of respiratory support given for the most hours was chosen. In addition, the total number of days of respiratory support was defined as total combined days of mechanical ventilation and CPAP. Discharge from the intensive care was based on

2 criteria: the infant required no mechanical ventilation and/or CPAP for 24 hours and weighed at least 1000 grams.

Infants were weighed at least biweekly; head circumference and length were measured within the first 2 days of life and thereafter weekly by trained medical students until the infant was either transferred or discharged. Short-term growth (weight, head circumference, length) was defined as measurement at birth and at term age as well as mean daily weight gain in grams and mean weekly length and head circumference growth in centimeters. Weight was measured on neonatal pediatric digital scales, length was measured from crown to heel and head circumference was measured around the largest area of the head, occipital-frontal circumference (OFC), using a non-stretch tape measure.

In addition, secondary outcomes were analyzed. Mortality was defined as early neonatal death when the infant died within the first 7 days of life and late neonatal death when the infant died after 7 days but before 28 days of life. Days of oxygen were calculated as total days of supplementary oxygen as well as the need for oxygen after 28 days of life.

Bronchopulmonary dysplasia (BPD) was defined as oxygen dependency at 36 weeks postconceptional age (PCA) according to the criteria of Shennan[12]. Postnatal steroids were divided into 3 classifications; 7 to 10, 15 to 20, and > 20 days. Intraventricular hemorrhage (IVH) was recorded according to Volpe[13]. Periventricular leukomalacia (PVL) was classified according to grades 1-4[14]. Sepsis was based on a positive blood culture (congenital infections excluded). Meningitis was defined as a positive cerebrospinal fluid (CSF) culture and/or pleocytosis. In addition, the incidence of necrotizing enterocolitis (NEC), persistent ductus arteriousus (PDA), retinopathy of prematurity (ROP), need for treatment of hypotension and hyperbilirubinemia was analyzed.

Follow-up

At term age, infants were seen in the follow-up clinics to assess growth, morbidity and neuromotor development by neonatologists who were experienced in developmental assessments and blinded to the group assignment of the infant. A standardized neurological examination according to Prechtl[15] was administered and was defined as definitely abnormal (DA), mildly abnormal (MA) or normal. Definitely abnormal means the presence of a full-blown neonatal neurological syndrome, such as apathy or hyperexcitability, hypotonia or hypertonia, hyporeflexia or hyperreflexia, hypokinesia or hyperkinesia, or a hemi-syndrome. Mildly abnormal denotes the presence of only part of such a syndrome. Examples of minor neurological signs are abnormal posture, abnormal head control and absent or abnormal responses or reflexes.

Statistical Analysis

Data was analyzed using SPSS 12.0 for Windows (SPSS Inc, Chicago, IL). The infant and parent characteristics were compared with the Chi-square test, the Chi-square test for trend or the two-sample t-test, where appropriate. Outcome parameters were compared between the two treatment groups with the t-test, Mann-Whitney test or Chi-square test where appropriate. A p-value of < 0.05 was considered significant. Linear regression was used to evaluate the influence of the duration of the intervention on term age outcomes by testing whether there was an interaction effect between the intervention duration and the 2 treatment groups.

Results

In total, 192 infants were originally included for the study: 98 in the DC group and 94 in the control group. Thirteen infants (DC: 7; control: 6) were excluded according to protocol because they were admitted less than 5 days or died within the first 5 days. One of the 6 infants in the control group was taken out of the study on day 3 at the parents' request. This left a total of 179 infants who met inclusion criteria. Of the 179 included infants, 12 (13.2%) of 91 in the DC group and 8 (9.1%) of 88 in the control group died during hospitalization, with the main cause of death being cerebral or pulmonary complications. The difference between the 2 groups was not significant (p=0.40). Two infants in each group died of NEC. One infant was lost to follow-up in the DC group and 5 infants in the control group because either they were transferred to hospitals out of the health region or parents did not want to come back for follow-up. Two infants from the DC group and 2 from the control group did not show up for the term age follow-up assessment, resulting in 76 infants in the DC group and 73 infants in the control group who were assessed at the outpatient clinic. All infants who were lost to follow-up survived. The mortality rate and loss to follow-up are shown in Figure 1. The data from the infants who were lost to follow-up were comparable to the infants who were assessed at follow-up (data not shown).

Parent characteristics for the study population were similar, with no significant differences found, and are shown in Table 1. There was no difference in infant characteristics between the DC and the control group, with the exception of more infants in the control group with grade 4 RDS, however the difference was not significant (Table 2).

Some of the infants were transferred to regional hospitals once stabilized. Seven infants (DC: 5; control: 2) were hospitalized temporarily elsewhere for surgical or other necessary treatment. These infants were included in the outcome under the intention-to-treat protocol.

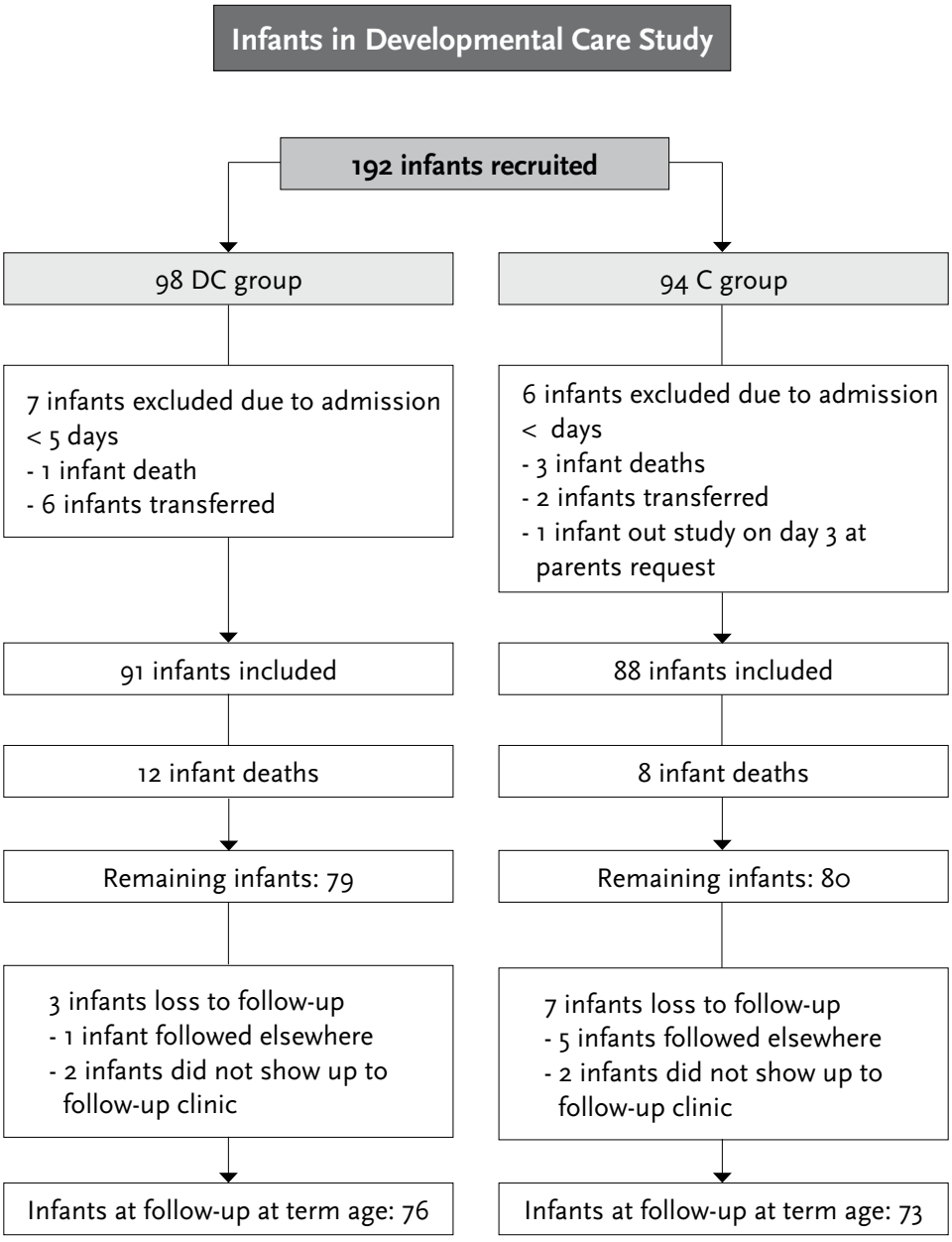
Infants in Developmental Care Study
192 infants recruited
98 DC group
94 C group
7 infants excluded due to admission < 5 days
- 1 infant death
- 6 infants transferred
6 infants excluded due to admission < days
- 3 infant deaths
- 2 infants transferred
- 1 infant out study on day 3 at parents request
91 infants included
88 infants included
12 infant deaths
8 infant deaths
Remaining infants: 79
Remaining infants: 80
3 infants loss to follow-up
- 1 infant followed elsewhere
- 2 infants did not show up to follow-up clinic
7 infants loss to follow-up
- 5 infants followed elsewhere
- 2 infants did not show up to follow-up clinic
Infants at follow-up at term age: 76
Infants at follow-up at term age: 73

Table 1. Maternal medical and parental demographic background variables

	DC n=91	Control n=88
Obstetrical history		
Pre-existing disease (diabetes, renal, hypertension, other)	8/82 (9.8)	11/82 (13.4)
Pregnancy induction	13/86 (15.1)	12/84 (14.3)
Diseases during pregnancy		
Diabetes mellitus gravidarum	4/87 (4.6)	5/84(6.0)
(Pre)eclampsia or HELLP syndrome	19/87 (21.8)	13/84 (15.5)
Medication during pregnancy		
Antihypertensives	12/91 (13.2)	14/84 (16.7)
Antibiotics	35/91 (38.5)	34/84 (40.5)
Tocolytics	46/91 (50.5)	48/84 (57.1)
Other	8/91 (8.8)	7/84 (8.3)
Antenatal glucocorticoids		
1 dose	17/90 (18.9)	28/88 (31.8)
1 course (2 doses)	47/90 (52.2)	41/88 (46.6)
Mode of delivery		
Vaginal	51/91 (56.0)	47/88 (53.4)
Caesarean section	40/91 (44.0)	41/88 (46.6)
PROM > 24 hours	16/91 (17.6)	22/88 (25.0)
Primipara	76/91 (83.5)	73/86 (84.9)
Parental demographic background		
Maternal age	n=89	n=85
(mean in years, sd)	30.1 (5.6)	30.4 (5.1)
Paternal age	n=70	n=69
(mean in years, sd)	34.3 (5.3)	35.0 (5.7)
Mother Caucasian	59/90 (65.6)	62/87 (71.3)
Father Caucasian	63/90 (70.0)	65/87 (74.7)
Mother's education level*		
Low	36/78 (46.2)	24/73 (32.9)
Intermediate	26/78 (33.3)	33/73 (45.2)
High	16/78 (20.5)	16/73 (21.9)
Father's education level*		
Low	30/78 (38.5)	21/73 (28.8)
Intermediate	30/78 (38.5)	29/73 (39.7)
High	18/78 (23.0)	23/73 (31.5)

Data shown is n (%), unless otherwise indicated
HELLP indicates hemolysis, elevated liver enzymes, and low platelet count; PROM: premature rupture of membrane
* Low indicates vocational training, intermediate = high school, high = college/university

Table 2. Infant medical background variables

Birth Characteristics	**DC n=91**	**Control n=88**
Gestational age, wk	n=91	n=88
Mean (SD)	29.3 (1.8)	28.9 (1.9)
Range	25.0-31.9	25.0-31.9
Birthweight,g	n=91	n=88
Mean (SD)	1216 (358)	1196 (354)
Range	538-2155	640-2080
Length,cm	n=79	n=79
Mean (SD)	37 (4.0)	37 (3.8)
Range	25.0-46.0	28.5-45.0
Head circumference	n=86	n=86
Mean in cm, sd	26.7 (2.4)	26.5 (2.3)
Range	22.0-33.6	22.0-31.6
Male gender	49/91 (54.0)	58/88 (65.9)
SGA p < 10 and p ≥ 3	8/91 (8.8)	8/88 (9.1)
SGA p < 3	8/91 (8.8)	6/88 (6.8)
Twin	26/91 (28.6)	18/88 (20.5)
Inborn	56/91 (61.5)	53/87 (60.9)
Apgar scores at 5 minutes		
Mean (SD)	8.1 (1.8)	8.1 (1.4)
Median (range)	9 (2-10)	8 (3-10)
CRIB Score	n = 91	n = 87
Median (range)	2 (0-20)	3 (0-12)
RDS		
Grade 1	15/91 (16.5)	15/87 (17.2)
Grade 2	16/91 (17.6)	17/87 (19.5)
Grade 3	19/91 (20.9)	14/87 (16.1)
Grade 4	9/91 (9.9)	17/87 (19.5)
Surfactant	41/91 (45.1)	50/88 (57.5)
Hyperbilirubinemia	82/91 (90.1)	81/88 (92.0)

Data shown is n (%), unless otherwise indicated

SGA indicates small for gestational age; p: percentile; CRIB: Clinical Risk Index for Babies; RDS: respiratory distress syndrome

Primary outcomes

No significant difference was found in the number of intensive care days, days of respiratory support or growth between the DC and control groups (Table 3). Eighty-six (94.5%) infants in the DC group and 79 (89.8%) infants in the control group required some form of respiratory support. A total of 149 infants (DC: 76; control: 73) of the surviving 159 (93.7%) infants were seen at the follow-up clinic at term age. One infant was too ill to undergo a Prechtl examination. No significant difference was found in the neurological outcomes between the DC and control groups. Of the 149 infants, 4 in the DC group and 3 in the control group were not measured or weighed at term age. Four surviving infants (DC: 3; control: 1) who had a diagnosis of post-hemorrhagic ventricular dilatation were excluded from the weekly and term age head circumference analysis. No significant difference was found between the DC and control groups in the growth parameters at term age or in daily weight gain (g), and weekly length and head circumference (cm) growth.

We also conducted a linear regression analysis to determine whether the number of days when infants received the DC intervention influenced the neuromotor outcome according to Prechtl and growth at term age by testing whether there was an interaction effect between the intervention duration and the 2 treatment groups. No significant effect on the neuromotor outcome (p=0.45), term age head circumference (p=0.56): term age weight (p=0.61) or term age length (p=0.92) was found.

Secondary outcomes

A total of 15 (19.2%) of 78 infants in the DC group required oxygen after 28 days of life as opposed to 22 (29.3%) of 75 infants in the control group; however, the difference was not significant (p=0.15). No difference was found in the incidence of BPD between the 2 groups. In total 4 (4.4%) of 91 infants in the DC group required postnatal corticosteroids as opposed to 10 (11.4%) of 88 infants in the control group (p=0.08). A total of 19 (20.9%) of 91 infants in the DC group had grade 1 or 2 IVH as opposed to 28 (31.8%) of 88 in the control group, and twice as many infants (11 of 91 [12.1%]) in the DC group had grade 3 IVH or grade 3 IVH and periventricular echodensity than in the control group (5 of 88 [5.7%]; p=0.12). At term age, there was no difference in the incidence of PVL or the number of infants who required physical therapy. Also, no significant differences were found in the remaining secondary outcomes (Table 4).

Table 3. Comparison of data of primary outcome measures

	DC n=91	**Control n=88**	***p*-value**
Days of hospitalization			
Mean (SD)	37.2 (29.1)	36.4 (28.1)	0.86
Median (range)	31 (6-142)	30 (5-165)	
Days intensive care			
Mean (SD)	15.9 (13.7)	16.7 (15.3)	0.74
Median (range)	12 (0-53)	11 (0-60)	
No. of infants requiring respiratory support	86/91 (94.5)	79/88 (89.8)	0.28
Days of mechanical ventilation			
Mean (SD)	6.1 (7.3)	6.9 (7.1)	0.45
Median (range)	3.5 (0-39)	4.0 (0-29)	
Days of CPAP			
Mean (SD)	8.6 (9.6)	10.1 (10.5)	0.34
Median (range)	4.5 (0-35)	6.0 (0-39)	
Total days ventilatory support			
Mean (SD)	14.6 (13.6)	17.0 (15.1)	0.30
Median (range)	10.0 (1-52)	12.0 (1-59)	
Growth parameters at term age	n = 72	n = 70	
Age, mean (SD), wk	40.8 (1.2)	40.7 (1.5)	0.72
Weight, mean (SD), kg	3.12 (0.64)	3.15 (0.50)	0.76
Head circumference*, mean (SD), cm	35.6 (1.8)	35.5 (1.6)	0.81
Length, mean (SD), cm	48.6 (3.3)	48.6 (2.3)	0.95
Daily weight gain, mean(SD), g	23.7 (4.9)	23.6 (4.8)	0.95
Weekly head circumference growth*, mean (SD), cm	0.78 (0.13)	0.75 (0.14)	0.38
Weekly growth in length, mean (SD), cm	1.00 (0.23)	0.97 (0.20)	0.34
Neurological outcome at term (Prechtl)			
Normal	42/76 (55.3)	43/72 (59.7)	0.46
Mildly abnormal	30/76 (39.5)	27/72 (37.5)	
Definitely abnormal	4/76 (5.2)	2/72 (2.8)	

Data shown is n (%), unless otherwise indicated
Comparisons were performed by using chi-square test (for linear trend), t-test or Mann-Whitney test where appropriate
* Infants with posthemorrhagic ventricular dilatation (DC: n=3,control: n=1) were excluded from head circumference analysis

Table 4. Comparison of data of secondary outcome measures

	DC n=91	**Control n=88**	***p*-value**
In-hospital mortality	12/91 (13.2)	8/88 (9.1)	0.40
Early neonatal death	3/91 (3.3)	2/88 (2.3)	
Late neonatal death	9/91 (9.9)	6/88 (6.8)	
Total days supplemental oxygen			
Mean (SD)	12.0 (17.7)	14.9 (20.5)	0.31
Median (range)	5 (0-93)	4.5 (0-90)	
Oxygen requirement > 28 days of life	15/78* (19.2)	22/75* (29.3)	0.15
BPD (oxygen dependent > 36 wk GA)	6/78 (7.7)	10/75 (13.3)	0.30
Postnatal corticosteroids			
7-10 days	2/91 (2.2)	1/88 (1.1)	0.08
15-20 days	1/91 (1.1)	8/88 (9.1)	
> 20 days	1/91 (1.1)	1/88 (1.1)	
IVH			
Grade 1-2	19/91 (20.9)	28/88 (31.8)	0.12
Grade 3 and periventricular echodensity	11/91 (12.1)	5/88 (5.7)	
Posthemorrhagic ventricular dilation	4/91 (4.4)	2/88 (2.3)	0.68
NEC	6/91 (6.6)	4/87 (4.6)	0.75
Sepsis	40/91 (44.0)	32/87 (36.8)	0.36
Meningitis	5/91 (5.5)	5/88 (5.7)	0.99
PDA (indomethacin and/or surgery)	19/91 (20.9)	23/88 (26.1)	0.48
Dopamine/Dobutamine	32/91 (35.2)	25/87 (28.7)	0.42
ROP	3/70 (4.3)	5/70 (7.1)	0.19
PVL at term age follow-up			
Grade 1	3/71 (4.2)	6/67 (9.0)	0.53
Grade 2	3/71 (4.2)	3/67 (4.5)	
Grade 3	0/71 (0.0)	0/67 (0.0)	
Grade 4	0/71 (0.0)	0/67 (0.0)	
Physical therapy required at term	14/76 (18.4)	9/74 (12.2)	0.49

Data shown is n (%), unless otherwise indicated
Comparisons were performed by using the chi-square test (for linear trend) or t-test where appropriate
* n is lower as a result of in-hospital deaths and loss to follow-up infants
BPD indicates bronchopulmonary dysplasia; GA: gestational age; IVH: intraventricular haemorrhage; NEC: necrotising enterocolitis; PDA: patent ductus arteriosus; ROP: retinopathy of prematurity; PVL: periventricular leukomalacia

Discussion

In this RCT to examine the short-term effects of basic DC (incubator covers, nests and positioning aids) on neonatal morbidity, neuromotor development and growth at term age of infants who were born at < 32 weeks gestation, we found no significant positive effects of the intervention on intensive care days or need for respiratory support. Although the control infants had more pulmonary problems than the infants in the DC group, the difference was not significant. There were also no differences between the DC and control groups in growth and neurological outcomes at term age, even when correcting for days of intervention. This study is to our knowledge the largest RCT to examine the effects of basic developmental care on preterm infants. Of the surviving 159 infants, 93.7% were seen at follow-up at term age.

The Cochrane Review[10] looked at 4 separate developmental care interventions (positioning, clustering of care, modification of external stimuli and individualized developmental care), but no studies that combined nesting, positioning aids and incubator covers have been published to our knowledge. Because NICU's may start with these basic elements when embarking on the implementation of a developmental care program, we believed that it was important to study the effects of these basic interventions. Most previous RCT's examined the effects of the more intensive, individually-focused NIDCAP program and although a few of them showed positive results [16-21], we were not able to duplicate this with the less intensive basic developmental care.

One limitation of our study was the variation in total days of hospital admission of studied infants. In the Netherlands' neonatal care system, infants may be transferred to regional hospitals once they no longer require intensive care. This was also the case with a number of infants in our study. This would not affect the short-term outcomes such as days of intensive care or respiratory support, because all infants remained in the participating hospitals during this period, but could have an effect on growth and secondary outcomes at term age. If this were true, then infants who received more days of developmental care would show less morbidity and better short-term growth and neurodevelopmental outcome; however, our analysis showed that this was not the case. It seems that at least concerning short-term outcomes, the duration of providing basic developmental care, whether only during the intensive care period or continuing developmental care until hospital discharge, has no significant effect.

The infants were randomly assigned in an appropriate manner; however, there could be no blinding of the intervention because the infants in de DC group had incubator covers and nesting. This did make it easier to ensure a strict control

group whereby control infants were not provided with any nesting or incubator covers, because this was the standard method of care when this trial began and so was easy to maintain during the study period. The amount of respiratory support given to an infant was decided on by several neonatologists and so was not influenced by the study group in which the infant was placed. Because the discharge from the intensive care was based on two criteria: the infant's requiring no mechanical ventilation and/or CPAP for 24 hours and weight at least 1000 grams, IC days also could not be influenced by group participation. In addition, the neonatologists who performed the term age assessments were blinded to group participation.

Conclusions

This was a RCT with a large sample size in comparison with previous developmental care studies; however, no significant results were found. Our findings showed that a less intensive, cost-saving form of developmental care (incubator covers, nests and positional aids) does not have a significant effect on short-term medical outcomes (respiratory support, intensive care days), growth or neurodevelopment at term age. Although some of the secondary analyses were suggestive of an advantage to developmental care, they did not reach a level of significance and would therefore need to be replicated in a larger sample to confirm a trend. Additional research of the developmental outcomes at 1 and 2 years of age of the children in this study will be addressed in future publications.

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CHAPTER 4

The Influence of Basic Developmental Care on Growth, Neurological, Cognitive and Psychomotor Development at 1 and 2 years of age in Very Preterm Infants

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Abstract

Objective: Randomized controlled trial investigating the effect of basic elements of developmental care (DC) on growth and neurodevelopment in infants born < 32 weeks.

Study design: Infants were randomized within 48 hours of birth to DC group or standard care (C) group. Outcome measures at 1 and 2 years corrected age (CA) were growth, standardized neurological exams and mental (MDI) and psychomotor (PDI) development (Dutch version of the Bayley Scales of Infant Development II). Outcome parameters were compared with the t-test, Mann-Whitney test or Chi-square test where appropriate. Linear regression was used to evaluate the influence of the duration of the intervention on 1 and 2 year outcomes.

Results: 192 infants were recruited (DC=98; C=94). Thirteen infants (DC=7, C=6) were excluded because they were admitted less than or died within the first 5 days. In total, 179 infants met inclusion criteria. In-hospital mortality was 12/91 (13.2%) in DC group and 8/88 (9.1%) in C group. 147 children (DC= 74, C= 73) at 1 year and 142 children (DC=72, C=70) at 2 years were assessed. No significant difference in growth, neurological outcomes or MDI was found. A positive trend in PDI at 1 year (p=0.05) did not continue once the children reached 2 years. When neurological and developmental scores were combined, the C group showed more definitely abnormal scores than the DC group at both ages, but this did not reach the level of significance.

Conclusions: Basic developmental care has a positive effect on psychomotor development at 1 CA, but this improvement does not continue at 2 years CA in infants born < 32 weeks. No significant difference in neurological and mental development or growth was found.

Introduction

The care and survival rate of preterm born infants has in recent years continued to improve [1-4]. Even as survival rates are improving, the risk of developmental disabilities remains high and increases as the gestational age at birth decreases [1,5-7]. The technological advances are improving the survival rates of preterm infants, but the question remains how these vulnerable infants can best be supported during their stay in the neonatal intensive care unit (NICU) in order to positively influence their developmental outcomes. Since the 1980's, programs have been created to support the infant's development in the NICU while at the same time providing the necessary medical and nursing interventions. Many of these programs are based on developmental care, with the most comprehensive being the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) developed by Als, an individual approach in which caregiving is based on the infant's behavior [8,9]. The first studies of the effectiveness of the NIDCAP developmental care program in the 1980's and 1990's showed promising results, however the sample size of the studies was small [10-14]. Follow-up studies published to date up to preschool age have been scarce and the results are conflicting[10,15-18]. In a recent Cochrane review of developmental care the need for larger trials, more follow-up and studying the effects of different aspects of developmental care was emphasized [19].

The aim of this randomized controlled trial (RCT) was to explore the effectiveness of the implementation of basic Developmental Care on growth, mental and psychomotor development and neurological outcome at 1 and 2 years CA of preterm infants born < 32 weeks gestational age. We hypothesized that by reducing stress and promoting physiological stability through the use of incubator covers and nesting, the stability provided to the infants during their NICU hospitalization would positively affect their later growth and development.

Patients and Methods

The study was carried out from April 2000 to June 2004 at a tertiary NICU at 2 locations in the Netherlands: Leiden University Medical Center in Leiden and Juliana Children's Hospital in The Hague. Inclusion criteria were: infants born with a gestational age < 32 (31+6) weeks. Exclusion criteria included: infants with major congenital anomalies, infants needing major surgery and infants of drug-addicted mothers. After parental informed consent was obtained by the resident or staff member on call, infants were randomized within 48 hours of birth to the Developmental care (DC) group or the Control (C) group using sealed envelopes made

in groups of 6 using a computer generated randomization allocation. According to protocol, infants in both groups who were admitted for less than 5 days were excluded from follow-up because the duration of the basic developmental care intervention was hypothesized not to be long enough to obtain an effect. A power analysis performed before the study showed that a sample size of 140 infants was needed to show a significant difference (p level < .05) with a power of 80%, based on the expected difference of half a standard deviation (7.5) on the developmental test scores at 1 and 2 years corrected age (CA).

The intervention included the reduction of light and sound through the use of standardized incubator covers and supporting motor development and physiological stability by positioning the infant in ways that encourage flexion and containment through the use of standardized nests and positioning aids. Infants in the control group received standard care, which at that time consisted of no covers or nesting[20]. The Ethical committees of both locations approved the study.

Measures

Infant characteristics (gestational age, birth weight, gender, small for gestational age, inborn, Apgar scores, CRIB score) and parental characteristics (age, ethnicity, educational level) were collected to compare groups (Tables 1 and 2). Inborn infants were infants born in the participating tertiary neonatal center. Severity of illness was analyzed using the CRIB (Clinical Risk Index for Babies) score which assesses initial neonatal risk. Scores are given for birth weight, gestational age, maximum and minimum fraction of inspired oxygen and maximum base excess during the first 12 hours, and the presence of congenital malformation [21].

Follow-Up

Children were assessed at 1 and 2 years of corrected age for prematurity (CA) for growth and neurodevelopment by neonatologists experienced in developmental assessments and blinded to the group assignment of the child. A standardized neurological exam according to Touwen [22,23] at one year CA and Hempel [24] at two years CA was administered and classified as definitely abnormal (DA) when there was definite neurological dysfunction such as cerebral palsy; mildly abnormal (MA) in the presence of mild deviations in muscle tone regulation, reflexes, fine or gross motor performance or cranial nerve function; or normal (N).

Weight was measured on a pediatric digital scale, length was measured from crown to heel on a standard measurement board and head circumference was measured around the largest area of the head, occipital-frontal circumference (OFC), using a non-stretch tape measure.

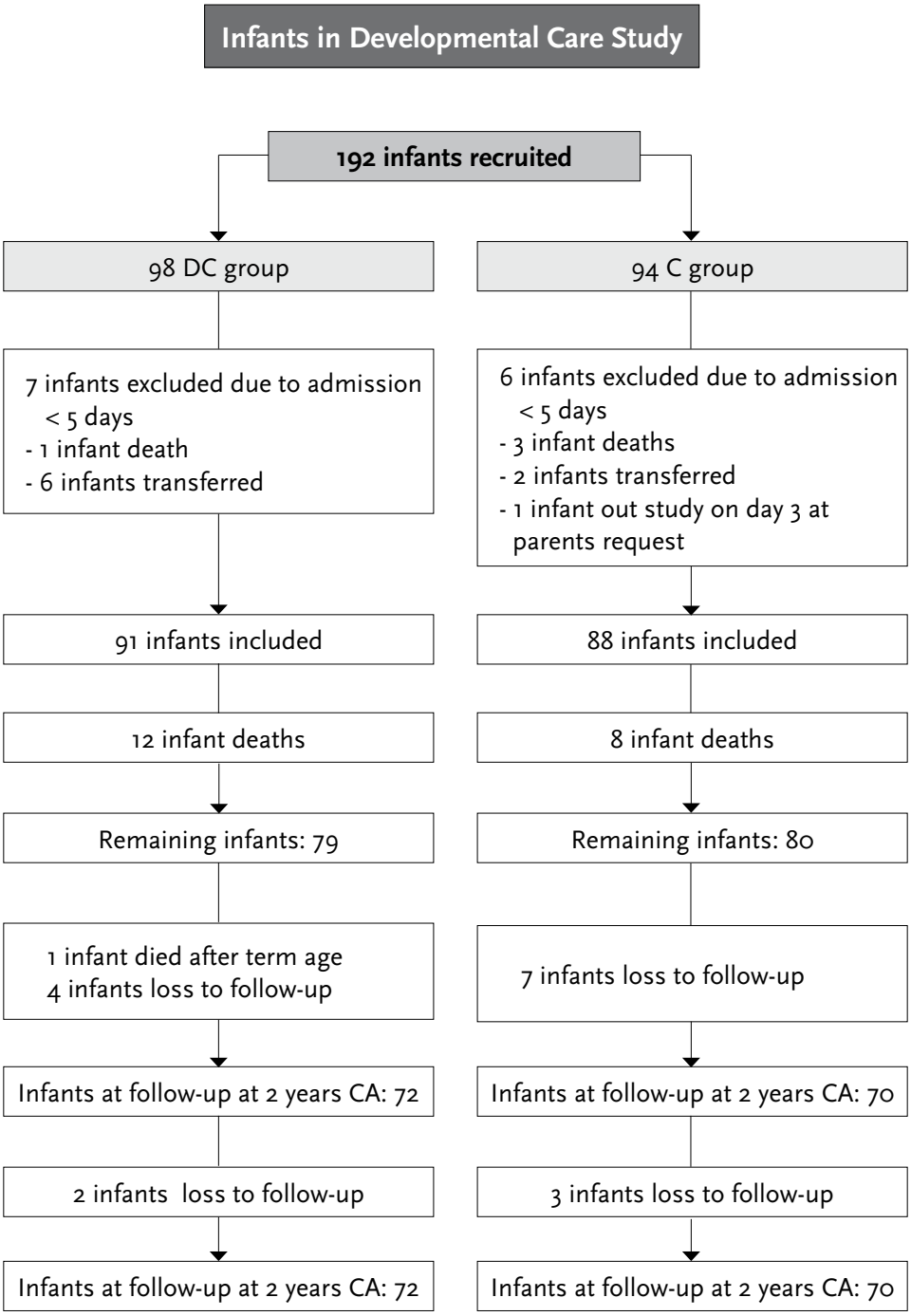
In addition, children were assessed at 1 and 2 years CA by psychology interns supervised by a clinical psychologist, who were blinded as to whether the child was in the DC or C group. Mental and psychomotor development was assessed using the Dutch version of the Bayley Scales of Infant Development II (BSID-II)[25,26]. The mean score of the mental developmental index (MDI) and the psychomotor developmental index (PDI) is 100, with 1 standard deviation (SD) of 15 points. An MDI or PDI ≥ 85 (≥ – 1 SD) is considered normal, an MDI or PDI between 70 and 84 (–2 to –1 SD) is considered mildly delayed and Index scores ≤ 69 (< – 2 SD) severely delayed. The Dutch norms, which had become available during our research, were used. To obtain a single outcome measure, neurological outcome, PDI and MDI were combined. When at least 1 of these 3 outcome measures was DA, children were considered DA, and when at least 1 outcome was MA, children were considered MA.

Statistical Analysis

Data was analyzed using SPSS 12.0 for Windows. The infant and parent characteristics were compared with the Chi-square test, the Chi-square test for trend or the two-sample t-test, where appropriate. Outcome parameters were compared between the two treatment groups with the t-test, Mann-Whitney test or Chi-square test where appropriate. P-values < 0.05 were considered significant. Linear regression was used to evaluate the influence of the duration of the intervention on 1 and 2 year outcomes by testing if there was an interaction effect between the intervention duration and the 2 treatment groups.

Results

In total 192 infants were recruited for the study; 98 in the DC group and 94 in the C group. Thirteen infants (DC=7, C=6) were excluded according to protocol because they were admitted less than 5 days or died within the first 5 days. One of the six infants in the C group was taken out of the study on day 3 at parents' request. This left a total of 179 infants that met inclusion criteria. Of the 179 included infants, 12/91 (13.2%) in the DC group and 8/88 (9.1%) in the C group died during hospitalization, with the main cause of death being cerebral or pulmonary complications. Two infants in each group died of NEC. There was no significant difference in the in-hospital mortality rate between the DC and C group (p=0.40). This left a remaining 159 infants (DC=79, C=80) for follow-up. At the 1 year assessment, there were 4 infants lost to follow-up in the DC group and 7 infants in the C group because they were either transferred to hospitals out of the health region or parents did not want


Infants in Developmental Care Study
192 infants recruited
98 DC group
94 C group
7 infants excluded due to admission < 5 days
- 1 infant death
- 6 infants transferred
6 infants excluded due to admission < 5 days
- 3 infant deaths
- 2 infants transferred
- 1 infant out study on day 3 at parents request
91 infants included
88 infants included
12 infant deaths
8 infant deaths
Remaining infants: 79
Remaining infants: 80
1 infant died after term age
4 infants loss to follow-up
7 infants loss to follow-up
Infants at follow-up at 2 years CA: 72
Infants at follow-up at 2 years CA: 70
2 infants loss to follow-up
3 infants loss to follow-up
Infants at follow-up at 2 years CA: 72
Infants at follow-up at 2 years CA: 70

to come back for follow-up. In addition, one infant in the DC group died between term age and 1 year. Between the 1 and 2 year assessment 2 children in the DC group and 3 children in the C group were lost to follow-up due to parents moving or not wanting to continue with the follow-up. The baseline data from the lost to follow-up infants was comparable to the infants that were assessed at follow-up (data not shown). There were 147 children: DC=74/79 (93.7%), C= 73/80 (91.3%) at 1 year corrected age and 142 children: DC=72/79 (91.1%), C=70/80 (87.5) at 2 years corrected age that were seen at the follow-up clinic of the total 159 surviving infants. The mortality rate and loss to follow up are shown in Figure 1.

There was no significant difference in infant characteristics between the DC and C groups assessed at 1 year or 2 years (Table 1). Parent characteristics (age, ethnicity and educational level) were similar in both groups with no significant differences found and are shown in Table 2.

Table 1. Infant medical background variables of children seen at 1 and 2 year follow-up

	DC n (%)	**C n (%)**	**DC n (%)**	**C n (%)**
	1 year		**2 years**	
Birth Characteristics	n=74	n=73	n=72	n=70
Gestational age mean in wks (sd) range	29.5 (1.6) 25.9-31.9	29.1 (1.9) 25.0-31.9	29.5 (1.6) 25.9-31.9	29.1 (1.9) 25.0-31.9
Birthweight mean in g, (sd) range	1248.4 (338.1) (585-2155)	1238.5 (337.2) (640-2080)	1266.3 (329.6) (585-2155)	1236.6 (338.5) (640-2080)
Male gender	39/74 (52.7)	46/73 (63.0)	38/72 (52.8)	44/70 (62.9)
SGA* SGA P < 10 and P ≥ 3 SGA P < 3	 8/74 (10.8) 6/74 (8.1)	 6/73 (8.2) 4/73 (5.5)	 8/72 (11.1) 4/72 (5.6)	 5/70 (7.1) 4/70 (5.7)
Inborn	46/74 (62.2)	46/72 (63.9)	45/72 (62.5)	44/70 (63.8)
Apgar scores at 5 minutes median (range)	n= 74 9.0 (2-10)	n= 72† 8.0 (5-10)	n= 72 9.0 (2-10)	n= 69† 8.0 (5-10)
CRIB Score mean (sd)* range	3.2 (2.9) 0-13	3.7 (2.9) 0-11	3.0 (2.7) 0-10	3.8 (3.0) 0-11

Data shown is n (%), unless otherwise indicated
Comparisons were done using chi-square test or t-tests where appropriate
* SGA: small for gestational age, P: percentile, CRIB: Clinical Risk Index for Babies
† Correct n is shown in table if there are missing values

Table 2. Parental demographic background variables

	DC n (%)	C n (%)	DC n (%)	C n (%)
	1 year follow-up		2 year follow-up	
Maternal age mean in years (sd)	n=74 31.3 (5.1)	n=73 31.4 (4.9)	n=72 32.5 (5.1)	n=73 31.4 (4.9)
Paternal age mean in years (sd)	n=70 34.3 (5.3)	n=69 35.0 (5.7)	n=67 35.0 (5.2)	n=69 35.0 (5.7)
Mother Caucasian	48/74 (64.9)	53/73 (72.6)	48/74 (64.9)	53/73 (72.6)
Father Caucasian	52/74 (70.3)	56/73 (76.7)	52/74 (70.3)	56/73 (76.7)
Education level mother*				
low	34/74 (46.0)	23/72 (32.0)	32/71 (45.1)	23/72 (32.0)
intermediate	24/74 (32.4)	33/72 (45.8)	23/71 (32.4)	33/72 (45.8)
high	16/74 (21.6)	16/72 (22.2)	16/71 (22.5)	16/72 (22.2)
Education level father*				
low	26/74 (35.2)	19/71 (26.8)	26/71 (36.6)	19/71 (26.8)
intermediate	30/74 (40.5)	29/71 (40.8)	28/71 (39.4)	29/71 (40.8)
high	18/74 (24.3)	23/71 (32.4)	17/71 (23.9)	23/71 (32.4)

Data shown is n (%), unless otherwise indicated
Comparisons were done using chi-square test (for linear trend) or t-tests where appropriate
* Low = vocational training, intermediate = high school, high = college/university

Growth

One child from the C group was not measured at 1 year of age. At 2 years of age one child from the DC group and one child from the C group were not measured. There was no significant difference found between the DC and C group in growth (weight in grams, height and head circumference in centimeters) at 1 or 2 years CA. When we calculated the standard deviation scores (SDS) using the Dutch growth charts, the DC group showed significantly better SDS for length than the C group and the weight (p=0.08) and head circumference (p=0.06) SDS showed a trend in favor of the DC group. There were however more infants in the C group (11.3 %) than in the DC group (4.4 %) that required postnatal corticosteroids (p=0.08), the usual dosage being 0.20 mg/kg/day in 2 doses with tapering of the dosage over a period of 16 days. As this may influence growth we corrected for use of postnatal steroids and then found no significant difference in growth SDS between the 2 groups (Table 3).

Developmental outcomes

At one year of age 145 children (DC=73, C=72) of the 147 children seen at follow-up were tested with the Bayley Scales-II-NL and at 2 years of age 140 (DC=70, C=70) of the 142 children seen at follow-up were tested. There were 3 children (DC=1, C=2) who were 13 or 14 months CA at the 1 year developmental follow-up and 8 children (DC=4, C=4) tested that were 26-27 months CA at the 2 year developmental follow-up, but their index scores were based on the norms for that age so we included them in the analysis. There was no significant difference in the mean age of all children assessed at the 1 and 2 year follow-up.

There were 2 children who did not have a developmental test due to illness or because they were uncooperative. At one year CA, the children in the DC group showed a trend of improvement (p=0.05) in the psychomotor developmental index (PDI) as compared to the C group but no significant difference (p=0.56) in their mental developmental index (MDI). At 2 years CA, this difference was no longer evident as both the MDI and PDI scores were comparable. While the PDI classifications at 12 and 24 months had a higher percentage of children in the C group with severe delays, this difference was not significant (p=0.27; p=0.20) (Table 4).

Neurological outcomes

There were 147 (DC=74, C=73) children who were assessed with a neurological exam at 1 year CA and 140 (DC=71, C=69) children at 2 years CA. Two children (DC=1, C=1) were not able to be tested at 2 years CA because they were uncooperative. There was no significant difference found between the DC and C group in neuromotor development at 1 year and 2 years CA. Although there were twice as many children in the C group with definitely abnormal scores at 1 year and more than 3 times as many C children at 2 years of age, the difference was not significant (Table 5).

Combining neurological development, MDI and PDI scores in a Total Outcome Score

When we combined the developmental and neurological score, the percentage of C group children that were definitely delayed at both 1 and 2 years compared to the DC group was much higher (1 year: DC=12.2%, C=23.3%; 2 year: DC=5.6%, C=18.3%), however the difference did not reach the level of significance (Table 5).

We then carried out a linear regression analysis to see if the number of days infants received the DC intervention influenced the neurological outcomes at 1 and 2 years according to Touwen and Hempel by testing if there was an interaction effect between the intervention duration and the two treatment groups. There was no

Table 3. Growth outcomes at 1 and 2 years CA

	1 year			2 years			
Growth outcomes	**DC**	**C**	***p* value**	**DC**	**C**	***p* value**	***p* value**§
Weight	n=74	n=72		n=72	n=69		0.18
mean in kg, sd	9.31 (1.38)	9.11 (1.28)	0.37	11.9 (1.5)	11.5 (1.4)	0.10	
SDS‡ (mean, sd)	-0.72 (1.27)	-0.94 (1.28)	0.31	-0.69 (1.12)	-1.03 (1.1)	0.08	
Head circumference	n=72†	n=71		n=71	n=68		0.10
mean in cm, sd	46.4 (1.7)	46.2 (1.7)	0.42	48.6 (1.7)	48.2 (1.7)	0.14	
SDS ‡ (mean, sd)	-0.15 (1.10)	-0.38 (1.11)	0.21	-0.06 (1.03)	-0.41 (1.09)	0.06	
Length	n=74	n=70		n=72	n=69		0.10
mean in cm, sd	74.7 (3.7)	74.1 (3.6)	0.36	87.3 (3.6)	86.0 (4.0)	0.06	
SDS‡ (mean, sd)	-0.54 (1.27)	-0.77 (1.31)	0.29	-0.36 (1.06)	-0.75 (1.24)	0.04*	

Comparisons were done using t-tests;
* *p* value significance = < 0.05
† Correct n is shown in table if there are missing values
‡ SDS (standard deviation scores) according to Fredriks et al [33]
§ *p* value after correction for postnatal steroid use

Table 4. Mental and psychomotor development at 1 and 2 years corrected age (CA)

	DC Mean (sd or %)	C n (sd or %)		DC Mean (sd or %)	C n (sd or %)	
	1 year CA			2 years CA		
	n=73	n=72	*p* value*	n=70	n=70	*p* value*
Age at test in months mean (sd) range	12.14 (0.34) 11.2-13.2	12.14 (0.40) 11.4-12.1	0.99	24.3 (0.68) 23.2-26.4	24.1 (0.47) 23.5-27.4	0.12
MDI mean (sd) range	102.3 (15.1) (57-138)	101.2 (15.7) (55-132)	0.66	100.9 (14.9) (55-130)	102.3 (16.2) (56-132)	0.58
PDI mean (sd) range	99.2 (17.0) (55-135)	93.7 (16.1) (55-124)	0.05	96.0 (14.6) (55-121)	92.3 (17.0) (55-145)	0.18
MDI classification scores† ≥ 85 70-84 ≤ 69	 64 (87.7) 7 (9.6) 2 (2.7)	 62 (86.1) 7 (9.7) 3 (4.2)	0.69	 61 (87.1) 7 (10.0) 2 (2.9)	 60 (85.7) 9 (12.9) 1 (1.4)	1.00
PDI classification scores† ≥ 85 70-84 ≤ 69	 62 (84.9) 6 (8.2) 5 (6.8)	 56 (77.8) 8 (11.1) 8 (11.1)	0.27	 54 (77.1) 13 (18.6) 3 (4.3)	 48 (68.6) 16 (22.9) 6 (8.6)	0.20

Comparisons were done using chi-square test (for linear trend) or t-tests where appropriate

* p value significance = < 0.05

† ≥ 85= normal or above normal, 70-84=mildly delayed, ≤ 69=significantly delayed

Table 5. Neurological outcomes and combined score of neurological outcomes, MDI and PDI at 1 and 2 years corrected age (CA)

	1 year CA				2 years CA		
	DC n (%)	**C n (%)**			**DC n (%)**	**C n (%)**	
	Neurological Outcome*				Neurological Outcome*		
	n=74	n=73	*p* value		n=71	n=69	*p* value
- N†	56 (75.7)	52 (71.2)	0.25	- N	50 (70.4)	46 (66.7)	0.18
- MA	13 (17.5)	10 (13.7)		- MA	17 (24.0)	11 (15.9)	
- DA	5 (6.8)	11 (15.1)		- DA	4 (5.6)	12 (17.4)	
	Combined neurological score MDI and PDI				Combined neurological score MDI and PDI‡		
	n=74	n=73			n=72	n=71	
- N†	48 (64.8)	45 (61.6)	0.26	- N	38 (52.8)	37 (52.1)	0.25
	17 (23.0)	11 (15.1)		- MA	30 (41.7)	21 (29.6)	
- MA	9 (12.2)	17 (23.3)		- DA	4 (5.6)	13 (18.3)	
- DA							

Comparisons were done using chi-square test (for linear trend) where appropriate

* neurological exam according to Touwen at 1 year and Hempel at 2 years

† N=normal, MA=mildly abnormal, DA=definitely abnormal (MDI/PDI scores ≥ 85 = N, 70-84=MA, ≤69=DA)

‡ one DC group child's en 2 C group children's combined scores were derived from the PDI and MDI

significant effect on the neurological outcome at 1 year (p=0.79) or 2 years (p=0.67) or on the combined neurological and developmental scores at 1 year (p=0.86) and 2 years (p=0.60) found.

Discussion

This randomized controlled trial showed that basic developmental care (incubator covers and positioning aids) for infants born < 32 weeks gestational age has a positive effect on psychomotor development at 1 CA, but this improvement does not continue at 2 years CA and no significant effect on MDI at 1 and 2 years CA. There may be some positive influence on neurological outcomes at 1 and 2 years as there were more DA scores in the C group than in de DC group; however the effect was not statistically significant.

There were also some differences seen between the neuromotor and the developmental scores. While the percentages of children scoring severely delayed on the PDI were comparable with scores of definitely abnormal on the Touwen exam at 1 year of age, there were twice as many children in the C group who scored 'definitely abnormal' in the Hempel neuromotor exam than children that scored 'severely delayed' in the PDI of the Bayley exam at 2 years of age. One explanation for this discrepancy is that the Touwen and Hempel measure qualitative minor neuromotor dysfunction whereas the BSID-II PDI measures motor skills and identifies motor delays and gives a quantitative score. We therefore combined the scores into a single 'mildly abnormal' or 'definitely abnormal' score in order to get a clearer picture of the outcomes. We observed more children in the C group with scores of definitely abnormal; however the difference was not significant. There appeared to be a shift to mildly abnormal in the DC group as both groups had comparable percentages of normal scores.

In addition, we looked at the amount of days infants had received developmental care when hospitalized to see if that positively influenced neurological and developmental outcomes at 1 and 2 years, but found no interaction effect.

To get a better picture of the growth outcomes, we corrected growth for CA by using standard deviation scores (SDS), which did show a significant improvement in length at 2 years in the DC group and a trend in improved head circumference growth at 2 years. However once SDS was corrected for postnatal steroid use, these differences were no longer apparent.

To date, there has been no large RCT examining growth and neurodevelopmental outcome of a basic developmental care program. Therefore comparison to other studies is not possible. Most of the studies examined the more intensive individualized NIDCAP developmental care program and had smaller sample sizes and mixed results [15-17,19]. Most outcomes of developmental care studies have focused on short term morbidity and growth or neurodevelopment up to 9-12 months[11,15,17] with only one study that followed the infants' development to 3 years which showed no significant difference in development between the two groups[16]. There were no

studies reported in the Cochrane meta-analysis examining the effect of basic developmental care programs such as ours on neurodevelopment[19].

We have tried with this study to answer some of the questions posed concerning developmental care and follow-up to 2 years of age. The percentage of lost to follow-up was low and the assessors were blinded to the treatment group the children participated in and the neurological outcomes were obtained using a standardized neurological examination.

Our conclusion is that a less intensive, cost-saving form of developmental care has a positive effect on psychomotor development at 1 year of age but no significant effect on neurodevelopment of preterm infants at 2 years of age. Perhaps a more intensive, individualized developmental care program such as the NIDCAP program based on a larger sample size than previous studies will show improved outcomes.

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CHAPTER 5

A Randomized Controlled Trial examining the Effects of NIDCAP compared to Basic Developmental Care on Preterm Infants Born < 32 Weeks to Term Age

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Abstract

Objective: To investigate the effect of the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) on days of respiratory support and intensive care, growth and neuromotor development at term age in infants born < 32 weeks.

Patients and methods: Infants were randomized within 48 hours of birth to a NIDCAP group or basic developmental care (C) group. The NIDCAP intervention consisted of weekly formal behavioral observations of the infants and caregiving recommendations for the staff and parents as well as incubator covers and positioning aids. The C group infants were given basic developmental care which consisted of only incubator covers and positioning aids. Outcome measures: respiratory support: days of mechanical ventilation and/or CPAP. Intensive care: days requiring mechanical ventilation and/or CPAP and/or weight <1000 grams. Growth parameters were measured (bi)weekly and at term age. Neuromotor development was assessed at term age by a standardized exam (Prechtl).

Results: A total of 164 infants met inclusion criteria (NIDCAP=81, C=83).
In-hospital mortality was 8/81 (9.9%) in the NIDCAP group and 3/83 (3.6%) in the C group. No difference in mean days respiratory support (13.9/16.3) or mean days IC (15.2/17.0) were found (NIDCAP/C, respectively). Short-term growth and neuromotor development at term age showed no differences even when correcting for the duration of the intervention.

Conclusions: NIDCAP developmental care has no effect on respiratory support, intensive care days or growth and neuromotor development at term age.

Introduction

Advanced technology in neonatal care has resulted in increasing survival rates of preterm infants[1-3] . This has not however led to either major improvements in morbidity rates or a decrease in the risk of developmental delays, physical disabilities and behavioral disorders[1,4,5]. Developmental care programs have been used to support the infant and family during their stay in the Neonatal Intensive Care Unit (NICU) with the premise that reducing the stress the infant experiences in the NICU and supporting the infant's development may have a positive impact on outcomes. Most research has been based on the NIDCAP (Newborn Individualized Developmental Care and Assessment Program), which is a comprehensive approach in which caregiving is based on the individual behavior of the infant [6]. A meta-analysis by Jacobs et al concluded that the evidence showing a positive effect from the NIDCAP program is inconclusive and they recommended further RCT studies with a larger sample size for appropriate power, long-term follow-up and the inclusion of cost effectiveness evaluations[7].

Between April 2000 and May 2002, our first randomized controlled trial was carried out comparing basic Developmental Care (incubator covers, nests and positioning aids) with standard care (no covers, nests or positioning aids), but no short-term significant effects were found[8]. We then wanted to explore the effects of a more comprehensive behavioral-based individualized developmental care program such as NIDCAP.

The aim of this randomized controlled trial (RCT) was to explore the effectiveness of the NIDCAP individualized developmental care program on neonatal morbidity, neuromotor development and growth at term age of preterm infants < 32 weeks GA as compared to basic developmental care.

Patients and Methods

The study was carried out at a tertiary NICU at 2 locations in the Netherlands: Leiden University Medical Center in Leiden and Juliana Children's Hospital in The Hague. Inclusion criteria were: infants born with a gestational age < 32 (31+6) weeks. Exclusion criteria included: infants with major congenital anomalies, infants needing major surgery and infants of drug-addicted mothers. After parental informed consent was obtained by the resident or staff member on call, infants were randomized within 48 hours of birth to the NIDCAP developmental care (NIDCAP) group or the Control (C) group using sealed envelopes made in groups of 6 using a computer generated randomization allocation. According to protocol, infants in both groups who were admitted for less then 5 days were excluded from follow-up

and outcome analysis, because the duration of the intervention was hypothesized not to be long enough to obtain an effect. A power analysis performed before the study showed that a total sample size of 140 infants was needed to show a significant difference (p level < .05) with a power of 80%; based on a difference of half a standard deviation on the Bayley developmental test scores at 1 and 2 years of age, corrected for prematurity and was deemed sufficient power for the short-term primary neonatal outcomes.

In addition to providing basic developmental care such as incubator covers and nests and positioning aids to encourage flexion and containment, formal behavioral observations of the infants in the NIDCAP group were carried out within 48 hours of birth and then weekly thereafter by trained certified NIDCAP developmental specialists. The observation was then discussed with parents and caregivers. Formal observation reports were available at the infants' bedside. Individual care plans based on these observations with caregiving recommendations for parents and staff were hanging clearly visible at the infant's bedside. Parents were supported in understanding their infant's behavior and how to approach and support their infant during caregiving interactions and procedures. They were also provided with photo booklets explaining preterm infant behavioral cues. The infants in the NIDCAP group were primarily cared for by nurses who had received extra training and support in behavioral-based individual developmental care. A NIDCAP certified developmental psychologist supervised the intervention as well as carried out observations and supported the parents and staff. If an infant was transferred to a regional hospital, a report was made with a behavioral summary and recommendations for caregiving for the parents.

Infants in the C group were given only basic developmental care which consisted of incubators covers and nests and positioning aids. Parents of both groups had regular access to a social worker for support. The Ethical Committees of both locations approved the study.

Definitions

Severity of illness was analyzed using the CRIB (Clinical Risk Index for Babies) score which assesses initial neonatal risk. Scores are given for birth weight, gestational age, maximum and minimum fraction of inspired oxygen and maximum base excess during the first 12 hours, and the presence of congenital malformation [9]. Inborn infants were infants born in the participating tertiary neonatal center. The primary medical outcome variables included: duration of respiratory support, number of intensive care days and short-term growth. Mechanical ventilation (SIMV and/or HFO) and/or CPAP were measured in days. If an infant received both

mechanical ventilation and CPAP in one day, the method of respiratory support given for the most hours was chosen. In addition, the total number of days of respiratory support was defined as total combined days of mechanical ventilation and CPAP.

Discharge from the intensive care was based on two criteria: the infant required no mechanical ventilation and/or CPAP for 24 hours and weighed at least 1000 grams.

Infants were weighed at least biweekly; head circumference and length were measured within the first 2 days of life and thereafter weekly by trained medical students until the infant was either transferred or discharged. Short-term growth (weight, head circumference, length) was defined as measurement at birth and at term age as well as mean daily weight gain in grams and mean weekly length and head circumference growth in centimeters. Weight was measured on neonatal pediatric digital scales, length was measured from crown to heel and head circumference was measured around the largest area of the head, occipital-frontal circumference (OFC), using a non-stretch tape measure.

Mortality was defined as early neonatal death if the infant died within the first 7 days of life and late neonatal death if the infant died after 7 days but before 28 days of life. In addition secondary outcomes were analyzed. Length of stay (LOS) was defined as total days of hospitalization in the participating hospital as well as the regional hospital until discharge to home. Days of oxygen were calculated as total days of supplementary oxygen as well as the need for oxygen after 28 days of life. Bronchopulmonary dysplasia (BPD) was defined as oxygen dependency at 36 weeks postconceptional age (PCA) according to the criteria of Shennan [10]. Postnatal steroids were divided into 3 classifications; 7-10 days, 15-20 days or more than 20 days (maximum dosage of 0.2 mg/kg/day, tapered off over a period of 16 days). Intraventricular hemorrhage (IVH) was recorded according to Volpe[11]. Periventricular leukomalacia (PVL) was classified according to grades 1-4[12]. Sepsis was based on a positive blood culture. Meningitis was defined as a positive cerebrospinal fluid (CSF) culture and/or pleocytosis. The incidence of necrotizing enterocolitis (NEC), persistent ductus arteriousus (PDA), retinopathy of prematurity (ROP), need for treatment of hypotension and hyperbilirubinemia was also analyzed.

Follow-up

At term age, infants were seen in the follow-up clinics to assess growth, morbidity and neuromotor development by neonatologists experienced in developmental assessments and blinded to the group assignment of the infant. A standardized neurological exam according to Prechtl[13] was administered and was defined as

definitely abnormal (DA), mildly abnormal (MA) or normal. Definitely abnormal is defined as the presence of a full-blown neonatal neurological syndrome, such as apathy or hyperexcitability, hypotonia or hypertonia, hyporeflexia or hyperreflexia, hypokinesia or hyperkinesia, or a hemi-syndrome. Mildly abnormal denotes the presence of only part of such a syndrome. Examples of minor neurological signs are abnormal posture, abnormal head control and absent or abnormal responses or reflexes.

Statistical Analysis

Data was analyzed using SPSS 14.0 for Windows. The infant and parent characteristics were compared with the Chi-square test (for trend) or the two-sample t-test where appropriate. Outcome parameters were compared between the two treatment groups with the t-test, Mann-Whitney test or Chi-square test (for trend) where appropriate. P-values < 0.05 were considered significant. Linear regression was used to evaluate the influence of the duration of the intervention on term age outcomes by testing if there was an interaction effect between the intervention duration and the 2 treatment groups. Median days of CPAP, days of respiratory support and IC days were obtained from Kaplan-Meier curves and compared using the log rank test, where measurements of infants who died were censored.

RESULTS

In total 168 infants were originally recruited between July 2002 and November 2004 for the study; 84 in the NIDCAP group and 84 in the C group. Four infants (NIDCAP: 3, C: 1) were excluded according to protocol because they were admitted less than 5 days or died within the first 5 days. This left a total of 164 infants that met inclusion criteria. Of the 164 included infants, 8/81 (9.9%) in the NIDCAP group and 3/83 (3.6%) in the C group died during hospitalization. The difference of the in-hospital mortality rate between the 2 groups was not significant (p=0.11). The majority of incidences of infant mortality (NIDCAP: 7/8, C: 3/3) was classified as late neonatal death, between 8 and 28 days of life, with the main cause of death being cerebral or pulmonary complications. Seventy-three infants in the NIDCAP group and 80 infants in the C group were assessed at term age. Two infants in the C group were followed at term age in another hospital not participating in the study, and were classified according to a different neurological exam by their pediatrician as normal and mildly abnormal respectively. These infants were not included in the neurological assessment outcome. Their growth parameters however were included in the growth analysis. The mortality rate and loss to follow up are shown in Figure 1.

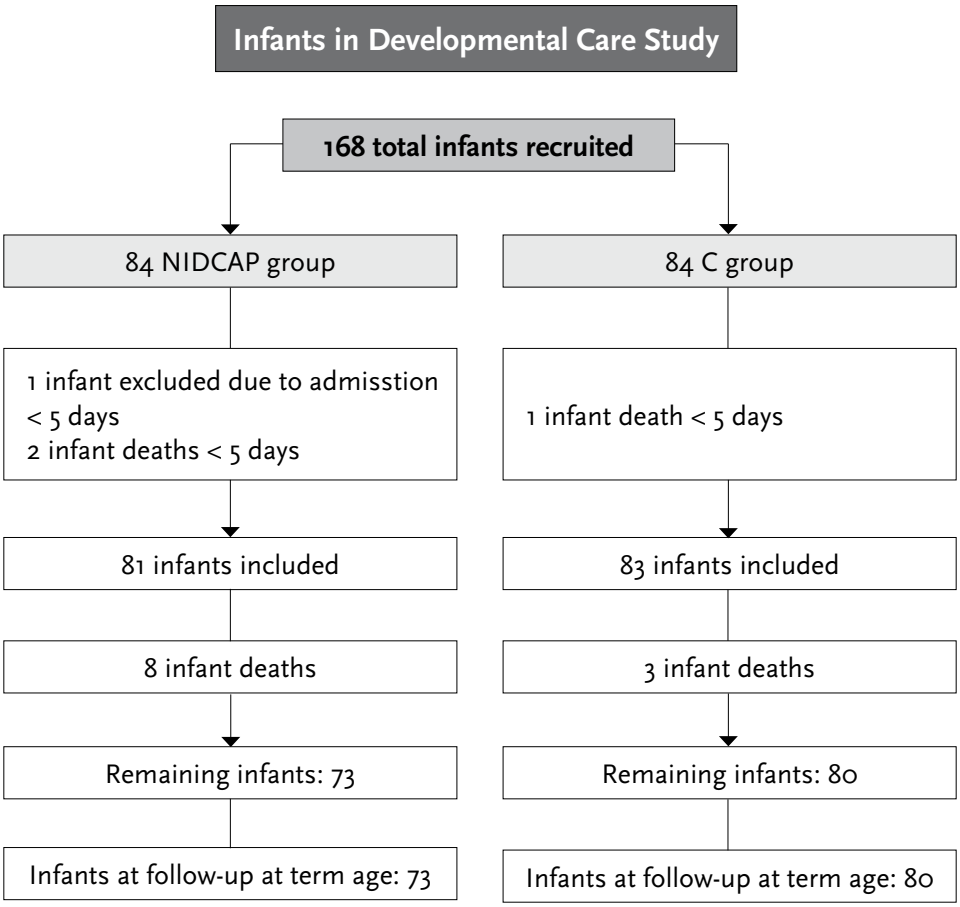


Figure 1

Parent characteristics for the study population were similar with no significant differences found and are shown in Table 1. There was no difference in infant characteristics between the NIDCAP and C group (Table 2). Five infants in the NIDCAP group were hospitalized temporarily elsewhere for surgical or other necessary treatment. These infants were included in the outcome under the intention-to-treat protocol.

Primary Outcomes

There was no significant difference found in the number of Intensive care (IC) days, days of respiratory support or growth between the NIDCAP and C groups.

Table 1. Maternal medical and parental demographic background variables

	NIDCAP n=81	**C n=83**
Obstetrical history		
Pre-existing disease (diabetes, hypertension, other)	9/81 (11.1)	14/83 (16.9)
Pregnancy induction	13/81 (16.0)	14/83 (16.9)
Diseases during pregnancy		
diabetes mellitus gravidarum	2/81 (2.5)	3/83 (3.6)
(pre)eclampsia or HELLP syndrome	13/81 (16.0)	16/83 (19.3)
Medication during pregnancy		
antihypertensives	14/81 (17.3)	19/83 (22.9)
antibiotics	32/81 (39.5)	25/83 (30.1)
tocolytics	45/81 (55.6)	43/83 (51.8)
other	7/81 (8.6)	14/83 (16.9)
Antenatal glucocorticoids		
one dose	29/80 (36.3)	35/83 (42.2)
1 course (2 doses)	33/80 (41.3)	29/83 (34.9)
Mode of delivery		
vaginal	41/81 (50.6)	45/83 (54.2)
caesarean section	40/81 (49.4)	38/83 (45.8)
PROM > 24 hours*	25/81 (30.9)	19/83 (22.9)
Primipara	54/81 (66.7)	42/83 (50.6)
Parental demographic background		
Maternal age	n=74	n=78
mean in years, sd	30.0 (5.2)	31.9 (5.0)
Paternal age	n=72	n=77
mean in years, sd	32.3 (5.6)	34.1 (5.5)
Mother Caucasian	66/80 (82.5)	70/80 (87.5)
Father Caucasian	63/79 (79.7)	64/80 (80.0)
Education level mother †		
low	26/72 (36.1)	19/77 (24.7)
intermediate	25/72 (34.7)	26/77 (33.8)
high	21/72 (29.2)	32/77 (41.6)
Education level father †		
low	19/69 (27.5)	15/76 (19.7)
intermediate	22/69 (31.9)	32/76 (42.1)
high	28/69 (40.6)	29/76 (38.2)

Data shown is n (%), unless otherwise indicated
* Premature rupture of membranes
† Low = vocational training, intermediate = high school, high = college/university

Table 2. Infant medical background variables of all participating infants

Birth Characteristics	**NIDCAP n=81**	**C n=83**
Gestational age	n=81	n=83
mean in wks, sd	29.3 (1.8)	29.2 (1.6)
range	24.7 – 31.9	25.6 - 31.6
Birthweight	n=81	n=83
mean in g, sd	1215 (328)	1226 (343)
range	577 - 1939	625 - 2060
Length	n=81	n=83
mean in cm, sd	37.1 (3.1)	36.8 (3.3)
range	29.0 - 43.0	29.0 - 44.0
Head circumference	n=81	n=83
mean in cm, sd	26.8 (2.2)	26.6 (2.3)
range	22.4 – 32.0	21.5 – 30.5
Male gender	46/81 (56.8)	43/83 (51.8)
SGA* P < 10 and P ≥ 3	15/81 (18.5)	10/83 (12.0)
SGA P < 3	3/81 (3.7)	5/83 (6.0)
Twin	27/81 (33.3)	34/83 (41.0)
Inborn	51/81 (63.0)	49/83 (59.0)
Apgar scores at 5 minutes	n=80	n=80
mean (sd)	8.1 (2.2)	8.3 (1.4)
median (range)	8 (3- 10)	8 (4 - 10)
CRIB Score	n=81	n=83
median (range)	2 (0 – 14)	3 (0 – 13)
RDS*		
grade 1	20/81 (24.7)	23/82 (28.0)
grade 2	11/81 (13.6)	13/82 (15.9)
grade 3	17/81 (21.0)	17/82 (20.7)
grade 4	6/81 (7.4)	8/82 (9.8)
Surfactant	41/81 (50.6)	39/83 (47.0)
Hyperbilirubinemia	73/81 (90.1)	76/83 (91.6)
Days of phototherapy (mean, sd)	4.4 (2.9)	4.8 (3.4)

Data shown is n (%), unless otherwise indicated
Comparisons were done using chi-square test (for linear trend) or t-tests where appropriate
* SGA: small for gestational age, RDS: respiratory distress syndrome

Seventy-three infants 73/81 (90.1%) in the NIDCAP group and 77/83 (92.8%) infants in the C group required some form of respiratory support. This analysis was based on all included infants. We performed the same analysis of the infants who survived, NIDCAP: 73/81(90%), C: 80/83 (96%). The infant characteristics as well as the primary and secondary outcomes showed no significant differences between groups (data not shown).

All of the surviving 153 infants (NIDCAP: 73, C: 80) were assessed at term age. Age at follow-up assessment was comparable for both groups. There was no significant difference found in the neurological outcomes between the NIDCAP and C group. Three surviving infants (NIDCAP: 2, C: 1) diagnosed with posthemorrhagic ventricle dilatation were excluded from the weekly and term age head circumference analysis. There was no significant difference found between the NIDCAP and C group in the growth parameters at term age or in daily weight gain (g), weekly length and head circumference (cm) growth (Table 3).

A linear regression analysis was carried out to analyze if the number of days infants received the NIDCAP intervention influenced the neuromotor outcome and growth at term age by testing if there was an interaction effect between the intervention duration and the two treatment groups. There was no significant effect on the neurological outcome (p=0.72), term age head circumference (p=0.94): term age weight (p=0.28) or term age length (p=0.54) found.

Secondary outcomes

The total length of stay (LOS) from birth to discharge to home or the gestational age of the infants when discharged from the hospital was not different in the 2 groups. There was no difference in the days of oxygen received or infants that required oxygen after 28 days or incidence of BPD between the two groups. In total 7/81 (8.6%) infants in the NIDCAP group required postnatal corticosteroids as opposed to 11/83 (13.3%) infants in the C group (p=0.35), with twice as many infants in the C group requiring corticosteroids for more than 2 weeks. There were significantly more infants in the NIDCAP group 25/81 (30.9%) with PDA requiring medication and/or surgery than in the C group 11/83 (13.3%). Of the 25 NIDCAP infants with PDA, 6/25 (24%) died in-hospital and 1/11 (9%) infant with PDA died in the C group. When we analyzed the surviving infants, the NIDCAP group 19/73 (26%) still had twice as many infants with PDA than the C group 10/80 (12.5 %); p=0.03. At term age there was no difference in the incidence of PVL or the number of infants requiring physical therapy. There were also no significant differences found in the remaining secondary outcomes (Table 4).

Table 3. Comparison of data of primary outcome measures

	NIDCAP n=81	**C n=83**	***p* value**
Days of hospitalization (mean, sd)	41.5* (30.9)	40.4 (37.9)	0.83
median (range)	37 (6-159)	30 (5-285)	
Days IC (mean, sd)	15.2 (14.8)	17.0 (16.5)	0.46
median (range)	9 (0-54)	11 (0-80)	
Number of infants requiring respiratory support	73/81 (90.1)	77/83 (92.8)	0.54
Days of mechanical ventilation** (mean, sd)			
median (range)	5.6 (7.0)	6.4 (9.3)	0.60
Days of CPAP (mean, sd)	2.0 (0-25)	2.0 (0-41)	
median (range)	8.4 (9.9)	10.0 (11.0)	0.35
Total days ventilatory support† (mean, sd)	4.0 (0-36)	6.0 (0-67)	
median (range)	13.9 (14.6)	16.3 (16.7)	0.35
	9.0 (1-52)	10.0 (1-79)	
Growth parameters at term age	n=72	n=80	
Age in weeks (mean, sd)	41.1 (1.9)	41.1 (2.0)	0.94
Weight in kg	n=72	n=80	
mean, sd	3.11 (0.63)	3.10 (0.57)	0.86
daily weight gain in grams (mean, sd)	23.9 (5.8)	22.9 (5.2)	0.25
Head circumference in cm ‡	n=70	n=79	
mean, sd	35.5 (1.6)	35.6 (1.5)	0.62
weekly head circumference growth in cm§	0.76 (0.14)	0.76 (0.12)	0.90
Length in cm	n=72	n=77	
mean, sd	49.0 (2.8)	48.5 (2.9)	0.23
weekly growth in length in cm (mean, sd)	1.00 (0.22)	0.99 (0.19)	0.29
Neurological outcome at term (Prechtl)	n=73	n=78§	
normal	39/73 (53.4)	40/78 (51.3)	0.47
mildly abnormal	23/73 (31.5)	34/78 (43.6)	
definitely abnormal	11/73 (15.1)	4/78 (5.1)	

Data shown is n (%), unless otherwise indicated
Comparisons were done using chi-square test (for linear trend), t-tests or Mann-Whitney tests where appropriate

* also indicates number of days intervention was given
** SIMV and or HFO
† Total days SIMV, HFO and CPAP combined
‡ Infants with posthemorrhagic ventricle dilatation (n=2 NIDCAP, n=1 C) were excluded from head circumference analysis
§ Two infants not assessed according to Prechtl

Table 4. Comparison of data of secondary outcome measures

	NIDCAP n=81	**C n=83**	***p* value**
In-hospital mortality	8/81 (9.9)	3/83 (3.6)	0.14
early neonatal death	1/81 (1.2)	0	
late neonatal death	7/81 (8.6)	3/83 (3.6)	
LOS† in days	n=70	n=74	0.24
mean (sd)	61.9 (24.5)	67.6 (34.2)	
median (range)	57.5 (32-159)	58.5 (30-285)	
GA† at discharge to home	n=70	n=74	0.50
mean in weeks (sd)	38.5 (2.7)	38.9 (4.4)	
Total days supplemental O2			
mean (sd)	17.2 (22.6)	16.4 (25.4)	0.84
median (range)	6 (0-100)	3 (0-121)	
O2 requirement > 28 days of life	25/81 (30.9)	24/82 (29.3)	0.82
BPD †	12/80 (15.0)	16/81 (19.8)	0.43
Postnatal corticosteroids			
< 7 days	1/81 (1.2)	1/83 (1.2)	0.37
7-14 days	2/81 (2.5)	2/83 (2.4)	
15-20 days	2/81 (2.5)	7/83 (8.4)	
> 20 days	2/81 (2.5)	1/81 (1.2)	
IVH †			
grade I - II	17/81 (21.0)	19/83 (22.9)	0.72
grade III (and periventricular echodensity)	6/81 (7.4)	4/83 (4.8)	
Posthemorrhagic ventricular dilatation	2/81 (2.5)	6/83 (7.2)	0.16
NEC †	3/81 (3.7)	3/83 (3.6)	0.86
Sepsis	38/81 (46.9)	45/83 (54.2)	0.35
Meningitis	1/81 (1.2)	1/83 (1.2)	0.99
PDA† (indomethacin and/or surgery)	25/81 (30.9)	11/83 (13.3)	0.01*
Dopamine/Dobutamine	22/81 (27.2)	23/83 (27.7)	0.94
ROP †	8/70 (11.4)	10/73 (13.7)	0.82
PVL † at term age follow-up			
grade 1	5/72 (6.9)	10/80 (12.5)	0.76
grade 2	1/72 (1.4)	0	
grade 3	1/72 (1.4)	1/80 (1.3)	
grade 4	0	0	
Physical therapy required at term	16/73 (21.9)	11/80 (13.8)	0.32

Data shown is n (%), unless otherwise indicated
Comparisons were done using chi-square test (for linear trend) or t-tests where appropriate
* *p* value < 0.05 was considered significant
† LOS: length of stay, BPD: bronchopulmonary dysplasia, IVH: intraventricular haemorrhage, NEC: necrotising enterocolitis, PDA: patent ductus arteriosus, ROP: retinopathy of prematurity, PVL: periventricular leukomalacia

Survivor Analysis

Because our primary outcomes were respiratory support and IC days, we also wanted to include the data from the infants who died in-hospital, so we carried out a Kaplan Meier analysis. No differences were found in the total population (Figures 2a-c). Because there was a significant difference in incidence of PDA between the groups (Table 4), we also carried out a post-hoc Kaplan Meier survival analysis and stratified for infants with PDA requiring medication or surgery, or infants without significant PDA. In the subgroup of infants with no PDA, the NIDCAP group required less median days of CPAP (p=0.02), total respiratory support (p=0.02) and total days intensive care (p=0.06) as compared to the C group (Figures 3a-b).

As phototherapy may influence the closure and/or reopening of a PDA we compared days of phototherapy but found no difference between the groups (NIDCAP: 4.4 mean days, C: 4.8 mean days)[14].

Discussion

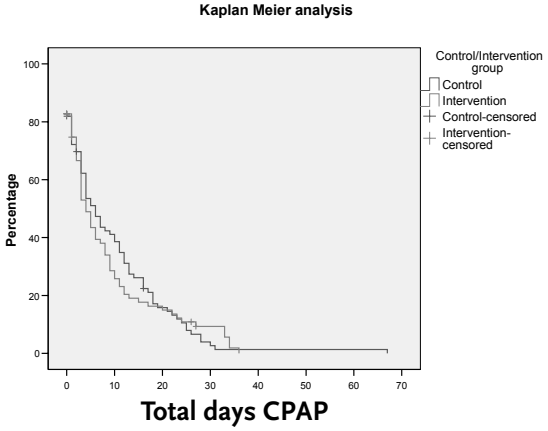
In this randomized controlled trial examining the short-term effects of the comprehensive NIDCAP developmental care program compared to basic developmental care on neonatal morbidity, neurological outcome and growth at term age of infants born < 32 weeks, we found no significant positive effects of the intervention on need for respiratory support or IC days. There were no differences between the NIDCAP and C group in growth and neurological outcomes at term age, even when correcting for days of intervention.

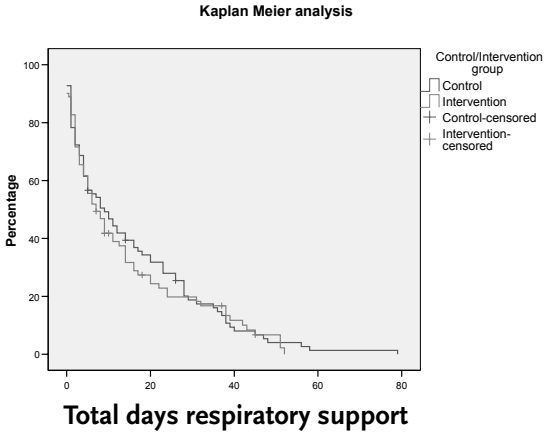
Respiratory Support

A Cochrane review meta-analysis found infants receiving NIDCAP had significantly fewer ventilation days and no differences in days of oxygen, however stated that the results were conflicting and the studies showed much heterogeneity and should be reviewed with caution[15]. An RCT by Westrup et al of 25 infants born with a gestational age < 32 weeks and with the need for ventilatory support at 24 hours showed no significant difference in days of mechanical ventilation and a trend (p=0.045) in days of CPAP in favor of the NIDCAP group (NIDCAP: 43.9, C: 26.1) as well as a younger PCA of oxygen withdrawal[16]. The number of included patients in this study was small (E: 12, C: 13) because the trial had to be terminated earlier than expected.

Earlier NIDCAP studies by Als and Fleischer have also shown positive results concerning the need for ventilatory support[17,18], however only infants born < 30 GA and birth weight < 1250 grams were included and they had specific ventilation

Figures 2a-c. Comparison of days CPAP, ventilatory support and IC days of all participating infants





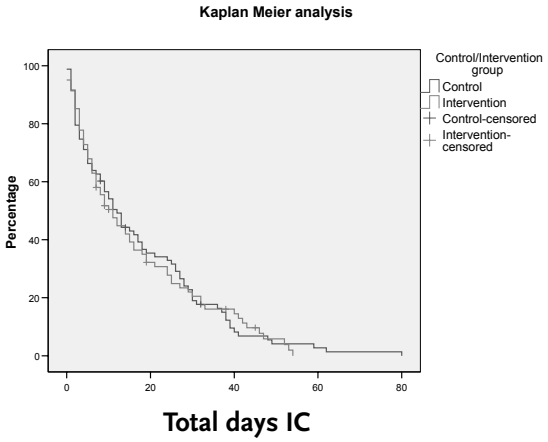


Figure 3a. Comparison of days of respiratory support in infants with no PDA

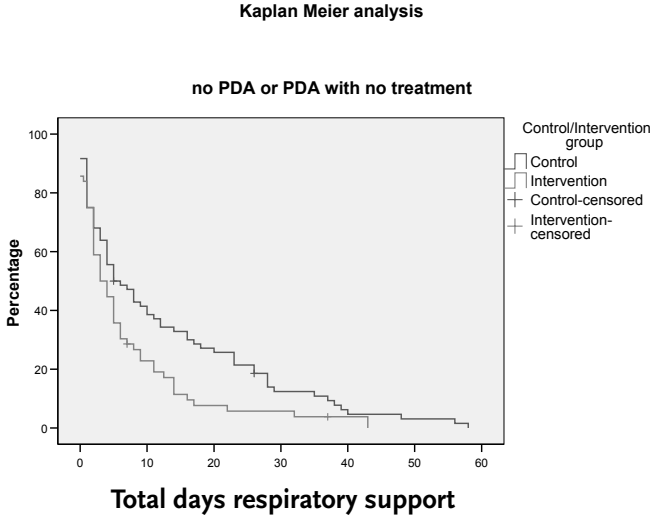
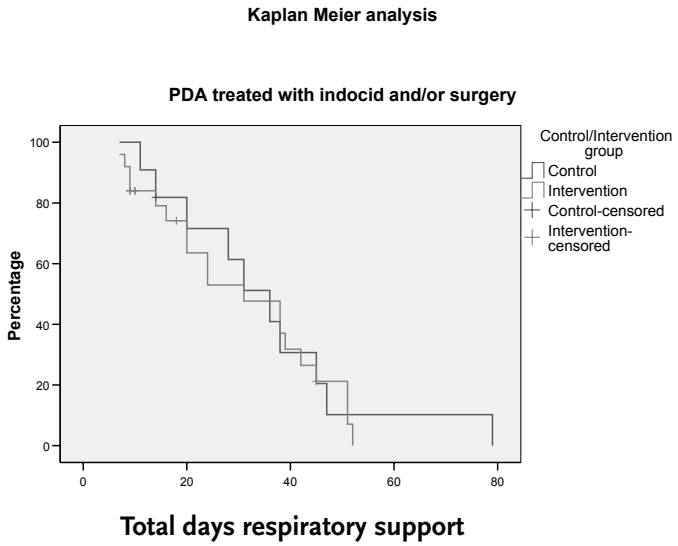


Figure 3b. Comparison of days of respiratory support in infants with PDA



inclusion criteria (Als: IMV within first 3 hours and IMV > 24 hours of first 48 hours of life; Fleisher: no IMV in first 3 hours of life or for > 24 hours in first 48 hours of life). A later three-center trial by Als showed no significant difference in respiratory support between the NIDCAP and control group but there were differences between sites (parental demographic and infant medical background variables)[15,19]. Our study included infants born < 32 weeks regardless of their need for ventilator support and had lower CRIB scores than Westrups's study, indicating they were more stable in the first 12 hours of life.

IC Days

The three-center RCT by Als et al of 92 preterm infants with a birth weight < 1250 grams and gestational age < 28 weeks showed significantly less days of intensive care in the infants receiving NIDCAP[19]. We were not able to duplicate those findings in our study, however our population was different in that we included older infants < 32 weeks gestational age with no restriction on birth weight. The total number of IC days in our study was considerably less than the above mentioned study, perhaps reflecting the difference in population or a different definition of IC days as the criteria for intensive care days was not defined in the study by Als. Wielenga et al found no significant difference in IC days between NIDCAP and conventional care, but also did not define their criteria for intensive care days[20]. Other NIDCAP studies looked at total days of hospitalization but did not report days of intensive care.

Growth

A study by Als et al showed a significantly better average daily weight gain and improved growth (weight, head circumference and height) to term age in the infants receiving NIDCAP[19]. Westrup's study showed no significant effect on growth (weight gain and head growth) up to 35 weeks PCA[16]. The Cochrane meta-analysis that did not include the above mentioned study by Als due to site differences concluded that NIDCAP did not effect growth in infants surviving to 9 months corrected age[15]. Our short-term growth results are comparable to these findings.

Neurobehavioral outcome

Another study by Als et al[21] of 30 stable preterm infants between 28-33 weeks GA showed significant improvements in neurobehavioral outcomes according to Prechtl at 2 weeks corrected age. The Prechtl outcome was defined by 12 summary variables and a total score showing the percentage of abnormal scores in each group. Buehler's study of stable preterm infants between 30-34 weeks GA and birth weight < 2500 grams showed significantly better scores in 3 of the 10 Prechtl

summary variable scores as well as the total score at term age in the NIDCAP infants as well[22]. We found no significant difference in our study in which neurobehavioral outcome according to Prechtl was defined as DA, MA or normal, so were not able to compare our results with theirs.

PDA

After randomization, our study showed significantly more infants in the NIDCAP group with PDA requiring medication or surgery (Table 4). The mean days of phototherapy, which can influence ductal reopening were similar for both groups so there is no plausible reason NIDCAP group infants had significantly more PDA that needed treatment[14]. Most of the infants (NIDCAP: 17/19, C: 9/10) were given a 3-dose course of Indomethacin which successfully closed the ductus. Two infants in the NIDCAP group and 2 infants in the control group were first given a course of Indomethacin and then treated with surgical ligation.

When we examined the subgroup of infants with no PDA (NIDCAP: 56, C: 72) using a Kaplan Meier analysis, we did find a significant difference in days of CPAP and total respiratory support in favor of the NIDCAP group. We assume on clinical grounds that most of the PDA's were diagnosed after inclusion (within 48 hours after birth) into the study. So while there may be a possible benefit from NIDCAP for a subgroup of infants without PDA in days of respiratory support, these findings should be interpreted with caution. The presence of PDA did appear to influence neurodevelopmental outcomes, as 7/11(64%) of the NIDCAP infants with a DA score on the Prechtl exam at term age had PDA, and only 1/4 (25%) of the C infants with a DA score had PDA, reflecting the higher incidence of PDA in the NIDCAP group. There were also more boys (57.9% vs 30%) and SGA infants (31.6% vs 20%) in the NIDCAP group with PDA than the C group.

Secondary outcomes

Wielenga et al showed NIDCAP infants had less incidence of severe cerebral damage[23] in a phase-lag study of infants born < 30 weeks gestation in which 26 infants received conventional treatment and after 6 months training, 25 infants received NIDCAP developmental care. There were significant differences in the neonatal background characteristics between the two groups in that the NIDCAP infants were smaller and had less multiples than the conventional care group and the NIDCAP infants developed significantly more pneumonia, possibly due to an outbreak of a nosocomial infection in the NICU during the NIDCAP implementation. One advantage of a phase-lag study is the ability to implement a program such as NIDCAP throughout the entire department; however the disadvantage of

having different periods of research in which there may be changes in the department may affect results. Therefore they have stated that these results should be interpreted with caution[23].

The Cochrane meta-analysis of 3 studies[17,21,24] showed no evidence that NIDCAP affected the incidence of IVH, grade 3 or 4[15], nor was there a significant difference in either the Swedish trial[16] or the 3-center trial[19]. Our study was comparable in that there were no differences in outcomes of IVH and or PVL between groups found.

In addition, a significant effect of NIDCAP was found on moderate-severe chronic lung disease according to the Cochrane review[15]. In this study, despite the fact that the C group required more postnatal corticosteroids than the NIDCAP group, there was no difference in the incidence of BPD.

The total days of intervention were less when compared to previous NIDCAP trials, which is a limitation of our study as this would impact the amount of days NIDCAP developmental care would be given. If we compare the number of intensive care days as well as the total days of hospitalization, the infants in our study required less days of intensive care and were transferred to regional hospitals earlier, so that the amount of days of the intervention was, with a percentage of our participating infants, less than in previously reported studies. Because of the regionalization of neonatal intensive care in the Dutch neonatal health care system, infants often are transferred to regional hospitals who can provide post-IC and intermediate care. There were 33/80 (41%) of the surviving C group and 37/73 (51%) of the surviving NIDCAP group infants who remained in the participating hospitals for at least 6 weeks. Because of this variation we did correct for amount of days of the intervention, but this did not change the term age outcomes.

This study is to our knowledge the largest RCT examining the effects of NIDCAP developmental care on preterm infants. All but 2 of the surviving 153 infants were seen at follow-up at term age. The infants were randomized in an appropriate manner; however there could be no blinding of the intervention as all infants were cared for in the same intensive care unit and the NIDCAP infants had recommendations for caregiving at their bedside. The amount of respiratory support given to an infant was decided upon by several neonatologists and was not influenced by the study group the infant participated in. Since the discharge from the intensive care was based on two criteria: the infant required no mechanical ventilation and/or CPAP for 24 hours and weighed at least 1000 grams, IC days could also not be influenced by group participation. In addition, the follow-up at term age was carried out by neonatologists blinded to the participation group.

Despite the large sample size compared to previous NIDCAP studies and well defined outcome measurements, we were not able to find any significant differences in our primary outcomes. In a previous study examining the effects of basic developmental care compared to controls[8], we also did not find any significant effects of the intervention in short-term outcomes to term age.

Future research in NIDCAP should include not only the neonatal intensive care centers but the regional hospitals where infants are transferred to as well. In addition, an intervention program where infants and parents are supported after discharge may help to improve outcomes, as it would provide a continuation of the support already given to infants and families in the hospital.

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CHAPTER 6

Follow-up Outcomes at 1 and 2 years of Infants < 32 weeks after NIDCAP Developmental Care

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Abstract

Objective: Randomized controlled trial investigating the effect of NIDCAP developmental care on growth, cognitive, psychomotor and neuromotor development in infants born < 32 weeks.

Methods: Infants were randomized within 48 hours of birth to the NIDCAP group or basic developmental care C group (incubator covers or nests). At 1 and 2 years corrected age (CA) growth was measured and standardized neurological exams were administered. Mental (MDI) and psychomotor (PDI) development was assessed using the Dutch version of the Bayley Scales of Infant Development II. To obtain a total outcome measure, neurological outcome, PDI and MDI scores were combined.

Results: 168 infants were recruited (NIDCAP: 84; C: 84). Four infants (NIDCAP: 3, C: 1) were excluded because they were admitted less than or died within the first 5 days, leaving a total of 164 infants that met inclusion criteria. In-hospital mortality was 8/81 (9.9%) in the NIDCAP group and 3/83 (3.6%) in the C group. At one year 148 children (NIDCAP: 70, C: 78) and at 2 years 146 children (NIDCAP: 68, C: 78) were assessed. There was no significant difference in growth at 1 and 2 years. There was no significant difference in neurological outcome or mental and psychomotor development at 1 and 2 years found. When neurological outcome, MDI and PDI scores were combined, there still remained no significant difference.

Conclusions: NIDCAP developmental care showed no effect on growth, neurological, mental and psychomotor development at 1 and 2 years in infants born < 32 weeks. Duration of the NIDCAP intervention was not associated with neurological and developmental outcome.

Introduction

Advances in the care of preterm infants have increased their survival rates, but the chance of later developmental and/or behavioral problems remains high for a considerable percentage of these infants and may continue into young adulthood[1-3]. Cerebral palsy rates have not fallen over the past 10 years although survival has improved and increasing survival at low gestations is associated with the highest prevalence of cerebral palsy[4]. The most common disability at two years is developmental or cognitive impairment, which assumes greater significance in the school years. Cognitive differences between ex-preterm infants and term born infants show a greater need for educational support and higher prevalence of school problems in children without severe disabilities[5]. In addition, VLBW children have an increased risk of developing attention deficit hyperactivity disorders (ADHD), generalized anxiety and symptomatic depression[6].

With the increasing technological advances has come the awareness that the intensive care and interventions used may also play a part in developmental disabilities. Developmental care programs have focused on changing the environment and caregiving of the preterm infant while providing these necessary life saving interventions. The philosophy behind developmental care is that by reducing stress and supporting the infants' developmental in the NICU, this in turn may impact their later developmental outcome. The most comprehensive and well known program is the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) developed by Als, an individual approach in which caregiving is based on the infant's behavior [7-9]. Follow-up studies of the effectiveness of the NIDCAP developmental care program have shown conflicting results and are based on trials with a small sample size [10-15]. A Cochrane meta analysis has therefore recommended conducting larger trials with more follow-up[15].

The aim of this randomized controlled trial (RCT) was to explore the effectiveness of the implementation of the comprehensive NIDCAP developmental care program on growth, mental and psychomotor development and neurological outcome at 1 and 2 years CA of preterm infants born < 32 weeks gestational age. We hypothesized that an individual developmental care approach, in which the caregiving during their NICU stay was guided by the behavior of the infant, would reduce stress and promote physiological stability and in turn would positively affect their later growth and development.

Patients and Methods

The study was carried out from July 2002 to November 2006 at a tertiary NICU at 2 locations in the Netherlands: Leiden University Medical Center in Leiden and Juliana Children's Hospital in The Hague. The inclusion period was from July 2002 to August 2004 and the 1 and 2 year follow-up was from September 2003 to November 2006. Inclusion criteria were: infants born with a gestational age < 32 completed weeks. Exclusion criteria included: infants with major congenital anomalies, infants needing major surgery and infants of drug-addicted mothers. After parental informed consent was obtained by the resident or staff member on call, infants were randomized within 48 hours of birth to the NIDCAP developmental care (NIDCAP) group or the Control (C) group (basic developmental care) using sealed envelopes made in groups of 6 using a computer generated randomization allocation. According to protocol, infants in both groups who were admitted for less then 5 days were excluded from follow-up because the duration of the NIDCAP intervention was hypothesized not to be long enough to obtain an effect. A power analysis performed before the study showed that a sample size of 140 infants was needed to show a significant difference (p value < .05) with a power of 80%, based on the expected difference of half a standard deviation (7.5) on the developmental test scores at 1 and 2 years of age.

The NIDCAP intervention consisted of weekly behavioral observations of the infants by trained certified NIDCAP developmental specialists, with the first observation being done within 48 hours of birth. Individual care plans based on these observations with caregiving recommendations were discussed with parents and caregivers and were available at the infant's bedside. Parents were supported in understanding their infant's behavior and how to approach and support their infant during caregiving interactions and procedures. The infants in the NIDCAP group were primarily cared for by nurses who had received extra training and support in behavioral-based individual developmental care. If an infant was transferred to a regional hospital, a report was made with a behavioral summary and recommendations for caregiving for the parents. In addition, incubator covers and nests and positioning aids were provided to encourage flexion and containment. A NIDCAP certified developmental psychologist supervised the intervention, carried out observations and supported the parents and staff. The C group consisted of basic developmental care which included the use of incubator covers and nests and positioning aids to encourage flexion and containment. The Ethical Committees of both locations approved the study.

Measures

Infant characteristics (gestational age, birth weight, gender, small for gestational age, inborn, Apgar scores, CRIB score) and parental characteristics (age, ethnicity, educational level) were collected to compare groups (Tables 1 and 2). Severity of illness was analyzed using the CRIB (Clinical Risk Index for Babies) score which assesses initial neonatal risk. Scores are given for birth weight, gestational age, maximum and minimum fraction of inspired oxygen and maximum base excess during the first 12 hours, and the presence of congenital malformation [16].

Follow-Up

Children were assessed at 1 and 2 years of corrected age for prematurity (CA) for growth and neurodevelopment by neonatologists experienced in developmental assessments and blinded to the group assignment of the child. All mention of age hereafter is corrected age for prematurity. A standardized neurological exam according to Touwen [17,18] at one year and Hempel [19] at two years was administered and classified as definitely abnormal (DA) when there was definite neurological dysfunction such as cerebral palsy; mildly abnormal (MA) in the presence of mild deviations in muscle tone regulation, reflexes, fine or gross motor performance or cranial nerve function; or normal (N).

Weight was measured on a pediatric digital scale, length was measured from crown to heel on a standard measurement board and head circumference was measured around the largest area of the head, occipital-frontal circumference (OFC), using a non-stretch tape measure.

In addition, children were assessed at 1 and 2 years by psychology interns supervised by a clinical psychologist, who were blinded as to whether the child was in the NIDCAP or C group. Mental and psychomotor development was assessed using the Dutch version of the Bayley Scales of Infant Development II (BSID-II)[20,21]. The mean score of the mental developmental index (MDI) and the psychomotor developmental index (PDI) is 100, with 1 standard deviation (SD) of 15 points. An MDI or PDI ≥ 85 (≥ - 1 SD) is considered normal, an MDI or PDI between 70 and 84 (–2 to –1 SD) is considered mildly delayed and Index scores ≤ 69 (< - 2 SD) severely delayed. The Dutch norms, which had become available during our research, were used. To obtain a single outcome measure, neurological outcome, PDI and MDI were combined. When at least 1 of these 3 outcome measures was DA, children were considered DA, and when at least 1 outcome was MA, children were considered MA.

Statistical Analysis

Data was analyzed using SPSS 12.0 for Windows. The infant and parent characteristics were compared with the Chi-square test, the Chi-square test for trend or the two-sample t-test, where appropriate. Outcome parameters were compared between the two treatment groups with the t-test, Mann-Whitney test or Chi-square test where appropriate. *P*-values < 0.05 were considered significant. Linear regression was used to evaluate the influence of the duration of the intervention on 1 and 2 year outcomes by testing if there was an interaction effect between the intervention duration and the 2 treatment groups. Linear regression was also used to evaluate the influence of postnatal steroids on growth outcomes at 1 and 2 years.

Results

In total 168 infants were recruited for the study; 84 in the NIDCAP group and 84 in the C group. Four infants (NIDCAP: 3, C: 1) were excluded according to protocol because they were admitted less than 5 days or died within the first 5 days. This left a total of 164 infants that met inclusion criteria. Of the 164 included infants, 8/81 (9.9%) in the NIDCAP group and 3/83 (3.6%) in the C group died during hospitalization, with the main cause of death being cerebral or pulmonary complications. There was no significant difference in the in-hospital mortality rate between the NIDCAP and C group (p=0.11). This left 156 infants (NIDCAP: 73, C: 80) for follow-up. At 1 year 148 [NIDCAP: 70/73 (95.9%), C: 78/80 (97.5%)] and at 2 years 146 children [NIDCAP: 68/73 (93.2%), C: 78/80 (97.5%)] were seen at the follow-up clinic out of a total of 153 surviving infants. At 1 year, 2 infants were lost to follow-up and the parents of 1 infant no longer wanted to participate in the NIDCAP group and 2 infants in the C group were lost to follow-up. Between the 1 and 2 year assessment two children in the NIDCAP group were lost to follow-up. There was no loss to follow-up in the C group at 2 years. The mortality rate and loss to follow-up are shown in Figure 1.

There was no significant difference in the primary infant characteristics between the NIDCAP and C groups. Despite randomization, there were significantly more surviving infants with PDA requiring medication or medication and ligation in the NIDCAP group, p=0.03 at 1 year and p=0.02 at 2 years (Table 1). Parent characteristics (age, ethnicity and educational level) were similar in both groups and are shown in Table 2.

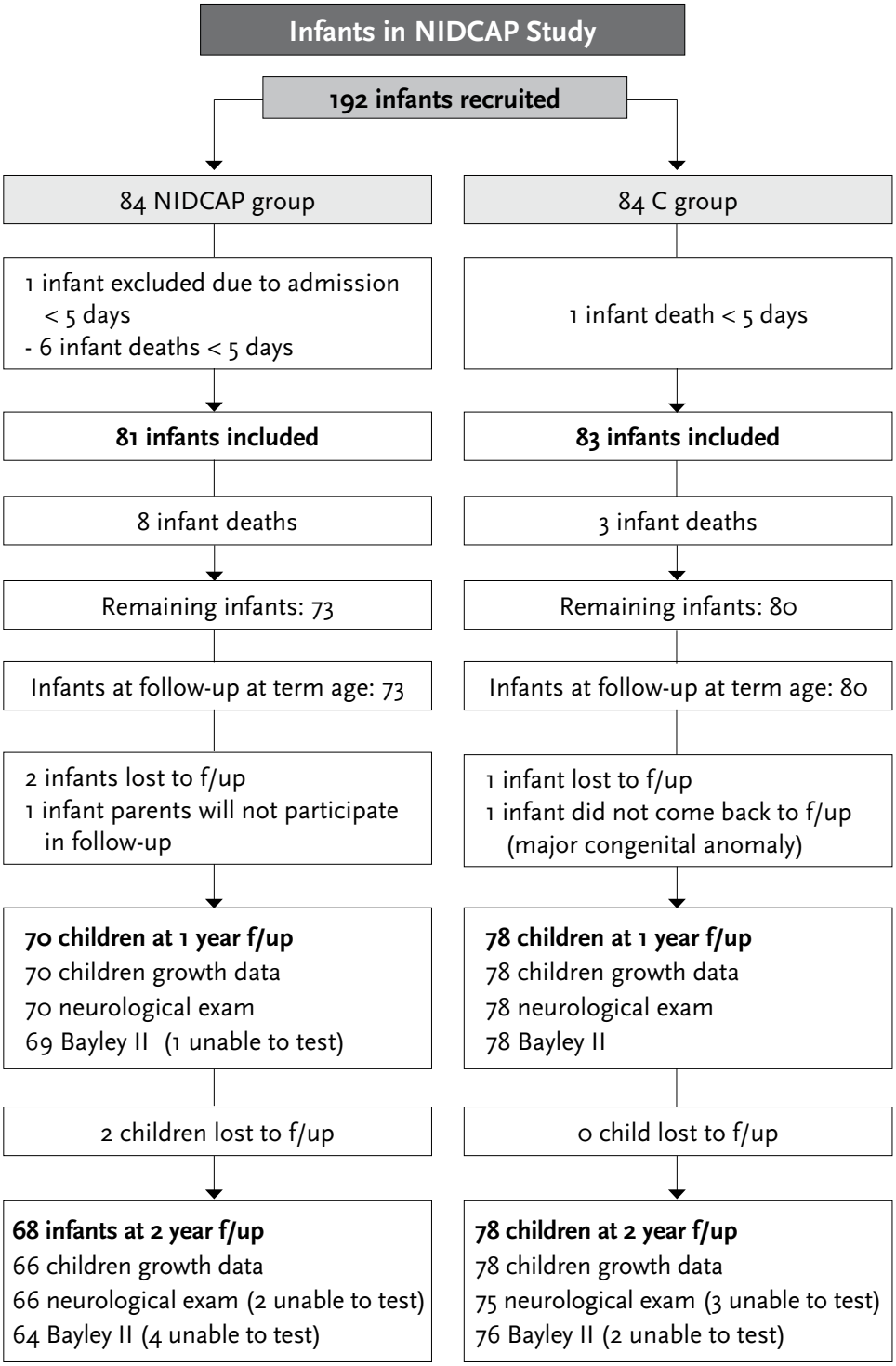
Infants in NIDCAP Study
192 infants recruited
84 NIDCAP group
84 C group
1 infant excluded due to admission < 5 days
- 6 infant deaths < 5 days
1 infant death < 5 days
81 infants included
83 infants included
8 infant deaths
3 infant deaths
Remaining infants: 73
Remaining infants: 80
Infants at follow-up at term age: 73
Infants at follow-up at term age: 80
2 infants lost to f/up
1 infant parents will not participate in follow-up
1 infant lost to f/up
1 infant did not come back to f/up (major congenital anomaly)
70 children at 1 year f/up
70 children growth data
70 neurological exam
69 Bayley II (1 unable to test)
78 children at 1 year f/up
78 children growth data
78 neurological exam
78 Bayley II
2 children lost to f/up
0 child lost to f/up
68 infants at 2 year f/up
66 children growth data
66 neurological exam (2 unable to test)
64 Bayley II (4 unable to test)
78 children at 2 year f/up
78 children growth data
75 neurological exam (3 unable to test)
76 Bayley II (2 unable to test)

Table 1. Infant medical background variables of children seen at 1 and 2 year follow-up

	NIDCAP n (%)	C n (%)	NIDCAP n (%)	C n (%)
	1 year		2 years	
Birth Characteristics	n=70	n=78	n=68	n=78
Gestational age mean in wks (sd) range	29.6 (1.5) 25.9-31.9	29.3 (1.6) 25.6-31.6	29.6 (1.6) 25.9-31.9	29.3 (1.6) 25.6-31.6
Birthweight mean in g, (sd) range	1263 (311) (655-1939)	1247 (340) (625-2060)	1260.8 (314.3) (655-1939)	1246.6 (339.6) (625-2060)
Male gender	41/70 (58.6)	40/78 (51.3)	41/68 (60.3)	40/78 (51.3)
SGA* SGA P* < 10 and P ≥ 3 SGA P < 3	13/70 (18.6) 2/70 (2.9)	10/78 (12.8) 4/78 (5.1)	13/68 (19.1) 2/68 (2.9)	10/78 (12.8) 4/78 (5.1)
Inborn	44/70 (62.9)	47/78 (60.3)	44/68 (64.7)	47/78 (60.3)
Apgar scores at 5 minutes median (range)	9.0 (4-10)	8.0 (4-10)	8.0 (4-10)	8.0 (4-10)
CRIB Score mean (sd)* Range	2.7 (2.9) 0-14	2.9 (2.9) 0-13	2.7 (2.9) 0-15	2.9 (3.0) 0-13
PDA* (indomethacin and/or surgery)	19/70 (27.1)	10/78 (12.8) ‡	19/68 (27.9)	10/78 (12.8) †

Data shown is n (%), unless otherwise indicated
Comparisons were done using chi-square test or t-tests where appropriate
* SGA: small for gestational age, P: percentile, CRIB: Clinical Risk Index for Babies, PDA: patent ductus arteriosus
† *p* value 0.03 at 1 year and 0.02 at 2 years; *p* value significance = < 0.05

Growth

There was no significant difference between the NIDCAP and C group in growth (weight in kilograms, height and head circumference in centimeters) at 1 or 2 years. When we calculated the SDS using the Dutch growth charts[23], there was again no difference between the 2 groups. As postnatal corticosteroids may influence growth, we corrected for days of postnatal steroids and then found no significant difference in growth SDS between the 2 groups (Table 3).

Table 2. Parental demographic background variables

	NIDCAP n (%)	C n (%)	NIDCAP n (%)	C n (%)
	1 year follow-up		2 year follow-up	
Maternal age	n=69	n=75	n=68*	n=75*
mean in years (sd)	31.3 (5.2)	32.9 (5.1)	32.3 (5.3)	33.9 (5.1)
Paternal age	n=67	n=74	n=66	n=74
mean in years (sd)	33.5 (5.7)	35.0 (5.6)	34.4 (5.6)	36.0 (5.6)
Mother Caucasian	55/69 (79.7)	65/74 (87.8)	54/68 (79.4)	65/74 (87.8)
Father Caucasian	52/68 (76.5)	58/74 (78.4)	51/67 (76.1)	58/74 (78.4)
Education level mother †				
low	23/67 (34.3)	19/74 (25.7)	22/66 (45.1)	19/74 (25.7)
intermediate	23/67 (34.3)	25/74 (33.8)	23/66 (32.4)	25/74 (33.8)
high	21/67 (31.3)	30/74 (40.5)	21/66 (22.5)	30/74 (40.5)
Education level father †				
low	16/64 (25.0)	15/73 (20.5)	15/63 (23.8)	15/73 (20.5)
intermediate	21/64 (32.8)	31/73 (42.5)	21/63 (33.3)	31/73 (42.5)
high	27/64 (42.2)	27/73 (37.0)	27/63 (42.9)	27/73 (37.0)

Data shown is n (%), unless otherwise indicated
Comparisons were done using chi-square test (for linear trend) or t-tests where appropriate
* Correct n is shown in table if there are missing values
† Low = vocational training, intermediate = high school, high = college/university

Table 3. Growth outcomes at 1 and 2 years CA

	1 year CA			2 years CA		
Growth outcomes	**NIDCAP**	**C**	***p* value**	**NIDCAP**	**C**	***p* value**
Weight	n=70	n=78		n=63*	n=78	
mean in kg, sd	9.26 (1.14)	9.44 (1.45)	0.40	12.0 (1.3)	12.3 (2.1)	0.32
SDS† (mean, sd)	-0.74 (1.10)	-0.59 (1.31)	0.43	-0.64 (0.98)	-0.48 (1.41)	0.42
Head circumference	n=70	n=77		n=66	n=77*	
mean in cm, sd	46.3 (1.9)	46.7 (1.8)	0.23	48.7 (1.6)	49.0 (1.9)	0.32
SDS† (mean, sd)	-0.26 (1.21)	0.05 (1.20)	0.13	-0.07 (0.94)	0.18 (1.18)	0.15
Length	n=70	n=78		n=64*	n=78	
mean in cm, sd	75.2 (2.4)	75.1 (3.4)	0.82	87.9 (3.3)	87.3 (4.1)	0.33
SDS† (mean, sd)	-0.33 (0.90)	-0.37 (1.23)	0.81	-0.19 (1.03)	-0.37 (1.19)	0.32

Comparisons were done using t-tests
* Correct n is shown in table if there are missing values
† SDS (standard deviation scores) according to Fredriks et al 2000[23]

Table 4. Mental and psychomotor development at 1 and 2 years CA

	NIDCAP n (%)	C n (%)		NIDCAP n (%)	C n (%)	
	1 year CA			2 years CA		
	n=69	n=78	*p* value	n=63†	n=76	*p* value
Age at test in months mean (sd) range	 12.2 (0.38) 10.9-13.5	 12.3 (0.57) 10.4-14.6	 0.97	 24.2 (0.37) 23.5-25.3	 24.1 (0.99) 19.3-26.0	 0.41
MDI mean (sd) range	100.7 (17.8) (55-145)	100.7 (17.7) (55-133)	0.99	99.1 (15.4) (55-132)	98.7 (16.6)‡ (66-140)	0.90
PDI mean (sd) range	97.3 (16.7) (55-134)	95.9 (16.3) (55-126)	0.60	89.1 (14.2) (55-123)	91.2 (11.7) (58-121)	0.35
MDI classification scores§ ≥ 85 70-84 ≤ 69	 60 (87.0) 6 (8.7) 3 (4.3)	 65 (83.3) 9 (11.6) 4 (5.1)	 0.60	 54 (85.7) 7 (11.1) 2 (3.2)	 59 (78.7)‡ 13 (17.3) 3 (4.0)	 0.35
PDI classification scores§ ≥ 85 70-84 ≤ 69	 58 (84.1) 4 (5.8) 7 (10.1)	 61 (78.2) 13 (16.7) 4 (5.1)	 0.93	 40 (63.5) 18 (28.6) 5 (7.9)	 52 (68.4) 21 (27.6) 3 (4.0)	 0.38

Data shown is n (%), unless otherwise indicated
Comparisons were done using chi-square test (for linear trend) or t-tests where appropriate
* *p* value significance = < 0.05
† One infant in NIDCAP group had only PDI score and 1 infant in NIDCAP group had only MDI score which changed the total n from 64 to 63 at 2 years
‡ One child in the C group had only a PDI score
§ ≥ 85= normal or above normal, 70-84=mildly delayed, ≤ 69=significantly delayed

Developmental outcomes

At one year of age 147 (NIDCAP: 69, C: 78) of the 148 children seen at follow-up and at 2 years of age 140 (NIDCAP: 64, C: 76) of the 146 children seen at follow-up were tested with the Bayley Scales-II-NL. There was no significant difference in the mean age of all children assessed at the 1 and 2 year follow-up. We were not able to obtain developmental scores at 1 year of age for one child in the NIDCAP group and at 2 years of age for 5 children in the NIDCAP group and 2 children in the C group because they were uncooperative. There was no difference in developmental outcomes at 1 and 2 years between the two groups (Table 4).

Neurological Outcomes and combined scores

There were 148 (NIDCAP: 70, C: 78) children assessed with a neurological exam at 1 year and 141 (NIDCAP: 66, C: 75) children at 2 years. Five children (NIDCAP: 2, C: 3) could not be tested at 2 years because they were uncooperative. There was no significant difference between the NIDCAP and C group in neuromotor development at 1 and 2 years or in the combined developmental and neurological scores (Table 5).

Table 5. Neurological outcomes and combined score of neurological outcomes, MDI and PDI at 1 and 2 years CA

	1 year CA				**2 years CA**		
	NIDCAP n (%)	**C n (%)**			**NIDCAP n (%)**	**C n (%)**	
	Neurological Outcome*				Neurological Outcome*		
	n=70	n=78	*p* value		n=66	n=75	*p* value
- N†	52 (74.3)	53 (67.9)	0.60	- N	52 (78.8)	54 (72.0)	0.99
- MA	12 (17.1)	19 (24.4)		- MA	5 (7.6)	16 (21.3)	
- DA	6 (8.6)	6 (7.7)		- DA	9 (13.6)	5 (6.7)	
	Combined neurological score MDI and PDI				Combined neurological score MDI and PDI‡		
	n=70	n=78			n=68	n=71	
- N†	44 (62.9)	44 (56.4)	0.78	- N	34 (50.0)	37 (47.4)	0.76
- MA	14 (20.0)	23 (29.5)		- MA	21 (30.9)	31 (39.7)	
- DA	12 (17.1)	11 (14.1)		- DA	13 (19.1)	10 (12.8)	

Comparisons were done using chi-square test (for linear trend) where appropriate

* neurological exam according to Touwen at 1 year and Hempel at 2 years

† N=normal, MA=mildly abnormal, DA=definitely abnormal

‡ one child from DC group and 2 children from C group's combined scores were derived from the PDI and MDI

Because there was a wide range in length of stay in the participating hospitals, we carried out a linear regression analysis to see if the number of days infants received the NIDCAP intervention influenced the neurological outcome at 1 and 2 years by testing if there was an interaction effect between the intervention duration and the 2 treatment groups. We found no significant effect on neurological outcome at 1 year (p=0.97) or 2 years (p=0.30) of age or on the combined neurological and developmental scores at 1 (p=0.27) and 2 years (p=0.73).

Discussion

In this study examining the effects of NIDCAP compared to basic developmental care on infants born < 32 weeks GA, we have been unable to show any differences in growth, neurological and developmental outcomes at 1 and 2 years of age. The percentage of lost to follow-up in this large RCT was low. The assessors were blinded to the treatment group the children participated in and the neurological outcome was assessed using a standardized neurological examination.

Few studies have examined short-term neurodevelopmental outcomes of NIDCAP and the results of these studies are conflicting[15]. Three studies by Als et al showed an effect of NIDCAP on Bayley Developmental Index scores up to 9 months of age. The first study examined the effect of NIDCAP on 16 (E: 8, C: 8) infants born < 28 weeks GA with a birth weight < 1250 grams and found a significant difference in PDI and MDI scores at 3, 6 and 9 months in favor of the NIDCAP group as compared to the control group[10]. A second study of 38 infants weighing less than 1250 grams and born < 30 weeks GA also showed improved PDI and MDI scores at 9 months in the NIDCAP group[24]. The most recent study of 30 low-risk preterm infants born between 28-33 weeks GA showed significantly better PDI and MDI developmental scores in the NIDCAP group at 9 months, however only 24 of the 30 infants returned to follow-up at 9 months[14]. These studies have not reported follow-up beyond 9 months of age so it is difficult to compare our results.

A few studies report follow-up at and beyond 1 year of age. Ariagno et al reported no difference at 1 and 2 years in the Bayley scores between the NIDCAP and control group, however there was a large loss to follow-up, as only 23 of the original 35 infants in the study were tested[13]. Kleberg et al showed higher MDI scores in 9 infants who received NIDCAP care as compared to 11 control infants at 12 months; however the PDI scores were not significantly different[11]. This study was based on an RCT of 25 infants born < 32 weeks with a need for ventilatory support 24 hours after birth[25]. A second follow-up study at 3 years of age based on a non-randomized, historical design trial of 42 infants showed no difference in the developmen-

tal quotients (DQ) according to the Griffiths Developmental Scale between the NIDCAP and control group. They did show a significant difference in mother-child interaction during videotaped structured and free play[12]. The preschool outcome of the RCT by Westrup showed no difference in cognition, but a possible positive impact of NIDCAP on behavior and is the only RCT to date to have published longer follow-up data[26]. They did state that because the recruitment was less than half of the anticipated subjects, their conclusions should be interpreted with caution[26]. All the above mentioned studies had relatively small sample sizes.

Another approach recommended would be to use qualitative research and benchmarking as well as RCT's, so that not only medical and developmental outcomes will be assessed but also additional information concerning the experience of parents and infants as well as staff when implementing a developmental care program[27]. Previous studies as well as our study have reported that parents and the nursing team were positive about the NIDCAP approach and felt that it contributed to the wellbeing of the infant [28-31].

There are a few factors to take into account in our study. The length of stay of the infants in this trial differed widely with previous NIDCAP studies as a result of the Dutch system to transfer infants to regional hospitals once stabilized. Because of this range of days of hospitalization, we examined if the number of days infants had received NIDCAP care influenced neurological and developmental outcomes at 1 and 2 years, but found no interaction effect between length of intervention and follow-up outcome.

Another consideration is the significantly higher incidence of PDA requiring medication or medication and ligation in the infants in the NIDCAP group. When we corrected for incidence of PDA, we found no significant difference in either 1 year neurological outcome (p=0.71) and combined scores (p=0.89) or 2 year neurological outcome (p=0.98) and combined scores (p=0.67).

We conclude that providing NIDCAP to preterm infants born < 32 weeks gestation in a system with regionalized NICU's and early transfer to local hospitals has no effect on their neurodevelopment or growth at 1 and 2 years of age. Perhaps follow-up studies at school age may be able to detect more subtle differences in cognition.

We had hoped that by providing parents with the tools to understand their infant's behavior and how to provide support, they would have been able to continue providing this individual approach when interacting with their infant once transferred out of the NICU, which would then have a continuing effect on their infant. It

appears, based on our results, that both infants and parents require longer periods of ongoing support in order to show any effect.

Recommendations for further research would be to continue the NIDCAP approach in the regional hospitals once infants are transferred to see if the effect would be greater. This however was beyond the scope of our present study. In addition, early intervention programs in which parents are supported once their infant is discharged home may help to build on the support and knowledge parents have received in the NICU and guide them in responding to their infants quickly changing developmental needs.

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CHAPTER 7

General Discussion

In this thesis we evaluated the effect of basic developmental care and the comprehensive NIDCAP developmental care program in preterm infants < 32 weeks gestational age born between April 2000 and August 2004 on short-term morbidity, growth and neurodevelopment at term age, as well as growth and neurodevelopment at 1 and 2 years corrected age.

Pilot study

We started with a pilot study in 1999 of a short-term, hospital based intervention with parents of preterm infants < 32 weeks in the NICU with the goal of positively influencing parental knowledge and responsiveness to premature infant signals and behavioral cues. This was a phase-lag study in which the control group parents were first included. They completed a questionnaire concerning confidence in caregiving when their child was 1 week old and again 2 weeks later. Once the inclusion of the control group parents was completed we began to include parents in the intervention group. Starting after the first week of their infant's birth, parents were given 4 lessons over a period of 2 weeks concerning preterm infant behavior with the emphasis on understanding their own infant's behavior. They were asked to complete questionnaires on knowledge of preterm infant behavior and also confidence in caregiving before and at the end of the intervention. The study showed that the instructions significantly increased their knowledge of preterm infant behavior, and while their level of confidence in caregiving improved, the difference was not significant. There was no improvement in confidence in caregiving found in the control group parents. Very few fathers in the intervention group completed the lessons and questionnaires, and even though mothers claimed to share what they had learned with their spouse, this "transferring" of knowledge was not measurable because most fathers did not complete the questionnaires after week 3. Interviews of parents after the intervention indicated that they appreciated having the lessons and being able to better understand their infant's behavior, as well as the support provided by a developmental specialist. Parents in the control group expressed the need for more knowledge of preterm infant behavior.

While this was a small study with only 10 sets of parents and 22 infants, it did indicate that it is feasible to start an intervention program with parents early on in the NICU period. The pilot study also raised the level of interest in developmental care in the neonatal team. We concluded that a longer, more intensive program with a larger sample size and finding ways of incorporating more participation from fathers was necessary.

Randomized Controlled Trial: Phase 1

In Phase 1, we examined the effect of basic developmental care, which we defined as the use of standardized incubator covers and nests and positioning aids, on short and long-term outcomes up to 2 years of age corrected for prematurity. We hypothesized that by providing protection from the environment with incubator covers and boundaries through the use of nesting, we would decrease the infants' stress and physiological instability, which would result in positive short-term outcomes. There was a wide range of the number of days infants spent in the participating NICU, which reflected days of intervention given. We hypothesized that infants receiving basic developmental care for a longer period would show better results in term age outcomes. However, we found no effect on short-term morbidity, growth or neurological outcomes up to term age, even when we corrected for length of stay.

We were able to report that there were no detrimental effects of basic developmental care, which was a concern of the neonatal staff when we first proposed this trial, as the use of incubator covers and nests for infants was a new concept. At that time, it was felt that perhaps it would be more difficult to observe the infants and that having an infant lie in a softly flexed position might alter the effect of ventilation. In fact, the intervention infants required less days of ventilation and oxygen although this difference was not significant. In addition two secondary outcomes (postnatal steroids and requiring oxygen after 28 days of life) while not reaching the level of significance, suggested that there may be an advantage of developmental care on pulmonary morbidity.

We did find a positive effect on psychomotor development (PDI) at 1 year CA, but this improvement did not continue at 2 years and we found no significant effect on mental development (MDI) at 1 and 2 years CA. We also found more infants in the control group with definitely abnormal neurological outcome, but since it was not statistically significant we could only conclude that developmental care may have a positive influence on neurological outcome at 1 and 2 years.

We could find no other study examining basic developmental care on neurodevelopment, so were unable to compare our results with other studies. Our findings did provide an answer to the question of whether a basic developmental care program, which does not entail major funding to implement, has an effect on development. We concluded that while it did have a positive effect on psychomotor development at 1 year of age, these effects did not continue up to 2 years of age.

Randomized Controlled Trial: Phase 2

In Phase 2, we examined the effect of the comprehensive NIDCAP program on short and long-term outcomes up to 2 years of age corrected for prematurity. This consisted of formal behavioral observations of the infant, individual care plans based on these observations and support to the parents in understanding and responding to their child's behavior. After inclusion in phase 1 was completed and before starting inclusion of infants into phase 2, we spent 2 months providing extra lessons to a team of nurses that would be primarily caring for the NIDCAP infants. This was done to try to prevent as much contamination of the control group as possible. There were 5 nurses in the group who were completing NIDCAP training and who became certified and were able to assist under guidance from the developmental psychologist in carrying out NIDCAP observations and supporting the care team, infants and parents.

Because we only found a transient significant positive effect of basic developmental care on psychomotor development at 1 year of age, we hypothesized that a more intensive, individualized developmental care program such as the NIDCAP program would show more improvement. This however was not the case and in fact the developmental outcomes and growth at 1 and 2 years CA did not much differ from the outcomes obtained in the first RCT, with the exception of the drop in PDI between 1 and 2 years of age in the phase 2 children.

There were significantly more infants in the NIDCAP group with PDA requiring medication or medication and surgical ligation. This was unexpected as the infants were randomized precisely in the same manner as in phase 1. As PDA usually develops in the first days of life we did not feel that the intervention played a significant role in the incidence of PDA, but realized that it could affect some of our short-term primary outcomes. There was no difference in days of phototherapy between the 2 groups, so that could not have affected the incidence of PDA. When we carried out a Kaplan Meier analysis we did indeed find that PDA had negatively affected the respiratory outcomes of the NIDCAP infants as after the analysis they required significantly less days (expressed in median) of CPAP and total ventilatory support as compared to the control infants.

We found no positive effects at 1 and 2 years of age on mental or psychomotor development or neurological outcomes in the NIDCAP group as compared to the control group. While the difference in developmental scores between the two groups was not significant, both groups' mean PDI scores were lower at 2 years

when compared to the 1 year PDI and the NIDCAP group was more than a half standard deviation lower. It should be noted that even with this drop all the mean PDI and MDI scores of both groups were classified in the normal range of development. The neurological outcomes were comparable at 1 year of age, but at 2 years of age, the NIDCAP group had a higher percentage of children with scores defined as definitely abnormal, however this difference was not significant.

Because of these outcomes, we concluded that NIDCAP had no effect on neurological outcome or development at 1 and 2 years of age. In addition, we found no effect on growth at 1 and 2 years of age.

Behavior at 1 year of age

In questionnaires completed by parents when children were 1 year of corrected age, children in the basic developmental care group had significantly higher behavior scores on the total competence domain and the competence subscale mastery motivation of the Infant–Toddler Social and Emotional Assessment (ITSEA) questionnaire, meaning that the children showed more curiosity, persistence, obedience and enjoyment with small accomplishments. No significant effects were found on problem behavior or parenting stress. We concluded that introducing a basic form of developmental care in the neonatal intensive care unit has a positive influence on the child's competence behavior at 1 year of age[1].

When parents completed questionnaires concerning their child's behavior and temperament at 1 year corrected age, the children in the NIDCAP group tended to show more social relatedness behavior than the children in the control group, especially when their length of admission was more than 1.5 months, which would reflect how long the NIDCAP intervention was given. In addition parents in the NIDCAP group reported more positive experiences and effects on the well-being of their infant during admission[2]. Further research when the children are school age will show if these effects remain.

Comparison to previous NIDCAP studies

We were not able to duplicate the findings of previous NIDCAP studies even with our large sample size. When we compared our Phase 2 RCT to other NIDCAP development care studies, our total days of intensive care for both groups was much less, which could be due to a difference in the population and care provided, or simply a difference in their definition of intensive care[3-6]. Days of intensive care were also less when we compared our outcome with a study from another NICU in

the Netherlands, however they did not provide a clear definition or criteria for days of intensive care[7] (Table 1).

Contrary to the inclusion criteria of many NIDCAP studies, we chose the inclusion criteria of infants < 32 weeks gestational age because we know from previous studies that infants < 32 weeks GA are vulnerable and have an increased risk of developmental problems[8,9]. This was different than other NIDCAP studies previously published in which the inclusion age was between < 28 and < 30 weeks and infants required some form of ventilation in the first 48 hours. Westrup's study also included infants < 32 weeks GA but had some restrictions on respiratory support in their inclusion criteria[10]. We did not make any restrictions concerning ventilation because we hypothesized that all infants < 32 weeks GA could benefit from this intervention.

We did not find significant differences in follow-up neurodevelopmental outcomes as reported in other NIDCAP studies[11-13]. In our study we chose 2 points of follow-up at 1 and 2 years corrected age as we wanted to be able to compare our results with previous NIDCAP studies. There have been questions raised, however, concerning the poor predictive value of the Bayley Scales of Infant Development as one large study reported that a subnormal MDI score at 20 months in ELBW infants is not predictive of a subnormal cognitive functioning at school age[14]. This could mean that decisions of whether to continue with an intervention in the NICU based on 1 and 2 year outcomes may not be appropriate, as effects may not be seen until the child is older.

To date only the Swedish studies have published developmental outcomes beyond 2 years, reporting positive effects on behavior and mother-child interaction at 3 years of age from their phase-lag study[12] and results at preschool age from their RCT which showed no difference in cognition and a possible positive effect on behavior in the NIDCAP group. Because the power was low and recruitment was half of what they had expected, caution was suggested when interpreting their results[12,15] (Table 1). It is therefore important that our cohort is followed to at least school age to see if there are any effects only evident as the children mature.

Meta-analysis

A Cochrane meta-analysis of NIDCAP trials found 3 studies with significantly fewer days of ventilation[4,10,16], 3 studies with no differences in days of oxygen[3,4,13] and one study with fewer days CPAP and a lower age for oxygen withdrawal[10], but concluded that results on respiratory support should be viewed with caution due to significant heterogeneity among the sites[17]. It should be noted that they did not

Table 1. NIDCAP studies published from 2000

Author and year	Design	Participant's	N	Intervention	Main outcomes
Westrup 2000	RCT	GA < 32 weeks Requiring ventilatory assistance at 24 hours of life	E=12 C=13	Caregiving by NIDCAP trained personnel and weekly observations until 36 weeks post-conception	Days CPAP PCA at O2 withdrawal BPD
Kleberg 2000	Phase lag	Birthweight ≤ 1500 g GA < 30 weeks Ventilated within first 3 hours and > 24 hours of first 48 hours	E=21 C=21	Caregiving by NIDCAP trained personnel starting within 3 days after birth and continuing until discharge. Control group was born prior to NIDCAP implementation.	No difference in DQ at 3 years Subscale hearing-speech Behavior scale Communication in "mother- infant" scale (ns)
Kleberg 2002	RCT	GA < 32 weeks Requiring ventilatory assistance by 24 hours of life	E=11 C=9	Follow-up of surviving participants of RCT by Westrup, 2000	MDI at 12 months
Als 2003	RCT	Birthweight < 1250 g GA < 28 weeks Ventilated within first 3 hours and > 24 hours of first 48 hours	E=45 C=47	3-center trial Caregiving by NIDCAP trained personnel until discharge	Ventilation days, days ICU and LOS Weight at 2 wk PCA Days parenteral feeding PCA at discharge, hospital costs Weight at 42 wk PCA, HC at 42 wks PCA
Als 2004	RCT	GA 28+ 4 – 33+3 weeks < 72 hours ventilation including CPAP	E=16 C=14	Caregiving by NIDCAP trained personnel until discharge	2 APIB system scores at term age 6 Prechtl summary scores and total Prechtl score at term age MDI and PDI at 9 months BRS scores at 9 months
Westrup 2004	RCT	GA < 32 weeks Requiring ventilatory assistance by 24 hours of life	E=11 C=15	Follow-up at 69.9 months of surviving participants of RCT including 4 C infants who originally declined to participate in study by Westrup, 2000	OR for surviving with normal behavior after correcting for group differences

All outcomes are significant in favor of the intervention group unless otherwise indicated.
E = experimental group, C =control group, GA= gestational age, PCA=postconceptional age, BPD=bronchopulmonary dysplasia, ICU-Intensive Care Unit, HC= head circumference, DQ= developmental quotient according to Griffiths' Developmental Scale II, MDI= Mental Development Index, PDI =Psychomotor Development Index, BRS= Behavioral Rating Score, LOS= length of stay of total hospitalization, OR = odds ratio

include the 3-center trial by Als[6] in this meta-analysis because they felt that there was too much heterogeneity between the 3 sites. They also reported that NIDCAP had a significant effect on moderate-severe chronic lung disease and incidence of necrotizing enterocolitis, no effect on length of hospitalization and no effect on feeding and growth in infants surviving to 9 months. The effects on neurodevelopment were conflicting with a significant difference in Bayley MDI at 12 months in a meta-analysis of 2 trials[11,18], but no difference in PDI. They found some positive evidence of the long-term effect of NIDCAP at 5 years on behavior and movement but no effect on cognition. The authors' final conclusion was that while there was limited benefit of developmental care and no major harmful effects, that the outcomes were conflicting and further studies were recommended[17].

Comparison of Phase 1 and 2

We then looked at the outcomes from both phases 1 and 2 of our study. Even though they were 2 separate RCT's, the level of developmental care given was progressive in each phase, as we started in phase 1 with a control group with no DC and then in phase 2 a control group of basic DC (nests and incubator covers), which was comparable to the DC intervention group in phase 1. We hypothesized that if the infant characteristics in both phases were comparable, then there would be an increasing improvement in outcomes with a more pronounced improvement seen between the control group of phase 1 who received no elements of developmental care and the intervention group of phase 2 who received the complete NIDCAP intervention. Comparing these 2 groups would be the equivalent of a phase-lag design.

However we decided not to perform such an comparison based on the following methodological reasons. The first reason was that these were 2 separate RCT's carried out over a period of 4 years in which clinical changes occurred between the implementation of the 2 phases. That could mean that the C group in phase 1 possibly had different medical care approaches than the NIDCAP intervention group in phase 2. The second reason was that although various infant characteristics such as birthweight, gestational age, Apgar scores at 5 minutes, CRIB scores and inborn at birth were comparable between the C group in phase 1 and the NIDCAP group in phase 2, there were some differences in infant characteristics between these 2 groups. There were more twins and SGA infants born in the NIDCAP group phase 2, and both characteristics can have a negative influence on developmental outcome. On the other hand, there were more males born and a higher percentage of RDS in the C group of phase 1 than in the NIDCAP group in phase 2 which could lead to poorer outcomes in the C group and an advantage for the outcomes

in the NIDCAP intervention group. We decided not to correct for these differences between the groups with statistical methods and to hold on to the original design of the study as 2 separate RCT's.

Strengths and limitations of the study

This was a large randomized controlled trial with a low percentage of lost to follow-up. In the phase 1 RCT there could be no blinding of the intervention as the developmental care infants had incubator covers and nesting, however it did make it possible to ensure a strict control group. The amount of respiratory support given to an infant was decided upon by several neonatologists so was not influenced by the study group the infant participated in. Discharge from the intensive care was based on two criteria: the infant required no mechanical ventilation and/or CPAP for 24 hours and weighed at least 1000 grams, so days of IC could also not be influenced by group participation. The assessors for both the neurological and developmental outcomes were blinded to the treatment group in which the children participated. The neurological outcomes were obtained using a standardized neurological examination and the Bayley Developmental Index scores were scored using the Dutch norms[19].

Length of the Intervention

The trial was carried out in a tertiary NICU in two locations. Both locations were able to provide intensive care as well as intermediate care, however the length of stay in one location was longer as most infants were not transferred to regional hospitals but discharged from the NICU nursery to home and only a small percentage of the infants in the other location stayed until discharge to home. This meant that there was a wide range in length of stay in the participating NICU's, which mainly reflected the period of hospitalization in the intermediate care unit. We had hypothesized that an increase in days that infants spent in the two participating locations and thereby more days of developmental care would positively affect growth and neuromotor outcomes. This however was not the case as was shown via an interaction analysis of the intervention duration and the term age outcomes.

It may be that there were not enough infants who received developmental care until discharge to home to show an effect, however we also did not find site differences in the IC days or days of ventilatory support, which would not be influenced by total length of stay. These results were disappointing and we can only conclude

that in a subsequent trial the intervention should continue when the infants are transferred to regional hospitals. This was beyond the scope of this study as our main goal was to look at the effect of developmental care in the Dutch neonatal system with centralization of perinatal care.

It could also be that an early intervention program provided only in the period of hospitalization of the preterm infant is not enough. Perhaps a subsequent study should be carried out in which the NIDCAP program is implemented along with another program such as the Infant Behavioral and Assessment Intervention Program (IBAIP)[20]. This is an early intervention program based on the NIDCAP approach which provides support to parents and their infant up to 6 months corrected age. This would be the logical continuation of an approach that would help parents in the difficult first months at home with their still fragile infant. It would also help to build on the support and knowledge parents received in the NICU and guide them in responding to their infant's quickly changing developmental needs.

Central Nervous System

We found no significant differences in IVH or PVL between the intervention and control groups in both RCT's. It is of course possible that some infants had already experienced an IVH prenatally or before entering the study as inclusion was allowed up to 48 hours after birth. It was not feasible to include all infants on day one as parents needed time to decide whether to participate in the study. It is possible that by decreasing the stress and physiological instability the infant experienced through providing developmental care may have helped to prevent more cerebral damage, but this was not something we were able to measure. A study by Wielenga showed a possible decrease in severe cerebral damage in favor of the NIDCAP group but stated that the results should be interpreted with caution as it was a phase-lag study and there were some differences between the 2 groups[21]. Als et al have published outcomes on MRI studies showing positive effects of NIDCAP on the developing brain, however it was a relatively small number of infants and not all infants underwent an MRI at term age[13]. It was unfortunately not feasible at the time of our study to perform MRI's at term age, however it is something that perhaps could be studied in future trials.

Practical considerations

At the onset of our study, little was known about developmental care and implementation had not yet begun to occur in our NICU's. This made it easier to have a pure control group in Phase 1 with no covers or nesting as that was the standard care at that time. As the use of these materials was very visible, it made it easy to prevent contamination of the control group. In Phase 2 both groups appeared much the same, as both were given basic developmental care which consisted of incubator covers and nesting, however the NIDCAP group infants were formally observed every 7-10 days and were given individualized developmental care plans based on these observations. It is possible to conceive that there was more of a chance for contamination as the parents and nurses of the control group infants would be able to see some of the interventions being carried out and apply them to the infants in the control group. We did feel that since it is an individual approach, the argument could be made that what works for one infant may not apply for another, however general methods of support during caregiving could conceivably be copied.

Both intervention and control infants were cared for in the same NICU nursery, which can create a greater chance for contamination. However Westrup's study had to be ended before inclusion was completed precisely because the infants were cared for in different rooms and it became harder to motivate parents and nurses to continue including infants in the control group as the difference in care was so obvious[10]. At the time we did not have the capacity to use two separate rooms and it ended up being to our advantage as we were able to include the number of infants required by the power analysis. Having all the participating infants in the same nursery appeared to actually make it easier for the parents as there was a wide variety of infants in the room, including older infants who did not participate in the study.

One way we tried to diminish the effect of contamination was to give extra training to the group of nurses who primarily cared for the infants in the NIDCAP group. This also permitted more continuation of the care and allowed the nurses to become more familiar with the infants' and parents' needs. There were only 5 nurses that underwent the formal NIDCAP training, the rest of the caregiving team were given extra instructions in caregiving based on the NIDCAP approach. As recommendations have been made to train at least 10% of the staff in order to generate a change it is possible that more formally trained nurses are necessary to have an effect.

Methods of studying developmental care

Perhaps a randomized controlled trial is not necessarily the best method to measure the effects of a complicated psychological intervention such as the NIDCAP program. It is much more difficult to measure than a study of the effect of a new medication. In these studies, often double blind, the infant either receives the medication or not with less chance of contamination and outcomes are quantifiable and therefore easier to measure. There have been recommendations made for future research of developmental care such as randomization by site instead of patients, evaluating neurobiological mechanisms or using other approaches to developmental care research such as qualitative research and continuous quality benchmarking as an alternative to RCT's[22]. It has been proposed that these approaches may be a more effective way of examining the effects developmental care has on infants in the NICU nursery[23]. However each approach has some methodological restrictions. For example, a trial in which sites are randomized instead of patients would be difficult to implement as there would be too many differences in medical and nursing practices at each site. It may be that a combination of outcomes based on various research methods will be needed to produce a body of evidence of the effects of developmental care.

Developmental care research in the Netherlands

Since we began our study there have been 2 other neonatal centers in the Netherlands carrying out research on NIDCAP developmental care. A phase-lag study of 51 infants < 30 weeks was carried out in the AMC/Emma Children's Hospital in Amsterdam in which first a group of 26 infants received conventional care, followed by a group of infants who received NIDCAP care. They found a decreased risk for more severe cerebral damage in the NIDCAP group after correcting for neonatal differences in the groups (birthweight, head circumference, incidence of twins, incidence of pneumonia) but did comment that these findings should be interpreted with caution[21]. In addition, parents of the NIDCAP group infants reported significantly more satisfaction in caregiving than the parents of the conventional care infants[24]. The neonatal department of the Erasmus-MC Sophia Children's Hospital in Rotterdam is currently carrying out an implementation research trial in which the effect of the implementation of the NIDCAP program on staff as well as parental stress is being studied. A pilot study carried out to evaluate parental stress in the NICU showed the following factors caused stress in parents: health status of the infant, parental role alteration, staff behaviors and communication and equipment and sound [25]. They are now in the process of completing their study

of providing NIDCAP for infants born ≤ 30 weeks. Once all results are published, we will be able to have a clearer view of the effect of implementing NIDCAP in the Dutch neonatal system.

Parents

One of the effects of the NIDCAP intervention was that fathers were encouraged to participate in the caregiving of their infant. This was a recommendation we made after our pilot study findings because fathers stated that they wanted to become more involved in their child's care and acquire more knowledge of preterm infant behavior[26]. We found that fathers of infants in the NIDCAP group exhibited more stress than fathers of infants in the control group and concluded that this was perhaps because they were more involved in their child's care, so would not be able to maintain the emotional distance that they would have if not so involved in the caregiving[27]. It is therefore important to not only find ways of including fathers in the caregiving in future programs but find ways of providing them with support.

Both parents and the nursing team were positive about NIDCAP and the nurses expressed an interest in receiving more developmental care in-services and bedside support[28]. This finding has been reported in previous trials as well as our study[24,29]. As NIDCAP is a humane way of caring for infants and does no harm[30], it is important that the wishes of parents and nurses should also be taken into consideration when deciding whether to implement this approach to caregiving. In a study of mothers of infants in the NIDCAP group, the mothers perceived more closeness to their infants at 36 weeks post menstrual age (PMA) than did the control mothers and rated the staff's ability to support them in their role as a mother somewhat higher. They also expressed more anxiety than did the control group mothers which was similar to our findings of fathers of the NIDCAP infants. Kleberg suggests that the reason may be that the mothers in the NIDCAP group had already bonded to their infants during the hospital stay[31]. We felt also that perhaps fathers were more involved in their infant's care and this raised their level of stress.

Developmental care in NICU's in the Netherlands

There has been an increasing centralization of perinatal care in the Netherlands, with a twofold increase in the number of very preterm infants being born in tertiary centers[9,32,33]. Infants are often transferred from the neonatal centers to regional hospitals with intermediate care once stable enough to be discharged from the

intensive care. This policy is used in order to ensure sufficient intensive care beds are available for new admissions but may also impact any programs implemented in the NICU, as infants may be transferred out within weeks after birth. Because this may directly affect outcomes of these early intervention programs in the NICU, the importance of a continuation of such programs once the infant is transferred to a regional hospital should be emphasized.

Conclusions

Based on our findings the following conclusions can be made concerning the implementation of developmental care and with emphasis on the NIDCAP developmental care program.

Basic developmental care has a positive effect on psychomotor development at 1 year of age in children born < 32 weeks. Since it is fairly inexpensive and not time consuming to implement, NICU nurseries should at least implement basic developmental care.

It is possible that the NIDCAP intervention was not provided long enough to be able to make any final conclusions concerning outcome effects. A subsequent study is needed involving not only the neonatal centers but also the regional hospitals with intermediate care since infants may be transferred to them within weeks after birth.

In addition, early intervention programs provided only in the period of hospitalization of the preterm infant are possibly not enough to produce results and that a subsequent study should be carried out in which the NIDCAP program is implemented along with a home-based intervention for parents and infants when they are discharged from the hospital.

We have examined the effects of developmental care in the NICU in the Dutch neonatal system of centralized perinatal care and hope that we have been able to answer some of the questions posed back when developmental care was first introduced in the Netherlands. However we feel that more research is warranted before a definite conclusion can be made concerning the effect of developmental care on preterm infants and families.

Recommendations for future research

Based on our conclusions, recommendations for further studies are:

1. A follow-up study at school age of the infants from our 2 RCT's to see if there are any later effects of the intervention and ideally continuing to follow these children as they mature; as this is a large cohort, they may reveal answers to long term effects of prematurity.
2. Examine the effect of developmental care provided not only in the neonatal centers but also in the regional hospitals in order to see if a longer intervention has an effect on outcomes.
3. Initiate a phase 3 study in which the NIDCAP intervention in the neonatal nursery is combined with an intervention program once infants are discharged to home to see if this continuing support of infants and families will show improved outcomes.
4. Measure the effect of developmental care on younger, sicker preterm infants such as ventilated infants born < 30 weeks GA to compare results with previous NIDCAP studies and to see if the effect is greater.
5. A developmental care study in which the biological effect on the brain such as in MRI studies or other quantifiable biological stress measurements are used to measure outcomes.

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Summary

This thesis examines the effect of a developmental care program in a tertiary NICU in 2 locations in the Netherlands on preterm infants born < 32 weeks gestational age.

Chapter 1. Introduction

Chapter 1 describes the incidence of preterm birth and risks associated with prematurity as well as the impact of the NICU on the infant and family. Research on the sensory development of the preterm infant have shown that many of the environmental factors and care practices in the NICU have a significant impact on infant sensory development. Developmental care programs have been developed to support the infant and family during their stay in the Neonatal Intensive Care Unit (NICU) with the premise that reducing the stress the infant experiences in the NICU and supporting the infant's development may have a positive impact on outcomes. The NIDCAP (Newborn Individualized Developmental Care and Assessment Program) is a comprehensive approach in which caregiving is based on the individual behavior of the infant. Developmental care is a fairly new concept in the Netherlands with little known about its effect in the neonatal system in the Netherlands where there is a centralization of perinatal care. To that aim, we carried out 2 consecutive randomized controlled trials to examine the effect of a basic development care program and the comprehensive NIDCAP program on short and long term growth, morbidity and neurodevelopment of preterm infants born < 32 weeks gestational age.

Chapter 2. Hospital based intervention with parents and their preterm infants

Chapter 2 describes a short-term, hospital based intervention study with 10 sets of parents and their preterm infants < 32 weeks in the NICU. This was a phase-lag pilot study in which parents in the intervention group were instructed in preterm infant behavior with the goal of increasing their responsiveness to their infant and therefore their confidence in caregiving. While the lessons significantly increased their knowledge of premature infant behavior, their level of confidence in caregiving increased but not significantly. Parents in the control group who did not receive the instructions showed no increase in confidence in caregiving. While no large effect was found, it did indicate that it is feasible to start an intervention program with parents early on in the NICU period. We concluded that a longer, more intensive program with a larger sample size was necessary.

Chapter 3. Short-term effects of Basic Developmental Care

In Chapter 3 we examined the effects of basic developmental care (DC), which we de-fined as the use of incubator covers and positioning aids, on short term morbidity, growth and neurodevelopmental outcomes to term age in preterm infants born < 32 weeks gestational age. 192 infants were recruited and a total of 179 infants (DC=91, C=88) met inclusion criteria. In-hospital mortality was 12/91 (13.2%) in the DC group and 8/88 (9.1%) in the C group. Ten (DC=3, C=7) infants were lost to follow-up. There was no significant difference in the number of days of respiratory support, number of intensive care days, short-term growth or neuromotor developmental outcome at term age between the DC and C groups. Duration of the intervention, whether only during the intensive care period or until hospital discharge, had no significant effect on outcome. We concluded that providing basic developmental care in the NICU has no effect on short-term physical and neurological outcomes in infants born < 32 weeks GA.

Chapter 4. Effect of Basic Developmental Care on 1 and 2 year outcomes

In Chapter 4 we report the effect of basic developmental care on growth and neurodevelopmental outcome at 1 and 2 years CA of preterm infants < 32 weeks.
Of the 159 surviving infants, 147 children (DC= 74, C= 73) at 1 year and 142 children (DC=72, C=70) at 2 years were assessed. No significant difference in growth, neurological outcomes or MDI was found. A positive trend in PDI at 1 year (p=0.05) did not continue once the children reached 2 years of age. When neurological and developmental scores were combined, the C group showed more "definitely abnormal" scores than the DC group at both ages, but this did not reach the level of significance. We concluded that basic developmental care has a positive effect on psychomotor development at 1 CA, but no effect on neurological and mental development or growth at 1 and 2 years CA.

Chapter 5. Short-term effects of NIDCAP Developmental Care

Chapter 5 describes the effect of the comprehensive NIDCAP developmental care program in preterm infants < 32 weeks GA on short term morbidity, growth and neurodevelopmental outcomes to term age. 168 infants were recruited (NIDCAP=84; C=84). Four infants (NIDCAP=3, C=1) were excluded because they were admitted less than or died within the first 5 days, leaving a total of 164 infants (NIDCAP=81, C=83) that met inclusion criteria. In-hospital mortality was 8/81 (9.9%) in the NIDCAP group and 3/83 (3.6%) in the C group. No difference in mean days respiratory support (13.9/16.3) or mean days IC (15.2/17.0) were found (NIDCAP/C, respectively). Short-term growth and neuromotor development at term age showed

no differences, even when correcting for the duration of the intervention. Our conclusion was that NIDCAP developmental care has no effect on respiratory support, intensive care days or growth and neuromotor development at term age.

Chapter 6. Effect of NIDCAP on 1 and 2 year outcomes

Chapter 6 examined the effect of NIDCAP in preterm infants < 32 weeks GA on 1 and 2 year growth and neurodevelopmental outcomes. Of the 153 surviving infants, 148 children (NIDCAP= 70, C= 78) at 1 year and 146 children (NIDCAP=68, C=78) at 2 years were assessed. There was no significant difference in growth, neurological outcome or mental and psychomotor development at 1 and 2 years found. When neurological outcome, MDI and PDI scores were combined, there still remained no significant difference. We concluded that NIDCAP developmental care showed no effect on growth, neurological, mental and psychomotor development at 1 and 2 years in infants born < 32 weeks. Duration of the NIDCAP intervention was not associated with neurological and developmental outcome.

Chapter 7. General Discussion

Chapter 7 contains the General Discussion of the results of this study. We examined the methodology of our RCT's and compared our results to previous NIDCAP trials. We suggested that more research is warranted before a definite conclusion can be made concerning the effect of developmental care on preterm infants and families. A recommendation for future research was studying the effect of developmental care not only in the neonatal centers but also continuing the intervention once infants are transferred to regional hospitals. There may also be an added effect to providing early intervention for parents and infants in the first months after discharge to home and therefore such programs should be evaluated in future trials.

Samenvatting

Dit proefschrift geeft de resultaten weer van het onderzoek naar het effect van ontwikkelingsgerichte zorg in een tertiaire Neonatale Intensive Care Unit (NICU) op 2 locaties in Nederland bij kinderen geboren na een zwangerschapsduur van minder dan 32 weken.

Hoofdstuk 1. Algemene Inleiding

Hoofdstuk 1 beschrijft de incidentie van vroeggeboorte en de daarmee verbonden risico's, alsmede het effect van de NICU omgeving op het kind en de familie. Onderzoek naar ontwikkeling van de te vroeg geborene heeft laten zien dat veel van de omgevingsfactoren en handelingen in de NICU effect hebben op de sensorische (zintuiglijke) ontwikkeling van het kind. Ontwikkelingsgerichte zorg programma's zijn ontwikkeld om het kind en het gezin te ondersteunen tijdens de opname in de NICU. Verondersteld wordt dat vermindering van de stress en ondersteuning van de ontwikkeling van het kind een positief effect kan hebben op de latere ontwikkeling.

Het Newborn Individualized Developmental Care and Assessment Program (NIDCAP) is een uitgebreide benadering waarin de zorg is gebaseerd op het individuele gedrag van het kind. Ontwikkelingsgerichte zorg is een betrekkelijk nieuw begrip in Nederland en er is weinig bekend van het effect op vroeggeborenen in Nederland. Wij hebben twee opvolgende gerandomiseerde onderzoeken gedaan naar het effect van basiselementen van Ontwikkelingsgerichte Zorg en het volledige NIDCAP programma. Korte termijn uitkomsten behelsden de neonatale morbiditeit en groei en de neuromotorische ontwikkeling op à terme leeftijd. Op de leeftijd van 1 en 2 jaar gecorrigeerd voor vroeggeboorte werden de neuromotorische ontwikkeling en de psychomotorische en mentale ontwikkeling van kinderen geboren < 32 weken zwangerschapsduur onderzocht.

Hoofdstuk 2. Pilot studie met ouders en hun te vroeg geboren kind

Hoofdstuk 2 behandelt een pilot studie in de NICU bij 10 ouderparen en hun kinderen geboren voor een zwangerschapsduur van 32 weken. Dit was een phaselag studie waarbij ouders in de interventie groep les kregen in het gedrag van te vroeggeborenen met het doel om het zelfvertrouwen in de zorg van hun kind te verbeteren. Hoewel de lessen de kennis van de ouders over het gedrag van premature kinderen significant verbeterden, was hun zelfvertrouwen, hoewel groter, niet significant gegroeid. Bij de ouders in de controle groep die geen lessen kregen zagen we

geen toename in het zelfvertrouwen. Hoewel er geen groot effect werd gevonden, liet deze pilot studie wel zien dat een interventieprogramma met ouders al vroeg in de NICU periode mogelijk is. Wij concludeerden dat een langere en intensievere interventie met een grotere populatie noodzakelijk was.

Hoofdstuk 3 Korte termijn effecten van basis Ontwikkelingsgerichte Zorg

Hoofdstuk 3 geeft het onderzoek weer naar de effecten van basis Ontwikkelingsgerichte Zorg (couveusehoezen, nestjes en ondersteunende hulpmiddelen) op morbiditeit, groei en neuromotorische ontwikkeling tot op de à terme leeftijd in kinderen < 32 weken zwangerschapsduur. Er werden 192 kinderen in het onderzoek opgenomen en 179 kinderen (DC=91, C=88) konden geïncludeerd worden. Er overleden 12/91 (13,2%) kinderen in de DC groep en 8/88 (9,1%) in de C groep tijdens de ziekenhuisopname.

Tien (DC=3, C=7) kinderen waren niet beschikbaar voor follow-up. Er werd geen significant verschil in het aantal dagen beademing, het aantal intensive care dagen, de groei vanaf geboorte tot aan à terme leeftijd en de neuromotorische ontwikkeling op à terme leeftijd, tussen de DC en C groepen gevonden. De duur van de interventie had geen effect op de uitkomsten.

Onze conclusie was dat basis Ontwikkelingsgerichte Zorg in de NICU geen effect heeft op de korte termijn morbiditeit, de groei en neuromotorische uitkomsten bij kinderen < 32 zwangerschapsweken.

Hoofdstuk 4. Effect van basis Ontwikkelingsgerichte Zorg op 1 and 2 jaar

In hoofdstuk 4 keken we naar het effect van basis Ontwikkelingsgerichte Zorg op groei, neuromotorische ontwikkeling en de mentale en psychomotorische ontwikkeling op 1 en 2 jaar gecorrigeerde leeftijd van kinderen < 32 weken. Van de 152 kinderen die overleefden werden 147 kinderen (DC=74, C=73) op 1 jaar en 142 kinderen (DC=72, C=70) op 2 jaar onderzocht. Er werd geen significant verschil in groei, neurologische uitkomsten en in de Mental Developmental Index (MDI) gevonden. Wel werd een positieve trend van de Psychomotor Developmental Index (PDI) op 1 jaar (p=0.05) vastgesteld, maar er was geen verschil meer te zien op 2 jaar. Na combinatie van de neuromotorische MDI en PDI scores tot één uitkomstvariabele, had de C groep meer "sterk abnormale" scores dan de DC groep op beide leeftijden, echter het verschil was niet significant. Wij concludeerden dat basis Ontwikkelingsgerichte Zorg een positief effect heeft op de psychomotorische ontwikkeling op de gecorrigeerde leeftijd van 1 jaar, maar geen effect op de neuromotorische en mentale ontwikkeling op de gecorrigeerde leeftijd van 1 en 2 jaar.

Hoofdstuk 5. Korte termijn effecten van NIDCAP ontwikkelingsgerichte zorg

Hoofdstuk 5 beschrijft het effect van het volledig NIDCAP programma voor prematuren < 32 weken op de korte termijn morbiditeit, groei en de neuromotorische ontwikkeling tot de à terme leeftijd. Er werden 168 kinderen in het onderzoek opgenomen (NIDCAP=84, C=84). Vier kinderen (NIDCAP=3, C=1) werden geëxcludeerd omdat ze minder dan vijf dagen waren opgenomen, of stierven binnen de eerste vijf dagen, zodat er een totaal van 164 (NIDCAP=81, C=83) kinderen overbleef. Er overleden 8/81 (9.9%) kinderen in de NIDCAP groep en 3/83 (3.6%) in the C groep tijdens de ziekenhuisopname.

Er was geen significant verschil in het aantal dagen beademing of intensive care. Er was ook geen verschil in korte termijn groei en neuromotorische ontwikkeling op à terme leeftijd, zelfs wanneer er gecorrigeerd werd voor interventieduur. Onze conclusie was dat NIDCAP geen effect heeft op beademings- en IC dagen, of op korte termijn morbiditeit en neuromotorische ontwikkeling.

Hoofdstuk 6. Het effect van NIDCAP op 1 en 2 jaar

In Hoofdstuk 6 worden de resultaten vermeld van het effect van NIDCAP op de gecorrigeerde leeftijd van 1 en 2 jaar bij kinderen geboren < 32 weken, op de groei, neuromotorische ontwikkeling en de mentale en psychomotorische ontwikkeling. Van de 153 overlevende kinderen werden 148 kinderen (NIDCAP=70, C=78) op 1 jaar en 146 kinderen (NIDCAP=68, C=78) op 2 jaar onderzocht. Er werd geen significant verschil in groei, neurologische uitkomsten of mentale en psychomotorische ontwikkeling op 1 en 2 jaar gevonden. Na combinatie van de neurologische uitkomsten, MDI en PDI scores tot één variabele, bleek er eveneens geen significant verschil tussen de groepen te zijn. De duur van de NIDCAP interventie had geen effect op de neurologische en ontwikkelingsuitkomsten. Wij concludeerden dat NIDCAP ontwikkelingsgerichte zorg geen effect op groei, neuromotorische, mentale en psychomotorische ontwikkeling op 1 en 2 jaar heeft bij kinderen geboren na een zwangerschapsduur van minder dan 32 weken.

Hoofdstuk 7. Algemene discussie

Hoofdstuk 7 bevat de algemene discussie van de resultaten van dit onderzoek. Wij onderzochten de methodologie van onze RCT's en vergeleken onze resultaten met eerdere NIDCAP trials. Wij menen dat meer onderzoek nodig is voordat een definitieve conclusie kan worden getrokken over het effect van ontwikkelingsgerichte zorg op premature kinderen en hun families. Aanbevelingen voor toekomstige trials zijn het onderzoeken van het effect van NIDCAP niet alleen in de neonatale centra maar ook wanneer de kinderen worden overgeplaatst naar perifere ziekenhuizen.

Het zou misschien ook van toegevoegde waarde kunnen zijn een interventieprogramma voor ouders en kinderen in de eerste maanden na ontslag uit het ziekenhuis te combineren met de NIDCAP interventie tijdens de opname. De effecten van dergelijke programma's dienen in toekomstige trials te worden onderzocht.

List of Abbreviations

ADHD	attention deficit hyperactivity disorder
BPD	bronchopulmonary dysplasia
BSID-II	Bayley Scales of Infant Development II
C	control
CA	corrected age
CPAP	continuous positive airway pressure
CRIB	Clinical Risk Index for Babies
CSF	cerebrospinal fluid
DA	definitely abnormal
DC	developmental care
E	experimental group
GA	gestational age
GC	Global Confidence
HELLP	hemolysis, elevated liver enzymes, and low platelet count
HFO	high frequency oscillation
IVH	intraventricular hemorrhage
LCC	Lack of Confidence in Caregiving
LOS	Length of stay
MA	mildly abnormal
MABS	Mother and Baby scale
MDI	mental developmental index
N	normal
NEC	necrotizing enterocolitis
NICU	Neonatal Intensive Care Unit
NIDCAP	Newborn Individualized Developmental Care and Assessment Program
OFC	occipital-frontal circumference
P	percentile
PCA	postconceptional age
PDA	patent ductus arteriousus
PDI	psychomotor developmental index
PROM	premature rupture of membrane
PVL	periventricular leukomalacia
RCT	randomized controlled trial
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
SDS	standard deviation scores
SGA	small for gestational age
SIMV	synchronized intermittent mandatory ventilation
VLBW	very low birth weight

Curriculum Vitae

Celeste M. Maguire was born on October 16, 1953 in Wilmington, Delaware, USA. She received her registered nursing degree in 1978 from the West Penn School of Nursing in Pennsylvania, and worked in intensive care at the University of New Mexico Hospital in Albuquerque, New Mexico, bone marrow transplant at the Leiden University Medical Center and later as a neonatology nurse at the Presbyterian Hospital NICU in Albuquerque, New Mexico. She returned to the Netherlands and began her study in psychology at Leiden University in 1992. After obtaining her Masters Degree in Clinical and Health Psychology and in Developmental Psychology in 1999, she worked at the Division of Neonatology of the Willem-Alexander Department of Pediatrics of the Leiden University Medical Center in Leiden and the Juliana Children's Hospital in The Hague as a developmental psychologist and infant developmental specialist. Her responsibility was to design, execute, analyze and report in a PhD thesis a randomized controlled clinical trial on the effects of developmental care and to implement a developmental care program in the NICU's. In addition she completed a 2 year postmasters training in zero-to three infant mental health in 2005. She became a NIDCAP (Newborn Individualized Developmental Care and Assessment Program) trainer and provides training in premature infant behavior for nurses, medical personnel and psychologists.