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

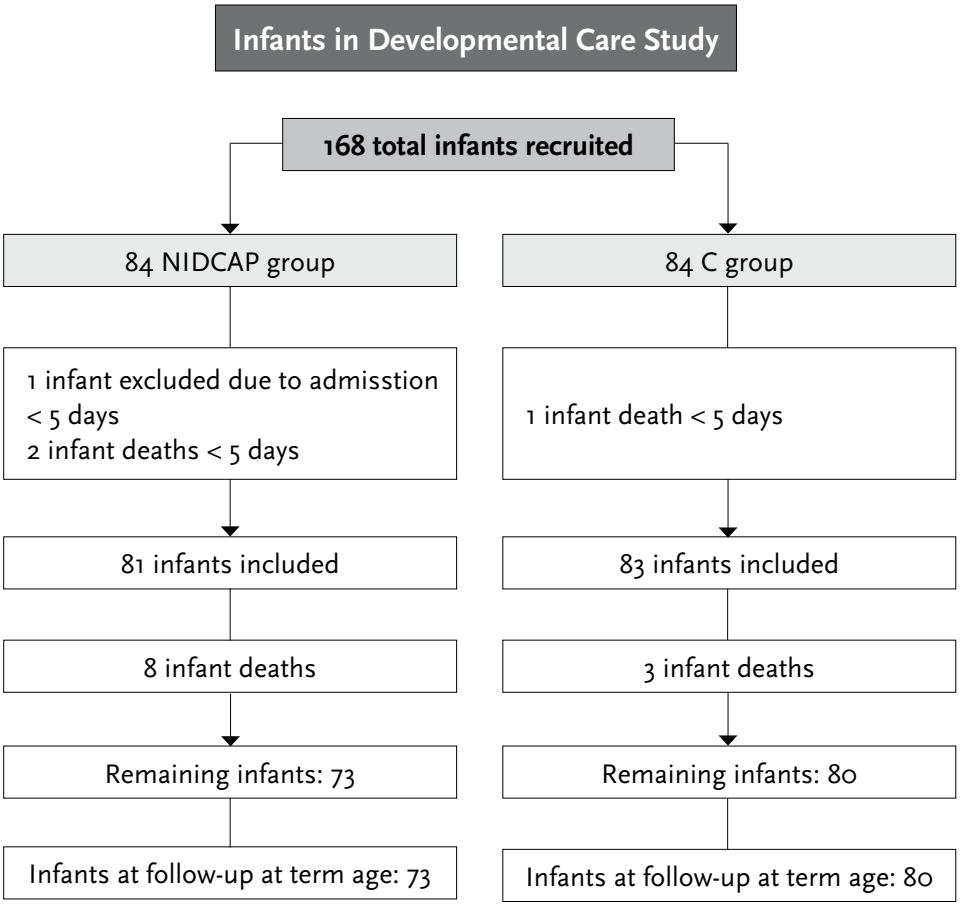


Figure 1

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

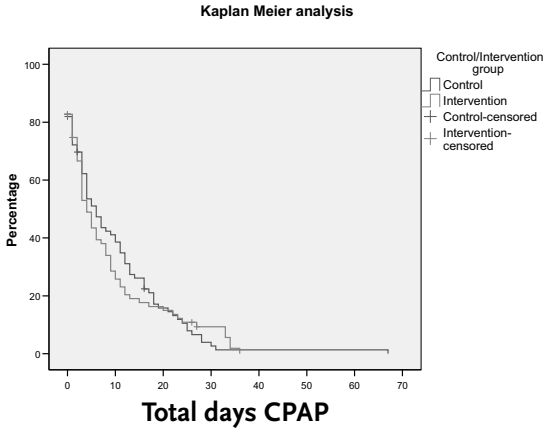
In this randomized controlled trial examining the short-term effects of the comprehensive NIDCAP developmental care program compared to basic developmental care on neonatal morbidity, neurological outcome and growth at term age of infants born < 32 weeks, we found no significant positive effects of the 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.

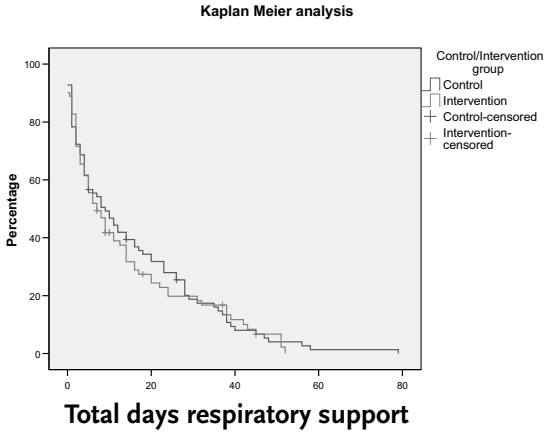
Respiratory Support

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





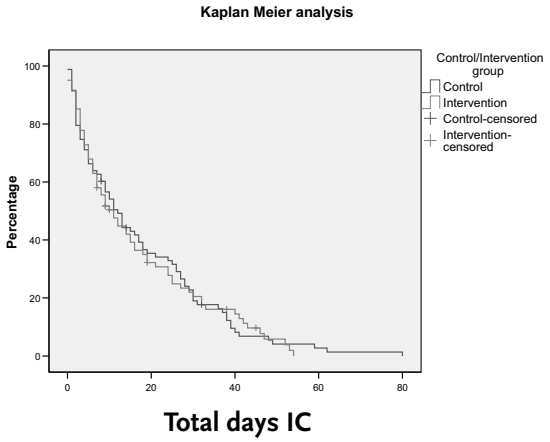


Figure 3a. Comparison of days of respiratory support in infants with no PDA

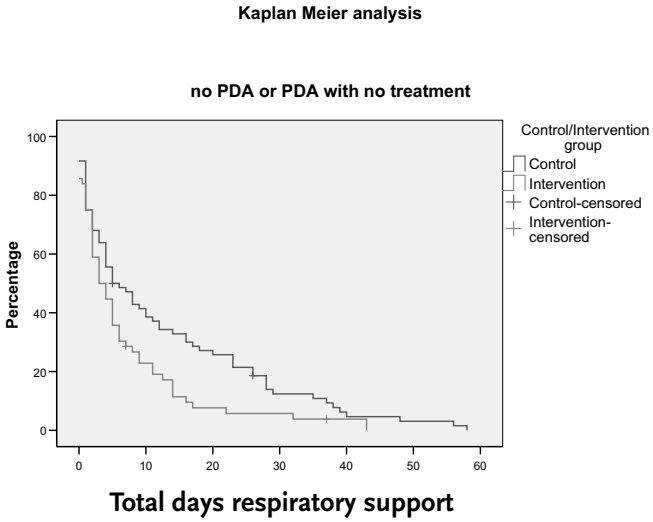
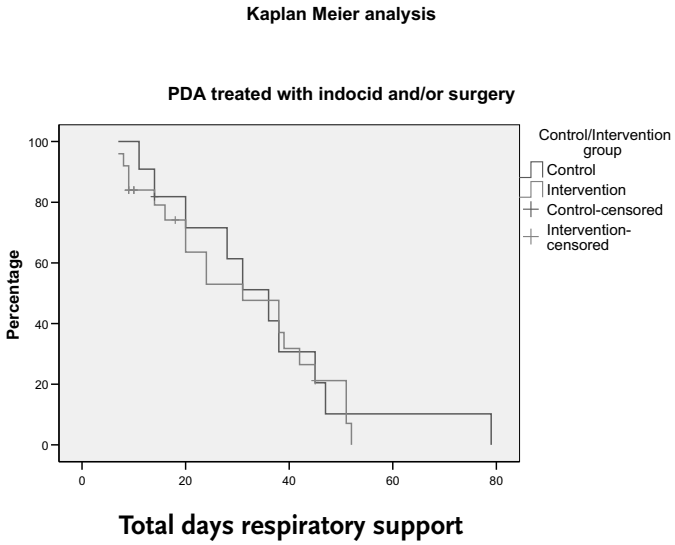


Figure 3b. Comparison of days of respiratory support in infants with PDA



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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