A regional follow-up study at two years of age in extremely preterm and very preterm infants.

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CHAPTER 6

Is hypotension a major risk factor for neurological morbidity at term age in very preterm infants?

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Abstract

Objective: To investigate the influence of perinatal risk factors, especially hypotension, on neuromotor status at term in surviving preterm infants born before 32 weeks of gestation.

Methods: This study is part of the Leiden Follow-Up Project on Prematurity: a prospective, regional study of 266 live born infants with a gestational age < 32 weeks born in 1996 – 1997. Twenty-eight infants died before term age. Two hundred and eleven infants were examined neurologically at term according to Prechtl. The findings were classified as normal (N), mildly abnormal (MA) or definitely abnormal (DA). Hypotension was defined as a mean arterial blood pressure < 30 mmHg on at least two occasions.

Results: One hundred and six (50%) infants were classified as neurologically N, 92 (44%) infants were classified as MA and 13 (6%) infants as DA. Hypotension, bronchopulmonary dysplasia, flaring and cystic periventricular leucomalacia were risk factors for neurological morbidity. Of the 68 infants with hypotension 33 (49%) were classified as MA and 7 (10%) as DA. Of the 141 infants without hypotension 58 (41%) were MA, and 5 (4%) were DA. The odds ratio of hypotension for neurological morbidity was 1.9 (95% CI 1.06 - 3.40), adjusted for gestational age, birth weight, small for gestational age and gender it was 1.96 (95% CI 1.02 - 3.77). The adjusted odds ratio of PVL was 18.6 (4.4 - 78.5), of flaring was 2.37 (1.18 - 4.74) and of BPD was 2.44 (1.08 - 5.5).

Conclusions: Apart from gestational age, periventricular leucomalacia, and bronchopulmonary dysplasia, hypotension in preterm infants is a major risk factor for neurological morbidity at term.

Introduction

Preterm birth is associated with an increased risk of neurological disorders[1;2], including cerebral palsy[3] and mental retardation[4;5], learning difficulties[6-8] and behavioural problems.[9] Due to major recent advances in neonatal intensive care, approximately 85% of preterm infants < 31 weeks gestational age (GA) now survives.[10] The purpose of the present study is to investigate the influence of perinatal risk factors on neurological condition at term.

Hypoxic-ischemic brain events and intracranial haemorrhages in the perinatal period are common complications associated with the development of cerebral palsy in preterm infants.[11] Disturbances of blood pressure play an important role in the pathogenesis of these intracranial lesions.[12-14] Previous studies in preterm infants < 31 weeks have shown a significant association between a mean arterial blood pressure (MABP) < 30 mmHg and severe cerebral haemorrhage or ischemia or death within 48 hours.[15;16]

This study addressed the question if hypotension, defined as a MABP < 30 mmHg irrespective of GA, affects neurological morbidity at term age in very preterm infants. Neurological morbidity at term was chosen as an outcome parameter because (a) it evaluates the functional status of the nervous system, (b) it is known to be a significant predictor of major and minor neurological dysfunction at school-age[17], and (c) in contrast to functional evaluations at older age, it has the advantage of the absence of interference with environmental factors and later occurring illnesses. Additional questions were: (a) does hypotension have a greater impact on immature infants (GA < 27 wks) than on more mature (GA ≥ 27 wks) ones, because of the higher vulnerability to cerebral haemorrhage and ischemia of more immature infants and (b) can other adverse neonatal events, possibly leading to hypotension, predict adverse neurological outcome equally well as hypotension, or is hypotension by itself the better predictor of the neurological condition.[18-20]

Patients and methods

Patients

The present study is part of the Leiden Follow-Up Project on Prematurity (LFUPP), which is a geographically defined collaborative follow-up study of preterm infants in the Dutch health regions The Hague, Leiden and Delft. Two hundred and sixty-six live born infants born between January 1996 and January 1998 with a GA < 32 weeks were included. The mean age at birth was 29.2 weeks (range of 23.4 – 31.6 wks), the mean BW was 1250 gram (SD 383 g). One hundred and sixty-three (61%) infants were born in a university centre and immediately admitted to a neonatal intensive care unit (NICU), 103 (39%) infants were delivered in centres without a NICU. These neonates were either transported to a NICU or stayed in a regional hospital, depending on whether or not they needed intensive care. The in-hospital mortality rate was 11% (29 of the 266 children died; 28 before term age, one after term age). From the remaining 237 children 211 were included in this analysis. These infants all had a detailed and age-specific neurological examination according to Prechtl.[21] Twenty-six infants were not examined according to Prechtl. They were excluded from the present analysis because we were of the opinion that a standard clinical neurological examination would overlook mild neurological findings. These 26 infants as a group did not differ in mean GA, mean BW, gender, PVL, BPD and SGA from the 211 infants included into the analysis. There was, however a significant difference in the percentage who suffered from hypotension; 33 % in the study group versus 12 % in the group of the 26 excluded infants (Chi-Square Test, $p < 0.035$). A detailed dataset of antenatal and perinatal factors was collected including mother's health, socio-economic status, pregnancy induction, disease and medication during pregnancy, reliability of GA, birth weight (BW), Apgar scores, cardiovascular and respiratory complications, neurological abnormalities and cerebral ultrasound findings.

Definitions

Cerebral ultrasound scans were performed as part of the clinical work-up. For study purposes an ultrasound scan was made in all infants at term. The ultrasound scans were performed through the anterior fontanel using an Ultramark 4-sector scanner with multifrequency head (5 or 7.5 MHz). Haemorrhages were graded according to Papile *et al.*[22] Flaring was defined as areas of increased echogenicity

in the periventricular region distinct from the ventricles. Periventricular leucomalacia (PVL) was defined as parenchymal lesions of increased echogenicity in the periventricular region distinct from the ventricles, which were replaced by cystic areas. Hypotension: MABP < 30 mmHg on at least two occasions, measured intra-arterially (umbilical) in 43% of the infants and/or with the oscillometric technique (Dinamap monitor, Critikon, Inc., Tampa, Fla.). Small for gestational age (SGA): birth weight < P10.[23] Patent ductus arteriosus: a clinical diagnosis confirmed by cardiac ultrasonography. Bronchopulmonary dysplasia (BPD): oxygen need at 36 weeks postconceptional age.[24] Sepsis: a clinical diagnosis confirmed by positive blood cultures.

Neurological examination

The remaining 211 infants were examined according to Prechtl by specially trained paediatricians. These infants were the subjects of the present paper. The neurological findings were classified as normal (N), mildly abnormal (MA), or definitely abnormal (DA). Definitely abnormal means the presence of a full-blown neonatal neurological syndrome, such as apathy or hyperexcitability, hypotonia or hypertonia, 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 an abnormal posture, abnormal head control, frequently occurring tremors or startles and absent or abnormal responses or reflexes.[25]

The study was approved by the Medical Ethics Committee of the Leiden University Medical Center. Parental informed consent was obtained.

Statistical analysis

The X^2 – test and the Student's *t* - test were used for univariate analyses, Fisher's exact test was used where appropriate. Correction for confounding variables was done with ordinal logistic regression analysis contrasting normal with mildly and definitely abnormal infants, using GA, BW, gender, SGA, BPD and PVL as confounders. P-values < 0.05 were considered significant.

Results

At term 106 (50%) of the 211 infants were classified as neurologically N, 92 (44%) infants as MA and 13 (6%) as DA. The risk factors for neurological morbidity at term age are summarised in Table 1. Infants born before 27 weeks of gestation showed more a DA outcome than infants born after 27 weeks of gestation (15% versus 5%) although the difference did not reach statistical significance ($p = 0.133$). Infants below 1250 grams at birth were more often categorised as neurologically MA and DA infants ($p = 0.02$). Also infants born SGA ($n = 28$) had a higher risk for neurological morbidity than the 182 AGA infants. Additional factors associated with neonatal neurological morbidity were flaring, PVL, BPD, diuretics, dexamethasone postnatal given and hypotension in the neonatal period. For example, of the 68 infants with hypotension 33 (49%) were classified as MA and 7 (10%) as DA, whereas in the group of 141 infants without hypotension 58 (41%) were MA and 5 (4%) were DA (Table 1, Fig. 1). Of two children the blood pressure variables were not available.

Gender, prolonged rupture of membranes, sepsis, meningitis, respiratory distress syndrome (RDS), pneumothorax, pneumonia, prolonged mechanical venti-

Figure 1. Distribution of neurological morbidity at term in infants with and without hypotension

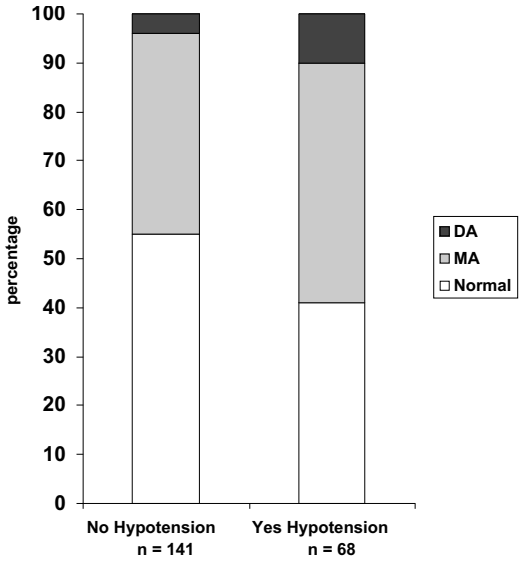

Table 1. Risk factors for neurological morbidity at term

	Neurological classification			
	Normal (n=106)	**Mildly Abnormal (n=92)**	**Definitely Abnormal (n=13)**	**P⋆**
GA, mean in wks (sd)	29.5 (1.9)	29.6 (1.9)	28.4 (2.1)	0.103
< 27 weeks n (%)	12 (44)	11 (41)	4 (15)	0.133
≥ 27 weeks n (%)	94 (51)	81 (44)	9 (5)	
Gender				
Female n (%)	50 (55)	36 (40)	5 (5)	0.49
Male n (%)	56 (47)	56 (46)	8 (7)	
BW, mean in gr (sd)	1332 (362)	1255 (364)	1101 (417)	0.062
< 1250 gr n (%)	43 (42)	50 (48)	10 (10)	0.020
≥ 1250 gr n (%)	62 (58)	42 (39)	3 (3)	
SGA n (%)	7 (25)	17 (61)	4 (14)	0.008
AGA n (%)	98 (54)	75 (41)	9 (5)	
Hypotension				
Yes n (%)	28 (41)	33 (49)	7 (10)	0.049
No n (%)	78 (55)	58 (41)	5 (4)	
IVH				
Grade 3 or 4 n (%)	5 (42)	5 (42)	2 (16)	0.305
Grade 1 or 2 n (%)	18 (50)	14 (39)	4 (11)	
No n (%)	80 (50)	72 (45)	7 (4)	
Flaring:Yes n (%)	16 (37)	21 (49)	6 (14)	0.025
No n (%)	89 (54)	70 (42)	7 (4)	
PVL				
Yes n (%)		3 (43)	4 (57)	< 0.001
No n (%)	105 (52)	87 (43)	9 (5)	
O_2 at 28 days				
Yes n (%)	23 (42)	26 (47)	6 (11)	0.145
No n (%)	81 (53)	64 (42)	7 (5)	
BPD				
Yes n (%)	14 (33)	24 (56)	5 (12)	0.005
No n (%)	91 (55)	66 (40)	8 (5)	
Diuretics**				
Yes n (%)	17 (37)	23 (50)	6 (13)	0.028
No n (%)	89 (54)	69 (42)	7 (4)	
Dexamethasone**				
Yes n (%)	12 (35)	17 (50)	5 (15)	0.030
No n (%)	94 (53)	74 (42)	8 (5)	
Bilirubin, mean in mmol/l(sd)	193 (41)	195 (39)	199 (45)	0.9

GA = gestational age; BW = birth weight; SGA = small for gestational age; IVH = intraventricular haemorrhage; PVL = cystic periventricular leucomalacia; BPD = bronchopulmonary dysplasia;
**Diuretics, Dexamethasone were given postnatal.
⋆ P-value of one-way ANOVA, or Fisher's exact test, where appropriate.

lation, surfactant therapy, patent ductus arteriosus, necrotising enterocolitis, intraventricular haemorrhage (IVH) and post haemorrhagic ventricular dilatation were not related to the neurological condition at term.

Table 2 summarises the raw odd ratios of the risk factors mentioned above and the odd ratio's adjusted for GA, BW, SGA and gender. After correction for the latter confounders, hypotension, PVL, flaring and BPD remained associated with neurological dysfunction at term. PVL was the most important factor. Adjusted for PVL, the odds ratio of hypotension was slightly smaller (OR = 1.87, 95% CI 0.94 -3.71, p = 0.07).

To increase our understanding of the role of hypotension, the characteristics of infants (and their mothers) with or without hypotension were compared (Table 3). This table presents available data of all the surviving infants. There were no significant differences between the two groups with respect to mater-

Table 2. Raw and adjusted Odds ratio's of risk factors for neurological morbidity at term age

		Adjusted for GA, BW, Gender, SGA
	Raw OR (95% CI)	**OR (95% CI)**
Gestational Age (wks) <27 wks	0.96 (0.83-1.10) 1.56 (0.70-3.48)	- -
Male gender	1.38 (0.80-2.37)	-
Birth weight (gr.) < 1250 gr	0.99 (0.99-1.00) 2.05 (1.19-3.53)	
SGA	3.41 (1.50-7.74)	
O_2 need at 28 days	1.70 (0.92-3.15)	1.49 (0.67-3.33)
BPD	2.60 (1.30-5.03)	2.44 (1.08-5.51)
IVH grade 3 and 4	13.87 (4.15-46.43)	1.53 (0.44-5.28)
PVL	20.1 (5.03-80.24)	18.60 (4.40-78.50)
Flaring	2.20 (1.13-4.32)	2.37 (1.18-4.74)
Hypotension	1.90 (1.06-3.40)	1.96 (1.02-3.77)
Diuretics	2.20 (1.10-4.20)	2.00 (0.93-4.31)
Dexamethasone*	2.37 (1.13-4.96)	2.36 (0.98-5.67)
Bilirubine	1.00 (0.99-1.00)	1.00 (0.99-1.01)

OR = odds ratio; GA = gestational age; SGA = small for gestational age; BPD = bronchopulmonary dysplasia; IVH = intra ventricular haemorrhage; PVL = cystic periventricular leucomalacia,
*Dexamethasone postnatal given.

nal and obstetrical complications like pre-eclampsia and intra-uterine growth retardation. Moreover, the use of anti-hypertensive medication in the mother was not associated with hypotension in the newborn. Substantial differences in neonatal morbidity were found. Infants with hypotension were of lower GA and BW than those without hypotension. In addition, the presence of hypotension was associated with RDS, oxygen need at 28 days, BPD, PVL, PDA, diuretics and postnatal treatment with dexamethasone and lower Apgar scores at both 5 and 10 minutes. Infants with hypotension did not have more IVH ($p = 0.13$). Infants with hypotension were more often of a multiple pregnancy, they were less often transported postnatal, they were less often born by caesarean section and the mothers of hypotensive infants were more often treated with Indomethacine medication before delivery. Except for postnatal transport, which is known to have a negative influence on outcome[26], none of these factors was significantly related to neurological morbidity at term.

Finally, we saw no difference in neurological outcome at term between the infants born with a GA < 27 weeks (MA + DA = 14 (61%)) having hypotension and the infants with hypotension and born with a GA ≥ 27 wks (MA + DA = 26 (58%)). This suggests that the more immature infants were not more susceptible to the adverse effect of hypotension.

Table 3. Characteristics of infants with and without hypotension

	HYPOTENSION		
	No N=163 (%)	**Yes N=70 (%)**	**P⋆**
INFANT			
Gestational Age <27 weeks	8 (5)	22 (31)	<0.001
Male Gender	96 (59)	37 (53)	0.47
Birth weight <1250 gr	66 (41)	47 (67)	<0.001
SGA	22 (14)	9 (13)	0.99
Apgar-score: 5 min.	8.0 (1.5)	7.5 (1.9)	0.02
10 min.	9.1 (1.1)	8.7 (1.5)	0.03
IVH	4 (3)	5 (8)	0.13
PVL	1 (1)	6 (9)	0.004
Flaring	31 (19)	21 (30)	0.09
RDS	79 (50)	52 (74)	<0.001
O_2 need at 28 days	27 (17)	37 (54)	<0.001
BPD	21 (13)	26 (38)	<0.001
Diuretics	21 (13)	25 (36)	<0.001
Postnatal Dexamethasone	13 (8)	22 (31)	<0.001
Patent ductus arteriosus	31 (19)	27 (39)	0.002
Meningitis	4 (3)	2 (3)	0.99
NEC	13 (8)	7 (10)	0.80
Sepsis (clin symptoms or positive blood culture)	131 (78)	54 (89)	0.06
Inotropics	3 (2)	49 (70)	<0.001
MOTHER:			
Pre-eclampsia	19 (12)	3 (4)	0.07
Indocid treatment	16 (10)	23 (33)	<0.001
Anti-hypertensive treatment	32 (21)	8 (12)	0.7
Antenatal Glucocorticosteroids	114 (74)	52 (80)	0.4
PROM	48 (30)	17 (25)	0.52
Caesarean Section	75 (46)	21 (30)	0.03
Multiple birth	46 (28)	29 (41)	0.07
Transport	64 (40)	13 (9)	0.002
SES	3.6 (1.3)	4.4 (1.3)	<0.001
Age	30.3 (4.7)	31.1 (4.6)	0.22
Smoking during pregnancy	18 (13)	12 (18)	0.41

⋆ P-value of Student's t-test, or Fisher's exact test, where appropriate.
SGA = small for gestational age; IVH = intraventricular haemorrhage; PVL = cystic periventricular leucomalacia; BPD = bronchopulmonary dysplasia; RDS = respiratory distress syndrome; NEC = necrotising enterocolitis; PROM = prolonged rupture of membranes; SES = socio-economic status.

Discussion

Our primary goal was to analyse the influence of perinatal risk factors on neurological morbidity at term. We found that infants who had a mean arterial blood pressure of < 30 mmHg more often showed neurological dysfunction at term than infants without hypotension. After adjustment for gestational age, birth weight, gender and SGA this association remained significant. We chose a MABP of less than 30 mmHg as definition of hypotension in line with other authors who pointed out the relevance of this cut-off point in premature infants < 31 weeks of GA.[15]

Several explanations for the association between hypotension and neurological morbidity can be delineated.

First, fluctuating patterns of cerebral blood flow (CBF) velocity can induce intraventricular haemorrhage.[14;27;28] In addition, sustained hypotension plays an important role in the pathogenesis of intracranial lesions.[15] In our study group, hypotension was clearly related to neurological morbidity at term. This neurological morbidity could not be attributed to IVH caused by hypotension, since IVH was not related to hypotension (Table 3). The relation between hypotension and PVL could explain only part of neonatal neurological morbidity. This implies that another part of neurological morbidity related to hypotension escapes the ultrasonic eye.[29]

Second, increased neurological morbidity in the hypotensive infants might have been due to disorders causing the hypotension. No association was found between hypotension and sepsis or prolonged rupture of membranes. However, the infants with hypotension had a lower GA and birth weight and more respiratory problems. Theoretically, changes in intrathoracic pressure associated with removal of spontaneous breathing effort may decrease venous return and cardiac output; these in turn may lead to hypotension if ventilator settings are not appropriately adjusted, particularly in the presence of hypovolemia.[30] These findings reinforce the concept that the overall condition of the infant and particularly RDS is an important determinant of cerebral pathology.[16] Furthermore, infants who developed hypotension had lower Apgar scores than those without hypotension. This illustrates the entanglement of risk factors, and reminds us of the danger of pinpointing only one factor as the major risk factor.

Third, the association between hypotension and neonatal neurological morbidity may have been induced by the treatment of the hypotension. The majority of

infants were treated with dopamine, some were treated with volume expansion only. Various studies have suggested that dopamine treatment may put preterm infants at risk for IVH and/or PVL, since they may have an increased responsiveness to the hemodynamic actions of dopamine and an inadequate auto regulation of CBF.[31-33]

This study showed no difference in neurological outcome at term comparing the more immature infants (GA < 27 wks) with the more mature ones. Especially, the younger infants were not more often categorised as MA than the older ones. Nevertheless they were somewhat more often classified as DA (15% versus 5%). Summarising, we found that hypotension in very preterm infants is associated with an increased neurological morbidity at term. At this point of time it is not clear whether this association persists with advancing age. We do know however, that neurological morbidity at term is a substantial risk factor for neurological dysfunction, behavioural and learning problems at school age.[17;34] Long-term follow-up is planned to study this correlation at school age.

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