Neonatal care bundles are associated with a reduction in the incidence of intraventricular haemorrhage in preterm infants: a multicentre cohort study

Karen de Bijl-Marcus,1 Annemieke Johanna Brouwer,2 Linda S De Vries,1 Floris Groenendaal,1 Gerda van Wezel-Meijler3

ABSTRACT
Objective To investigate the effect of a nursing intervention bundle, applied during the first 72 hours of life, on the incidence of germinal matrix-intraventricular haemorrhage (GMH-IVH) in very preterm infants.
Design Multicentre cohort study.
Setting Two Dutch tertiary neonatal intensive care units.
Patients The intervention group consisted of 281 neonates, whereas 280 infants served as historical controls (gestational age for both groups <30 weeks).
Interventions After a training period, the nursing intervention bundle was implemented and applied during the first 72 hours after birth. The bundle consisted of maintaining the head in the midline, tilting the head of the incubator and avoidance of flushing/rapid withdrawal of blood and sudden elevation of the legs.
Main outcome measures The incidence of GMH-IVH occurring and/or increasing after the first ultrasound (but within 72 hours), cystic periventricular leucomalacia and/or in-hospital death was the primary composite outcome measure. Logistic regression analysis was used to explore differences between groups.
Results The nursing intervention bundle was associated with a lower risk of developing a GMH-IVH (any degree), cystic periventricular leucomalacia and/or mortality (adjusted OR 0.42, 95% CI 0.27 to 0.65). In the group receiving the bundle, also severe GMH-IVH, cystic periventricular leucomalacia and/or death were less often observed (adjusted OR 0.54, 95% CI 0.33 to 0.91).
Conclusions The application of a bundle of nursing interventions is associated with reduced risk of developing a new/progressive (severe) GMH-IVH, cystic periventricular leucomalacia and/or mortality in very preterm infants when applied during the first 72 hours postnatally.

BACKGROUND
Germinal matrix-intraventricular haemorrhage (GMH-IVH) is a major, frequently occurring complication of preterm birth associated with serious complications such as periventricular haemorrhagic infarction (PVHI) and posthaemorrhagic ventricular dilatation (PHVD).1–5 Like cystic periventricular leucomalacia (c-PVL), complicated GMH-IVH is strongly associated with adverse outcome, including disabilities and death.1 6–8 The incidence of c-PVL has declined over the last decades and is now <5%. However, the incidence of moderate-to-severe GMH-IVH in premature infants has not declined during the last few decades.2 9 10 Seemingly insignificant, routine caregiving events may affect cerebral perfusion and oxygenation in preterm neonates and thereby increase the risk of a GMH-IVH.11–15 To avoid (rapid) fluctuations in cerebral blood flow (CBF) during routine care, nursing interventions have been proposed. These nursing interventions are especially important during the first 72 postnatal hours, since GMH-IVH mostly develops during this time window.6 16 The first of four interventions under current investigation is positioning the head in the midline position, enabling optimal cerebral venous drainage. Head rotation to either side may lead to complete occlusion or obstruction of the jugular venous-drainage system at the ipsilateral side.17–19 In preterm neonates, hampered venous drainage due to head rotation could lead to venous congestion, altered cerebral oxygenation and ultimately GMH-IVH.20 21 The second proposed intervention is elevating the head of the incubator 15–30 degrees upwards to facilitate cerebral venous outflow by promoting hydrostatic cerebral venous drainage.22 A focus group has identified maintaining a midline head position together with tilting as one of 10 potential better practices for the prevention of GMH-IVH. Rationale behind this recommendation

What is already known on this topic?
► Germinal matrix-intraventricular haemorrhage (GMH-IVH) is a frequent complication of prematurity and associated with adverse neurodevelopmental outcome.
► Routine caregiving events affect cerebral perfusion.

What this study adds?
► A bundle of nursing interventions decreases the risk of GMH-IVH.
► The beneficial effect was more pronounced in extremely preterm infants.
was the finding that the benchmark site with the lowest rate of GMH-IVH used this practice.23 24 The results of a recently published randomised controlled trial (RCT) indicate that maintaining an elevated head position during the first four postnatal days is associated with a lower risk of developing a GMH-IVH and may improve survival.25 The final intervention is avoidance of elevation of the legs during diaper change that may result in abrupt increased venous return and cardiac preload which may alter cerebral perfusion.11

The last intervention is slow arterial/intravenous flushing and slow arterial blood withdrawal. Rapidly withdrawing blood from an arterial line has been associated with a temporary, significant decrease in cerebral oxygenation through a rapid steal of blood. Prolonging sampling time can prevent this phenomenon.26

The aim of our study was to investigate the effect of a nursing intervention bundle (NIB), aimed at maintaining a more stable CBF and less cerebral venous congestion on the incidence of GMH-IVH in preterm neonates. In addition, we studied the effect of the intervention on the incidence of c-PVL and mortality.

METHODS
Design
This is an intervention cohort study conducted in two Dutch tertiary neonatal intensive care units (NICUs); (NICU1) Wilhelmina Children’s Hospital, University Medical Center Utrecht, The Netherlands; (NICU2) Isala Women and Children’s Hospital, Zwolle, The Netherlands. The Medical Ethical Committees of both hospitals considered the study an evaluation of an adaptation in nursing care. Since anonymised data were analysed, a waiver of informed consent was granted according to Dutch/European legislation. The study had a stepwise design (figure 1). In each NICU two patient groups were included. The first group corresponded to the pre-intervention period when patients received standard care (control group). After this first period nursing staff received a 1 month training period on how to apply the NIB. During this period, theory and practice lessons were organised in addition to bedside teaching. To increase compliance, stickers were placed as a reminder on the incubator. Parents were instructed as well. Afterwards, NIB was applied to all patients who fulfilled the inclusion criteria and were admitted to one of the NICUs. The time periods of recruitment for NICU2 were longer than for NICU1, as NICU2 is smaller than NICU1.

Study population
The study population included all preterm neonates (<30 weeks gestation) consecutively admitted to one of the NICUs. Outborn infants (n=5), infants who died in the delivery room (n=0) and/or infants with major congenital and/or chromosomal abnormalities and/or major congenital abnormalities of the central nervous system (n=2) were excluded from the study.

Control group
The control group received standard, routine care. Patients were positioned in various positions without attention to the position of the head. Often in prone position or supine with 45–90 degrees flexion of the head to either side. Tilting the incubator was not part of routine care, neither were standard minimal time periods in which flushing/arterial blood withdrawal took place. During diaper change the legs were often suddenly lifted. Blood product transfusion protocols, sedation protocols and ventilation strategies were similar for both units.

Intervention group
The NIB consisted of:
1. Posture:
   a. Maintaining midline head position.
   b. Incubator tilted 15–30 degrees.
   c. Avoidance of head down position and sudden elevation of the legs.
2. Avoiding rapid intravenous/arterial flushes and rapid arterial blood withdrawal (<30 s).

The NIB was applied directly after birth starting in the delivery room and was continued during the first 72 postnatal hours. After 72 hours, all aspects of the NIB were still carried out with the exception that a prone position was allowed. The head was maintained in the midline when the infants were positioned in a supine position.

Neuroimaging
In all infants, cranial ultrasound scanning (cUS) was performed within 6 hours after admission and additionally two to three times during the first 72 postnatal hours. Thereafter, cUS was performed at least once a week until discharge. GMH-IVH was classified according to Volpe.6 Severe GMH-IVH was defined as IVH grade 3, haemorrhages complicated by PVIH (GMH-IVH grade 4) and/or PHVD with need for intervention since these types of haemorrhages are strongly associated with adverse outcome.1 6–8 Ultrasound images were analysed offline by two experts in neuroimaging (LSDeV and GvW-M) blinded for the type of nursing care the patients received.

Outcome
The primary outcome was a composite of the incidence of a GMH-IVH occurring and/or increasing after the first ultrasound (but within 72 hours postnatally), c-PVL and/or in-hospital death. Secondary outcomes were: 1) GMH-IVH occurring and/or increasing after the first ultrasound (but within 72 hours postnatally), 2) c-PVL, 3) in-hospital mortality.

Statistical analysis
Interobserver and intraobserver reliability of presence and classification of GMH-IVH was assessed, using respectively the multiple rater kappa k and Cohen’s kappa statistic method. The cUS examinations of 15 patients were analysed by both experts blinded for previous interpretations. Intraobserver reliability was assessed by repeating the analysis of the same 15 exams by GvW-M 3 months after the first. Statistical analysis was performed using binary logistic regression analysis with backward selection of the outcome parameters, with the NIB as intervention, and gestational age (GA, continuous), Apgar score at 5 min (AS5), the clinical risk index for babies (CRIB) score (continuous),27 gender, birth weight z-score (dichotomised <1 or ≥ –1 SD), centre, treatment of a patent ductus arteriosus, mode of delivery, breech position, antenatal steroids and multiple birth
as covariates. Statistical Package for Social Sciences for Windows, V.21 (Chicago, Illinois, USA) was used. Results are presented as adjusted ORs. Statistical significance is set at a p value of 0.05. We estimated that the proportion of patients/infants with the primary outcome would be around 30%. With a sample size of 280 patients receiving standard care and 280 patients treated with the NIB, we were able to detect a reduction of >33% of the primary outcome with a power of 0.80 and alpha of 0.05.

RESULTS
Patient characteristics
Patient characteristics are described in table 1. Characteristics of the control and intervention groups of the two NICUs were comparable except for the number and percentage of infants receiving minimal invasive surfactant replacement therapy. All infants underwent serial cUS examinations. In 53 patients, a GMH-IVH was diagnosed on the first cUS (25 patients in the control group vs 28 in the NIB group).

Outcome parameters
The outcome parameters are shown in table 2. Mortality rate was equal in both patient groups. The primary outcome (composite of the incidence of any GMH-IVH occurring and/or increasing after the first ultrasound (but within 72 hours), c-PVL and/or in-hospital death) was less frequently observed in the NIB group (adjusted OR 0.42 95% CI 0.27 to 0.65, p<0.001, see section logistic regression for adjustment for confounders). The composite outcome of the development of a severe GMH-IVH occurring and/or increasing after the first ultrasound (but within 72 hours), c-PVL or mortality was also less frequent in the NIB group (adjusted OR 0.54, 95% CI 0.33 to 0.91, p = 0.02, see section logistic regression for adjustment for confounders). The difference was slightly, but not significantly more pronounced in NICU1 compared with NICU2 (adjusted OR 1.40, 95% CI 0.92 to 2.12, p 0.1, see section logistic regression for adjustment for confounders) when all grades of GMH-IVH were included, however the effect of NIB on the incidence of severe GMH-IVH occurring and/or increasing after the first ultrasound (but within 72 hours) was equal in both NICUs (adjusted OR 1.14, 95% CI 0.69 to 1.89, p 0.65, see section logistic regression for adjustment for confounders). The effect of the intervention on the primary outcome was stronger in the subgroup of infants born after a gestation of <27 weeks (figure 2). No undesirable effects of the NIB were observed. In 27 patients, a new GMH-IVH or progression of a known bleed after the first 72 hours (median day 8; range 4–56) was observed (15 NICU1 vs 12 NICU2; 11 control group vs 16 intervention group; five patients with a severe GMH-IVH). All five patients who developed a late severe GMH-IVH suffered from serious, acute illness at that time (sepsis, necrotising enterocolitis). In 3 of the 27 patients, a newly formed GMH-IVH was diagnosed more than >1 month after birth (33, 37 and 56 days). All three had extremely low birth weights and/or were born extremely prematurely and suffered from severe illness at time of onset of the haemorrhage. Exclusion of patients diagnosed with a GMH-IVH on the first cUS did not affect the logistic regression model, nor did the inclusion of patients in whom a new/progressive GMH-IVH occurred after the first 72 postnatal hours.

Intraobserver and interobserver reliability
For the assessment of the presence of a haemorrhage (yes vs no), we found excellent reliability with a Cohen’s kappa 0.86 (intraobserver) and 0.76 (interobserver). The average intraobserver agreement of the grade of the GMH-IVH was 60% (moderate). The average interobserver agreement of the grade of the GMH-IVH was also 60% (moderate). For the assessment of the presence of a severe haemorrhage (yes or no), we found

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics of both control groups and intervention groups in NICU1 and NICU2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Control group NICU1 (n=140)</td>
</tr>
<tr>
<td>Gestational age in weeks, mean±SD</td>
<td>27.3±1.7</td>
</tr>
<tr>
<td>Gender, number (%)</td>
<td>72 male (51)</td>
</tr>
<tr>
<td>Birth weight z-score, mean±SD</td>
<td>−0.8±1.3</td>
</tr>
<tr>
<td>Apgar score at 5 min, median (IQR)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Antenatal corticosteroids, % of cases</td>
<td>69%</td>
</tr>
<tr>
<td>Breech position, % of cases</td>
<td>19%</td>
</tr>
<tr>
<td>Caesarean section, % of cases</td>
<td>55%</td>
</tr>
<tr>
<td>CRIB score, median (IQR)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Intubation rate, % of infants intubated at least once in first 72 hours after birth</td>
<td>62%</td>
</tr>
<tr>
<td>Duration of endotracheal mechanical ventilation in hours, median (IQR) during first 72 hours after birth</td>
<td>31 (70)</td>
</tr>
<tr>
<td>Surfactant therapy, % of cases</td>
<td>66%</td>
</tr>
<tr>
<td>Of which: using minimal invasive surfactant replacement therapy</td>
<td>0%</td>
</tr>
<tr>
<td>Necrotising enterocolitis, number of infants (%)</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Sepsis, number of infants (%)</td>
<td>29 (21%)</td>
</tr>
<tr>
<td>Posthaemorrhagic ventricular dilatation with need of intervention, number of infants (%)</td>
<td>3 (2%)</td>
</tr>
</tbody>
</table>

CRIB, clinical risk index for babies; NIB, nursing intervention bundle; NICU, neonatal intensive care unit.

---

presence and treatment of a
the delivery, multiple birth, birth weight z-
model: gender, breech position, antenatal steroids, mode of
following parameters did no improve the logistic regression
haemorrhage occurring and/or
severe
F422 de Bijl-
nursing intervention bundle group) stratified by gestational age (GA).

Table 2 Outcome parameters of control group and intervention group in both NICUs

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control group (280 infants: NICU1+NICU2)</th>
<th>NIB intervention group (281 infants: NICU1+NICU2)</th>
<th>aORs and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome: new or progressive GMH-IVH within first 72 hours, in-hospital death or c-PVL, number of patients (%)</td>
<td>86 (31%)</td>
<td>49 (17%)</td>
<td>aOR 0.42; 95% CI 0.27 to 0.65, p&lt;0.001</td>
</tr>
<tr>
<td>New or progressive GMH-IVH within first 72 hours after birth, number of patients (%)</td>
<td>65 (23%)</td>
<td>27 (10%)</td>
<td>aOR 0.34; 95% CI 0.20 to 0.56, p&lt;0.001</td>
</tr>
<tr>
<td>c-PVL, number of patients (%)</td>
<td>3 (1%)</td>
<td>2 (1%)</td>
<td>aOR 0.71; 95% CI 0.11 to 4.43, p=0.71</td>
</tr>
<tr>
<td>In-hospital death, number of patients (%)</td>
<td>28 (10%)</td>
<td>29 (10%)</td>
<td>aOR 1.04; 95% CI 0.55 to 1.95, p=0.90</td>
</tr>
<tr>
<td>Composite outcome: new or progressive severe* GMH-IVH within first 72 hours, in-hospital death or c-PVL, number of patients (%)</td>
<td>55 (20%)</td>
<td>37 (13%)</td>
<td>aOR 0.54, 95% CI 0.33 to 0.91, p=0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control group survivors (252 infants: NICU1+NICU2)</th>
<th>NIB intervention group survivors (252 infants: NICU1+NICU2)</th>
<th>aORs and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>New or progressive severe* GMH-IVH within first 72 hours after birth, number of patients (%)</td>
<td>26 (9%)</td>
<td>6 (2%)</td>
<td>aOR 0.20, 95% CI 0.08 to 0.51, p&lt;0.001</td>
</tr>
</tbody>
</table>

*Severe GMH-IVH defined as a grade III haemorrhage, haemorrhages accompanied by periventricular haemorrhagic infarction and/or resulting in ventricular dilatation with need of intervention; Apgar score at 5 min, centre, and CRIB score.
aOR, adjusted OR; c-PVL, cystic periventricular leukomalacia; GMH-IVH, germinal matrix-intraventricular haemorrhage; NIB, nursing intervention bundle; NICU, neonatal intensive care unit.

excellent reliability with kappa 1.0 (intraobserver) and 0.91 (interobserver).

Logistic regression

Binary logistic regression analysis demonstrated that NIB strongly reduced the risk of adverse primary outcome after adjustment for GA, centre, AS5 and CRIB, although the R² of the model was not high (R²=0.21). Adding one or more of the following parameters did no improve the logistic regression model: gender, breech position, antenatal steroids, mode of the delivery, multiple birth, birth weight z-score (<1SD) and presence and treatment of a patent ductus arteriosus. For the composite outcome of severe haemorrhage occurring and/or increasing after the first ultrasound (but within 72 hours), c-PVL and/or in-hospital death, the best model also consisted of NIB, centre, GA, AS5 and CRIB score with an R² of 0.27. According to the model for an infant with a GA of 24 weeks and a CRIB score of 3, the NIB reduces the risk of developing a new/progressive severe GMH-IVH, c-PVL or mortality from 24% to 14%. For an infant with a GA of 24 weeks and a CRIB score of 6 this risk reduced from 35% to 23%, while for an infant with a GA of 29 weeks and a CRIB score of 3 the risk reduced from 9% to 5%.

DISCUSSION

We have shown that the NIB applied during the first 72 postnatal hours decreased the risk of GMH-IVH in preterm infants (<30 weeks gestation). The incidence of low-grade haemorrhages as well as severe haemorrhages was significantly decreased in the intervention group. The effect of the intervention was more pronounced in the subgroup of infants born after a gestation of <27 weeks. We postulate that the NIB contributes to a more stable perfusion of the vulnerable preterm brain and decreases the risk of venous congestion. One key factor in the aetiology of GMH-IVH is the intrinsic fragility of the germinal matrix vasculature which causes the delicate blood vessels to easily rupture when rapid changes in cerebral perfusion occur.8,28 Autoregulation of cerebral perfusion is impaired in preterm infants, especially when they are ill.29,30 Preterm infants are thus less able to maintain a relatively constant blood flow to the brain when changes in cerebral perfusion pressure occur. A second contributing factor to GMH-IVH is the U-shaped alignment of the venous vessels that are hereby prone to venous congestion and stasis, which can cause vessel damage and bleeding.8,33 The NIB in the current study aimed at a more stable cerebral perfusion and preventing cerebral venous congestion. Maintaining a midline head position.
during the early transition period has been included in GMH-IVH prevention bundles at several institutions. However, so far strong data to support the practice are lacking. 23–32–34 Two RCTs have been performed by the same group. 35,36 Their first pilot study analysed the effect of head position on the incidence of GMH-IVH and mortality of preterm infants and found no difference between different head positions. However, no cUS examinations were conducted prior to inclusion. 37,38 The second study was a multicentre RCT. 39 Infants who were diagnosed with a GMH-IVH within the first 12 postnatal hours were excluded. The intervention was identical to their previous study. However, the study was terminated prematurely owing to low accrual rate. They found no difference in risk of GMH-IVH or mortality between the groups. Unfortunately, both RCTs are characterised by small sample sizes, few events and wide CIs. A recent retrospective cohort study investigated differences of incidence of GMH-IVH when comparing two NICUs that had established a protocol to maintain a midline head position during the first 72 postnatal hours with two NICUs that provided routine care. They included a total of 1226 preterm infants and did not find a difference in the incidence of GMH-IVH. However, there were significant differences between groups regarding A55, patent ductus arteriosus, mode of delivery and inborn/outborn which may have influenced the results. No information was given regarding whether or not the GMH-IVH was already present at time of the first cUS. 40 A study performed by Ancora et al did not show significant changes in either the tissue haemoglobin index (which reflects changes in cerebral blood volume) or cerebral oxygenation after rotation of the head. Only the most immature infants (<26 weeks gestation) showed a reduction in cerebral blood volume with head rotation. 38 As the latter group represents the infants with the greatest risk of developing a GMH-IVH, this reduction may therefore be of clinical importance. Our findings also indicate that extremely premature infants (<27 weeks gestation) benefit most from the NIB intervention. One RCT investigated the effect of tilting on the incidence of GMH-IVH and mortality. They found significantly fewer grade 4 haemorrhages and lower mortality rates in the group with tilted heads. 41 To the best of our knowledge, there are no previous studies that analysed the combined effect and/or the other components of the NIB under investigation in the present study (avoidance of rapid flushes/blood withdrawal, avoidance of elevating legs/head down position) on the incidence of GMH-IVH, c-PVL and/or mortality in preterm infants. We have shown that the application of a NIB during the first 72 postnatal hours reduces the risk of developing a (severe) GMH-IVH in very preterm infants. The effect of NIB on the incidence of low-grade haemorrhages differed between both NICUs. In NICU1, a larger reduction of the incidence of low-grade GMH-IVH was observed when compared with NICU2. A possible explanation for this difference could be protocol adherence and/or parent participation. The effect of NIB on the incidence of severe GMH-IVH was equal in both NICUs.

**Limitations of the study**

Our study has several limitations. The first being the study design as it is a cohort study and not an RCT. The implementation of two simultaneous nursing protocols was considered not feasible in our units. Due to the nature of the intervention blinding was only feasible for the outcome assessors. The second limitation is the study period (NICU1 2 years, NICU2 4 years). It is possible that improvements in overall neonatal care contributed to a reduction in GMH-IVH. However, previous studies have indicated that the incidence of GMH-IVH has remained stable for the last few decades. 2,9,10 There was no difference in mortality between the control and NIB groups. Third, our intervention consists of a bundle of interventions. The individual contribution of each of the interventions remains therefore unclear in the current study. Fourth, the intrareporter and interobserver agreement of the assessment of the grade of the GMH-IVH was moderate despite the fact that cUS was evaluated by experts. These findings are consistent with previous studies. 19 However, intrareporter and interobserver agreement for the presence of a haemorrhage (any grade), as well as the diagnosis of a severe GMH-IVH were excellent.

In conclusion, the use of a NIB was associated with a reduction in the composite outcome of in-hospital death, GMH-IVH or c-PVL. We recommend conducting a large multicentre RCT to further investigate the effect of the NIB on the incidence of GMH-IVH.

**Funding**

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests**

None declared.

**Patient consent for publication**

Not required.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data availability statement**

Data are available on reasonable request.

**ORCID ID**

Linda S de Vries http://orcid.org/0000-0002-7282-8304

**REFERENCES**