Early Human Development 116 (2018) 1–8

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Ante-, peri- and postnatal factors associated with intraventricular hemorrhage in very premature infants

Martin Poryo[a,*], Judith Caroline Boeckh[b], Ludwig Gortner[c], Michael Zemlin[c], Perrine Duppré[d], Daniel Ebrahimi-Fakhari[d], Stefan Wagenpfeil[e], Matthias Heckmann[f], Eva Mildenberger[g], Anne Hilgendorff[h,1], Andreas W. Flemmer[h,1], Georg Frey[i], Sascha Meyer[c,j], On behalf of the PROGRESS study consortium and NGFN - Nationales Genomforschungsnetz Deutschland

[a] Department of Pediatric Cardiology, Saarland University Medical Center, Homburg/Saar, Germany
[b] Department of Internal Medicine, Katharinenhospital Klinikum Stuttgart, Stuttgart, Germany
[c] Department of Pediatrics and Neonatology, Saarland University Medical Center, Homburg/Saar, Germany
[d] University of Saarland, Medical School, Homburg/Saar, Germany
[e] Institute for Medical Biometry, Epidemiology and Medical Informatics, Saarland University, Campus Homburg/Saar, Germany
[f] Department of Neonatology and Pediatric Intensive Care, University Medicine Greifswald, Germany
[g] Department of Neonatology, University Medical Center, Johannes Gutenberg University Mainz, Germany
[h] Department of Neonatology, University Medical Center, Ludwig-Maximilian-University Munich, Germany
[i] Department of Pediatric Cardiology and Neonatology, Darmstaedter Kinderkliniken Prinzessin Margaret, Darmstadt, Germany
[j] Department of Pediatric Neurology, Saarland University Medical Center, Homburg/Saar, Germany

ARTICLE INFO

Keywords:
Premature infants
Intraventricular hemorrhage
Neonatal complications

ABSTRACT

Background: Intraventricular hemorrhage (IVH) is one of the most serious complications in preterm infants and is associated with neurological sequelae and mortality. Over the past few decades, the rate of IVH has decreased due to improved neonatal intensive care. However, up to 15–25% of very and extremely premature infants (< 32 and < 28 weeks of pregnancy (WOP) respectively) still suffer from IVH.

Study purpose.

The aim of this study was to perform an updated, multicenter analysis to identify ante-, peri, and postnatal factors other than gestational age/birth weight associated with IVH of any grade in a large cohort of very and extremely premature infants.

Methods: We performed a retrospective analysis in a prospectively conducted multicenter cohort study between 01/01/1998–31/12/2012 at 5 level 3 perinatal centers. All relevant ante-, peri- and neonatal data were collected and univariate as well as multivariate logistic regression analysis was performed.

Results: 765 inborn infants with a gestational age < 32 WOP were enrolled into this study (369 (48.2%) female; 396 (51.8%) male). Birth weight ranged from 315 g to 2200 g (mean 1149.7 g, SD 371.9 g); 279 (36.5%) were born ≤ 27 + 6 WOP and 486 (63.5%) ≥ 28 + 0 WOP. IVH was seen in 177 (23.1%) patients.

Multivariate analysis revealed that in addition to higher gestational age (OR 0.7, CI [0.6–0.8]), antenatal steroid treatment (OR 0.3, CI [0.2–0.6]) and caesarian section without uterine contraction (OR 0.6, CI [0.4–0.9]) were associated with a lower rate of IVH while RDS (OR 5.6, CI [1.3–24.2]), pneumothorax (OR 2.8, CI [1.4–5.5]) and use of catecholamines (OR 2.7, CI [1.7–4.5]) were associated with an increased risk of IVH. After exclusion of gestational age and birth weight from multivariate analysis, early onset sepsis (OR 1.6, CI [1.01–2.7]) and patent ductus arteriosus (OR 1.9, CI [1.1–3.1]) were associated with a higher rate of IVH. In addition, univariate analysis revealed that Apgar scores at 5 min ($p < 0.001$), BDP/ROP/NEC (p < 0.001),

Abbreviations: AIS, amniotic infection syndrome; ANS, antenatal steroids; BPD, bronchopulmonary dysplasia; CBF, cerebral blood flow; CI, confidence interval; CRIB score, critical risk index for babies score; CPAP, continuous positive airway pressure; CRP, C-reactive protein; CUSS, cranial ultrasonography scans; EOS, early onset sepsis; ELBW infants, extremely low birth weight infants; ELGAN, extremely low gestational age neonates; GA, gestational age; g, grams; IVH, intraventricular hemorrhage; LBW infants, low birth weight infants; UA-pH, umbilical arterial pH; NGFN, Nationales Genomforschungsnetz Deutschland; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; iNO, inhalative nitric oxide; PDA, patent ductus arteriosus; pPROM, preterm premature rupture of membranes; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; SD, standard deviation; US, ultrasound; VLBW infants, very low birth weight infants; VLGAN, very low gestational age neonates; WOP, weeks of pregnancy

* Corresponding author at: Department of Pediatric Cardiology, Saarland University Medical Center, Kirrberger Straße, 66421 Homburg/Saar, Germany.
E-mail address: martin.poryo@uks.eu (M. Poryo).
[1] Member of the German Center for Lung Diseases (DZL), Germany.

http://dx.doi.org/10.1016/j.earlhumdev.2017.08.010
Received 13 July 2017; Received in revised form 21 August 2017; Accepted 25 August 2017

mechanical ventilation ($p < 0.001$) and inhalative nitric oxide ($p < 0.001$) were significantly associated with IVH.

Conclusions: Our comprehensive analysis demonstrated that the occurrence of IVH in very premature infants is significantly associated with ante-, peri- and postnatal factors being either related to the degree of immaturity or indicating a critical clinical course after birth. The analysis reiterates the necessity for a very close cooperation between obstetricians and neonatologists to reduce the incidence of IVH in this susceptible cohort.

1. Introduction

Intraventricular hemorrhage (IVH) in preterm neonates is one of the most serious complications seen in this high risk patient cohort, and it is associated with significant long-term morbidity and mortality. The etiology for IVH is thought to be multifactorial [1] and related to both ante- and post-natal factors including altered hemostasis [2].

One of the main reasons for morbidity and mortality in very low and extremely low gestational age neonates (< 32 weeks of pregnancy (WOP) = VLGAN; < 28 WOP = ELGAN) is the occurrence of intraventricular hemorrhage (IVH) [3–6]. A significant decline of the incidence of IVH could be seen in the 1980–1990s [5] when routine implementation of antenatal steroids (ANS) increased. Nowadays the rate of IVH is estimated at around 15–25% in VLGAN [5,7,8].

A number of ante-, peri-, and postnatal factors have been linked to the occurrence of IVH [7,9–13]. Pharmacologic prevention trials have been conducted [14] because of the importance of IVH for long-term prognosis, but so far they delivered unconvincing and conflicting data with regard to the effective reduction of IVH.

Moreover, other studies examined the importance of coagulopathy and their potential treatment on the development and severity of IVH [2,15]. The lowest activities of many coagulation factors were seen in extremely low birth weight infants (ELBW) infants, but results from these studies are conflicting. Nevertheless, recommendations with regard to the use of platelets and humoral clotting factors in this susceptible cohort have been published [16–20].

Of note, previous data sets referred to specific subsets of risk factors (either ante-, peri- or postnatal) for the occurrence of IVH in premature infants [2] or relied on older data [10] obtained from more mature neonates often collected before the year 2000. These studies included analyses of potentially relevant clinical parameters (e.g., Apgar score, body temperature at admission, etc.), specific laboratory findings (e.g., clotting factors, etc.) as well as specific interventions (ANS, administration of clotting factors, mechanical ventilation, use of catecholamines). Thus, the main aim of this study was to present an updated, comprehensive and integrative analysis of potential ante-, peri- and postnatal factors associated with the occurrence of IVH in a highly susceptible cohort of VLGAN and ELGAN. Moreover, it was our aim to analyze changes over time by comparing two a priori defined time intervals.

2. Patients and methods

This retrospective study was performed as a multicenter cohort study in five large tertiary neonatal intensive care units (NICU) with annual admission rates of VLGAN between 50 and 100, located mainly in German university hospitals (University Medical Center Giessen; Saarland University Medical Center, Homburg/Saar; University Medical Center of the Johannes Gutenberg University Mainz; Darmstaedter Kinderkliniken Prinzessin Margaret; University Medical Center of the Ludwig-Maximilian-University, Grosshadern/Munich). Standard neonatal intensive care treatment was comparable between participating centers. Data evaluation was a sub-project within the prospective Pneumonia Research Network on Genetic Resistance and Susceptibility for the Evolution of Severe Sepsis (PROGRESS), and the Nationales Genomforschungsnetz Deutschland (NGFN) sponsored by the German Federal Ministry of Education and Research (BMBF).

Data were collected from infants born from 01/01/1998 to 31/12/2012. The study was approved by the local ethics committee (Ethikkommission des Saarlandes, Saarbrücken, Germany) as well as by the local ethics committees of all participating centers. Inclusion criteria were: gestational age (GA) of < 32 WOP, informed parental consent. Patients were not included in study analysis in case of early neonatal death (< 12 h of life) because of lack to obtain parental consent, or if missing data was in excess of 25%.

All relevant ante-, peri- and postnatal data were retrieved from an electronic database (SAP, Walldorf, Germany) and included information about the course of pregnancy as well as the delivery, perinatal maternal infectious parameters (amniotic infection syndrome (AIS) and/or preterm premature rupture of membranes (pPROM)), peri- and neonatal information, the critical risk index for babies score (CRIB score), laboratory parameters within the first 72 h of life, the clinical course and diagnoses (e.g. retinopathy of prematurity (ROP), IVH, hemodynamically relevant patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD)), parameters related to respiratory support (e.g. continuous positive airway pressure (CPAP), mechanical ventilation, etc.) as well as pharmacological therapies. Definitions of ROP, BPD, IVH, PVL and NEC have been provided previously [2]. Hemodynamically relevant PDA was characterized by echocardiography and either the need for a change in medical treatment (e.g. fluid restriction, use of inotropes, escalation of ventilatory support), the use of either ibuprofen or indomethacin for PDA closure or surgical PDA ligation.

Included neonates were subdivided into two groups with regard to GA: group 1 corresponded to neonates delivered ≤ 27 + 6 WOP (ELGAN) and group 2 were all neonates born between ≥ 28 + 0 and < 32 + 0 WOP (VLGAN).

Furthermore, two a priori defined time intervals, 1998–2005 and 2006–2012, were used to examine changes in the occurrence of IVH over time.

In all NICUs, serial cranial ultrasonography scans (CUSS) were performed based on the unit protocol by the attending neonatologist with expertise and training in ultrasonography on at least day 1, 3, and 7. Routinely, ultrasound studies were then repeated at 14, 21, 42 days of life, and then at term-corrected gestation with individual modifications made as deemed necessary. The *Papile* grading system for IVH [21] was used for assessment of IVH. The definition is as follows:

(1) Grade 1: Blood in the periventricular germinal matrix regions or germinal matrix hemorrhage.
(2) Grade 2: Blood within the lateral ventricular system without ventricular dilatation.
(3) Grade 3: Blood acutely distending the lateral ventricles.
(4) Grade 4: Blood within the ventricular system and parenchyma.

Primary data were entered into Microsoft Excel 2010 and further statistical analysis was performed using IBM SPSS Statistics (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Data are presented as minimum, maximum, mean, median and standard deviation, as appropriate. Comparison of variables between the groups of presence and absence of associated factors was performed using contingency tables, Chi^2-test, Mann-Whitney-U test and t-test for two independent samples, respectively. Two-sided *p*-values < 0.05 were defined as statistical significant. Due to the