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Perinatal risk factors for neonatal intracerebral hemorrhage in preterm infants

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Abstract

Objective: To investigate the perinatal factors related to neonatal intracerebral hemorrhage (ICH) and possibly to define obstetric and perinatal risk factors. *Study design:* All medical records of women who delivered in the period from 1 January 1991 to 1 January 2000 were reviewed for intracerebral hemorrhages in infants born between 24 and 34 weeks of gestation and treated in the postnatal period. Sixty infants with ICH (Group I) and 60 infants without ICH (Group II, matched controls) were determined for comparison. Obstetrical parameters and risk factors and perinatal outcome parameters were evaluated and statistically analyzed. *Results:* Neonatal intracerebral hemorrhage prevalence was 0.8% (60/7635 births). Betamethasone administration was significantly less in Group I than in Group II (27% versus 46%). Although Doppler-sonography of the middle cerebral artery was performed in a minority of the cases, it showed a significant tendency of lower resistance indices (brain sparing) in the intracerebral hemorrhage group (66.7% versus 21.1%). Postnatally, infants with intracerebral hemorrhage showed a significantly more often umbilical arterial acidosis (18% versus 10%), a greater base deficit, lower median 5 min Apgar scores (6 and 8, respectively for Groups I and II), and a lower thrombocyte count (Group I 190,000 ± 76,000 μl−1, and Group II 227,000 ± 96,000 μl−1). Infants in Group I were more often (93% versus 76%) and longer (26.7 ± 30.5 days versus 15.4 ± 11.7 days) dependent on ventilatory support than infants in Group II. Mortality rate in Group I (35%) was significantly higher compared to Group II (17%). *Conclusions:* Antenatal Doppler sonography in predicting intracerebral hemorrhage in preterm infants should be investigated in large scale prospective studies. Postnatal low pH-values (pH < 7.1) and a base deficit of more than −16 mmol/L in the umbilical artery, low Apgar scores and thrombocytopenia are associated with a neonatal intracerebral hemorrhage and prophylaxis with corticosteroids reduces the risk for it. A higher neonatal mortality and morbidity, including neurological and neuromotoric dysfunctions is expected in this clinical entity.

Keywords: Neonatal intracerebral hemorrhage; Doppler sonography; Perinatal outcome; Risk factors

1. Introduction

The magnitude of the problem of brain injury in the premature infant and, particularly, the prevention of that injury is enormous. Because of major advances in perinatal medicine and neonatal intensive care, approximately 85% of these infants survive. Of the survivors, approximately 5–15% exhibit major spastic motor deficits, grouped under the rubric 'cerebral palsy', and an additional 25–50% exhibit less prominent developmental disabilities, involving not only motility but also cognition and behavior, with school disturbance the nearly uniform result [1]. Prevention and early management of these manifestations of the brain injury will require determining the perinatal risk factors associated with this clinical entity.

Besides the main risk factors, such as gestational age and birth weight, studies on neonatal intracranial hemorrhage (ICH) denoted low Apgar scores, acidosis, and birth asphyxia as further risk factors [2,3]. Consequences of

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ICH are a higher mortality rate, as well as ventricular dilatation, hydrocephalus, spastic paresis and disorders in the neurological development [4–6].

The aim of this study is to investigate the perinatal factors related to neonatal intracerebral hemorrhage and possibly to define obstetric and perinatal risk factors.

2. Patients and methods

After approval of the clinical ethical committee all medical records of women who delivered in the period from 1 January 1991 to 1 January 2000 at the University Hospital, Department of Obstetrics and Gynecology, Homburg/Saar, a tertiary obstetrical referral hospital in Saarland/Germany, were reviewed for intracerebral hemorrhages in infants born between 24 and 34 weeks of gestation and treated in the Department of Pediatrics in the postnatal period. Sixty infants with ICH (Group I) and 60 infants without ICH (Group II, matched controls) were determined for comparison.

For matching of Group II fetuses to Group I, same gestational ages at diagnosis, maternal age, gestational ages at delivery, mode of delivery and birth weights were assigned as criteria. Each group consisted of 36 boys and 24 girls. Gestational age was calculated from the first day of the last menstrual cycle and, if necessary, adjusted by early ultrasound estimates of gestational age.

Cranial ultrasound, according to the clinical protocol of the neonatal intensive care unit (NICU), was performed within 24 h to admission to the NICU on all neonates and at the end of first week of life and twice a week until discharge from the NICU. The severity of intraventricular hemorrhage was graded according to Papile et al. [7] (Table 1). The findings of the final cranial ultrasonography were used in analyses.

From those that were selected for the study the following variables were recorded from maternal and neonatal medical records:

- Obstetric parameters: Gestational age at birth, previous miscarriages, ultrasound scan, Doppler-sonographic examination, use of antenatal corticosteroids (betamethasone) in either an incomplete or a full course of antenatal corticosteroids (two doses given with an interval of 24 h at least 48 h before birth), delivery time and mode.
- Obstetric risk factors: Preeclampsia/HELLP-syndrome, premature rupture of membranes, premature labour, smoking, pathological fetal heart rate monitoring.

Table 1
Classification of neonatal intracerebral hemorrhage [7]

Grade 1	Hemorrhage limited to the germinal matrix
Grade 2	Hemorrhage with extension to the ventricles, without dilatation of the ventricles
Grade 3	Hemorrhage with extension to the ventricles, with dilatation of the ventricles
Grade 4	Hemorrhage with parenchymal extension

- Fetal outcome: Acid/base status, Apgar scores, birthweights, hematological parameters of the newborn and CRP levels.
- Postnatal progress: Duration of hospitalization, assisted ventilation and duration of ventilation, results of cranial ultrasonography (normal or abnormal), mortality.

An acidosis was defined as an umbilical arterial pH value lower than 7.10 and an umbilical arterial base deficit was defined as values greater than −16 mmol/L at birth.

In patients who underwent a Doppler sonographic examination during their pregnancy, data concerning the RI, the existence of absent enddiastolic flow (AEDF) and reverse flow (RF) of the fetoplacental vessels were collected. AEDF and RF of the umbilical artery and fetal aorta were directly considered as pathologic if the values of the fetal aorta, umbilical artery and uterine artery were >90th, and for the middle cerebral artery (MCA) ≤10th percentile [8].

Statistical analysis: For quantitative characteristics, the mean value, median and standard deviation were determined. The statistic procedures deployed were the *t*-test for unlinked random samples, and if appropriate the Mann–Whitney *U*-test. Partly the quantitative characteristics were further classified. For these classes, as well as for the qualitative characteristics, frequencies were determined, contingency tables were compiled and the Chi-square test and if appropriate the Mantel–Haenzel test were applied. In all applied statistical procedures, *P*-values ≤0.05 were considered as statistically significant.

3. Results

During the study period an ICH was determined in 60 infants (total 7635 births); corresponding to a prevalence of 0.8%. Gestational age at delivery was 29 weeks' (S.D. ± 27 days), and the mean birth weight was 1224 ± 675 g. In Group II, gestational age at delivery was 29 weeks (S.D. ± 26 days), and the birth weight was 1257 ± 655 g. There was no difference of gestational age and birthweights at the time of delivery between the groups.

Fifteen patients in Group I, and 19 in Group II underwent a Doppler sonographic examination during their pregnancy. The relative low number of antenatal Doppler sonographic examinations was due to the retrospective construction of the study. In Group I, the examination of the fetal aorta and umbilical artery showed a tendency towards serious pathologies (enddiastolic zero flow), while the findings in Group II were mostly inconspicuous or slightly pathological (raised RI). However, Doppler sonography of the middle cerebral artery showed significant differences between the groups ($P = 0.004$) (Table 2). Doppler sonography of the uterine artery showed no differences between the groups.

The groups were not different regarding frequencies of high risk pregnancies (preeclampsia, Hellp syndrome,