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REDUCTION IN DEATH OR MODERATE/SEVERE DISABILITY BY WHOLE BODY HYPOTHERMIA FOR HYPOXIC-ISCHEMIC ENCEPHALOPATHY (HIE)

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Background: Post-asphyxial hypothermia is protective in experimental animals; however, there have been no RCT evaluating safety and effectiveness of whole body hypothermia in term infants with HIE.

Objective: To assess safety and effectiveness of whole body hypothermia in term infants with moderate and severe HIE.

Design/Methods: A RCT was conducted of infants 36 weeks GA admitted 6 h of age with either a) a cord or first (<1 hour) pH <7.0 or BD >16 mEq/dl or b) a perinatal event and need for resuscitation, AND evidence of moderate or severe HIE by a certified examiner. Infants were randomized to normothermia (NORMO) or whole body cooling to 33.5 C esophageal (HYPO) for 72 h followed by rewarming by on site-research personnel using the Cincinnati Sub-Zero system. Primary outcome was death or disability at 18 mos: severe disability defined as ANY: Bayley MDI<70, Gross Motor Function (GMF) level 3–5, hearing impairment requiring aids, or blindness or moderate disability defined as MDI 85–70 AND either GMF 2, hearing impairment with no amplification or seizure disorder.

Results: Of 798 screened infants, 239 were eligible, and 208 were randomized; 102 to HYPO and 106 to NORMO. Target temperature was achieved in HYPO within 90 min and remained constant throughout 72 h. Adverse events were similar among HYPO infants (n=19) and NORMO (n=15), p=0.38. At 18 mos, primary outcome data were available for 204 of the 208 infants. Death or moderate/severe disability occurred in 45 (45%) infants in HYPO and 64 (62%) in NORMO: Risk Ratio (RR) (95%CI) 0.72 (0.55–0.93) with # needed treat (NNT)=6. The risk of death was 24% in HYPO and 36% in NORMO, RR 0.66 (0.43–1.01). The risk of death or disability after moderate HIE was RR 0.67 (0.44–1.03) and after severe HIE was 0.82 (0.64–1.06). For HYPO and NORMO respectively, the risks of disabling CP was 19.7% and 28.6%, RR 0.69 (0.38–1.26), blindness was 5.5% and 14.3%, RR 0.38(0.12–1.19) and hearing impairment requiring aids was 4.0% and 6.3%, RR 0.64 (0.15–2.75).

Conclusions: We have demonstrated the effectiveness and safety of whole body hypothermia in term infants with moderate and severe HIE, defined by rigorous criteria, using certified examiners and trained personnel to implement and monitor the intervention and outcome.

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PREDICTION OF ADVERSE OUTCOME BY THALAMIC AND BASAL GANGLIA MRI T2 RELAXOMETRY AND THALAMIC PROTON MRS IN NEONATAL ENCEPHALOPATHY

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Background: Robust quantitative methods are needed to assess the severity of cerebral injury following perinatal hypoxia-ischaemia and to ascertain the efficacy of neuroprotective therapies.

Aim: To compare the prognostic efficacies of early magnetic resonance imaging (MRI) spin-spin (T2) relaxometry and proton (1H) magnetic resonance spectroscopy (MRS) in infants with neonatal encephalopathy (NE).

Methods: Twenty-three term infants with NE were studied with MRI and MRS at 2.4Tesla within 5 days of birth (mean age at scan 3.09 (sd 1.35) days). Mean MRI T2s were calculated for basal ganglia (BG) and thalamic (TH) regions of interest. Thalamic metabolite 1H-MRS peak area-ratios were determined using an 8ml cubic voxel (PRESS; echo time 270ms; repetition time 2s). Infants were divided into 3 outcome groups based on 1 year assessment: i) normal; ii) moderate outcome (neuromotor signs or Griffiths quotient (DQ) 75–84); iii) severe outcome (functional neuromotor deficit or DQ<75 or death). Logistic regression was used to examine the predictive efficacies of MRI T2 and MRS metabolite ratios at differentiating between normal and adverse outcome (moderate and severe groups combined). Prognostic sensitivities and specificities were determined using a threshold probability for group assignment of 50%.

Results: TH and BG T2 correlated with outcome (r=0.594, p=0.003; r=0.493, p=0.017 respectively). Thalamic lactate/ N-acetylaspartate (lac/NAA) and Lac/ total creatine (Cr) correlated positively and NAA/Cr correlated negatively with outcome (r=0.707, p<0.001; r=0.636, p=0.001; r= -0.668, p<0.001 respectively). TH and BG T2 were significant predictors for adverse outcome (p=0.002) as were Lac/NAA, Lac/Cr and NAA/Cr (all p<0.001). Lac/NAA demonstrated highest sensitivity and specificity (88% and 87% respectively) for adverse outcome and was better than TH and BG T2 (87% and 63%, and 80% and 63% respectively).

Discussion: Increased Lac/NAA was most predictive of outcome. However if 1H-MRS is unavailable, MRI T2 relaxometry can provide useful early prognostic information.

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THE NEWBORN RAT MODEL OF NECROTIZING ENTEROCOLITIS AND EXPRESSION OF ENDOGENOUS PEPTIDE ANTIBIOTICS IN SMALL BOWEL

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Background: Necrotizing enterocolitis [NEC] is a deadly disease in preterm human neonates. Since 1975, the newborn rat has been the preferred animal model of human NEC. Why the newborn rat model develops manifestations like human NEC remains elusive.

Objective: We hypothesized that the newborn rat has a deficiency in the expression of endogenous peptide antibiotics in the ileum, the major site of NEC, and thus renders the ileum susceptible to intra-luminal bacterial overgrowth.

Design/Methods: Stomach, jejunum, ileum, and colon were recovered from 3-day-old, 7-day-old, and adult rats. Bowel specimens were pooled from 4 or more newborn rats. At least 3 separate litters of rats were studied. RNA was isolated from bowel and copy counts of cryptdin-5 and -7 [alpha-defensins], lysozyme, and secretory phospholipase A2 per microgram of RNA were quantified using the Roche Light Cycler.

Results: Cryptdins were found mostly in the small bowel. In 3-day-old rats, cryptdin-5 was not detected compared to the ileum of adult rats (P<.001), while cryptdin-7 was 25% of adult expression (P<.01). By 7 days of age, cryptdin-5 and -7 were 50 to 60% of the expression in adult ileum. Lysozyme and phospholipase A2 expression in ileum was similar in 3- and 7-day-old rats, and their expression was ~70% and ~45%, respectively, of the ileal RNA content for these antimicrobial peptides in adult rats.

Conclusions: Since cryptdins account for 70% of the antimicrobial activity against Escherichia coli in the ileum of adult mice, the low expression of cryptdins in 3-day-old rats correlates with the pathogenesis of NEC in this species. Moreover, this finding agrees with low expression of alpha-defensins in the human fetus at 24 weeks of gestation. We speculate these observations have meaning for the development of NEC in extremely preterm human infants.

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EXTREME PREMATURITY, FETAL GROWTH RESTRICTION, AND NON-IMMUNE ERYTHROBLASTOSIS

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Background: Fetal monitoring may prolong pregnancies with fetal growth restriction [FGR]. Infants with extreme prematurity and FGR may have elevated nucleated red blood cells [NRBC] and negative tests for isoimmunization [termed non-immune erythroblastosis or NIE].

Objective: This study correlated the magnitude of NIE in infants <29 wk of gestation with jaundice at <24 h of age, low platelet counts, intracranial hemorrhage [ICH], hypoglycemia, blood potassium at <72 h of age, cardiomyopathy, pulmonary hypertension, delayed passage of meconium, feeding intolerance, and necrotizing enterocolitis [NEC].

Design/Methods: A case-control, retrospective study examined admissions to a University NICU. Multivariate analysis determined differences between groups. The Holm sequential Bonferroni approach controlled for type I error across tests.

Results: There were 18 cases with FGR. The FGR + NIE group had a lower birth weight (P<.001) and elevated NRBC counts (P<.001) compared to gestational age matched controls. FGR compared to control had a higher occurrence of feeding intolerance [P = .007], ICH [P = .02], and NEC [P = .07]. Odds ratios were 3.4, 4.0, 7.0, and 8.1 for intestinal perforation, NEC, feeding intolerance, and ICH, respectively, in the extremely preterm infants with FGR + NIE v. control.

Conclusions: Extremely preterm infants with FGR and NIE have an increased prevalence of certain neonatal complications compared to normally grown, yet extremely preterm infants without NIE. NIE is a marker for identifying risks of certain conditions in extremely preterm and growth restricted infants.

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THE VALUE OF DIFFUSION-WEIGHTED MAGNETIC RESONANCE IMAGING, ULTRASONOGRAPHY AND ELECTROENCEPAHLOGRAPHY FOR EARLY DIAGNOSIS OF NEONATAL ENCEPHALOPATHY

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High-risk and preterm infants are likely to develop germinal matrix hemorrhage (GMH), intraventricular hemorrhage (IVH), cystic periventricular leukomalacia (PVL) and diffuse white matter injury. The aim of this study is to compare the usefulness of ultrasonography (USG), diffusion-weighted MR imaging (DWMRI) and electroencephalography (EEG) for the early diagnosis of ischemic brain injury and their prognostic value. Among the total of 89 infants who were diagnosed as suffering from perinatal asphyxia, hypoxic ischemic encephalopathy (HIE) or seizure, admitted to NICU in Seoul National University Bundang hospital between May 2003 and August 2004, 28 infants were examined using conventional and DWMRI during the early period of injury. Four infants were excluded based on exclusion criteria before analysis. The study population included 45.8% (11/24) male and 54.2% (13/24) female infants. Their gestational age was 38¡3/4 3 weeks and birth weight was 3.09¡3/4 0.82kg (range: 1.52~4.86kg). The 5-min APGAR score ranged from 1 to 10 (median 7). Forty-five% (11/24) infants were delivered by cesarean section and 54.2% (13/24) infants were delivered vaginally. The first examinations were performed at 3.17¡3/4 1.64 days (1~7 days) for USG, 5.74¡3/4 3.44 days (2~13 days) for MRI and 4.19¡3/4 2.71 days (1~13 days) for EEG. The rate of abnormal findings on their first examinations was 30.4% (7/23) on USG, 50.0% (12/24) on DWMRI and 90.4% (19/21) on EEG. Based on follow-up medical records especially in view of neurologic sequelae and treatment, EEG showed the highest sensitivity, specificity and negative predictive value. While DWMRI was more sensitive but less specific than USG. In conclusion, DWMRI showed higher correlation with subsequent neurologic sequelae than conventional MRI and USG. In addition, both EEG and DWMRI, when performed in the acute phase of the disease in high-risk newborn infants, are expected to be useful for treatment planning and for the earlier prediction of the neurologic prognosis.

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PERINATAL CHARACTERISTICS AND THE EFFECT OF ERYTHROMYCIN IN THE NEONATE COLONIZED WITH UREAPLASMA UREALYTICUM

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Ureaplasma urealyticum is a common inhabitant of the urogenital tract of pregnant women and over the years, have been often implicated in chorioamnionitis, preterm birth, and perinatal morbidity and mortality. In up to 50% of infants<34 week of gestational age, Ureaplasma urealyticum is isolated from urine, blood, CSF, tracheal aspirates, pleural fluid and lung tissue, causing respiratory insufficiency and development of bronchopulmonary dysplasia. This study examines the perinatal charateristics, respiratory morbidity and the usefulness of erythromycin in the newborn infants, those colonized with ureaplasma urealyticum.

Population and methods: A urine specimen for ureaplasma urealyticum culture was obtained from 90 infants admitted consecutively to NICU in Seoul national university Bundang hospital immediately after birth and their medical records were reviewed. Placental biopsy was performed to examine the presence of histologic chorioamnionitis. For all infants colonized with ureaplasma urealyticum, we treated with intravenous erythromycin for 2 weeks.

Results: 13 (14.4%) infants had growth of Ureaplasma urealyticum, 77 (85.6%) had negative culture results. Mean gestational age (32¡3/4 2 weeks vs 32¡3/4 3 weeks) and birth weight (1.83¡3/4 0.53kg vs 1.83¡3/4 0.65kg) were not different between the two groups (p=0.412, p=0.739). The presence of acute respiratory morbidity and the development of symptomatic bronchopulmonary dysplasia were not different (OR 0.225 CI 0.57–0.883 vs OR 1.509 CI 0.381–5.984) even though the radiologic abnormalities suggestive of bronchopulmonary dysplasia were higher in infants colonized with ureaplasma (OR 39.33 CI 4.782–323.509). Chorioamnionitis (OR 9.167 CI 1.887–44.521) and the level of CRP (0.51¡3/4 1.15mg/dL vs 0.17¡3/4 0.35mg/dL, p=0.029) showed the significant association with ureaplasma colonization.

Conclusion: This data indicates colonization with ureaplasma can be explained to be closely associated with chorioamnionitis and perinatal morbidity as well as development of bronchopulmonary dysplasia. And therapy with erythromycin might play a role to prevent symptomatic bronchopulmonary dysplasia, but our data needs further case-control study to support the effects of therapy.