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EARLY AND LATE ADVERSE EFFECTS FOLLOWING SURFACTANT THERAPY

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Background: Exogenous surfactant (S) therapy improved mortality and morbidity of premature babies with respiratory distress syndrome. The commercial S preparation used in our NICU is natural "bovine" type. The adverse effects of this therapy have not been clarified yet. **Objective:** To estimate the early and later risks of S therapy for respiratory distress syndrome (RDS).

Methods: Data from all premature newborns with or without RDS treated or not with S in our NICU the last 10 years were analyzed. The incidence and the relative risk(RR) of the lung and intracerebral hemorrhage as well as of the infection were calculated. Three hundred ninenty three of them accepted to participate in a retrospective study and were examined for allergic disorders, such as allergic rhinitis, asthma and adverse food reactions.

Results: Three thousands forty premature newborns graduated our NICU from 1994 to 2004.Pulmonary hemorrhage was observed in the 57 of the 330 newborns with RDS who received S and the 6 over 198 of those newborns untreated with S,chi squared=19.489, p=0.00001,RR=5.756. Intraventricular hemorrhage was diagnosed in 106 of the 281 and 20 over 184, respectively, chi square =24.629, p=0.00001,RR=3.490.Infection in 115 of 272 and 87 in 117,respectively, chi squared =9.291,p=0.00167,RR=1.768. Positive history of allergy was estimated in the 44% of the children treated with S for RDS and in the 25% of those with RDS not treated with S, chi squared=11.363, p=0.000749.From the premature babies without RDS allergy was noted in 28%,x=0.8061,p=0.3692.

Conclusion: Despite the undoubtfull benefits of the S therapy for RDS attention should be paid to its possible early and late adverse effects. The S therapy increases the risk for severe even lethal complications such as pulmonary or intraventricular hemorrhage and infection. It is impressive the almost two-fold increase in the incidence of allergy during childhood in babies treated with S compared to non-treated ones. Prospective clinical trials and basic research would help to minimize the early risks and optimize late prognosis in newborns treated with S.

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DELAYED HYPOYHERMIA IS NEUROPROTECTIVE IN MODERATE, BUT NOT SEVERE, PERINATAL HYPOXIC-ISCHAEMIC BRAIN INJURY

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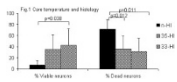
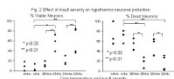
Background: Hypothermic neuronal rescue therapy is a potent treatment for the newborn infant with hypoxic-ischaemic (HI) brain injury; the degree of neuroprotection, however, may be dependent on the delay, duration and depth of hypothermia and on the severity of the HI injury. A precise definition of the patient group who will respond to neuroprotective intervention is urgently required. **Objective:** The purpose of this study was to assess the relationship between the severity of the HI insult and the efficacy of hypothermic neuroprotection assessed histologically in an experimental model. **Design/Methods:** 19 piglets were randomised to 3 groups within 24 hr of birth; (i) normothermic (n-HI, n=6); (ii) core temperature 35°C (35-HI n=6); and (iii) core temperature 33°C (33-HI n=7). Animals were then subjected to a transient HI insult (bilateral carotid occlusion and FiO2 12–16% for approximately 1 hr). Phosphorus magnetic resonance spectroscopy gave a measure of the duration and magnitude of acute depletion of nucleotide triphosphate (NTP) relative to the exchangeable high energy phosphate pool (EPP): Animals were subgrouped: (i) moderate insult (n-HI-m, 35-HI-m, 33-HI-m); and (ii) severe insult (n-HI-s, 35-HI-s, 33-HI-s). Animals were maintained at target temperature for 24hr commencing 2hr after the end of the insult and then rendered normothermic. At 48hr the animal was sacrificed and the brain perfusion fixed. Hematoxylin and eosin stained slices were assessed in 10 regions in the cortex and 6 regions in the deep grey matter. Percentages of viable and necrotic neurons in each region were compared in subgroups.

Results: Consolidating all grades of HI insult, compared to the n-HI group, 33-HI and 35-HI animals both had less dead neurons; only the 33-HI group had more viable neurons (Fig 1, all $p < 0.05$). In the normothermic group histological scores were similar in moderate and severe insults (Fig 2). Hypothermic intervention improved histological scores in the moderate insult groups (35-HI-m, 33-HI-m) but not in the severe insult groups (Fig 2).

Conclusion: These data suggest that HI insult severity affects the efficacy of subsequent hypothermic intervention; systemic hypothermia of 35°C and 33°C were neuroprotective only after moderate HI insults.





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DOPPLER ASSESSMENT OF PULMONARY ARTERY PRESSURE IN VERY LOW BIRTH WEIGHT INFANTS AT RISK OF CHRONIC LUNG DISEASE

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Background: Chronic lung disease (CLD) is mainly confined to very low birthweight (VLBW) infants and is a significant cause of morbidity and mortality. It appears that pulmonary hypertension plays an important part in the physiopathology of CLD and has been linked to the increased incidence of death in infants with CLD. Doppler echocardiography allows to assess non-invasively pulmonary artery pressure in these infants. The objectives are: first, to evaluate the pulmonary artery pressure changes in VLBW infants at risk of CLD, and second, to determine whether Doppler evaluation can detect the infants at risk to develop CLD.

Methods: In a prospective study, all infants with a birth weight of less than 1500g were studied by serial Doppler echocardiography on day 15, 28 of life and at 36 weeks corrected age. Pulmonary artery pressure was assessed by its inverse relationship with the ratio of pulmonary artery Doppler time to peak velocity: right ventricular ejection time which was corrected for heart rate (TPV: RVET (c)). CLD was defined as oxygen dependency at 36 weeks corrected age with characteristic chest X-ray.

Results: One hundred eleven infants have been studied over one year. Thirteen infants developed CLD. The TPV: RVET(c) ratios were only significantly different between the CLD group and the control group at 36 weeks corrected age. Data are presented as median [minimal-maximal] range. (* p value by Mann-Whitney test)

Group	BW (g)	GA (weeks)	TPV: RVET (c) 15 d	TPV: RVET (c) 28 d	TPV: RVET (c) 36 weeks
Control (n=98)	1250 [560–1500]	30 [23–36]	0.71[0.36–1.03]	0.68[0.36–1.21]	0.67[0.36–0.90]
CLD (n=13)	830 [570–1280]	27 [25–31]	0.73[0.45–0.88]	0.71[0.48–0.98]	0.58[0.33–0.71]
p *	<0.01	<0.01	0.70	0.83	<0.01

Conclusion: This study shows that infants with CLD develop signs of elevated pulmonary artery pressure at 36 weeks corrected age, but Doppler examination at 15 and 28 d post natal age failed to predict CLD.

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FREQUENCY-SPECIFIC HEARING IMPAIRMENT IN NEONATES AFTER PERINATAL HYPOXIA-ISCHAEMIA

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Background/Aim: Perinatal hypoxia-ischaemia (HI) is one of the major risk factors of acquired sensorineural hearing impairment in infants. So far, little is known about which frequencies on the audiogram of the cochlea in newborn infants are highly susceptible to perinatal HI. By measuring distortion product otoacoustic emissions (DPOAEs), this study aimed to identify the frequencies that are impaired in neonates after HI.

Methods: The subjects were 46 term neonates who suffered perinatal HI (5 min Apgar score ≥7 and clinical evidence of HI). Normal controls were 35 healthy term neonates without problems. DPOAE was elicited by two pure tones ($f1$ and $f2$; $f2/f1$ = 1.22) presented simultaneously, with the lower frequency primary tone ($f1$) at 65 dB SPL and the higher frequency primary tone ($f2$) at 55 dB SPL. The $f2$ primary tone was presented at 10 frequencies between 0.5 and 10 kHz. In individual subjects, a testing result that 6 or more out of the 10 frequencies passed the criteria was classified as a total pass. Both the left and right ears were tested. DPOAE was measured on day 3–5 after birth. One month later, all neonates after HI who had normal acoustic impedance (n = 41, 82 ears), and the normal controls who failed in the first DPOA testing were re-tested.

Results: On day 3–5 after birth, the pass rates across the frequencies, mainly 1–5 kHz, in the neonates after HI were all lower than in the controls. The total pass rate was 77.2% (71/92 ears), compared with 95.7% (67/70 ears) in the controls. The patterns of $2f1$- $f2$ DPOAE amplitudes at different frequencies in both the neonates after HI and the controls were generally similar to those of the pass rates, with a 'dip' at the frequencies 750 Hz and 1 kHz. The difference in the patterns between the two groups was also similar to that in the pass rates. One month later, all the 3 ears which did not pass the first DPOAE testing in the controls passed the re-test. Of the 92 ears in neonates after HI, 80 had Type A tympanogram, and the remaining had Type B (n=2) or Type As/C (n=10), suggesting middle ear disorders. The DPOAE pass rates in the 80 neonates with Type A tympanogram tended to decrease slightly further at all frequencies. The total pass rate also decreased further to 62.5%.

Conclusions: The neonatal cochlea, mainly at the frequency range of 1–5 kHz, was impaired after perinatal HI. One month later, the impairment did not show any improvement. The findings may have important implication to early intervention. Follow-up study is needed to detect any permanent frequency-specific impairment.

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DYNAMIC CHANGES IN CEREBRAL BLOOD FLOW DURING SELECTIVE HEAD COOLING IN NEWBORN PIGLETS

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Background/Aim: Selective head cooling (SHC) is a promising therapy for hypoxic-ischaemic brain damage (HIBD) in neonates. Disturbance of cerebral blood flow (CBF) plays an important role in neonatal HIBD. Safe application of SHC will depend on a better understanding of the effects of hypothermia on CBF which is influenced by temperature. This research aimed to study dynamic changes in CBF following SHC in newborn piglets.

Methods: Sixteen newborn piglets, 5 to 7 day old, were randomly assigned to one of the following groups: SHC in normal piglets (n=4), SHC after HI (n=6) and normal temperature after HI (n=6). HI was induced using temporary occlusion of the bilateral carotid arteries and mechanical ventilation with low concentration of oxygen (6%) for 30 minutes. In SHC nasopharyngeal temperature was reduced to 35 °C, and then to 32 °C. During HI and SHC, heart rate, respiratory rate, arteria blood pressure, SpO2, blood glucose and haemoglobin were monitored. CBF was measured with colour microspheres before HI (as baseline) and 2, 4 (35 °C), 6 (32 °C) and 8 hours (rewarming) after HI.

Results: During HI and SHC, no differences in arteria blood pressure, SpO2, blood glucose and haemoglobin were seen among the three groups studied. In normal piglets during SHC, global CBF decreased to 68% and 50% of baseline at 35 °C and 32 °C, respectively, particularly in temporal lobe, parietal lobe, brainstem and cerebellum. In normal temperature newborn piglets after HI, global CBF was decreased to 78% and 60% of baseline at 2h and 4h, respectively, after HI, particularly in temporal lobe, parietal lobe, hippocampus and thalamus. In SHC piglets after HI, similar decrease in global CBF was observed at the same time point at 35 °C and 32 °C, but local CBF was increased at 35 °C, particularly in the hippocampus, striatum and thalamus. At 32 °C, however, local CBF tended to decrease, particularly in the cerebellum, brainstem and parietal lobe.

Conclusion: Global CBF was decreased in piglets at 2h and 4h after HI. The decrease was not influenced by SHC, although global CBF was decreased in normal piglets during SHC. Local CBF in HI piglets during SHC was improved at 35 °C, and tended to decrease when temperature was reduced to 32 °C. Thus, after HI although SHC does not improve global CBF, it improves local CBF when the temperature remains at 35 °C.

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NEONATES WITH LOW APGAR SCORE BUT WITHOUT HYPOXIC-ISCHAEMIC ENCEPHALOPATHY: SUB-OPTIMAL BRAINSTEM FUNCTION

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Background/Aim: The Apgar score has been widely used as an indicator of immediate newborn condition to guide appropriate delivery room management and intervention. It is not clear whether the neonate who have low Apgar score and do not demonstrate clinical signs of hypoxic-ischaemic encephalopathy (HIE) have any degree of brain damage. We have previously found no abnormalities in conventional brainstem auditory evoked response (BAER) in these neonates. However, we cannot exclude some possible abnormalities in the brainstem that cannot be shown by conventional BAER but may be revealed by a relatively new technique – the maximum length sequence (MLS) BAER, which can present acoustic stimuli at much higher rates than is possible using conventional BAER.

Methods: The study group included 34 term infants who had low Apgar score (1 min ≤7 and 10 min ≥8) but no clinical signs of HIE. Normal controls were 38 healthy term infants without any perinatal problems. MLS BAER was serially recorded on day 1, 3, 5, and 7 and 1 month after birth in the study group and on day 1–3 and 1 month in the controls. The click stimuli to elicit MLS BAER were presented at 91–910/sec and 40 dB above the BAER threshold of each subjects.

Results: No significant differences in wave I and III latencies were found between the study and controls groups at any repetition rates of clicks (91–910/sec) on any day studied. Wave V latency in the study group did not differ significantly from the normal controls at 91–455/sec on any day, but increased significantly at 910/sec on day 1 (ANOVA $p < 0.01$). The increase in I-V interval with the increase in click rate was slightly more in the study group than in the controls on day 1 and 3. The interval increased significantly at 455/sec and 910/sec on day 1 ($p < 0.01$ and 0.001, respectively) and day 3 ($p < 0.05$ and 0.01). Similar changes were found in I-III and III-V intervals. From day 5, wave III and V latencies and the I-V interval decreased slightly at all rates of clicks. On day 5, 7, and 1 month, none of the MLS BAER latencies and intervals differed from the controls. No systematic abnormalities were seen in V/I and V/III amplitude ratios during the first month after birth.

Conclusions: During the first 3 days of life there is sub-optional brainstem auditory function in neonates who have low Apgar score but no HIE, which can only be revealed at very high rates of clicks in MLS BAER. Thereafter, the function returns to normal. The findings suggest that such neonates have short-term sub-clinical neural impairment after birth.