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INCREASE OF IGFBP1 FOLLOWING HYPOXIA IN THE PIGLET

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Background:: Insulin Like Growth Factor Binding Proteins (IGFBPs) may be more directly related to ischaemic injury than factors such as pH and lactate, which relate to hypoxia and anaerobic metabolism. We sought to determine if IGFBP1 increases following a hypoxic insult in an animal model and to establish its possible role as an early predictor of outcome.

Methods: 26 piglets were anaesthetised and ventilated. The oxygen intake was decreased to 3 to 7%, in order to create a hypoxic insult. Measurements of IGFBP1 were made before and in regular intervals after the insult. At 72 hours the piglets were sacrificed, the brains perfusion fixed and histologically examined.

Results: There was no difference of birth weight or postnatal age of the animals between the groups. The histology score in the severe insult group was significantly higher than in the control or mild insult group (15.6 vs 0, $p<0.001$). At 48 and 72 hours there was a significant difference of IGFBP1 between the groups with the short and prolonged hypoxia group having higher IGFBP1 levels (43.31 vs 77.9 μmol/L at 48 hours, 30.13 vs 79.68 μmol/L at 72 hours, $p<0.05$)

Conclusion: IGFBP1 is expressed after a hypoxic insult. The sustained increase may represent hepatic damage as is often seen in neonates following perinatal asphyxia. These findings need to be verified in neonates, however, timing of the insult is often not possible in babies. It may be that IGFBP1 may be used as a predictor of outcome following perinatal asphyxia in neonates.

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HYPOXIA ALTERS GABAA-SUBUNIT COMPOSITION: IMPLICATIONS FOR NEURAL RESCUE THERAPY?

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Background: Neuronal death following a hypoxic/ischaemic insult is thought to be caused by excitotoxicity, mediated via glutamate, the major excitatory neurotransmitter found in the central nervous system. ã-amino butyric acid (GABA) is the major inhibitory neurotransmitter in the brain. The GABA receptor is the target of many antiepileptic drugs used in neonates and infants. To date there are no studies examining the changes on the composition of the GABAA receptors by hypoxia in an animal model.

Methods: Eighteen 1-day old piglets were anaesthetised and ventilated. Following a standardised stabilisation period, the oxygen intake was decreased to 3 to 7%, in order to create a hypoxic insult as measured by suppressed EEG. The piglets were sacrificed 6 hours after the insult, the brain removed, sections taken and frozen. Subunits of the GABAA-receptor were quantified by Western Blot.

Results: There were no differences in birth weight, gender or postnatal age between the groups. Two central (hippocampus and thalamus) and two cortical regions (superior frontal and parietal cortex) were examined for the presence and changes of the GABAA subunits alpha 1, 2 and beta 2. At this short period of time following a hypoxic insult (6 hours), changes were evident in the alpha 2 and beta 2 subunits of the GABAA receptor in three regions.

Conclusion: Hypoxia alters subunits of the GABAA receptor; this may affect its inhibitory function and exacerbate hypoxic/ischaemic brain injury.

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THE EFFECT OF SERUM FROM PREECLAMPSIA MOTHER AND HER NEONATAL CORD BLOOD ON THE ACTIVITY OF SOLUBLE ADHESION MOLECULES AND APOPTOSIS IN CULTURED HUVEC

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Purpose: In this study we tested the effect of serum from preeclampsia mother and her neonatal umbilical cord bood on the activity of soluble intercellular adhesion molecule-1(sICAM-1) and apoptosis in cultured human umbilical venous endothelial cells(HUVEC). We also determined if unknown circulating factors in preeclamptic women may influence to the endothelial cells of her fetus. **Study design:** Maternal serum samples were collected before delivery from women with preterm and term preeclampsia (preeclamptic term mother group, n=14, preeclamptic preterm mother group, n=12) and uncomplicated control pregnancies (control term mother group, n=12, control preterm mother group, n=11). Neonatal serum samples of these women were also collected from the umbilical veins(preeclamptic term cord group, n=13, preeclamptic preterm cord group, n=12, control term cord group, n=12, control preterm cord group, n=11). The sICAM-1 were measured with a sandwich ELISA technique in isolated

Results: 1) In sICAM-1 levels: Each mother groups determined significantly higher levels compared to each neonatal cord groups($p<0.001$). Preeclamptic mother groups showed increased levels compaired to control mother groups but have no statistical differences(p0.05). However, the preterm mother groups determined increased levels compaired to term mother groups($p<0.001$). In between each mother groups, preterm preeclampsia mother groups were significantly elevated compared to other mother groups($p<0.001$). In between neonatal cord groups, there were no statistical differences in each groups. 2) In TUNEL stain: Preterm preeclampsia mother group showed significantly increased number of apoptotic nuclei and decreased number of cells compaired to other groups. Especially, the neonatal cord groups of preterm preeclampsia showed no apoptotic body on cultured HUVEC.

Conclusions: Unknown circulating factors in preterm preeclampsia mother activate expression of ICAM-1 and apoptosis in cultured human umbilical venous endothelial cells. But the fetal circulation may not be affected by the factor(s) that lead to disturbed endothelial cell function in women with preterm preeclampsia.

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MOTHERS' ATTITUDES TOWARDS FAMILY CENTERED CARE ACCORDING TO NEWBORN INDIVIDUALIZED DEVELOPMENTAL CARE AND ASSESSMENT PROGRAM (NIDCAP) VERSUS CONVENTIONAL CARE

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Aim: Has family centred care (NIDCAP) impact on mother's perception of caregivers, herself, the infant and the care? Subjects: inborn infants <32 weeks of gestation at the Karolinska Hospital September 1994 to April 1997 randomly assigned to either NIDCAP intervention (n=12) or conventional care (n=13). The two groups were comparable [median, (range)] as to female/male ratio 3/9 vs. 5/8, birth weight 1083 (630–1411) vs. 840 (636–1939), head circumference 24.0 (22.3–26.5) vs. 24.0 (21.1–30.0), gestational age 27.6 (24.0–28.7) vs. 26.1(23.9–30.3) and Clinical Risk Index for Babies 4.0 (0–11) vs. 6.0 (2–15). Infants in interventions group were cared for in a separate room. Weekly observations during hospital stay, with recommendations to attune care and environment according to the infant's current developmental stage and to support the family participation were performed.

Methods: Attitude scale on mother's opinion during hospital stay was created. "Face validity" used to test scale validity and Cronbach's alpha to increase internal consistency. Subgroups of questions studied: mother's perception of staffs' ability to interpret infant's signals and needs; staffs' ability to support motherhood; own ability to interpret infant's signals and needs; closeness with infant; her motherhood; staffs' attitudes towards her; her fear and the care. Ten mothers from each group answered questionnaire at infants' age of 36 weeks PMA.

Results: Mothers in NIDCAP-group estimated closeness between her and infant higher than control mothers [median (range)] (4 (3–4) vs. 3.5 (2–4), p=0.022. No correlation was found between gestational age or birthweight with mother's perception of closeness to baby. Mothers in NIDCAP-group also estimated fear higher than control mothers 3.2 (2.0–3.7] vs. 2.5 (1.3–3.3) p= 0.033. No correlation was found between infant's gestational age or birthweight and mother's perception of "fear".There was a tendency that mothers in NIDCAP-group estimated staffs' ability to support her motherhood somewhat higher than mothers in the control group 3.5 (2.9–3.9) vs. 3.2 (2.3–3.7) p=0.066. A weak correlation between infant's birthweight and mother's perception of staffs' ability to support her motherhood was found (r= -0.436; p=0.054).

Conclusion: NIDCAP early intervention appears to support mother-infant contact during hospital stay.

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PHENOTYPIC AND GENOTYPIC AMINOGLYCOSIDE RESISTANCE IN BLOOD CULTURE ISOLATES OF COAGULASE NEGATIVE STAPHYLOCOCCI FROM A SINGLE NEONATAL INTENSIVE CARE UNIT, 1989–2000

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Background/aims: Coagulase-negative staphylococci (CONS) are the most prevalent pathogen causing late onset sepsis in neonates. A combination therapy including aminoglycosides is often used for empiric treatment of this condition. The aims of the study were to determine the susceptibility of neonatal CONS blood culture isolates to different aminoglycosides and to correlate the presence of genes encoding aminoglycoside modifying enzymes (AME) to aminoglycoside susceptibility pattern and methicillin resistance.

Methods: Over a 12 years period 180 CONS blood culture isolates from one single neonatal unit were collected. According to standard definitions 95 isolates were classified as contaminants and 85 as invasive isolates. Susceptibility testing with Etest or the paper disk diffusion method was done for gentamicin, amikacin, netilmicin, tobramycin, arbekacin and oxacillin. Three different genes encoding AME [aac(6')-Ie- aph(2")-Ia, ant(4')-I and aph(3')-IIIa] and the methicillin resistance gene, mecA, were detected with PCR.

Results: For tobramycin, gentamicin, netilmicin and amikacin 57 (32 %), 61 (34 %), 85 (47 %) and 110 (61 %) of all isolates, respectively, remained susceptible. No increase in aminoglycoside resistance rate was detected during the study period. The susceptibility rates were significant lower among invasive isolates versus contaminants. aac(6')-Ie-aph(2")-Ia was encountered in 125 isolates (69 %), and 22 isolates (12 %) carried this gene in combination with the ant(4')-Ia gene. Only 10 of 125 aac(6')-Ie-aph(2")-Ia positive strains had gentamicin MIC≤ 2 mg/L, but 124 strains remained susceptible to arbekacin. However, 57 isolates highly resistant to gentamicin (MIC ≥ 128 mg/L) showed smaller arbekacin zone diameter ($p < 0,001$) than other isolates. Only 9 % of methicillin resistant strains were susceptible to gentamicin compared to 79 % of methicillin susceptible strains. Methicillin resistant strains remained susceptible to netilmicin (28 %), amikacin (48 %) and arbekacin (99 %).

Conclusion: A high prevalence of aminoglycoside resistance was detected. Among the traditional aminoglycosides netilmicin or amikacin seems a better choice compared to gentamicin in the treatment of neonatal CONS infections. An optimal dosing regimen with high peak concentration will ensure best coverage for borderline resistant CONS strains. Arbekacin showed superior performance with antibacterial activity to 99.4 % of all isolates. We advocate including arbekacin in future clinical trials of empiric therapy of late onset neonatal sepsis.

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PILOT STUDY OF MILRINONE FOR PREVENTION OF LOW SYSTEMIC BLOOD FLOW IN VERY PRETERM INFANTS

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Background: Low systemic blood flow as measured by superior vena cava (SVC) flow is common in very preterm infants. It is strongly associated with IVH and disability and may be caused by poor cardiac adaptation to high vascular resistance (VR)[1]. Because of limited efficacy of therapeutic circulatory support using traditional inotropes[2], we are exploring a preventative approach using Milrinone, an inodilator that increases contractility and reduces VR. The aim of this study was to examine the safety and pharmacokinetics (PK) of Milrinone infusion given prophylactically from 3 hours to very preterm infants (median GA 26w) at risk of low blood flow.

Methods: A dose escalation and PK study was undertaken, starting with low dose infusion (0.25mcg/kg/min) followed by a higher dose (0.5mcg/kg/min) from 3 until 24 hours of age. Monitoring was with serial echocardiography and head ultrasound (HUS). Serial blood Milrinone levels were taken for PK analysis. Using this data, a population modelling and simulation approach established an optimal dosing profile that fulfilled our preventative aim and achieved target drug levels. This regimen was to load with 0.75mcg/kg/min for 3 hours and maintain with 0.2mcg/kg/min until 18 hours of age. The primary outcome was maintenance of SVC flow >45ml/kg/min in the absence of severe hypotension. Secondary outcomes included intraventricular haemorrhage (IVH). Exit criteria: BP <24mmHg for over 30 mins unresponsive to inotropes.

Results: At both infusion rates in the dose escalation phase of study, target blood levels were not achieved quickly enough, only 64% of babies maintained SVC flow and Milrinone levels were high by 24 hrs. Ten infants were then studied using the optimised regimen. All maintained SVC flow >45 ml/kg/min (compared to 40% in an historical cohort) and had drug concentrations within the target therapeutic range. No infant met exit criteria. No immediate adverse effects attributable to Milrinone were noted. There were 3 late deaths attributable to severe respiratory failure and NEC and one from late diagnosis of lethal congenital malformation.

Table: Comparison of haemodynamic parameters and IVH

Milrinone Dose (µg/kg/min)	n	SVC flow >45 ml/kg/min	MBP >24 mmHg	Early IVH (first US)	Late IVH (later US)
0.25	8	5 (63%)	6 (75%)	2 (grade1)	1 (grade 4)
0.5	11	7 (64%)	6 (55%)	2 (grade1)	2 (grade 3)
0.75\0.2	10	10 (100%)	7 (70%)	0	1 (grade 2)

Conclusion: Population PK modelling in the preterm infant has been able to establish an optimal dose regimen for Milrinone that fulfils preventative aims. These encouraging results are currently being investigated for therapeutic efficacy within a pilot RCT.

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