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A RANDOMIZED PROSPECTIVE COMPARATIVE TRIAL OF ELECTIVE EARLY HIGH FREQUENCY OSCILLATORY VENTILATION (HFOV) IN PRETERM INFANTS WITH RESPIRATORY DISTRESS SYNDROME (RDS)

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Background: Chronic lung disease (CLD) is a major clinical problem in very low birth weight infants. It has been reported that by combining early use of HFOV (at high lung volumes) with exogenous surfactant, a further reduction in CLD could be achieved. Aim: the aim of this study was to examine the effect of applying an elective early HFOV at birth combined with surfactant treatment on improving the severity and rate of chronic lung disease.

Methods: Preterm infants enrolled in this study were with gestational age of 32 weeks and birth weight of 2000 grams or less who required mechanical ventilation soon after birth and surfactant therapy to treat surfactant deficient respiratory distress syndrome (RDS). They were randomized into 2 groups, synchronized intermittent mechanical ventilation (SIMV) and HFOV. Infants, who had lethal anomalies, congenital infection or received conventional ventilation for more than 2 hours prior to enrollment, were excluded from the study. The study was conducted between August 2002 and December 2003. Data included were demographic data, complications of prematurity (CLD at 28 days and 36 weeks corrected age, PIE, PVL, IVH, ROP, NEC, PDA), days of ventilation and oxygenation, mode of delivery, antenatal steroids, PROM, failure of mechanical ventilation, sepsis, maternal age and death.

Results: The two groups of patients (SIMV, N=29 & HFOV, N=32) were similar in demographic distribution of birth weight (959.55 ± 379.65, 906 ± 248.30) , gestational age (27.58 ± 2.78, , 27.25 ± 1.95) and gender (M=17, F=12, M=20, F=12), and mode of delivery, antenatal steroids, Apgar score, sepsis, PIE, pneumothorax, IVH, PVL, NEC, PDA and ROP. There were significant statistical differences in days of ventilation between the two groups (SIMV=11.140± 16.56, HFOV=3.79± 5.91, P = 0.001) and in failure of SIMV, P= 0.047. There were no significant statistical differences between the 2 groups in terms of CLD at 28 days and 36 weeks corrected age, P = 0.372, 0.919 and in mortality rate.

Conclusion: The elective early use of HFOV at birth did not improve the severity and rate of chronic lung disease. However, there was significant reduction in days of HFOV in comparison to SIMV.

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IMPACT OF ADMINISTRATION OF ANALGESICS DURING NEONATAL STAY ON PAIN EXPRESSION FOLLOWING NEONATAL STAY IN FORMER PRETERM INFANTS

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Introduction: There are still few data on the impact of pharmacologic treatment of pain during neonatal stay in preterm infants on pain expression after neonatal stay. We therefore investigated pain expression in former preterm infants at first immunisation with Palivisumab (Synagis®) in a cohort of former preterm infants who were treated with NICU-specific analgesia protocol, based on systematic evaluation of pain and an algorithm based use of intravenous analgesics.

Methods: Videotapes were made in former premature infants at first intramuscular administration of Palivizumab. Crying time (seconds) was registered based on these video recordings. Characteristics at time of immunisation and data on neonatal stay (surgery, ventilation, fentanyl administration) were retrospectively collected. Mann-Whitney U test, t test or Spearman rank correlation were used to study potential effects of neonatal variables on crying time.

Results: Videotapes at immunisation were collected in 42 infants of a median gestational age (GA) of 28 (range 25–32) weeks. Median duration of ventilation was 10 (range 0–46) days and median duration of fentanyl administration was 22 (0–672) hours. Thirteen infants received at least one surgical intervention during their neonatal stay. Median postconceptional age at immunisation was 60 (34–90) weeks. Median crying time at immunisation was 44 (range 0–112) seconds. There was no significant correlation of either GA or duration of ventilation or duration of fentanyl administration on crying time. There was no significant difference in crying time between infants who underwent surgery or not.

Conclusions: In a cohort of preterm infants in whom systematic evaluation of pain and an algorithm based administration of analgesics was part of their routine neonatal care, no significant differences in pain expression were observed at immunisation in their first year of life. These findings are suggestive for appropriate analgesia during intensive care, i.e. to treat pain when documented by pain score, while at the same time, such an approach can avoid systematic administration of analgesics.

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ONTOGENY OF UDP-GLUCURONOSYLTRANSFERASE ACTIVITY DURING REPEATED ADMINISTRATION OF PROPACETAMOL IN NEONATES

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Background: Major changes in drug clearance are observed during infancy, at least partially based on ontogenic regulation of metabolic pathways but data on maturation of UDP-glucuronosyltransferase (UGT)-activity in term and especially in preterm neonates are still limited. Since paracetamol provides a good substrate to study ontogeny of UGT-1A6 activity, urinary metabolites of propacetamol were determined in neonates in whom repeated administration of propacetamol (a prodrug of paracetamol for intravenous use) was part of their routine clinical care.

Methods: Following informed parental consent, urine samples were collected during consecutive time intervals in neonates who received consecutive administrations of propacetamol. In these urine samples, paracetamol-glucuronide, paracetamol-sulfate and free paracetamol were determined using High Performance Liquid Chromatography. Spearman rank and linear multiple regression (MedCalc®) were used to study correlations of postnatal age, of postmenstrual age and of repeated administration on the relative contribution of paracetamol-glucuronide to overall urine paracetamol elimination (G/T ratio).

Results: 142 samples were collected in 18 neonates with a median postnatal age of 19 days (range 1–173) and a median postmenstrual age of 39 weeks (range 29–60). Median urine G/T ratio was 14 % (range 1–53). Besides increasing G/T ratio with increasing postnatal ($p<0.0001$) and postmenstrual age ($p<0.01$), repeated administration ($p<0.01$) also correlated with an increasing G/T ratio and this observation remained significant ($p<0.01$) when these 3 perinatal variables were entered in a multiple linear regression model.

Conclusions: The range of urine G/T ratio's documented in this study reflects the major variability in the ontogeny of UGT-activity in neonates of various postnatal and postmenstrual ages. Besides the significant effect of postnatal and postmenstrual age on UGT-activity, an additional independent significant effect of repeated administration of propacetamol was documented. Therefore, observed variability in paracetamol clearance can not only be explained by postnatal and postmenstrual age, but also in part by the number of administered doses of this drug, reflecting an inductive effect of paracetamol on UGT-activity.

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NEONATAL HYPERAMMONEMIA SUCCESSFULLY TREATED WITH CARBAGLU® IN A NEONATE WITH N-ACETYL-GLUTAMATE SYNTASE DEFICIENCY

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Background: Neonatal hyperammonemia is often a sign of a severe urea cycle disorder with fatal outcome. With the introduction of Carbaglu® a new treatment option is available for neonatal hyperammonemia due to N-acetyl glutamate synthase (NAGS) deficiency .

Patient: We report of a child with severe neonatal hyperammonemia due to NAGS deficiency successfully treated with Carbaglu® .The boy, the first child to healthy, related parents, was born full term after a normal pregnancy. At 2½ days of age the child's general condition rapidly deteriorated. He became comatose and had convulsions. Laboratory work up showed normal acid-base balance, normal liver- and kidney function tests but P-NH3 was 926 umol/L. The boy was transferred to ICU, required mechanical ventilation and treatment was initiated with i.v. sodium-benzoate, arginine and glucose. Carbaglu® 100 mg/kg x day was given orally and hemofiltration was started. Within 2 days P- NH3 was < 30 umol/L. U-orotic acid was normal. At 6 days of age the boy was taken off the ventilator, protein intake was gradually increased and he started to breastfeed. Genetic analysis showed that he was homozygous and the parents both heterozygous for the novel mutation R414P in exon 7 of the NAGS gene. Carbaglu® therapy has been maintained at 50mg/kg x day. The boy is breastfed without protein restriction and has normal P- NH3 levels. At 5 months of age he has achieved normal developmental milestones.

Conclusion: This case emphasizes the importance to include Carbaglu® early in the treatment of all patients with neonatal hyperammonemia. With Carbaglu® treatment this boy with NAGS deficiency could be breastfed normally.

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DEVIATIONS FROM REGULAR RESTING ENERGY EXPENDITURE IN SEVERELY DISABLED CHILDREN

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Background: The resting energy expenditure (REE) in children is well investigated and has been clearly defined by the WHO in normative values. Measured data of REE in severely disabled, tetraspastic or -plegic children are not sufficiently available. But especially in this group we quite often realize excessive gain of weight and / or pathological deviations in body composition while the children receive a normocaloric diet according to age.

Methods: In seven severely disabled (tetraspastic/-plegic) patients (age: 4 mo-14y) nine measurements of REE by indirect calorimetry were performed (sober in the morning). The collected data were compared with the normative values of the WHO according to age, weight and height. Further a randomised controll group of healthy children was investigated (n=10, age 2–11 mo) and the results were also compared with the WHO normative values. Statistics: Wilcoxon signed rank sum test, $p<0,05$.

Results: Measured REE in the controll group was within the normal range of the suggested WHO values (59 kcal / kg body weight (BW) median, difference –0,9 median, p0,05). Measured REE in the severely disabled patients (33,3 kcal / kg BW, median) was statistically significant lower than the suggested WHO values (60 kcal / kg BW median, difference –16,8 median, $p<0,01$). In one patient with excessive gain of weight we even found only 1/8 of the suggested WHO REE.

Conclusion: The agreement of the measured with the calculated REE in healthy children is a proof for the validity of the method. In disabled patients a significant difference to the normative values seems to exist. The underlying cause for this remains unclear. We speculate: 1) A different body composition (less fat free mass) leads to a reduced REE per kg BW in chronic immobile patients. 2) A higher metabolic level even in rest is found in healthy persons with regular physical activity due to bodily regeneration and therefore the REE in chronic immobile probands might be lower despite the same conditions during the measurement (30 min rest, thermoneutral surrounding, etc.).

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MEAN CEREBRAL OXYGEN SATURATION INCREASES WITH GESTATIONAL AGE IN PRETERM INFANTS

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Background: Ensuring the adequacy of cerebral oxygen delivery to meet metabolic demand is important in the brain orientated intensive care of preterm infants. Spatially resolved near-infrared spectroscopy allows continuous quantitative assessment of the mean cerebral oxygen saturation (SmcO2). This is a composite measure dependent on cerebral oxygen delivery and extraction. The aim of this study was to measure SmcO2 in a cohort of preterm infants in the first 36 hours of life.

Methods: Seventeen preterm infants born at a median (range) gestational age of 25 (23–32) weeks were studied. The median age at study was 10 (3–35) hours following delivery. All infants were receiving ventilatory support. Four infants had evidence of intracranial haemorrhage on cranial ultrasound examination. A NIRO300 spectrophotometer was used (Hamamatsu Photonics K.K, Japan) with the optodes placed over the parietal region. Continuous SmcO2 data was collected for 30 minutes. Other physiological variables were simultaneously recorded, including the mean arterial blood pressure (MABP) and the partial pressure of carbon dioxide (PaCO2) from a transcutaneous electrode. In 7 infants studied within the first 12 hours of life repeated measures were made at 34 (24–59) hours. The relationship between SmcO2 and gestational age, postnatal age, MABP and PaCO2 was analysed using Pearson Product Moment Correlation. Consecutive measurements were analysed using a t-test (SigmaStat, SPSS Inc).

Results: The median SmcO2 was 57.4 (43–77.7)%. There was a significant relationship between SmcO2 and gestational age(correlation coefficient 0.6, $P=0.01$). There was no significant relationship between SmcO2 and MABP, PaCO2 and age at study. There was no difference in SmcO2 between infants with and without intraventricular haemorrhage. In the infants in whom consecutive measurements were made there was a significant increase in SmcO2 between first and second measurement ($t=-2.5$, $P<0.03$).

Conclusion: SmcO2 is lower in extremely preterm infants and increases with gestational age. Consecutive measurements reveal an increase in SmcO2 in the first 72 hours of life consistent with an increase in cerebral blood flow. Cerebral metabolic rate is known to be low in the preterm infant and to increase with gestational age. In the extremely preterm infant it is likely that the low cerebral oxygen saturation is a consequence of low cerebral perfusion and as a consequence these infants are more vulnerable to hypoxic-ischaemic cerebral injury in the first day of life.