40

FOREGOING OF TREATMENT OF CRITICALLY ILL NEWBORN INFANTS. A DECISION-THEORETICAL APPROACH

D Bratlid St. Olav University Hospital, Department of Pediatrics, Trondheim, Norway

Background: Improvements in diagnostics and treatment have made it possible to save more premature and critically ill newborn infants as well as infants born with severe congenital anomalies. However, some of these infants often develop complication with a poor prognosis for survaval and later quality of life. An active decision to withdraw treatment is often made in such cases. The process of such decisions are, however, often weakly structured and regulated with respect to; who makes the decision, how and when are such decisions taken, and which ethical platform is used. In most cases the etical considerations are based on a combination of duty based and consequence based ethics. In such cases a decision-theoretical approach migh be useful in the decision process.

Methods: The decision-theoretical approach takes into account; who are the persons who will be affected by the decision (infant, parents, staff), what are the different alternatives (continue treatment, extubate), what are the consequences of these alternatives (death, severe handicap), what is the possibility that these consequences will happen (very likely, not likely), and what is the value of these consequences (positive or negative). On this background a decision theoretical approach was used in the evaluation of treatment of a case report of a critically ill newborn infant, where the parents had asked for the treatment to be stopped. The treatment alternatives were considered to be; continue full treatment, immediately extubate, and, continue treatment at present level but not escalate to treat deteriorations or complications.

Results: The analysis showed that considering both the infant and the parents, to continue treatment at the present level came out as the best alternative, with immediate extubation as the the second best. The best alternative for the infant alone was, however, to continue full treatment. The best alternative for the medical staff would be to extubate the infant to die. For all parts (infant, parents, staff) the best decision would be to continue treatment at the present level.

Conclusion: A decision-theoretical approach is useful by its possibility to highlight the different elements which the final decision will be based upon. It will therefore make the decision takers more conscious about the basis for their decision and illustrate how differences in evaluation of consequences and their values might explain any disagreements between the different persons who will be responsible for the final decision.

41

COMPARISON OF CRIB SCORE AND SNAPPE-II SCORE AS PREDICTORS OF MORTALITY AND MORBIDITY IN PREMATURE INFANTS WITH BIRTHWEIGHT < 1501 GRAMS

S L Bratlli, D Bratlid St. Olav University Hospital, Department of Pediatrics, Trondheim, Norway

Background: Neonatal risk scoring systems are designed to predict illness severity and mortality through observations made shortly after birth. The two systems CRIB score and SNAPPE-II score have previously not been compared applied to very low birth weight (VLBW) and extremely low birth weight (ELBW) infants.

Methods:CRIB score and SNAPPE-II score were applied in a retrospective study on two cohorts of premature infants with BW<1501 grams, born in 1990–91 and 2000–01. Validity of risk scores to mortality and morbidity was assessed through analysis of ROC-curves on both cohorts. Furthermore, the scoring systems were used to analyse the immediate severity of illness in the two cohorts

Results:213 infants were included. CRIB score showed outstanding discrimination of mortality with an area under the ROC-curve of 0.91. For the subgroups VLBW- and ELBW infants the area under the curve was 0.85 and 0.90 respectively. SNAPPE-II score had an excellent discrimination of mortality with an area under the curve of 0.83. For the subgroups VLBW- and ELBW infants the discrimination was excellent and acceptable, respectively; areas of 0.80 and 0,73. BW and gestational age (GA) also offered acceptable discrimination of mortality; areas of 0.74 and 0.73 respectively. As predictors of short-term morbidity, defined as intraventricular hemorrhage (IVH), CRIB score was acceptable for the whole study group and for VLBW infants, but not for ELBW infants; areas of 0.77, 0.78 and 0.66 respectively. The same was found for SNAPPE-II score, with areas of 0.74, 0.73 and 0.62, respectively. BW and GA also had acceptable discrimination of morbidity; areas of 0.72 and 0.77, respectively. Infants born in 2000–01 had significantly better respiratory status and CRIB score (4 vs. 1, p<0.01) but not better SNAPPE-II score (30 vs. 24, p=0,26) than infants born in 1990–91. Despite homogeneity in important risk factors there were significantly fewer hospital deaths but no significant change in the frequency of IVH among infants born in 2000–01 compared to infants born in 1990–91.

Conclusion: Both CRIB and SNAPPE-II are better predictors of mortality than BW and GA, but not of morbidity, in VLBW- and ELBW infants than BW and GA. Furthermore, infants born in 2000–01 seemed to be less severely ill during the first twelve hours after birth than infants born in 1990–91, based on CRIB score, mainly because of improved respiratory status. This improvement was not reflected in the SNAPPE-II score.

42

IL-1 DECREASES THE PRODUCTION OF CELLULAR RETINOIC ACID BINDING PROTEIN-I (CRABP-I) IN THE LUNGS OF TRANSGENIC MICE: A POSSIBLE LINK BETWEEN INFLAMMATION AND THE RETINOIC ACID PATHWAY IN THE PATHOGENESIS OF BRONCHOPULMONARY DYSPLASIA (BPD)

K Bry, S Jägevall, U Lappalainen Göteborg University, Pediatrics, Göteborg, Sweden

Background: Pulmonary inflammation, increased production of the inflammatory cytokine IL-1, and vitamin A deficiency are associated with the development of BPD. In order to determine the mechanisms by which IL-1 influences lung development, we have developed a transgenic mouse overexpressing IL-1 in the lung epithelium in an externally regulatable manner. Lung histology of these mice after perinatal induction of IL-1 production shows impaired alveolar and vascular development of the lung, similar to the histological characteristics of BPD. Retinoic acid (RA), one of the most biologically active derivatives of vitamin A, increases septation. We hypothesized that a mechanism by which IL-1 decreases septation, is inhibition of RA action. Cellular retinoic acid binding protein I (CRABP-I) is an intracellular protein that binds RA with high affinity. Lack of CRABP-I results in decreased intracellular RA concentrations when the extracellular RA level is low. OBJECTIVE: To study CRABP-I mRNA expression and protein production in the lungs of fetal and newborn IL-1 overexpressing mice and their wild-type littermates.

Methods: IL-1 expression was induced in transgenic fetuses and newborns. Nontransgenic littermates were used as controls. CRABP-I mRNA expression was studied with real-time RT-PCR on Ed 18, and postnatal days 0, 5 and 9. Immunohistochemistry for CRABP-I was performed using a monoclonal antibody (Abcam).

Results: In control mice, CRABP-I mRNA expression and protein production increased at the beginning of alveolarization, reaching a maximum on postnatal day 9 (Table, arbitrary units). In contrast, in IL-1 overexpressing mice, the CRABP-I mRNA levels remained low. Immunohistochemistry for CRABP-I showed presence of CRABP-I protein in alveolar septae. Immunostaining was weaker in IL-1-overexpressing mice than in controls.

Conclusion: During alveolarization, CRABP-I production increases in the lungs of wild-type mice. This increase fails to occur in mice overexpressing IL-1. Decreased production of CRABP-I may be a mechanism by which inflammation inhibits alveolar septation. Lack of CRABP-I limits intracellular availability of RA when extracellular RA levels are low. Thus, inhibition of CRABP-I by IL-1 may be of particular importance in vitamin A deficiency, which is common in premature newborns. The present results suggest a possible link between inflammation and the RA pathway in the pathogenesis of BPD. Whether RA treatment improves alveolar development in the inflamed lung remains to be studied.

(* p < 0,05)	Ed 18	pn 0	pn 5	pn 9
Control	38±6	34±6	95±15	280±50
Transgenic	28±5	15±5*	17±8*	13±9*

43

INCREASED MMP-9 AND MMP-12 PRODUCTION IN THE LUNGS OF FETAL AND NEWBORN TRANSGENIC MICE EXPRESSING IL-1 IN THE PULMONARY EPITHELIUM

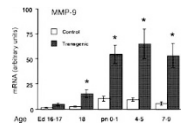
U Lappalainen, K Bry Göteborg University, Pediatrics, Göteborg, Sweden

Background: Increased IL-1 production is associated with chronic obstructive pulmonary disease (COPD) in the adult and with bronchopulmonary dysplasia (BPD) in the premature newborns. We have studied the actions of IL-1 in developing and mature lungs using a transgenic mouse with regulatable IL-1 expression in the lung epithelium. Induction of IL-1 expression in the lungs of fetal and newborn mice leads to impaired alveolarization (decreased alveolar number and increased alveolar size). Induction of IL-1 expression in the adult mouse, on the other hand, causes emphysema. Clinical studies and studies in adult animals provide convincing evidence that MMP-9 and MMP-12 play important roles in emphysema in the adult. We hypothesize that MMP-9 and MMP-12 are mediators of lung remodeling also in the developing lung. Objective: To study the mRNA expression and protein production of MMP-9 and MMP-12 in fetal and newborn mice overexpressing IL-1 and in their nontransgenic littermates.

Methods: MMP-9 and MMP-12 mRNA expression was studied by real-time RT-PCR using primers specific for murine MMP-9 and -12. Immunohistochemistry was used to detect MMP-9 and -12 protein in paraffin-embedded lung sections (antibodies from R&D Systems and Santa Cruz Biotechnology, respectively).

Results: MMP-9 and –12 mRNA expression at different antenatal and postnatal ages is shown below (figure; statistical significance (p<0,05) indicated by asterisk). Immunostaining for both MMPs was increased in transgenic animals at all ages studied.

Conclusion: 1) The production of MMP-9 and MMP-12 is higher in IL-1 overexpressing mice than in their nontransgenic littermates both antenatally and postnatally. 2) In both IL-1 overexpressing and wild-type mice, the expression of MMP-9 and MMP-12 increases at birth. The possibility that inhibiting MMP action prevents or alleviates lung injury caused by inflammatory mediators in the newborn remains to be explored.



44

OXIDATIVE STRESS IN AMNIOTIC FLUID OF PREGNANCIES WITH FETAL GROWTH RETARDATION

M Longini, S Perrone, A Kenanidis, P Vezzosi, B Marzocchi, F Petraglia, G Centini, G Buonocore University of Siena, Italy, Dept of Pediatrics, Obstetrics and Reproductive Medicine, Siena, Italy

Background: Isoprostanes (IP) are a novel marker of free radical-catalyzed lipid peroxidation. Recent evidence suggests that oxidative DNA damage occurs in pregnancies with fetal growth retardation (FGR). The aim of the present study was to analyse oxidative stress (OS) in amniotic fluid of pregnancies with FGR between weeks 15 and 18 week by evaluating IP concentrations.

Methods: We studied 236 women who underwent amniocentesis motivated by advanced maternal age. After exclusion criteria were considered, 78 women were enrolled: 54 had normal pregnancy with normal fetal growth (group I); 24 had IUGR (group II); 15 out of 24 IUGR fetuses were born AGA (subgroup IIa) and 9 were born SGA (subgroup IIb). Ultrasound criteria were applied to assess fetal growth on admission, two weeks later and at weeks 32–34. IP were determined in 2.0 ml of amniotic fluid. Data, expressed as mean ± SD, median and confidence interval were analysed using the STATA 6 statistical package.

Results: IP were higher in group II (154.05±43.32 pg/ml), subgroup IIa (158.27±58.17 pg/ml) and subgroup IIb (150.49±27.33 pg/ml) than group I (68.18±23.68 pg/ml; p<0.0001). The area under the ROC was 0.976 (95% CI: 0.913 - 0.997), showing 100% sensitivity (95% CI: 85.6 - 100) and 90.7% specificity (95% CI: 79.7 - 96.9) at a cutoff of 94 pg/ml. ROCs also enabled subgroup IIa and subgroup IIb to be distinguished. The area was 0.901 (95% CI: 0.812 - 0.957), showing a sensitivity of 100% (95%CI: 75.1 - 100) and a specificity of 75.5% (95%CI: 63.1 - 85.2) at a cutoff value of 94 pg/ml. Comparison of AGA percentiles between group I (F2-IP: 68.18±23.68 pg/ml) and subgroup IIa (F2-IP: 158.27±58.17 pg/ml) showed that 14 out of 15 babies in subgroup IIa and 7 out of 54 babies in group I were born AGA in the 10–25 centile range. The relative risk index between these two groups was 7.2 (CI: 3.42 - 14.34) indicating a risk of AGA (10–25°) 7.2 times higher in subgroup IIa.

Conclusion: This is the first report of elevated IP concentrations in amniotic fluid of pregnancies with IUGR. These results indicate that OS occurs early in fetal life in pregnancies with IUGR fetus.

45

NEAR-INFRARED-SPECTROSCOPY: SPONTANEOUS FLUCTUATIONS OF CEREBRAL OXYGENATION AND HEMODYNAMICS IN PRETERM INFANTS

W Burkhardt, M Rüdiger, H Hammer, H Proquitté, R R Wauer Otto-Heubner-Centrum, Charité-Universitätsmedizin, Klinik für Neonatologie Campus Mitte, Berlin, Germany

Background: Near-Infrared-Spectroscopy (NIRS) is a reliable noninvasive method and has been widely used in neonatology to measure acute changes of cerebral hemodynamics (i.e. during surfactant application - Edwards et al.). But clinical interpretation of NIRS data is still difficult. During long-time monitoring (2h) in healthy term newborns cyclical fluctuations of NIRS parameters were seen (Urlesberger et al.). In preterm and sick infants an impaired cerebral autoregulation can be found, that will most likely influence NIRS data (Boylan et al.). The aim of the study was to investigate, how NIRS parameters vary over time in preterm infants during quiet periods under NICU conditions.

Methods: In 5 ventilated preterms (26. – 29.weeks) NIRS measurements with a Niro 200 monitor (Hamamatsu Photonics Germany) during 90 min (± 5) were performed. Time periods of 60 undisturbed minutes were evaluated. Changes of NIRS data (oxygenated and total Hb, Tissue Oxygenation Index, Tissue Haemoglobin Index) were calculated as a difference between the maximum and base line values. For subsequent analysis the monitoring period was divided into 5 minutes intervals.

Results: During quiet periods over 60 min a mean of 4.5 (± 0.9) spontaneous fluctuations per interval of 5 minutes were recorded. The mean amplitude of these simultaneous fluctuations was: oxyHb 2.07 (± 0.4)imol/l, total Hb 2.9 (± 0.6)imol/l, TOI 2.5% (± 0.2) und THI 4.5% (± 0.5) . The vital parameters remained stable during the entire period.

Conclusion: We found NIRS easy to use in preterms, it did not affect the infants well being. Long periods of an undisturbed cerebral monitoring were obtained. During repeated measurements we could reproduce the NIRS data. We think it is necessary to record the individual spontaneous fluctuations under quiet conditions. So an intraindividual comparsion with NIRS measurments of acute changes is possibel and can help to evaluate and interpret this data. This could help to create a valuable cerebral longtime monitoring and to guide clinical decisions.