[1]S Yurttutan, [1]R Ozdemir, [1]FE Canpolat, [1]MY Oncel, [2]HG Unverdi, [3]B Uysal, [1]O Erdeve, [1]U Dilmen. *[1]Neonatal Intensive Care Unit, Zekai Tahir Burak Maternity Teaching Hospital; [2]Department of Pathology, Ankara Etlik Ihtisas Training and Research Hospital; [3]Department of Physiology, Gulhane Military Medical Academy, Ankara, Turkey*

Introduction The pathophysiology of necrotizing enterocolitis (NEC) includes massive production of endogenous cytokines with exaggerated activation of inflammatory pathways. Colchicine has been used as an anti-inflammatory agent. The aim of this study was to investigate the possible beneficial effects of colchicine in a neonatal rat model of NEC.
Methods Rats were randomly divided into 3 groups: control group; saline-treated NECgroup; colchicine-treated NEC group. NEC was induced by hyperosmolar enteral formula feeding and exposure to hypoxia/reoxygenation after cold stress. Intestinal samples were harvested for biochemical and histopathological analysis.
Results The grade of intestinal injury of pups in the saline-treated NEC group was found to be significantly higher than in the control or the colchicine-treated groups ($p<0.001$, $p=0.003$; respectively). Median level of intestinal malondialdehyde was significantly higher in the saline-treated NEC group compared to the control group ($p=0.006$) and the colchicine-treated group ($p=0.015$). Significantly higher activities of intestinal superoxide dismutase and glutathione peroxidase activities were observed in the colchicine-treated NEC group compared to the saline-treated group ($p=0.033$ and $p=0.030$; respectively). Tissue levels of tumor necrosis factor- α and interleukin 1β were significantly higher in the saline-treated NEC group compared to rats in the colchicine-treated group ($p<0.001$, $p=0.003$; respectively). A comparison of saline-treated and colchicine-treated NEC pups revealed that treatment with colchicine was associated with significantly lower tissue levels of TNF- α and IL-1β ($p<0.01$, both).
Conclusion We observed that; in this model of NEC**,** colchicine has favorable effects onintestinal histological and biochemical changes.

187 SYSTEMATIC REVIEW OF RANDOMIZED CONTROL TRIALS TO REVIEW THE ROLE OF PREBIOTICS IN PREVENTION OF NECROTIZING ENTEROCOLOITIS IN PRETERM NEWBORNS

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[1]S Ali, [2]L Faruque, [3]M Kumar. *[1]Neonatal Perinatal Medicine, Department of Pediatrics, University of Alberta; [2]Epidemiology; School of Public Health; [3]Department of Pediatrics, University of Alberta, Edmonton, AB, Canada*

Background and aims Necrotizing enterocolitis (NEC) is an important cause of mortality and serious morbidity in preterm infants. Prebiotics are specific oligosaccharides which have been shown to promote proliferation of beneficial bacteria in gut. This systematic review aims to review the literature to investigate the role of prebiotics in the prevention of NEC in preterm infants.
Methods Electronic databases CSDR-DARE, MEDLINE, CINAHL, EMBASE, Scopus, Web of science were serached from the date of inception to March 27, 2012. Additional citations were retrieved from the bibliography of the selected articles, Google scholarand abstracts of conference proceedings. The eligible studies were RCTs or quasi-RCTs enrolling inpatient preterm infants that compared use of Prebiotics (any dose and duration) with control (placebo/no treatment) for the outcomes of NEC (stage >=2 Bell's classification, perforation and any stage), growth and any other potentially beneficial effect or serious side-effects. Two independent reviewers extracted the data and assessed the risk of bias in included studies. Descripencies were resolved with consensus.
Results 14 studies fulfilled the inclusion criteria. None reported on the primary outcome of stage>=2 NEC. Two RCT reported on NEC (any stage) and showed no significant difference between the groups. There was no difference noted in the growth parameters [(weight & length (3 studies); head growth (2 studies)]. There was a trend towards higher stool frequency (one study) and higher Bifidobacterium count in stool (2 studies) in the Prebiotic group.
Conclusion Current data is insufficient to recommend the use of Prebiotics in preterm infants for prevention of NEC.

188 ANALGESIA AND SEDATION IN CRITICALLY ILL CHILDREN; LOCAL RELIGION OR EVIDENCE BASED?

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D Tibboel. *Pain Research Team, Erasmus MC - Sophia Childrens Hospital, Rotterdam, The Netherlands*

Over the last decade increasingly RCT's have been published about optimal dosing of opioids and benzodiazepines in critically ill children of different age groups.

In this way progress is made about optimal dosing as well as combination of therapies against the background of the use of novel ways of trial design.

To this effect the application of population pharmacokinetics-pharmacodynamics (NON-MEM) using spare data have guided the design of trials preceded by in vitro simulation and prediction of dose effect responses.

Both in the premature infant as well as in the so-called surgical newborn, dosages have been adjusted based on solid observational and experimental data sets for which the results should be evaluated. Apart from short term pharmacodynamic parameters such as validated pain scores, and eventually pharmacokinetic data analysis potentially equally important is the evaluation of long term consequences both of neonatal pain and the use of opioids. Experimental data have revealed increased neuro apoptosis in the developing brain. The data of a number of RCT's conducted by our group will be combined with prospective longitudinal data recently acquired combining quantitative sensory testing (QST) under conditions of fMRI.

In this way the question whether neonatal pain and/or opioid use results in altered pain response and long term negative sequelae can be answered.

189 STILL HURTING NEWBORN BABIES EIGHT YEARS AFTER WE FOUND OUT!

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[1]D Roofthooft, [1]S Simons, [2]K Anand, [3]D Tibboel, [3]M van Dijk. *[1]Neonatology, Erasmus MC - Sophia Children's Hospital, Rotterdam, The Netherlands; [2]Pediatrics, University of Tennessee Health Science Center ** Le Bonheur, Memphis, TN, USA; [3]Intensive Care, Erasmus MC - Sophia Children's Hospital, Rotterdam, The Netherlands*

Objective To study whether new pharmacological and non-pharmacological guidelines lowered numbers of painful procedures in neonates and changed the amount and frequency of analgesic therapy as compared to the results of our previous study in 2001.
Design A prospective observational study.Setting: Level III NICU of the Erasmus MC-Sophia Children's Hospital, Rotterdam.
Participants Neonates admitted at postnatal ages less than 3 days with length of stay at least 72 hours.
Main outcome measures Number of all potentially painful procedures and analgesic therapy recorded at the bedside during the first 14 days of NICU stay.
Results A total number of 21076 procedures were performed in the 175 neonates studied during 1730 patient-days (mean 12.2). The mean number of painful procedures per neonate per day was 11.4 (SD 5.7), significantly lower than the number of 14.3 (SD 4.0) in 2001 ($p<0.001$). The use of analgesics was 36.6% compared to 60.3% in 2001. Failed procedures encompassed sixty-three percent of all peripheral arterial line insertions vs. 37.5% in 2001 and 9.1% venipunctures vs. 21% in 2001.

Conclusions The mean number of painful procedures per NICU patient per day declined and analgesic treatment changed to a more tailored or individualized approach. Non-pharmacological pain- or stress reducing strategies like NIDCAP and sucrose were fully embedded in our pain management. As further reduction of the number of painful procedures is unlikely we should explore newer pharmacological agents and apply non-pharmacological interventions more frequently.

190 PREDICTING THE EFFICACY OF ORAL SUCROSE IN REDUCING PAIN DURING OPHTALMOLOGICAL EXAMINATION FOR RETINOPATHY OF PREMATURITY: A PROSPECTIVE RANDOMISED STUDY

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[1]N Cullas Ilarslan, [1]D Dilli, [2]EU Kabataş, [1]S Beken, [1]B Aydın, [1]A Zenciroğlu, [1]N Okumuş. *1Neonatology, Dr Sami Ulus Maternity, Childrens Education and Research Hospital, Division of Neonatology; [2]Opthalmology, Dr Sami Ulus Maternity, Childrens Education and Research Hospital, Ankara, Turkey*

Background and aim Retinopathy of prematurity (ROP) is one of the major morbidity among preterm infants. Although, local anesthetics reduce pain to some extent, eye examination still remains as a painful procedure. We aimed to evaluate the effect of oral sucrose combined with local anesthetics for pain relief during ophthalmological examination.

Method A total of forty patients under 32 weeks of gestational age were included in the study. Infants were randomly assigned to receive either oral sucrose solution (Group-1; n=21) or sterile water (Group-2; n=19) combined with topical proparacaine hydrochloride two minutes before examination. Pacifier was used in all patients as non-nutritive sucking during the study. Pain score was evaluated by premature infant pain profile (PIPP) scale. Each infant was video-recorded during and after the procedure.

Results Both groups were similar in terms of gestational age, birth weight, postnatal age and actual weight. There was no significant difference between groups in behavioral state, heart rate and oxygen saturation before the examination. At speculum insertion, heart rate variability was similar in both groups whereas oxygen desaturation was apparent in Group-2 (Group-1: 1.7±0.8 and Group-2: 2.5±0.6, p=0.001) and PIPP scores were also lower in Group-1 (Group-1: 14.5±1.8 and Group-2: 17.2±1.7, p=0.001). Total time of crying was significantly shorter in Group-1 (Group-1: 58.8±12.1 and Group-2: 96.3±24, p=0.001).

Conclusion Procedural pain is known to have acute and even long term negative. behavioral and developmental effects in neonates. In our study, use of sucrose in addition to local anesthetics during ophthalmological examination is shown to attenuate pain.

191 MORPHINE PREMEDICATION FOR INTUBATION IN PRETERM INFANTS - A PHARMACOKINETIC AND PHARMACOGENETIC REPORT

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[1]E Norman, [2]L Elens, [3]M Anderssson, [3]O Beck, [2]R van Shaik, [3]A Rane, [1,4]V Fellman. *[1]Department of Pediatrics, Lund University and Skåne University Hospital Lund, Lund, Sweden; [2]Department of Clinical Chemistry, Erasmus MC, Rotterdam, Netherlands Antilles; [3]Division of Clinical Pharmacology, Lab Medicine, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden; [4]Children's Hospital, University of Helsinki, Helsinki, Finland*

Background and aims Morphine is used in preterm infants, but data are scars on pharmacokinetics (PK), pharmacodynamics (PD) and pharmacogenetics (PG). We aimed to study PK and PD/PG relation of morphine in infants included in a RCT comparing morphine with short-acting analgosedation as premedication for intubation.

Methods 17 preterm infants with a median (IQR) gestational age of 26.6 (25.1–28.7) w, birth weight 924 (721–1240) g and postnatal age 136 (17.5–322) h were randomized to receive morphine (0.3 mg/kg).

Blood samples for morphine, M6G and M3G concentrations were collected before administration, 20 min, 6 and 24 h after intubation. DNA was isolated from salivary swabs to genotype 18 polymorphisms in 12 genes using Taqman assays. Pain assessment (ALPS-0 and EDIN scales) was performed and additional morphine boluses were offered accordingly. The morphine level/pain score relation and the genotype influence on time to achieve a low pain score was calculated.

Results In infants receiving no additional doses, clearance was 1.5–3.3 ml/kg/min in 5 infants of 5–34 h and 9.9 in one infant of 332 h postnatal age.

Both morphine and morphine+M6G/5 correlated with mean ALPS-0 score at 6h (p=0.02 and 0.04) and 24 h (p=0.01 and 0.02). The COMT rs4680G>A (Val158Met) SNP was significantly correlated with time to reach the lowest pain score. COMT rs4680A patients experienced a faster response to opioids compared to rs4680GG patients in both groups (p=0.001 and p=0.072).

Conclusions Morphine clearance is dependent on postnatal age in premature infants. Genotyping would improve individual dosing of opioids during NICU-care.

192 ANALGESIA MODULATES CORTICAL RESPONSE TO PAINFUL PROCEDURES IN EXTREMELY PRETERM NEWBORN INFANTS

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M Bartocci, E Thorn, H Lagercrantz. *Dept. of Neonatology, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden*

Introduction Proper pain management in the neonatal intensive care unit (NICU) is essential. The clinical pain assessment depends on objective measurement of indirect behavioural and physiological pain indicators. Cortical pain processing has been observed in preterm infants from 24 weeks gestational age but no study has focused exclusively on cortical pain response in extremely premature infants (≤28 weeks gestational age).

Aims This study aimed to demonstrate cortical pain processing in extremely preterm infants. Furthermore, the study aimed to investigate the impact of analgesic drugs on cerebral haemodynamics and the relationship between behavioural and cortical pain responses.

Material and Methods A clinical study was performed in the NICU, including preterm infants ≤28 weeks gestational age or with a birth weight ≤1500 grams. Patients with severe on-going intraventricular haemorrhage or hydrocephalus were excluded. The infants were studied during routinely performed venepunctures and endotracheal tube suctions. Near-infrared spectroscopy was used for the study of cortical activity, parallel to observation of systemic haemodynamics and pain assessment with the *Premature Infant Pain Profile* and *Échelle Douleur Inconfort Nouveau-Né*.

Results During the procedures significant increases in the cerebral concentration of oxygenated haemoglobin were observed bilaterally during venepuncture and unilaterally during endotracheal tube suctions. Simultaneously, minor alterations in systemic haemodynamics occurred. The cerebral pain response was significantly reduced by analgesia.

Conclusions These results indicate the existence of cortical pain processing in very premature infants. Analgesia reduces this cortical response.

193 IMAGING TOOLS TO ASSESS THE DEVELOPMENT OF CORTICAL MORPHOLOGY AND CONNECTIVITY

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