Neonatal Society Spring Meeting
30th March, 2017
Royal Society of Medicine
1 Wimpole Street, London, W1G 0AE
Spring Meeting, 30th March 2017

Royal Society of Medicine, 1 Wimpole Street, London, W1G 0AE

09.15 Coffee

Session 1: Chair – Dr James Boardman, General Secretary

09.45. Y Hodovanets, Bukovinian State Medical University, Ukraine
Diagnostic and Predictive Value of Serum Cystatin C in a case of Neonatal Acute Kidney Injury in Critically Ill Full-term Infants.

10.00. L Osbourne, Royal London Hospital
Development and External Evaluation of a Population Pharmacokinetic Model for Vancomycin in Neonates using Prospectively Collected Data

10.15. R Nallianan, University Hospital, Southampton
Cumulative Index of Exposure to Hypocarbia during Transport in Neonates with Hypoxic Ischaemic Encephalopathy receiving Therapeutic Hypothermia

10.30. S Ali, Imperial College London
Outcome Reporting in Neonatal Clinical Trials: a Systematic Review

10.45. P Rowsome, Imperial College London/ University of Edinburgh
Infant Feeding at 3 months of age in a Prospective Cohort Born in a UNICEF UK Baby Friendly Hospital: the Impact of Maternal and Delivery related Variables

11.00. Tea / coffee

Session 2: Chair – Professor Helen Budge, Treasurer

11.30. K Beardsall, University of Cambridge
Feasibility of Real Time Continuous Glucose Monitoring in Neonatal Intensive Care

11.45. P Mikrou, Birmingham Women’s Hospital
Pulse Oximetry Screening For Critical Congenital Heart Defects: a Repeat UK National Survey
12.00. Keynote lecture: Professor John Achermann, Institute of Child Health, UCL. What's new in sex development?

13.00. Lunch break

**Session 3: Chair – Dr Karen Luyt, Committee member**

14.15. R Lee-Kelland, University of Bristol

Children Who Receive Therapeutic Hypothermia for HIE but did not develop Cerebral Palsy, have Reduce Cognitive and Motor Performance at 6-8 years

14.30. M Thoresen, University of Oslo

Delivering Human Umbilical Cord Blood Cells after Hypothermia Augments Neuroprotection after Severe Brain Injury in the Vannucci seven day old Rat Model.

14.45. I Panayotidis, University College London

The Distribution of Pain-Related Activity across the Neonatal Cerebral Cortex

15.00. C Gale, Imperial College London.


15.15. J Webbe, Imperial College London

Parents, Patients and Health Professionals Report Different Outcomes of Neonatal Care as important: a Systematic Review of Qualitative Research

15.30. Afternoon Tea / Coffee

**Session 3: Chair – Professor Howard Clark, President**

16.00. M Kong, University of Southampton

The Impact of Necrotising Enterocolitis on Brain Development in Preterm Infants: Preliminary Report
16.15. H Jenkins, Imperial College London

The Exoenzyme Activity of the Preterm Gut

16.30. The McCance Lecture. Professor Frances Cowan, Visiting Professor, University of Bristol.

30 years of Neonatal MRI: Lessons Learned about Prognosis following Perinatal Brain Injury.

17.30 Drinks and close of meeting
## Diagnostic and predictive value of serum cystatin C in case of neonatal acute kidney injury in critically ill full-term infants

### Authors
Hodovanets Yuliya, Babintseva Anastasiya, Agaphonova Ludmila

Corresponding author e-mail address: Langus76@mail.ru

### Institution(s)
Bukovinian State Medical University, Department of Pediatrics, Neonatology and Perinatal Medicine

### Introduction (include hypothesis)
Serum cystatin C (SCysC) is a proteinase inhibitor involved in intracellular catabolism of proteins, produced by all nucleated cells, freely filtrated across glomeruli, and completely catabolized and reabsorbed in the proximal tubule. Several authors found that SCysC is a better marker of neonatal acute kidney injury (AKI) than creatinine but there are limited studies available on reference values of SCysC in healthy and ill neonates [1-4]. The objective of the work was to determine diagnostic and predictive value of SCysC in case of acute kidney injury (AKI) in critically ill full-term newborns.

### Methods (include source of funding and ethical approval if required)
A comprehensive paraclinical examination of 67 critically ill full-term newborns including 36 infants without AKI (I group), and 31 ones with diagnosed AKI (II group). AKI was detected by means of recommendations Kidney Disease: Improving Global Outcomes with modification by J. G. Jetton and D. J. Askenazi [5]. The level of SCysC was measured by immunonephelometric methods on the basis of the laboratory Gemeinschaftslabor Cottbus (Germany). The results of each group are expressed as mean and 95% confidence interval (95% CI). Where data were available, 2×2 tables were constructed to derive sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) and cut-off level of SCysC. Area under the receiver operating characteristic (ROC) curves (AUROCs) was used to deduce the diagnostic accuracies of the SCysC. Ethical approval was obtained from the research ethics committee of the Bukovinian State Medical University.

### Results
The newborns of the first group of level of SCysC was 1.56 mg/l (1.517-1.62), in the second group – 1.78 mg/l (1.73-1.82), p<0.05. A high sensitivity (100.0 (88.8-100.0)% of SCysC has been found during diagnostics of AKI in critically ill full-term newborns. High diagnostic value of this index is proved by diagnostic accuracy (82.1%) and high AUROC index (0.86, p<0.05); high predictive value – by high readings of a PPV (70.5 (60.7-78.6)% and NPV (100.0%), and also PLR (2.8 (1.8-4.3)). A cut-off level of SCysC which is indicative of the formation of AKI in full-term newborns with severe perinatal pathology was detected to be higher than 1.59 mg/l.

### Conclusions
Considering a high predictive and diagnostic value the authors recommend to measure SCysC level for identification of AKI in full-term infant into the practical work of neonatal intensive care units.

### References (include acknowledgement here if appropriate)
DEVELOPMENT AND EXTERNAL EVALUATION OF A POPULATION PHARMACOKINETIC MODEL FOR VANCOMYCIN IN NEONATES USING PROSPECTIVELY COLLECTED DATA

Authors (Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)

Leanne Osborne (1), Shehrazed A Lounis (2), Eva Germovsek (3), Flora Gunaratnam (2), Ferran Bossacoma Busquets (3), Joseph F Standing (3), Ajay Sinha (1,2)

Corresponding author e-mail address: leanneosborne@doctors.org.uk

Institution(s)

(1) Neonatal Unit, Royal London Hospital, London, UK; (2) Barts and the London School of Medicine and Dentistry, London, UK; (3) Inflammation, Infection and Rheumatology section, Institute of Child Health, University College London, London, UK;

Introduction (include hypothesis)

Vancomycin is commonly used for nosocomial bacterial pathogens causing late-onset sepsicaemia in preterm infants. There is limited data on optimum dosing regimens for vancomycin based on population pharmacokinetic analyses. We therefore aimed to develop and externally validate a pharmacokinetic model for continuous and intermittent vancomycin dosing regimens in neonates.

Methods (include source of funding and ethical approval if required)

New-borns receiving vancomycin for suspected or confirmed late onset sepsis were included. Peak and trough levels for intermittent vancomycin dosing and a random level for continuous vancomycin dosing were measured. The vancomycin assay was performed using COBA 702 platform (linear range was 1.7-80ug/mL). NONMEM 7.3 was used to perform the population pharmacokinetic analysis. Initial data collected over 12 months from September 2014 was used for model development and subsequent data collected between January and May 2016 for evaluation. The study was approved by Barts Health Clinical Effectiveness.

Results

Patient demographic and number of vancomycin samples for both model development stage and evaluation stage are given in Table. The final model was a 1-compartment model. Weight and PMA were included a priori; and after that no additional covariate significantly improved the model fit. Vancomycin volume of distribution (V) was fixed to the value from the intermittent administration; and clearance (CL) was estimated using both intermittent and continuous data. Internal evaluation showed the model is able to adequately describe the data. Final model parameter estimates (mean (relative standard error)): CL 5.4 L/h/70kg (7.0%), V 31.6 L/70kg. Values for a typical neonate from the studied population (weight 1.7kg, PMA 35.7 weeks): CL 0.10 L/h, V 0.77 L.

<table>
<thead>
<tr>
<th>Model development (n=54)</th>
<th>Evaluation dataset (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>infants on Intermittent/continuous regimen (n)</td>
<td>23/31</td>
</tr>
<tr>
<td>vancomycin samples on Intermittent/continuous regimen (n)</td>
<td>81/102</td>
</tr>
<tr>
<td>Corrected gestational age (weeks)</td>
<td>29 (23.7-41.9)</td>
</tr>
<tr>
<td>Postnatal age (days)</td>
<td>26 (1-156)</td>
</tr>
</tbody>
</table>

Visual predictive check on evaluation dataset using 1,000 simulated datasets confirmed that the model is able to predict external data.

Conclusions

A population PK model for continuous and intermittent vancomycin administration in neonates was developed. External evaluation showed that the model can predict external data that were not used in the model development. This confirms that the model could be used for simulations. This could be used to develop a new dosing scheme which could be prospectively evaluated.

References (include acknowledgement here if appropriate)

CUMULATIVE INDEX OF EXPOSURE TO HYPOCARBIA DURING TRANSPORT IN NEONATES WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY RECEIVING THERAPEUTIC HYPOTHERMIA

Authors (Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)
Regina Nalliannan¹; Nasreen Banu Shaik¹; Alison Le Poidevin¹; Richard Thwaites²; Mark Johnson³; Neelam Gupta

Corresponding author e-mail address: regelle83@yahoo.com

Institution(s)
¹Department of Neonatal Medicine, University Hospital Southampton NHS Foundation Trust and Southampton Oxford Neonatal Transport Service (SONeT)
²Neonatal Unit, Portsmouth Hospitals NHS Trust
³NIHR Biomedical research Centre Southampton, University Hospital Southampton NHS Foundation Trust and University of Southampton

Introduction (include hypothesis)
Early periods of hypocarbia in hypoxic ischemic encephalopathy (HIE) have been associated with adverse neurodevelopment outcomes. Avoidance of hypocarbia in these neonates during transfer to cooling centres can be challenging. The aim of the study was to determine the cumulative index of exposure (CIE) to hypocarbia during transfer of neonates with HIE requiring therapeutic hypothermia and its correlation to clinical outcome.

Methods (include source of funding and ethical approval if required)
Retrospective study over a 4-year period including neonates with HIE requiring therapeutic hypothermia who were transferred to a cooling centre. Ventilation, blood gas and transport details were collected. Hypocarbia was defined as pCO₂<4.5kPa and CIE was calculated by multiplying the extent of the hypocarbia (4.5kPa minus the lowest pCO₂) by the number of hours until normocarbia was achieved. Regression modelling was carried out to ascertain the relationship between CIE and outcomes.

Results
Fifty infants were included in the study. Hypocarbia occurred in 68% neonates with median pCO₂ of 4.1kPa(range 2.1-7.8). Linear regression modelling with adjustment for cord gas base deficit and ventilation mode demonstrated that an increase in CIE of 1kPa.hour was associated with an increase in HIE grade of 0.02 (p=0.018). Modelling CIE as a 5-level variable demonstrated that only the highest quartile for CIE (>14.2kPa.hours) was significantly associated with grade of HIE (p=0.002, see figure). There were no significant associations between CIE with ventilation mode.

Conclusions
Increase in CIE to hypocarbia was associated with severity of HIE. Avoidance of hypocarbia poses a challenge not only due to ventilatory support, but also clinical state. Therapeutic interventions to avoid hypocarbia besides ventilatory strategy need to be explored.

References (include acknowledgement here if appropriate)
1) Azzopardi D et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. NEJM. 2009; 361; 1349-1358
Title (Upper case)
OUTCOME REPORTING IN NEONATAL CLINICAL TRIALS: A SYSTEMATIC REVIEW

Authors
Shohaib Ali¹, James Webbe¹, James M N Duffy², Neena Modi¹, Chris Gale³

Corresponding author e-mail address: Shohaib.ali14@imperial.ac.uk

Institution(s)
¹ Section of Neonatal Medicine, Imperial College London, Chelsea and Westminster campus, London, UK
² Balliol College, University of Oxford, Oxford, OX2 6GG, United Kingdom.

Introduction (include hypothesis)
Inconsistent outcome reporting in clinical trials is wasteful, limiting comparability and evidence synthesis¹. In preterm infants, clinical trial interventions have the potential to affect other organ systems in addition to the therapeutic target organ²; preterm neonatal clinical trial outcomes should reflect this. We hypothesised:
1. Trials reported a consistent set of outcomes
2. That outcomes reported span the major organ systems
We also examined whether trials reported parent or patient involvement in outcomes selection.
This work will aid the development of a core outcome set for neonatology.

Methods (include source of funding and ethical approval if required)
Design: Systematic review of randomised trials and cluster randomised trials.
Data sources: We searched major bibliographic databases from their June 2011 to June 2016.
Study selection and data extraction: All trials including preterm (<37 gestational weeks at birth) neonates (0-28 days) requiring admission to a neonatal intensive care unit or special care baby unit. We systematically extracted and categorised primary and secondary outcomes and outcome measures.
Funding: SA was funded through a UROP Fellowship.

Results
We included 119 randomised trials involving 21,824 infants, reported 161 different primary outcomes and 1,210 different secondary outcomes. No studies reported parental involvement in outcome selection. Mortality was reported in 72 (61%) trials.
Major outcome domains were reported as follows: respiratory outcomes in 74 trials (62%), gastrointestinal in 62 trials (52%), infection in 50 trials (42%), genitourinary in 12 trials (10%) and psychosocial in 12 trials (10%).
Commonly reported secondary outcomes included: chronic lung disease (CLD) in 55 trials (45%), necrotising enterocolitis in 54 trials (45%), intraventricular haemorrhage in 46 trials (39%), sepsis in 46 trials (39%), patent ductus arteriosus in 44 trials (36%) and retinopathy of prematurity in 44 trials (37%). Among these common secondary outcomes there was variation in outcome measures used: CLD was reported using 7 different outcome measures. Neurodevelopmental outcomes after discharge were reported by 21 trials (18%); 17 different tools were used.

Conclusions
Outcome reporting in preterm neonatal trials is inconsistent. Trials do not consistently report outcomes across key organ systems and only a minority report development after discharge. Where outcomes are commonly reported, there is inconsistency in outcome measures. There is no evidence of parent involvement in outcome selection. Developing and implementing a neonatal core outcome set will address these issues.

References (include acknowledgement here if appropriate)
2. Doyle LW, Et al., Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochrane Database Sys Rev. 2014 May 13;(5)
INFANT FEEDING AT 3 MONTHS OF AGE IN A PROSPECTIVE COHORT BORN IN A UNICEF UK BABY FRIENDLY HOSPITAL: THE IMPACT OF MATERNAL AND DELIVERY RELATED VARIABLES

Authors (Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)


Corresponding author e-mail address: matthew.hyde02@imperial.ac.uk

Institution(s)

Section of Neonatal Medicine, Imperial College London, Chelsea and Westminster Hospital campus, 369 Fulham Road, London, SW10 9NH, UK

Introduction (include hypothesis)

We previously presented evidence that Caesarean section (CS) is associated with lower rate of breastfeeding initiation1 and that pre-labour CS (PLCS) is associated with increased rate of exclusive formula feeding at 3 months post-partum. Here we explore the relationship between six key maternal or delivery related variables and exclusive breastfeeding at 3 months post-partum.

Methods (include source of funding and ethical approval if required)

In February 2014 we commenced recruitment of a prospective cohort of babies to examine the association between mode of delivery and atopy at 1 year of age (Research Ethics Approval 13/LO/1793). Babies were recruited on the post-natal ward at Chelsea and Westminster Hospital following informed maternal consent. We collected data on the following variables: maternal age, booking BMI, Index of Multiple Deprivation (IMD) (based on mother’s postcode at recruitment), smoking status (yes/no), use of analgesia during labour (yes/no), and type of delivery (PLCS, In-labour CS, vaginal delivery). We recorded data on feeding prior to discharge, and at 3 months post-partum we telephoned mothers to obtain follow-up information. We classified infant feeding as 1) exclusively breast-fed (EBF); 2) mixed feeding (MF); 3) exclusively formula-fed (EFF). For analysis we looked at A) exposure to breast milk (1&2 v 3) and B) exclusive breastfeeding (1 v 2&3). We applied logistic regression to breastfeeding status at 3 months in terms of the mode of delivery CS, vaginal delivery)

Results

We have to-date recruited 680 infants and have follow-up data on feeding at age 3 months on 561 (87% follow-up rate at 3 months). Of these 248 (44%) mothers reported exclusive breastfeeding at 3 months, 175 (31%) were mixed feeding, and 138 (25%) were exclusively using formula. Our final model included maternal BMI, smoking status (yes/no), IMD (decile) and mode of delivery (PLCS, In-labour CS, vaginal delivery). The model suggests that higher maternal BMI, maternal smoking, and CS delivery are all associated with reduced rate of exclusive breastfeeding at 3 months of age.

Conclusions

The Unicef UK baby friendly hospital initiative has been widely implemented in the UK. Despite this, exclusive breastfeeding to 6 months (as recommended by the WHO) remains below 5%. We show that only 44% of women giving birth in a Unicef UK baby friendly hospital are exclusively breastfeeding at 3 months post-partum, but this is twice that in the 2010 NHS Infant Feeding Survey (national average of 17%). Implementation of the Unicef UK baby friendly hospital initiative alone does not appear to achieve WHO standards for exclusive breastfeeding. Here we report clear risk factors for failure to continuing exclusive breastfeeding to three months. Given pressures on healthcare funding and cuts to post-partum care in the community, it is possible that additional breastfeeding support targeted at women at high risk of stopping breastfeeding early may help to achieve WHO standards for breastfeeding in the UK. Validity of maternally reported feeding data is a caveat in our conclusions, but the prospective design is a strength.

References (include acknowledgement here if appropriate)

Feasibility of Real Time Continuous Glucose monitoring in Neonatal Intensive Care

Thomson L, Howlett J, Bond S, Hovorka, R, Dunger DB, Beardsall K

Corresponding author e-mail address: kb274@cam.ac.uk

University of Cambridge and University of Cambridge Addenbrookes Hospital NHS Trust, Cambridge Biomedical Campus, Cambridge, CB2 0QQ

Introduction (include hypothesis)

Extremely preterm infants are at high risk of glucose dysregulation and this is associated with increased mortality and morbidity. In these babies the desire to reduce frequency of blood sampling and handling means glucose monitoring is infrequent and controlling glucose levels is challenging. This study aimed to determine the feasibility of real time continuous glucose monitoring (CGM) to support glucose control in extremely preterm infants requiring intensive care.

Methods (include source of funding and ethical approval if required)

A single center feasibility study (n=21) in infants with a birth weight <1200g. The enhanced enlite glucose sensor was inserted subcutaneously manually and connected to a transmitter sending data via Bluetooth connection to a CGM reader device. CGM information was combined with a specifically designed paper based algorithm to guide glucose control. Accuracy of the CGM was assessed by comparison with blood glucose measurements from the point of care Stat Strip (Novobiomed) and the blood gas analyser (Radiometer). Safety was assessed in terms of episodes of hypoglycaemia (sensor or blood glucose <2.6mmol/l) and utility with a staff questionnaire. Cambridge Central Ethics committee provided approval for this study which is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership and equipment was provided by Medtronic.

Results

There were 21 babies recruited. Comparative data was available at 247 time points. The sensor performed well compared to the point of care blood glucose with mean difference 0.31 (95%CI 0.14, 0.49). Three babies were recorded clinically to have a single episode of hypoglycaemia (BG <2.6mmol/l >1 hour). In two of these it was the CGM that highlighted unanticipated falling glucose levels. The CGM data documented 3 babies each with a single episode (SG<2.6mmol/l >10 minutes), one of which was not detected clinically. Despite initial concerns about impact on workload the clinical staff reported a positive impact on clinical care.

Conclusions

CGM glucose values with enhanced enlite appear sufficiently accurate to be used to support clinical management in the preterm infant. Clinical staff reported a beneficial impact on patient care, but larger studies are required to determine impact on targeting glucose control.

References (include acknowledgement here if appropriate)

Disclaimer: “The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NHS, NIHR or the Department of Health.”
Title (Upper case)

PULSE OXIMETRY SCREENING FOR CRITICAL CONGENITAL HEART DEFECTS: A REPEAT UK NATIONAL SURVEY

Authors (Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)

Paraskevi Mikrou¹, Anju Singh¹, Andrew K Ewer¹²

Corresponding author e-mail address: voulamik@doctors.org.uk

Institution(s)

1. Neonatal Intensive Care Unit, Birmingham Women's Hospital, Birmingham, UK
2. Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK

Introduction (include hypothesis)

Pulse oximetry (PO) is a simple, safe and reproducible screening tool that identifies critical congenital heart defects missed by existing screening methods.¹² PO has been incorporated into the national screening programme of some countries (including the USA in 2011) while the debate whether it should be part of the national screening programme in the UK continues. In 2012 only 18% of UK units used PO screening.³ We aimed to assess how practice has changed over the last 4 years.

Methods (include source of funding and ethical approval if required)

Lead clinicians from all 193 neonatal units in the UK were contacted by email (with telephone follow-up for non-responders) and invited to complete a short online survey.

Results

All 193 UK neonatal units responded. PO screening was performed in 78/193 neonatal units (40%, compared to 18% in 2012). Uptake of PO screening was more likely in level 3 units (50%) compared to level 1 and 2 units (38% and 34% respectively) and there was evidence of regional variation: Wales and the North West of England had the highest uptake (75% and 73% respectively) and the South West of England had the lowest (11%). The majority of screening units (72%) used pre- and post-ductal saturations although there was wide variation in the cut-off for a positive result and only 33% reported using the PulseOx algorithm¹ limits (<95% in either limb and/or difference >=3%). Of the 115 units that did not perform PO screening, 12 were in the process of starting and 75 of the remaining units (73%) expressed an interest in adopting the practice. The most commonly perceived obstacles were similar to the previous survey: staffing issues (51%), cost (28%), availability of echocardiography (23%) and concerns regarding false positives (12%). Nineteen per cent of units are waiting a national recommendation.

Conclusions

The UK National Screening Committee is currently considering the possibility of introducing PO screening as national policy. In the meantime practice across the UK appears to be changing with more neonatal units adopting or willing to adopt PO as a routine screening tool. There is still significant variation in the protocols used. This may be resolved by a national recommendation.

References (include acknowledgement here if appropriate)

CHILDREN WHO RECEIVED THERAPEUTIC HYPOTHERMIA FOR HIE, BUT DID NOT DEVELOP CEREBRAL PALSY, HAVE REDUCED COGNITIVE AND MOTOR PERFORMANCE AT 6-8 YEARS.

Authors (Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)

Richard Lee-Kelland¹, James Tonks¹, Sally Jary¹, Frances Cowan¹, Marianne Thoresen¹,², Ela Chakkarapani¹

Corresponding author e-mail address: Ela.Chakkarapani@bristol.ac.uk

Introduction (include hypothesis)

In the pre-therapeutic hypothermia (TH) era, school aged children who had hypoxic-ischaemic encephalopathy (HIE) in the newborn period, even in the absence of cerebral palsy (CP), were reported to have lower cognitive scores than typically developing peers. [1] No equivalent data exists for non-CP related motor performance. It is unknown whether the cognitive and motor performance of this group, having received TH would differ from typically developing children. We hypothesize that children who received TH for HIE, but who did not develop CP would have reduced cognitive and motor performance at 6 to 8 years.

Methods (include source of funding and ethical approval if required)

Forty-eight children (28 cases and 20 age, sex and social class matched controls) were assessed between 6-8 years of age. All cases were treated for moderate/severe HIE with TH at St Michael’s Hospital, Bristol. The children completed a cognitive assessment administered by psychologists blinded to case/control status using the Wechsler Intelligence Scales (WISC-IV). A paediatrician administered the Movement ABC-2 (MABC-2) to assess motor performance and a neurological examination to exclude CP. The study was funded by the Bailly Thomas, David Telling, Moulton and SPARKS Charitable Trusts and received ethical approval (14.sw.0148). Mann-Whitney U test was used to compare the distribution of test scores.

Results

Children who received TH for HIE had significantly lower distributions of WISC-IV full-scale IQ scores than the control group (median (IQR)): 92 (85-99) vs 103.5 (96.25-117.75) p=0.001). This included the subscales of verbal comprehension, (median (IQR): 95 (89-99) vs 104 (96.25-109.5) p=0.003), perceptual reasoning (90 (82-98) vs 100 (92.5-112) p=0.001) and processing speed (97 (88-103) 106 (97-122.5) p=0.021). MABC-2 total scaled scores were also significantly lower (median (IQR) 8 (6-10.75) vs 10 (8-11.75) p=0.047) compared to typically developing children as well as manual dexterity scores (median (IQR): 8 (5-10.75) vs 10 (9-12) p=0.017) No statistically significant difference was found in the MABC-2 aiming or catching or balance subscales.

Conclusions

Despite the improvement in outcomes in HIE following the introduction of TH [2], affected children, even those who do not develop CP, remain at increased risk of cognitive and motor difficulties compared to age-matched controls.

References (include acknowledgement here if appropriate)

DELIVERING HUMAN UMBILICAL CORD BLOOD CELLS AFTER HYPOTHERMIA AUGMENTS NEUROPROTECTION AFTER SEVERE BRAIN INJURY IN THE VANNUCCI SEVEN DAY OLD RAT MODEL

Authors (Presenting author underlined. Is a member)

Marianne Thoresen 1,3, Mari Falck 1,2 Elke Maes 1, Hege Brinker Fjerdingstad 1,2, Hemmen Sabir,1, Joel Glover 1,2, Joanne Kurtzberg 4, Michael Cotton 4, Thomas Wood 1,

Corresponding author e-mail address: marianne.thoresen@medisin.uio.no

Institution(s)

1).Div. For Physiology, Inst. Basic Medical Sciences, Univ. of Oslo 2) Oslo Univ. Hospitals, Norway, 3) Neonatal Neuroscience, School of Clinical Medicine, Univ of Bristol, UK, 4) Pediatric Blood and Marrow Transplant Program and Department of Pediatrics Duke University, US

Introduction (include hypothesis)

After severe injury in the Vannucci neonatal rat unilateral hypoxic-ischaemic (HI) brain injury model, 5h of immediate postinsult hypothermia (TH) is not neuroprotective (1,2). Recently, human umbilical cord blood cells (hUBCs) have been proposed as a neuroprotective therapy for HI brain injury with the potential to extend the therapeutic window and stimulate repair processes. hUBC delivered by direct injection into the brain has shown added neuroprotection in neonatal rats (3). Direct intracerebral injection of hUBC is however not feasible in a clinical setting. We hypothesize that delivering hUBC intraperitoneally starting after the postinsult hypothermic period will reduce severe brain injury when hypothermia alone do not.

Methods (include source of funding and ethical approval if required)

Postnatal-day-7 (N=130, n=27-35) Wistar rats-pups underwent ligation of the left carotid artery followed by subsequent hypoxia (8% oxygen). After HI, pups were immediately randomised to either NT (37°C) or TH (32°C) for 5h, followed by an i.p. injection of hUBCs (2x10^7 cells/kg in 10ml/kg; NTcell and THcell groups) or an equivalent volume of vehicle (NTveh and THveh). Brains were harvested on P14 and processed for H&E and immunohistochemistry. Relative (ligated vs unligated) hemispheric area loss was calculated, and hippocampal pyramidal cell numbers were counted in the CA1 region. The project was funded by The Norwegian Research Council, The University of Oslo, Norway, Duke University, US, and the German Research Council (travel fund HS).

Results

A severe insult was confirmed by the presence of a median (interquartile range) 58.6% (12.7-64.9%) hemispheric area loss in the NT+V group (1). Neither hUBCs alone (NT+Cell) nor TH alone (TH+Veh) reduced hemispheric area loss significantly (NT+Cell: 54.8% (14.3-66.2%), TH+Veh: 48.2% (8.1-58.0%)). However, significant neuroprotection (median 37.5% (3.4-54.9%) area loss) was seen in the TH+Cell group (p=0.02). The median (interquartile range) number of NeuN positive cells in the CA1 hippocampal region was also higher in the TH+Cell (74.5 (15.5-123)) group compared to the both the NT+Veh (7 (0-64)) and NT+Cell (8 (0-89)) groups (p<0.05 for both).

Conclusions

(1) The combination of peripheral delivery of hUBCs after 5h of TH is the first treatment that results in significant neuroprotection in severe HI brain injury in the neonatal rat, where TH alone or hUBC at Normothermia did not offer neuroprotection. We aim to develop cell-based treatments combined with TH to reduce inflammation and promote long-term cellular repair and regeneration.

References (include acknowledgement here if appropriate)

THE DISTRIBUTION OF PAIN-RELATED ACTIVITY ACROSS THE NEONATAL CEREBRAL CORTEX

Panayotidis I\textsuperscript{a}, Jones L\textsuperscript{a}, Fabrizi L\textsuperscript{a}, Fitzgerald M\textsuperscript{a}, Meek J\textsuperscript{b} & Verriotis M\textsuperscript{a}

Corresponding author e-mail address: m.verriotis@ucl.ac.uk

Dept. Neuroscience, Physiology and Pharmacology, University College London, London WC1E 6BT, UK.

Elizabeth Garrett Anderson Obstetric Wing, University College London Hospital, London, WC1E 6DB, UK.

Previous EEG studies\textsuperscript{1} have identified a nociceptive-specific event-related potential (nERP) in the newborn brain following a clinically-required noxious heel lance. This nERP is maximal at the vertex (Cz and CPz electrodes) and well localised on a group average basis\textsuperscript{2}. However, we observed that the distribution of this response across the scalp could differ between subjects. Here we test the hypothesis that there is significant individual variability in the topographical distribution of the infant nERP and that this depends upon gestational age (GA).

Participants were 96 babies (23-42 weeks GA; 30-43 weeks corrected GA) recruited between 2007 and 2016. Brain activity was recorded using 9-22 EEG electrodes placed according to the international 10:20 system. The noxious stimulus was a clinically required routine heel lance, which was time-locked to the EEG recording. Ethical approval was obtained from the UCLH ethics committee and informed written parental consent was obtained prior to each study. This work was supported by the Wellcome Trust (090245/Z/09/Z), the Medical Research Council (MR/M006468/1), and the NIHR UCLH Biomedical Research Centre.

There was considerable individual variability in the topographical distribution of the nERP. In 54/96 babies (56%), the nERP could be identified at 9 or more electrodes and was considered to be widespread. The incidence of widespread nERP was greater in babies born and studied at premature age (Prem-Prem; <37 weeks GA; 25/37, 68%) compared to babies born and studied at term age (Term-Term; 37+ weeks GA; 14/33, 42%). Chi-square analysis indicates a significant effect of gestational age ($\chi^2 = 4.47, p=0.053$). There was no difference in the incidence of widespread nERP between babies born prematurely and studied at term age (Prem-Term) and the Term-Term babies (12/19, 63% vs. 14/33, 42%; $\chi^2 = 2.1, NS$).

A widespread pattern of distribution of the nERP is common in premature babies, with the response becoming more localized with increasing GA. A widespread nERP is likely to be due to the structural and functional immaturity of the premature brain and indicates age-related changes in cortical pain processing in prematurity.

References (include acknowledgement here if appropriate)

NATIONAL INCIDENCE OF BRAIN INJURIES OCCURRING AT OR SOON AFTER BIRTH IN ENGLAND: A REPORT OF WORK UNDERTAKEN FOR THE DEPARTMENT OF HEALTH NATIONAL MATERNITY AMBITION

Authors

Chris Gale¹, Eugene Statnikov¹, Sena Jawad¹, Sabita Uthaya¹, Neena Modi¹

Corresponding author e-mail address: christopher.gale@imperial.ac.uk

Introduction (include hypothesis)

In November 2015, the Secretary of State for Health announced a national ambition to halve the annual rates of brain injuries occurring during or soon after birth in England, by 2030, with a reduction of 20% by 2020¹. The reference year, 2010. Here we describe how a consensus working definition for brain injuries occurring during or soon after birth, based on existing, routinely recorded data was developed. We use this definition of calculate national incidence rates for England over the period 2010-2015.

Methods (include source of funding and ethical approval if required)

An expert group of neonatologists, obstetricians, policy and other health professionals was convened by the Department of Health to agree a working definition for brain injuries occurring during or soon after birth. To calculate national incidence rates, we extracted data from the National Neonatal Research Database (NNRD) in England for the period 2010-2015. The NNRD contains data from clinician-entered, point-of-care electronic patient records. The NNRD did not receive data from all NHS neonatal units in England in 2010-2011, so upper and lower incidence rates were estimated for these years as the NNRD did not receive data from all NHS neonatal units in England for these years. We estimated lower and upper margins of increase based on 2012-2015 data, and estimated the upper and lower incidence rates using a two standard deviation range above and below estimated incidence values to account for uncertainty. Denominator data was all live births in England².

Results

The agreed consensus definition for brain injuries occurring during or soon after birth comprised infants of all gestational ages with the following conditions: seizures, hypoxic ischaemic encephalopathy, stroke, intracranial haemorrhage, central nervous system infection and kernicterus, and preterm infants with white matter disease (periventricular leucomalacia). Annual incidence figures and rates are shown in the table below.

<table>
<thead>
<tr>
<th>Year</th>
<th>Infants with brain injury</th>
<th>Infants with brain injury adjusted for incomplete NNRD coverage</th>
<th>Live births in England</th>
<th>Rate of brain injuries per 1000 live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>3,006</td>
<td>3,160 to 3,616</td>
<td>687,007</td>
<td>4.60 to 5.26</td>
</tr>
<tr>
<td>2011</td>
<td>3,378</td>
<td>3,431 to 3,627</td>
<td>688,120</td>
<td>4.99 to 5.27</td>
</tr>
<tr>
<td>2012</td>
<td>3,397</td>
<td>3,397</td>
<td>694,241</td>
<td>4.89</td>
</tr>
<tr>
<td>2013</td>
<td>3,385</td>
<td>3,385</td>
<td>664,517</td>
<td>5.09</td>
</tr>
<tr>
<td>2014</td>
<td>3,561</td>
<td>3,561</td>
<td>661,496</td>
<td>5.38</td>
</tr>
<tr>
<td>2015</td>
<td>3,436</td>
<td>3,436</td>
<td>664,399</td>
<td>5.17</td>
</tr>
</tbody>
</table>

Conclusions

Annual incidence figures for brain injuries occurring during or soon after birth can be obtained from data held in the NNRD; annual incidence rates for individual conditions are consistent with published rates from similar settings. Routinely recorded data, captured as part of clinical care, can be used for national surveillance and to support quality improvement, offering efficiencies over traditional approaches.

References (include acknowledgement here if appropriate)

2. Office for National Statistics (ONS) Birth Summary Tables - England and Wales;
This work was commissioned and funded by the Department of Health in England; we thank them for permission to submit this work for presentation at the Neonatal Society Spring Meeting
PARENTS, PATIENTS AND HEALTH PROFESSIONALS REPORT DIFFERENT OUTCOMES OF NEONATAL CARE AS IMPORTANT: A SYSTEMATIC REVIEW OF QUALITATIVE RESEARCH

Authors
James Webbe¹, Ginny Brunton², Shohaib Ali¹, Nick Longford¹, Louise Wann³, Neena Modi¹, Chris Gale¹

Corresponding author e-mail address: j.webbe@imperial.ac.uk

Institution(s)
1. Section of Neonatal Medicine, Imperial College London, Chelsea and Westminster campus, London, UK
2. UCL Institute of Education, London, UK.
3. West Middlesex University Hospital, Middlesex, London, UK.

Introduction (include hypothesis)
Clinical trials have a greater potential to improve care if they measure outcomes that are meaningful and important. Research in other fields has shown that outcomes identified by patients differ from those identified by researchers or clinicians (1). Patient and parent input in outcome selection fosters public involvement in setting the research agenda (2). We aimed to review systematically published qualitative research to determine whether the outcomes of neonatal care that are important to the major stakeholder groups (patients, parents and health professionals) differ between groups. This is part of wider work to identify a neonatal core outcome set.

Methods (include source of funding and ethical approval if required)
The review was pre-registered on PROSPERO (CRD42016037874). The following databases were searched: MEDLINE; CINAHL; EMBASE; PSYCINFO; ASSIA. Peer reviewed papers published in the last 20 years (1997-2016) were considered. Where available, transcribed data were extracted verbatim. Narrative text describing stakeholders’ experiences, perspectives or opinions of the infant-related outcomes of neonatal care were analysed and grouped thematically according to the physiological system to which they related. If an outcome was discussed by a member of a stakeholder group this was assumed to reflect the importance of this outcome to them. Any new outcomes identified in the text were added to the framework of outcomes applied iteratively to all studies. Permutation testing was performed to test the null hypothesis that parents, patients and health professionals identified the same outcomes as important.

Results
Initial searches yielded 1130 papers. After screening, 62 papers containing the views of 4345 stakeholders (including 1952 parents and 368 former patients) were included in the final synthesis. We identified 186 discrete outcomes: 69 outcomes related to 9 physiological systems and 117 outcomes related to 10 other concepts. The most common physiological outcome domain was the gastrointestinal system. Thematic synthesis of non-physiological outcomes identified outcomes relating to themes such as ‘normality’ and ‘suffering’. Permutation testing showed that the frequency with which outcomes were reported differed between parents, ex-neonatal patients and health professionals group (p=0.037). Ex-neonatal patients discussed outcomes relating to surgical processes and neurodevelopment more frequently while doctors and nurses both discussed outcomes relating to suffering more often than expected.

Conclusions
Parents, patients and clinicians report a wide range of important infant outcomes; these differed significantly between parents, ex-neonatal patients and health professionals. Many outcomes identified in this review are not commonly reported in neonatal clinical trials. I recommend the development of a core outcome set to ensure that clinical trial outcomes are aligned with the priorities of wider stakeholder groups.

References (include acknowledgement here if appropriate)
THE IMPACT OF NECROTISING ENTEROCOLITIS ON BRAIN DEVELOPMENT IN PRETERM INFANTS: PRELIMINARY REPORT

Mark Kong, Finn Lennartsson, Angela Darekar, Nigel Hall, Brigitte Vollmer

Corresponding author e-mail address: matk1g12@soton.ac.uk

Clinical Neurosciences, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton; Neonatal and Paediatric Neurology, Southampton Children's Hospital. Department of Medical Physics, University Hospital Southampton NHS Foundation Trust. University Surgery Unit, Faculty of Medicine, University of Southampton.

Introduction (include hypothesis)
Necrotising Enterocolitis (NEC) is an inflammatory bowel disease causing intestinal gangrene, resulting in septicaemia. Infants born very preterm (<32 weeks of gestation; GA) are at high risk of developing NEC; around 50% of these infants require surgery[1]. Surgically treated infants have 60% greater risk of neurodevelopmental impairment than other babies born at similar GA. Here, we explore the hypothesis that brain white matter development is impaired in preterm infants with NEC, which might explain poorer neurodevelopmental outcome in these infants.

Methods (include source of funding and ethical approval if required)
This study included 8 preterm born infants (3 male, mean GA 27 weeks, SD=14.95 days) with confirmed NEC (Bell stage II/III), treated at a tertiary neonatal centre. Two control groups were recruited; a preterm control group without NEC (PTC; n=8, matched for at least two; GA +/-2 weeks, birth weight Z-score, sex, and intraventricular haemorrhage), and a term control (TC) group of n=11 healthy term-born infants. Infants were scanned on a 1.5T MRI scanner at term equivalent age (37-44 weeks GA). Diffusion MRI data were acquired and Tract-Based Spatial Statistics (TBSS) adapted for newborns was used to compare fractional anisotropy (FA) in white-matter tracts on a whole-brain level between groups.


Results
Correcting for post-menstrual age at scan, preliminary findings indicate that infants in the NEC and PTC groups have a significantly lower FA in central WM tracts compared to term-born infants (p<0.05 and p<0.05 respectively). Gestational age corrected comparisons found a weak trend of decreased FA in the splenium of the corpus callosum in NEC infants compared to preterm controls (p<0.12). At age 3 months, poorer motor development (Alberta Infant Motor Scale) and more atypical neurological signs (Hammersmith Infant Neurological Examination) are observed in the NEC group compared to the TC and PTC group.

Conclusions
These preliminary findings indicate microstructural white-matter changes associated with NEC, particularly in the corpus callosum. However, a larger sample is required for further confirmation. Thereafter, associations with neurodevelopmental outcome measures can be examined.

References (include acknowledgement here if appropriate)

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously:

Senior author supporting presentation on day of meeting: Brigitte Vollmer
THE EXOENZYME ACTIVITY OF THE PRETERM GUT

Jenkins, HJ1, Marchesi J2, Modi N1 and Hyde MJ1

Corresponding author e-mail address: holly.jenkins14@imperial.ac.uk

1 Section of Neonatal Medicine, Imperial College London, Chelsea and Westminster Hospital campus, 369 Fulham Road, London, SW10 9NH, UK; 2 Centre for Digestive and Gut Health, Imperial College London, St Mary's Hospital campus, London, W2 1NY, UK

Introduction (include hypothesis)

Extremely preterm infants are at high risk of invasive infection; potential drivers include overrepresentation of pathogenic intestinal microbial communities, and immature gut barrier defences including enzymatic activity.1,2 The protease family, a group of enzymes produced by both host and bacterial species, are believed to be central to intestinal integrity. Studies in adults have reported high levels of protease activity in association with bacterial translocation.3 A review of the literature showed that protease activity has not been longitudinally investigated in preterm neonates. The aim of this project is to explore protease activity and microbial diversity in faecal and meconium samples from very preterm infants.

Methods (include source of funding and ethical approval if required)

We are prospectively recruiting a cohort of 100 preterm babies (<32 weeks' gestation) from Chelsea and Westminster Hospital Neonatal Unit. Babies are enrolled unless parents opt-out (Research Ethics Approval 16/LO/0973). Daily stool samples are collected until death or discharge. Samples are frozen at -80°C and thawed prior to laboratory analysis. Five infants were selected for method development according to predefined criteria that excluded them from the proposed analysis. Protease activity was measured using a fluorescent assay (Pierce), protease origin was determined by inhibitor assays (G-Biosciences) and 16S gene sequencing, using the MiSeq Illumina platform to identify bacterial species.

Results

Samples from 2 girls and 3 boys have been analysed to-date; mean (range) gestational age was 28±3 weeks (24–31). At least 5 stool samples that spanned the infant's time in the Neonatal Unit were analysed (57 in total; 1 meconium). Protease activity ranged between 12 and 998 U of trypsin equivalent per 1 mg of stool protein. In each infant, protease levels were found to be low, but increased over time. Results from inhibitor analysis showed samples were predominately composed of host proteases. 16S gene sequencing revealed that the main phylum detected in stool was Proteobacteria, with samples becoming populated with more Firmicutes as time after birth increased. The genus Bifidobacterium was poorly represented. At the species level, Shigella, E. coli and other unclassified Enterobacter spp. were most commonly isolated. The meconium sample had the widest diversity of species and one of the highest levels of protease activity (513 U of trypsin).

Conclusions

These novel data indicate that preterm endogenous protease activity increases over time; the relevance of this is not as yet known. The finding that proteases are predominantly mammalian in origin may reflect a lower microbial load in the gut. The bacterial species we found are well recognised components of the preterm gut microbiome. The discovery of a microbial presence in meconium is not novel and has been previously reported. However, this is the first time total protease levels have been measured in meconium. It is possible that protease activity in meconium is due to the presence of protease producing bacteria, although this requires further investigation.

References (include acknowledgement here if appropriate)

Self Certificate of Attendance

Please complete the form below and have it signed by a member of the neonatal society committee if you wish to claim RCPCH CPD points

Neonatal Society Spring Meeting
Royal Society of Medicine, London
30th March, 2017

Name of person claiming CPD points:
(Blockletters)………………………………………………

Place of Work:……………………………………………………………………

Number of CPD points claimed :………………………………………………
(1 point per hour of attendance – up to a maximum of 5 CPD Points)

Claimant’s Signature…………………………..

Name and signature of Neonatal Society Committee member

………………………………………………………………
Howard Clark/Helen Budge//James Boardman/Andrew Ewer
Divyen Shah/Karen Luyt/Chris Gale
(please delete as appropriate)