ID: 82

TITLE: DOES PRONE SLEEPING AFFECT CARDIOVASCULAR CONTROL IN PRETERM INFANTS IN NICU?

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CONTENT:

Preterm infants are frequently placed prone in the neonatal intensive care unit (NICU) to improve respiratory function. However, prone sleeping is associated with impaired cardiovascular control in both term infants and preterm infants after term-corrected age. In term infants, heart rate (HR) is increased and HR variability (HRV) is decreased when infants sleep prone. Currently, there is a paucity of data on the effect of prone sleeping on HRV in preterm infants during their early postnatal weeks in NICU when they are most vulnerable to cardiovascular instability. We assessed the effects of position and sleep state on HRV in preterm infants longitudinally over the first 6 weeks of life.

Fifty-five preterm infants (born between 24-34 weeks of gestation) were studied weekly for 6 weeks after birth with cardiorespiratory monitoring, including electrocardiogram (ECG). Infants slept for 1 hr in both the prone and supine positions and data were analysed for both active sleep (AS) and quiet sleep (QS). Spectral analysis was performed on R-R interval series in a low frequency band (LF, 0.04-0.15 Hz, related sympathetic + parasympathetic changes) and a high frequency band (HF, 0.4-1.5 Hz, related to respiratory and parasympathetic modulation). HRV LF, HF and total power (TP) and LF/HF were calculated. Effects of sleep position, state and postnatal age were analysed using a linear mixed model approach.

Overall, LF, HF and TP were lower when prone compared to supine across the first 6 weeks of life (LF: 76.3 ±4.7 vs 61.8 ±3.8 ms2, p<0.05; HF: 10.8 ±2.1 vs 18.5 ±2.6 ms2, p<0.05; TP: 109.9 ± 8.5 vs 136.3 ±10.8 ms2, p<0.05), with no interaction between position and postnatal week in any of the parameters. R-R interval was shorter in the prone compared to supine position (379.1±1.5 vs 388.1±1.5 ms, p<0.01). LF and TP were lower during QS compared to AS (LF: 58.6 ±3.7 vs 81.4 ±4.9 ms2, p<0.001; TP: 95.9 ±8.2 vs 150.2 ±11.2 ms2, p<0.001). TP decreased in the first 3 weeks, being higher at week 1 compared to week 3 (160.1± 19.3 vs 92.2 ±11.7 ms2, p<0.05). LF also decreased initially, being lower at week 3 compared to weeks 2 and 4 (51.1 ±4.6 vs 77.8 ±6.5 and 80.6 ±7.8 respectively, p<0.05 for both).

The prone position was associated with reduced HRV and higher HR in preterm infants in the NICU. These results suggest dampened autonomic activity, which could increase the vulnerability to hypertensive/hypotensive events by limiting the compensatory HR responses. Further studies are required to determine the clinical significance of impaired HRV in the prone position in clinically unstable preterm infants.

COI: None declared
ID: 92
TITLE: ASSOCIATION BETWEEN HOSPITAL VOLUME AND MORTALITY OF CONGENITAL DIAPHRAGMATIC HERNIA REPAIR SURGERY IN JAPAN
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CONTENT:

Congenital diaphragmatic hernia (CDH) is one of the most common major congenital anomalies, with an annual incidence of 1 in 2,500 to 5,000 live birth. Hospital surgical volume is one of the important hospital factors which often influenced quality improvements and several health policy initiatives, usually high-volume hospitals achieved better outcome. However, only a few studies have investigated the effect of the hospital surgical volume on the outcomes of CDH repair surgery. The aim of this study was to examine the relationship between the hospital surgical volume and in-hospital mortality of these patients.

Data pertaining to CDH infants (age in day <28) who underwent CDH repair surgery between April 2010 and March 2017 were retrieved from the Japanese national inpatient database and retrospectively analyzed. Hospitals were classified into 4 categories by the quartile of surgical volume of CDH. The risk for in-hospital mortality were estimated by the Cox regression. Each patient had the records of baseline characteristics, comorbidity at admission and all medical practices based on daily basis among the hospital stay, which were used as the covariates. Differences of characteristics among the hospitals were considered in the Cox regression by the clustering method based on generalized estimating equation, where correlations of each hospital are accounted by the robust sandwich estimator.

The patients received CDH repair surgery and distribution of the case numbers were widely spread across 114 hospitals in Japan. Mean (sd) surgical volume of CDH in each hospital was 1.2 (1.6) cases per year and 8.7 (10.9) cases among 7 years in total. Overall mortality in this study was 9.5%. Very low volume hospitals had highest mortality (11.9%) among the four categories of hospitals. The Cox regression analysis in our study presented the surgical volume of CDH in middle-volume and high-volume hospitals were associated with decreasing in-hospital mortality. The hazard ratio were 0.82 (95% confidence interval [95% CI], 0.72-0.93, p = 0.003) in the second volume quartile, 0.65 (95% CI 0.58-0.72, p < 0.001) in the third volume quartile, and those of high-volume hospitals was 0.66 (95% CI 0.53-0.82, p < 0.001).

The present study indicated a volume-outcome relationship in CDH repair surgery cases, although there are several unmeasured confounding variables. Further centralization of surgeries should be considered to achieve better outcome.

COI: none declar
ID: 875
TITLE: SOCIAL ADJUSTMENT IN ADOLESCENTS BORN VERY PRETERM: UNDERLYING MECHANISMS OF IMPAIRMENT
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CONTENT:

Accumulating evidence shows neurodevelopmental impairments in adolescents and young adults born very preterm (VP). Less attention has been devoted to social functioning after VP birth, especially during adolescence. This is surprising since achieving adult levels of social competence is a fundamental maturational task during adolescence and poor social competence in adolescence is associated with increased psychiatric morbidity. The aim of our study was to increase the understanding of social adjustment and autism spectrum disorder (ASD) symptoms in adolescents born VP by studying the role of emotion recognition and cognitive control in the relation between VP birth and social adjustment.

A Dutch cohort of 61 VP and 61 full-term adolescents aged 13 years participated. Social adjustment was rated by parents, teachers, and adolescents and ASD symptoms by parents. Emotion recognition was assessed with a computerized task including pictures of child faces expressing anger, fear, sadness, and happiness with varying intensity. Cognitive control was assessed using a visuospatial span, antisaccade, and sustained attention to response task. Performance measures derived from these tasks served as indicators of a latent cognitive control construct, which was tested using confirmatory factor analysis. Mediation analyses were conducted with emotion recognition and cognitive control as mediators of the relation between VP birth and social problems.

VP adolescents showed more parent- and teacher-rated social problems and increased ASD symptomatology than controls. No difference in self-reported social problems was observed. Moreover, VP adolescents showed deficits in emotion recognition and cognitive control compared to full-term adolescents. The relation between VP birth and parent-rated social problems was significantly mediated by cognitive control but not by emotion recognition (see Figure). VP birth was associated with a 0.67-SD increase in parent-rated social problems through its negative effect on cognitive control. The model accounted for 35% of the variance in parent-rated social problems, while 11% of the variance was explained by VP birth alone.

The findings provide strong evidence for a central role of impaired cognitive control in the social problems of VP adolescents. Social problems are associated with psychiatric morbidity and should receive more attention in follow-up after VP birth. Since follow up in clinical practice mostly ends far before puberty onset, the focus on social development of VP children should be increased to detect and act on social impairments early in life.

IMAGES:
https://www.eiseverywhere.com/eselectv3/v3/events/351149/submission/files/download?fileID=f1b01c84f81f9dac026f56a1e4bde212-MjAxAOS0wNSM1Y2UyNjY2DE1MzUw

Path model of the effect of very preterm birth on parent-rated social problems mediated by cognitive control and emotion recognition. Standardized regression coefficients are related to the association between very preterm birth and the mediator (path a), the mediator and parent-rated social problems (path b), and the direct effect of very preterm birth on
parent-rated social problems controlling for the mediators (path c’). Significant paths (p<.05) are depicted in black and non-significant paths in gray.
SART = sustained attention to response task; VWM = visuospatial working memory.

COI: Prof. dr. Ruurd van Elburg is an employee at Danone Nutricia Research, Utrecht, the Netherlands. The other authors have no conflicts of interest to disclose.
ID: 246
TITLE: NEAR INFRARED SPECTROSCOPY AND GUT BIOMARKERS IN PRETERM INFANTS – CAN THEY PREDICT NEC?
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CONTENT:
We previously established normal ranges of regional tissue oxygenation in preterm infants using Near Infrared Spectroscopy (NIRS). Survival of very preterm infants has improved but the incidence of NEC has not changed. Progress in the prevention of Necrotising Enterocolitis (NEC) has been limited by difficulties in clearly defining high risk groups of preterm infants and because there are no routinely used effective gut biomarkers. There is an unmet need to identify prospective biomarkers to create a window of opportunity for prevention.

We aimed to establish if gut biomarkers of tissue injury and splanchnic NIRS measurements differed in infants with NEC compared to those without NEC.

We examined 48 infants <30w gestation admitted to our tertiary level NICU (after ethical approval and informed consent) from Oct 2016 to May 2018. Exclusion criteria: birthweight ≤2nd centile, abnormal antenatal dopplers, major congenital anomalies or Twin to Twin Transfusion Syndrome. For 60 minutes each week splanchnic (sTOI) and cerebral (cTOI) Tissue Oxygenation Index was measured simultaneously using NIRO-300 (Hamamatsu KK, Japan). Subsequently splanchnic Fractional Tissue Oxygen Extraction (sFTOE) and Splanchnic Cerebral Oxygenation Ratio (SCOR) were calculated. Weekly urinary intestinal and liver fatty acid binding proteins (I-FABP, L-FABP), Trefoil Factor 3 (TTF3) and stool Calprotectin were measured by ELISA and weekly clinical status recorded. NEC was defined as ≥ Bells stage 2.

Median birthweight was 884g (460-1600), median gestational age 26+3 weeks (23+0-29+6) and 52% female. 7 infants developed NEC.

Over the first 7 weeks of life none of the biomarkers were affected by presence of PDA, enteric feed volumes or haemoglobin level. There were no statistically significant differences in I-FABP, L-FABP, TFF3 and Calprotectin levels between those infants with and without NEC.

sTOI was significantly lower and sFTOE was significantly higher in those infants who developed NEC compared to those without NEC. The SCOR was lower in infants who developed NEC (Table 1). sTOI, and sFTOE were significantly associated with NEC even after adjusting for confounding factors such as gender, PDA, enteral feed, ethnicity and haemoglobin.

Infants who developed NEC had significantly lower splanchnic oxygenation. If preterm infants at the highest risk of NEC had continuous NIRS measurements and individual trends examined, then a reduction in sTOI and corresponding increase in sFTOE could herald the onset of NEC. This novel finding could help clinicians diagnose NEC sooner. In the future an algorithm could provide more sophisticated information than a single biomarker alone.
Table 1: Splanchnic NIRS measurements in those infants with NEC compared with infants without NEC (excluding those infants who developed Haemorrhagic Parenchymal Infarcts).

**COI:** None declared
ID: 839

**TITLE:** PRETERM NEONATES BENEFIT FROM LOW PROPHYLACTIC PLATELET TRANSFUSION THRESHOLD DESPITE VARYING RISK OF BLEEDING OR DEATH

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**CONTENT:**

The Platelets for Neonatal Thrombocytopenia (PlaNeT-2) trial reported an overall unexpected benefit of a prophylactic platelet transfusion threshold of 25x10^9/L compared to 50x10^9/L for major bleeding and/or mortality in preterm neonates (7% absolute risk reduction). However, some neonates in the trial may have experienced little benefit or even harm from the 25x10^9/L threshold. We aimed to assess this heterogeneity of treatment effect in the PlaNet-2 trial, in order to investigate whether all preterm neonates benefit from the low threshold.

We developed a multivariable logistic regression model in the PlaNet-2 data to predict baseline risk of major bleeding and/or mortality for all 653 neonates. We then ranked the neonates based on their predicted baseline risk and categorized
them into four risk quartiles. Within these quartiles we assessed the absolute risk difference between the 50x10^9/L and 25x10^9/L threshold group.

A total of 146 neonates died or developed major bleeding. The internally validated C-statistic was 0.63 (95% confidence interval 0.58 – 0.68). The 25x10^9/L threshold was associated with absolute risk reduction in all risk groups, varying from 4.9% in the lowest to 12.3% in the highest risk group.

These results suggest that a 25x10^9/L prophylactic platelet count threshold can be adopted in all preterm neonates, irrespective of predicted baseline outcome risk. Future studies are needed to improve the predictive accuracy of the baseline risk model.

IMAGES:
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Image title: Absolute risk difference (ARD) between a high (50x10^9/L) and low (25x10^9/L) threshold for prophylactic platelet transfusion thresholds in preterm neonates with respect to major bleeding and/or mortality within 28 days after randomization.

Image legend: Event rates (panel A), odds ratios (panel B) and absolute risk differences (panel C) are presented for all four risk categories, vertical lines represent 95% confidence intervals, horizontal lines represent overall trial results. A negative absolute risk reduction represents the risk decrease for a low prophylactic platelet transfusion threshold as compared to a high threshold.

COI: None declared.
ID: 847

**TITLE:** THE EFFECT OF PRENATAL SILDENAFIL ADMINISTRATION ON POSTNATAL CEREBRAL AND RENAL TISSUE OXYGENATION IN SEVERE EARLY-ONSET FETAL GROWTH RESTRICTION

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**CONTENT:**

Neonates born after fetal growth restriction (FGR) show higher cerebral oxygenation (rSO2) and ongoing redistribution of cerebral-renal blood flow during the first 3 days after birth. Sildenafil has been under investigation as a potential agent to improve utero-placental blood flow and thereby fetal growth. This could affect cerebral redistribution associated with placental insufficiency. Previous studies showed effects on fetal flow profiles after prenatal sildenafil treatment. However, a large RCT (STRIDER) was halted during interim analysis due to futility and potential neonatal side effects. This sub-study investigated the effect of prenatal sildenafil on cerebral and renal oxygenation.

Within the Dutch STRIDER trial, pregnant women with severe early-onset FGR received 25 mg tablets of placebo or sildenafil three times daily. In a random subset of neonates admitted to two neonatal intensive care units, frontal cerebral (n=14 vs n=14) and renal (n=5 vs n=6) rSO2 was continuously measured with near-infrared spectroscopy during the first 72 hours after birth. Arterial oxygen saturation (SaO2) was measured simultaneously and fractional tissue oxygen extraction (FTOE=(SaO2-rSO2)/SaO2) was calculated. One hour of good quality of rSO2 per 3-hour intervals was manually selected. Heart rate (HR) and mean arterial blood pressure (MAP) during these periods were extracted. A linear mixed model approach was used providing an intercept ± slope per 3 hour interval (=r) per group.

Neonates were born with comparable birthweight (707±46g vs 659±48g; p=0.48) and gestational age (28.1±0.4wk vs 28.4±0.7wk; p=0.72). Cerebral rSO2 and FTOE levels were similar between the placebo and sildenafil group and had comparable trends during the first 72 hours after birth (Figure 1). Renal rSO2 was similar between groups, but during the first 72 hours renal rSO2 decreased less in the sildenafil group (r: -0.91% vs -0.28%; p<0.01). Renal FTOE was elevated in the sildenafil group (intercept: -0.03 vs 0.13; p=0.02) and increased less over time compared with the placebo group (r: 0.015 vs 0.003; p<0.001). HR and MAP were similar between groups, but HR increased slightly more during the first 72 hours after birth in the sildenafil group (r: 0.6 bpm vs 1.1 bpm; p<0.001), while MAP increased less over time in the sildenafil group (r: 0.2 mmHg vs 0.1 mmHg; p<0.05).

In this small group of neonates born after severe early-onset FGR, we observed a renal but no cerebral effect in tissue oxygenation during the first 72 hours after birth in the sildenafil group compared with the placebo group. These data suggest that prenatal sildenafil may not prevent postnatal cerebral redistribution associated with placental insufficiency and that a different mechanism underlies the observed difference in renal oxygenation.
Figure 1: Cerebral and renal tissue oxygenation and oxygen extraction during the first 72 hours after birth in prenatal sildenafil and placebo treated neonates. Data expressed as mean ± SEM. FTOE, fractional tissue oxygen extraction; rSO2, regional oxygenation, r=slope per 3-hour intervals. Vertical dotted lines indicate days after birth.

COI: None declared.
ID: 909

TITLE: EFFECT OF 90 VERSUS 60 MINUTES OF EARLY SKIN-TO-SKIN CONTACT ON EXCLUSIVE BREASTFEEDING RATE IN HEALTHY INFANTS ≥ 35 WEEKS: AN OPEN-LABEL RANDOMIZED CONTROLLED TRIAL

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CONTENT:

Breastfeeding is one of the most cost-effective intervention to decrease under-5 mortality rate. Early skin-to-skin contact (SSC) is one of the key interventions around birth to promote breastfeeding practices and is a standard of care. World Health Organisation (WHO) currently recommends early SSC for a duration of at least 60 minutes however; the advantage of prolonging this duration is unknown. There is only one retrospective study which concluded that the longer periods of early SSC leads to increased likelihood of exclusive breastfeeding rate during the hospital stay immediately after birth however; there is no randomized controlled trial (RCT) assessing this dose-response relationship.

The objective was to evaluate if 90 minutes of early SSC improves exclusive breastfeeding rate in infants ≥35 weeks of gestation as compared to standard 60 minutes. Healthy infants ≥35 weeks of gestation born by vaginal delivery were randomized at birth to either 90 minutes (intervention) or 60 minutes (control) of early SSC. The infants in the intervention group received early SSC for 90 minutes immediately after birth whereas the control group received standard of care. The infants were followed until 14 weeks of age. The primary outcome was exclusive breastfeeding rate, which was assessed using standard WHO definition at 60±12 hours of age before discharge. The secondary outcome was breastfeeding behaviour as measured using modified infant Breast-Feeding Assessment Tool (IBFT).

Both groups had 99 infants each with similar baseline characteristics including maternal age, education, parity, previous breastfeeding experience, socio-economic status and time of first breastfeeding. The mean gestational age and birth weight of the infants were also similar [39 (±1.5) vs. 39 (±1.3) weeks and 3113 (±394) vs. 3055 (±428) in intervention and control group respectively]. The exclusive breastfeeding rate was significantly higher in intervention group as compared to control group at 60±12 hours of age [75.7% (75/99) vs. 52.5% (52/99) relative risk (RR): 1.44, 95% confidence interval (95% CI): 1.15 – 1.79; p = 0.003]. The exclusive breastfeeding rate at the time of discharge from the hospital was also same. The IBFT score was also significantly higher in the intervention group as compared to control group [9 [8, 10] vs. 8 [7, 10]; p = 0.03].

Ninety minutes of early SSC significantly improved the exclusive breastfeeding rates at 60±12 hours of age and at discharge. The infants who received prolonged early SSC were 1.4 times more likely to be on exclusive breastfeeding at the time of discharge than those who received 60 minutes of early SSC. Moreover, the breastfeeding behaviour as assessed by IBFT tool also significantly better in the prolonged early SSC group (CTRI/2018/09/015632).

COI: None declared