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**THE IMPACT OF A SEPSIS QUALITY IMPROVEMENT PROJECT (QIP)
ON NEURODISABILITY RATES IN VERY LOW BIRTH WEIGHT
INFANTS.**

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Abstract

Objective

Very low birth weight infants (VLBW; <1500g) with late onset sepsis have an increased risk of neurodisability. Care bundles to reduce bloodstream infections in NICU are effective in reducing late onset sepsis. Our aim was to determine if a sepsis reduction bundle introduced through a QIP would impact neurodevelopmental outcomes in VLBW infants.

Design

Cohort study

Setting

Level 3 regional NICU in the South West of England

Patients

VLBW infants born between 2002 — 2011.

Interventions

A sepsis reduction care bundle implemented between July '06 - December '07.

Main outcome measures

The primary outcome was risk of coagulase negative *Staphylococcus* (CONS) infection diagnosed > 3 days of age. Secondary outcomes were death and moderate cognitive impairment. A logistic regression model was derived using the birth era as the independent variable with adjustment for typical confounders.

Results

In total, 379 infants were born in the pre- and 378 in the post-intervention cohort. The CONS infection rate was reduced after the intervention (26.7% vs. 14.1% $p<0.001$). Death prior to discharge reduced without reaching statistical significance (14.1% vs. 10.9%, $p=0.195$). The rate of cognitive disability reduced in the post intervention cohort (18.8% vs. 6.1%, $p=0.042$). The adjusted odd ratios (95% confidence interval) for CONS infection, death and cognitive impairment were 0.46 (0.29 – 0.72), 0.73 (0.43 – 1.24) and 0.3 (0.07 – 1.33) respectively.

Conclusions

There appears to be an association between reduced cognitive disability and the implementation of a sepsis –reduction bundle. Further study in larger series are required to confirm these findings.

Introduction

Very low birth weight infants (VLBW, <1500g) are at high risk of infection during their stay in neonatal intensive care (NICU) (1), and importantly, infections in VLBW infants have an additive detrimental effect on neurodevelopmental outcomes. (2,3)

Late onset sepsis (LOS) is defined as infection commencing after 48 - 72 hours of age (1). The prevalence of LOS as reported by large data collections such as the Vermont Oxford Network (VON) and the National Institute of Child Health and Development (NICHD) is between 10 – 20% (4–6). VLBW infants are at increased risk of infection because of their immunological immaturity (1), exacerbated by intensive care interventions such as central venous catheterisation and ventilation. (7)

Care bundles are defined as a limited number of specific practices essential for effective and safe patient care and that implemented together result in additional improvements (8). Studies have demonstrated the effectiveness of ‘care bundles’ on the overall incidence of infection in the NICU population, mainly in state wide collaborations(8–10), although no study has to date demonstrated improvement in neurodevelopmental outcome or survival.

This work is based in a 31 bedded tertiary level neonatal unit with approximately 100 VLBW infants born per annum. Between 2001–2004, the rate of late onset sepsis in VLBW infants was 40%, compared to 20% (4) for the Vermont Oxford Network (VON) average and hence an ‘infection care bundle’ was developed and introduced through a Quality Improvement Project (QIP) in an attempt to improve infection rates.

Our aim was to determine the impact of the introduction of an infection reduction bundle in a tertiary neonatal unit on VLBW infants’ survival and neurodevelopmental outcomes.

Methods

The measures introduced were based on the iNICQ Quality improvement programme from the Vermont Oxford Network (11). The quality improvement strategy began with a broad assessment of practice by a small group of cross-discipline individuals and lead to the identification of a series of potentially better practices (PBPs) (Fig. 1).

The bundle consisted of improving hand washing and cleanliness of incubator environment, targeted aseptic intervention for venous and arterial line insertion, as well as the introduction of the aseptic non-touch technique (ANTT) for the access of central and arterial lines (12). In addition closed systems were introduced on all arterial access sets and microclaved ports on venous sets. All these measures were underpinned with regular, rapid cycle audits to identify and rectify areas of improvement. Rapid cycle audits were performed around hand and environmental cleanliness and aseptic non-touch technique, with immediate display of results to staff. Monthly compliance rates were displayed on run charts, which were visible to all staff on the unit. (Fig 2.)

The population investigated was all inborn infants, less than 1500g at St Michael's Hospital, Bristol, UK between 2002 and 2011. The care bundle was introduced to the unit in stages over 18 months between July 2006 and December 2007. Exposure was defined as before the intervention (Jan 2002 to Dec 2007) or after the intervention had been fully implemented (July 2008 to Dec 2011). The period between December 2007 and July 2008 was omitted from analysis to allow comparison of full practice implementation. The primary outcome was risk of coagulase negative *Staphylococcus* (CONS) infection diagnosed after 3 days of age. Secondary outcomes were any late (>3 days old) bacterial infection, death, cerebral palsy or moderate cognitive impairment. Moderate cognitive disability was defined as a Bayley Scales of Infant Development second edition (BSIDII) MDI below 70 or Bayley Scales of

Infant Development third edition (BSIDIII) combined language and cognitive scales below 80 at corrected age of 24 months (13).

The Vermont Oxford Network definition of a CONS infection was used. That being a CONS recovered from a blood culture from either a central line, or peripheral blood sample, and one or more signs of generalized infection (such as apnoea, temperature instability, feeding intolerance, worsening respiratory distress or hemodynamic instability), and initiation of intravenous antibiotics treatment for 5 or more days after blood cultures were obtained. If the infant died, was discharged, or transferred prior to the completion of 5 days of intravenous antibiotics, this condition would still be met if the intention were to treat for 5 or more days. Late bacterial infection was defined as a recognised bacterial pathogen (excluding CONS) recovered from blood culture after day 3 of life.

Initially the absolute risk of infection was assessed by year of birth. A logistic regression model was derived using the era of birth as the independent variable initially, and then adjusting for the confounders. Confounders were defined a-priori as antenatal steroids (completed course), gender, birth-weight, multiple birth, gestational age at birth and Apgar scores (at 1 and 5 minutes). No tests were performed to 'test' for confounders. Ordinal variables were checked that categorical terms did not show better fit than the linear terms (all Wald tests >0.05). This was repeated for the primary and secondary outcomes listed above. Univariable comparisons were made using the t-test or Wilcoxon-Mann-Whitney test as appropriate. All analyses performed using STATA10.

Ethical approval was not specifically requested as this intervention was part of a quality improvement project, and was registered as a service evaluation with University Hospitals Bristol NHS Trust.

Results

The results are described first by the baseline characteristics for each group which were additionally used as confounders to adjust for the odds ratios later in this section (Table 1). In total 757 patients were born during the study period at birth weight <1500g. The number of patients in the two cohorts was 379 and 378 in the early (2002 – 2007) and late (2008 – 2011) periods respectively.

Although birth weight, gestation and Apgar score were statistically different there was little numerical difference between the cohorts. The use of antenatal steroids improved significantly between the two time periods (78.1% vs. 89.1%, $p<0.001$).

Measure	Early Cohort (2002-2007) <i>n</i> =379	Late Cohort (2008- 2011) <i>n</i> = 378	<i>p</i> -value
Birth weight	1055 (795-1319)	1130 (880-1360)	0.0369
Gestation	28 (27-31)	29 (27-31)	0.0177
Male	176 (48.6%)	181 (50.4%)	0.629
Antenatal Steroids	281 (78.1%)	314 (89.0%)	<0.001
Multiple Birth	117 (32.3%)	103 (28.7%)	0.290
Apgar 1 minute	6 (5-8)	6 (5-8)	0.2093
Apgar 5 minutes	9 (8-10)	8 (7-9)	<0.001

Measures are *n* (%), mean (SD) or median (IQR)

Table 1. Characteristics of the study population (*n*= 757)

CONS and any other late infection were significantly reduced between the epochs (26.7% vs. 14.1%, $p<0.001$; 18.8% vs. 8.7%, $p<0.001$ respectively) (Table 2, Fig 3). On univariate analysis the rate of cognitive disability was significantly lower in the post intervention cohort

(18.8% vs. 6.1%, $p=0.042$) (Table 2). The adjusted odds ratios (95% confidence interval) for CONS infection, death and cognitive impairment were 0.46 (0.29 – 0.72), 0.73 (0.43 – 1.24) and 0.3 (0.07 – 1.33) respectively (Table 3).

Measure	Early Cohort (2002-2007)	Late Cohort (2008-2011)	<i>p</i> -value
CoNS infection	85 (26.7%)	44 (14.1%)	<0.001
Any other late infection	60 (18.8%)	27 (8.7%)	<0.001
Death prior to discharge	51 (14.1%)	39 (10.9%)	0.195
Cognitive Disability	16 (18.8%)	3 (6.1%)	0.042
Cerebral Palsy	10 (10.8%)	7 (12.1%)	0.803

Measures are *n*(%)

Table 2. Outcome measures, split by era of birth

Measure	Unadjusted	Adjusted*
CoNS Infection	0.45 (0.30-0.67)	0.46 (0.29-0.72)
Any other Late Infection	0.41 (0.25-0.66)	0.43 (0.25-0.73)
Death prior to discharge	0.75 (0.48-1.16)	0.73 (0.43-1.24)
Cognitive Disability	0.28 (0.08-1.02)	0.30 (0.07-1.33)
Cerebral Palsy	1.14 (0.41-3.18)	1.26 (0.34- 4.72)

Measures are OR (95% CI) for poor outcome

Table 3. Association between era of birth and outcome measure

* Adjusted for antenatal steroids, gender, birth-weight, multiple birth, gestational and Apgar scores.

Discussion

This is the first description of the long term impact of a sepsis reduction bundle on neurodevelopmental outcomes in VLBW infants. A reduced rate of cognitive disability will be important if confirmed in larger series. This QIP achieved its primary outcome in reducing coagulase negative *Staphylococcal* infection by nearly 50%. In addition, all other late bacterial infections were significantly reduced by the intervention. The intervention has demonstrated sustained impact as the rates of coagulase negative *Staphylococcus* infection in 2013 was 2.1%.

The link between systemic neonatal infection and cerebral white matter injury has been described for more than 40 years. (2,14) In a population of over 6000 extremely low birth weight infants Stoll et al. (3), reported that one or more episodes of infection significantly increased the risk of cognitive, motor and sensory disability. In this study there was some evidence of a reduction in cognitive disability without significant changes in death or cerebral palsy. After adjustment for potential confounders the confidence interval around cognitive disability widened, although the point estimate remained similar. While this effect may have been due to chance, it remains consistent with the published literature.

We were limited by the size of the population, and the fact that other changes in care may have occurred over the study period, not identified in this work. Although we do know that neuroprotective interventions such as intrapartum magnesium sulphate, delayed cord clamping and enhanced nutrition were not adopted on our unit before 2012 (after the end of the study period). In addition, the neurodevelopmental assessment changed during the study. It is well recognized that the BSIDIII cognitive and language scales overestimate cognitive ability compared to the BSIDII MDI. For this reason we used a validated (13) cut-off of 80 for moderate cognitive disability when using the BSIDIII cognitive and language composite to allow comparison across time (13). There is no validated alignment of cut offs for BSIDII PDI and BSIDIII motor score, therefore BSID motor score was not included in the analysis.

This is the first report where reduction in proven infection and cognitive disability have been associated. This effect needs to be studied and corroborated in larger populations and between institutions before more definite conclusions can be made.

What is already known on this topic?

Nosocomial infection in very low birth weight infants remains problematic

Infection in very low birth weight infants substantially increases the risk of neurodisability

Infection reduction care bundles are effective in reducing late onset sepsis

What this study adds

Infection reduction bundles reduce CONS and other late onset infections in VLBW infants.

We describe an association between reduced infection rates and cognitive disability at 2 years of age.

Figures

Figure 1. Examples of PBP identified and implemented

Figure 2. Example of compliance chart August 2006 – January 2007

Figure 3. Rates of Coagulase Negative *Staphylococcus* Infection by year, demonstrating impact of the intervention.

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Contribution statement:

The study was conceived by Dr Karen Luyt.

Dr Jary performed the neurodevelopment assessments

The data was analysed by Dr David Odd.

The significance of the findings were discussed by all four authors.

The initially manuscript was written by Dr J Davis with input from the other authors.

Dr J Davis and Dr D Odd contributed equally to the production of the manuscript.