Risk of severe intraventricular haemorrhage in the first week of life in preterm infants transported before 72 hours of age

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Objective

Evaluate the risk of severe intraventricular haemorrhage (IVH), in the first week of life, in preterm infants undergoing early inter-hospital transport.

Design

Retrospective cohort study

Setting

Tertiary neonatal centres of the Trent Perinatal Network in the UK.

Patients

Preterm infants <32 weeks gestation, who were either born within and remained at the tertiary neonatal centre (inborn), or were transferred (transported) between centres in the first 72 hours of life.

Methods

Multivariable logistic regression models adjusting for key confounders were used to calculate odds ratios (OR) for IVH with 95% confidence intervals (CI) for comparison of inborn and transported infants.

Interventions

None

Measurements

Cranial ultrasound findings on day 7 of life. Secondary analyses were performed for antenatal steroid course and gestational age subgroups.

Main Results

A total of 1047 preterm infants were included in the main analysis. Transported infants (n=391) had a significantly higher risk of severe (grade III/IV) IVH compared with inborns (n=656) (9.7% vs 5.8%, aOR 1.69, 95%CI 1.04-2.76), especially for infants born at <28 weeks gestation (aOR 1.83, 95%CI 1.03-3.21). Transported infants were less likely to receive a full antenatal steroid course (47.8% vs 64.3%, $p<0.001$). A full antenatal steroid course significantly decreased the risk of severe IVH irrespective of transport status (OR 0.33, 95%CI 0.2-0.55). However, transported infants <28 weeks gestation remained significantly more likely to develop a severe IVH despite a full antenatal steroid course (aOR 2.84, 95%CI 1.08-7.47).

Conclusion

Preterm infants transported in the first 72 hours of life have an increased risk of early-life severe IVH even when maternal antenatal steroids are given. The additional burden of postnatal transport could be an important component in the pathway to severe IVH. As timely in-utero transfer isn't always possible, we need to focus research on improving the transport pathway to reduce this additional risk.

Introduction

Centralisation of neonatal intensive care has improved preterm mortality, however, morbidity such as neurodisability remains unchanged [1]. Preterm infants have an increased risk of intraventricular haemorrhage (IVH) [2] [3], although the aetiology is multifactorial the principle cause is due to the fragility of the germinal matrix and fluctuations in cerebral blood flow [4]. However, this risk can be significantly reduced by administration of antenatal steroids prior to delivery [5]. Severe IVH (grades III and IV) is associated with increased mortality and an estimated 70% of survivors develop cerebral palsy or cognitive impairment [6]. This has a significant impact not only on quality of life, but on society with an estimated lifetime cost per child with cerebral palsy of \$1.3 million (£1 million) [7] [8]. Furthermore, infants with mild IVH have lower developmental scores compared to those with no IVH [6] [9].

The majority of IVHs start within the first hours and days of life [3], coincident with the period when inter-hospital transport frequently occurs [10] and, in many instances, grade 1 or 2 haemorrhages extend to the more severe grade [11]. This is of particular concern as 1 in 6 preterm infants <32 weeks gestation (~1400 infants) born in the UK are transported in the first 72 hours of life [10] and up to 1 in 5 are transported in Canada [12]. The EPICure 2 study found only 7% of extremely preterm infants, transported on the first day of life, survived without significant morbidity, lower than those born and cared for in level 2 (17%) and level 3 units (15%) [1]. Many historical cohort studies have reported an increased risk of severe IVH with postnatal inter-hospital transport [8] [13] [14] [15] but others have not [16] [17]. These have a number of limitations including exclusion of high risk patients and omission of important confounders including the role of antenatal steroids (ANS) as a

potentially neuroprotective agent and proxy of good quality antenatal care. More importantly, none account for the lack of differentiation between early perinatal (in the first week) and later brain injury; the latter could be attributed to other risk factors associated with longer-term neonatal care.

A recent Canadian study, of almost 3000 infants <29 weeks, found outborn (transported) infants were more likely to have a poor neurodevelopmental outcome at 2 years of age [12]. . The authors postulated that the outborn infants were sicker initially but not 12 hours after transfer and suggested the illness severity after delivery and during transport may have a major impact on these outcomes. However, no data were presented on the day of transfer or risk of severe IVH in the first week of life which could better reflect early perinatal risks including inter-hospital transport.

Understanding the incidence of IVH and the associated perinatal factors in the first week of life could provide useful data for studies aimed at reducing this during the period of greatest risk. Our primary aim was to evaluate the relationship between neonatal transport, early severe IVH and antenatal steroid administration in preterm infants born <32 weeks gestation who were transferred within the first 72 hours of life.

Materials and Methods

Study design and participants

This retrospective cohort study used prospectively collected anonymised clinical data from a validated online national UK database [18], BadgerNet (Clevermed), between 2007 (the start of the database in this network) and 2016 as well as local clinical records where appropriate. Data were collected on all preterm

infants born <32 weeks gestational age (GA), who were either born in (inborn), or transferred into (from regional centres of any care level) or between one of the two Nottingham University Hospitals (NUH) tertiary neonatal intensive care units (NICU). These are the two regional tertiary referral centres for the UK Trent Perinatal Network.

BadgerNet creates a single record of care for every newborn admitted to the NICU and includes information on obstetric care and subsequent postnatal management. In order to assess IVH potentially related to transport within 72 hours of birth, we included infants who had a cranial ultrasound scan (CrUSS) on day 7($\pm$ 1) after birth as per the standard tertiary centre protocol; those who died or were transported out of NUH before this scan were excluded. Ethical approval was given by the School of Medicine Ethics Committee, University of Nottingham.

Outcome

The primary outcome was CrUSS findings taken on day 7($\pm$ 1) of life. All CrUSSs used a standardised protocol with a pre-defined series of anatomical views obtained. These were then evaluated by a consultant paediatric neuro-radiologist or neonatal consultant and graded using the Papile classification [19]. Infants were categorised as having no IVH or any grade of IVH, which was further divided into no or mild IVH (grade 1 or 2) and severe IVH (grade 3 or 4).

Statistical Analysis

Infants were grouped according to transport status: inborn vs transported. The two groups were further divided into <28 week and 28 to 32 week GA subgroups. Initial assessment of the association between transport, within 72 hours of birth, and IVH outcome was conducted using a chi-squared test. Associations between

demographic and clinical variables with transport and with IVH were assessed using chi-squared tests for categorical data and Mann U Whitney for non-normally distributed continuous data.

Multivariable logistic regression was used to calculate the adjusted odds ratio (aOR) for the association between transport and IVH, controlling for confounding factors. A priori confounders (gender, gestation and birth weight) were included in the logistic model in addition to any variable that had a statistically significant association with both exposure (transport) and outcome (IVH) at the 5% level. Variables that were not statistically significant on univariate testing were individually added back into the model and included as potential confounders if there was a change in the aOR for IVH in either direction by $\geq 10\%$. Confounding factors evaluated for inclusion in the regression model were mode of delivery, intrauterine growth restriction (based on serial fetal ultrasound), maternal infection risk (maternal intravenous antibiotics or sepsis, prolonged rupture of membranes >18 hours, maternal pyrexia and group B-streptococcus), antepartum haemorrhage, maternal recreational drug use, intubation at birth, surfactant administration, chest compressions at birth, delivery room adrenaline, APGAR scores at 1 and 5 minutes and NICU inotrope treatment. Similar models were created with the main outcome severe IVH only, with the baseline group including those with no or mild IVH.

To evaluate whether ANS administration modified the effect of transport within 72 hours of birth on IVH, infants were stratified by whether they had received no or an incomplete course of ANS or a complete course of ANS at least 24 hours prior to delivery. Logistic multivariable models were also used to evaluate the association between transportation and IVH or severe IVH adjusting for confounding factors,

depending on ANS status. All statistical analyses were performed using Stata SE (StataCorp, Version 14).

Results

A total of 1114 preterm infants met the inclusion criteria (inborn n=713 and transported n=401, Figure 1). Sixty five infants died prior to day 7 CrUSS, 1 infant had a missing CrUSS and 1 infant was transferred out of the network before day 7, leaving 1047 for analysis. Extreme prematurity and respiratory causes were identified as the main factors contributing to the cause of death in infants who died before day 7 in both groups (Supplementary Tables 1, 2, 3). Both groups had similar median birth weights and GA at birth (Table 1). Overall, 51.9% (n=203) of transfers occurred between level 3 units (n=71 <28 weeks GA). Transported infants were more likely to be male, have a greater incidence of maternal infection risk factors, and were more likely to be intubated or receive surfactant compared with inborn infants. Over the period of the study, the incidence of mild and severe IVH did not change (data not shown).

Irrespective of transport group, infants <28 weeks GA were significantly more likely to develop any IVH (58.6% vs 25.4%, $p<0.001$) and severe IVH (12% vs 3%, $p<0.001$) compared with those born 28 to 32 weeks GA. The prevalence of any grade IVH was similar between transported (n=165, 42.2%) and inborn infants (n=264, 40.1%) and the OR was not statistically significant before (OR 1.08, 95% CI 0.84-1.4, $p=0.51$) or following adjustment (aOR 0.99, 95% CI 0.75-1.35, $p=0.96$). Overall, when including transfer status, transported infants were more likely to develop severe IVH compared to inborns (Table 2 and Figure 2). However,

secondary analysis demonstrated this association only persisted for transported infants <28 weeks GA following multivariate logistical regression analysis when accounting for the variables listed in Table 1 (excluding ANS, which were included in subsequent analysis). For transported infants, 310 had pre-transfer CrUSS performed with 2.3% (n=7) having a diagnosis of severe IVH but by day 7 this proportion had increased to 9.7% (n=38) compared with inborns (5.8%) (Table 4). Furthermore, of the 38 transported infants with severe IVH, 35 occurred in those transported in the first 48hrs of life with 27 of these infants <28 weeks GA (Supplementary Table 4).

For the assessment of ANS, 19 infants were excluded as they had missing data, leaving 1028 for analysis. Of these, 610 (58.2%) infants received a full course of ANS (Supplementary Figure 1), 228 (37.4%) were subsequently diagnosed with an IVH with 26 (4.3%) developing severe IVH. Inborn infants were significantly more likely to receive a full course of ANS compared to transported infants ($p<0.001$, Table 1). Irrespective of transport status, a full course of ANS was associated with a 33% decrease in odds of any IVH (OR 0.67, 95%CI 0.52-0.87, $p=0.003$) and 67% reduction of severe IVH (OR 0.33, 95%CI 0.2-0.55, $p<0.001$). Overall, transported infants who received no or an incomplete course of ANS were at increased odds of developing any IVH (OR 1.47, 95% CI 1.10-2.17, $p<0.05$) although this was not statistically significant following multivariable adjustment (aOR 1.37, 95% CI 0.88-2.14).

Subgroup analysis of infants <28 weeks GA showed a complete course of ANS was associated with significantly reduced odds of both any grade IVH by 41% (OR 0.59, 95% CI 0.40-0.86, $p<0.001$) and severe IVH by 63% (OR 0.37, 95% CI

0.21-0.66, $p < 0.001$) irrespective of transport status. However, inclusion of ANS in the multivariable regression model demonstrated transported infants < 28 weeks remained significantly more likely to have severe IVH despite a full course of ANS (Figure 3 & Table 3). Transported infants 28 to 32 weeks GA, irrespective of maternal antenatal steroid treatment, had a greater proportion of severe IVH overall (2.3% vs 1.2%) but this was not statistically significant (Table 3 & Supplementary Figures 1 & 2).

Discussion

This study aimed to evaluate the association between early inter-hospital transport of preterm infants and severe IVH in the first week of life. We found transported infants, particularly those < 28 weeks GA, were significantly more likely to develop severe IVH compared to inborns and this association remained following adjustment for major confounding factors. ANSs reduce the risk of IVH [5] but previous preterm transport studies have not been able to include these in their modelling [8] [14] [15]. This UK regional network transport study is one of the largest to date and demonstrates a 67% reduction in severe IVH for all preterm infants following a full course of ANS as expected [19]. However, infants < 28 weeks GA undergoing early inter-hospital transport were still more likely to develop a severe IVH despite a full course of ANS.

This is the first study to demonstrate the association between early transport of preterm infants and the risk of significant brain injury in the first week of life. Our results are consistent with previous studies [2] [3] [8] demonstrating an increased risk of severe IVH at discharge in preterm infants transported early in life, however,

none of these studies prove causation. The perinatal period is a high risk window for the development of IVH and our study raises the possibility that the postnatal transport pathway itself may contribute to the increased prevalence observed as we were able to adjust for many of the known obstetric and early neonatal risks. Our findings are similar to a recent Canadian study of tertiary centre inborn and outborn infants, <29 weeks gestation, demonstrating significantly greater mortality, severe IVH and poorer long-term neurodevelopmental outcomes in outborn infants [12]. Their study also controlled for a number of perinatal factors but didn't report CrUSS findings in the first week of life which may explain why the prevalence of severe IVH was higher than we report in the first week of life. Additional explanations for the difference could include later neonatal factors, such as sepsis, impacting on the progression of mild IVH into more severe IVH or the transport distances between Canadian centres are far greater than in the UK resulting in longer exposure to the noxious effects of transport including air transfer [20].

The mechanism for the association between IVH and transportation is not yet fully understood, but is likely to be multifactorial due to suboptimal ventilation [8], temperature instability [21], and the ambulance environment. The preterm infant is exposed to many noxious agents including noise, handling and vibration which increase discomfort [22]. Excess noise adversely impacts cardiorespiratory stability and significantly decreases cerebral oxygen saturations relative to baseline which could contribute to adverse neurological outcomes through resultant changes in cerebral vasculature and blood flow [23] [4]. Vibration is known to result in cerebral capillary wall thickening, constriction and destruction as well as induce neuronal injury in animal models [24] [25]. During neonatal ambulance transfer the newborn's head is exposed to excessive vibration far in excess of that deemed safe and known

to cause illness in well adults [26]. Combined with our data, these studies potentially implicate excess vibration and noise as an additional risk factor for the development of IVH.

In this study, the higher prevalence of severe IVH in transported infants <28 weeks GA (4.9% vs 2.7%) for no or an incomplete ANS course lacked statistical significance. This could be as a consequence of the smaller overall numbers and a lower event rate of severe IVH in this group compared to those with a full ANS course.

Strengths and Limitations

This study has several strengths compared to previous studies [8] [13] [14] [15]. Our study included only infants who were <32 weeks gestation, transferred within the first 72 hours and had a standardised day 7 CrUSS. These infants are those most at risk of IVH as the fragile germinal matrix is most prominent in this GA group [4]. Using early CrUSS for outcome analysis allows for the potential inflammatory process associated with the transportation process to evolve but minimises the influence of exposure to other postnatal events with later brain injury. Multivariate logistic regression analyses allowed adjustment for major risk factors for IVH and any group imbalance. However, we acknowledge some residual confounding effect may remain due to variable data entry error or imprecision, such as inotrope use to represent hypotension rather than actual values.

The main limitation of studies comparing inborn to transported infants is selection bias, as critically ill infants who are not stable enough to survive transport are often excluded. Our study highlights this, as inborn infants who died before day 7 were more likely to die within the first 2 days of life than transported infants. These

infants were extremely premature, died shortly after delivery and if delivered in a non-tertiary centre may not have survived transportation. We aimed to minimise this bias by excluding infants who died in the first week of life as many died from causes related to extreme prematurity and respiratory conditions rather than IVH. However, we cannot exclude all bias due to the increased level of care offered in tertiary centres as inborn infants, who would otherwise be too unstable for transfer if born elsewhere, have an increased chance of survival and are more likely to develop severe IVH [1] although both groups analysed were well matched for gestation and birth weight.

A further limitation of this study was the exact timing of occurrence of IVH could not be established, although the inclusion of all infants who survived to day 7 CrUSS decreased the chance of selection bias. A prospective study could obtain a pre-transfer CrUSS to aid with interpretation in this setting. Although we used a standardised CrUSS protocol, inter-assessor interpretation could introduce differences in grading of IVH. Pragmatically, this is what happens in clinical practice but we did try to mitigate this by subgrouping into mild (grade 1 or 2) or severe IVH (grade 3 or 4).

The limitations of retrospective cohort studies also make it difficult to account for evolving practices over the timeframe of the study. For example, the gradual introduction of magnesium sulphate, known to reduce the incidence of cerebral palsy [27], could not be assessed although this is unlikely to affect the prevalence of early IVH.

Conclusion

Our UK Trent perinatal network study highlights that, despite the increased survival observed with centralised neonatal care [28] [29], the early postnatal transport of extremely preterm infants is associated with an increased risk of severe IVH in the first week of life. This risk is not completely mitigated by the known neuroprotective effects of ANS, although receiving a full course of ANS was beneficial over having either no or an incomplete course. Women presenting with threatened preterm delivery should be given prompt ANS [30] and ideally transferred in-utero to an appropriate centre, a measure that could be used as a quality benchmark for perinatal network delivery of care.

With the centralisation of neonatal intensive care we have seen investment in postnatal transport services. However, the in-utero transfer process remains a time consuming process for healthcare staff potentially resulting in missed transfer opportunities [31]. Development of a co-ordinated, in-utero transfer service, with both obstetric and neonatal services, could result in not only better service provision and allocation of facilities based on clinical needs but could help reduce adverse outcomes associated with postnatal transfer. However, in-utero transfer is not always achievable, therefore the associated risks of postnatal transfer need to be explored and addressed where possible to improve the comfort of the infant and minimise any risk of neurological insult. This could include reducing noxious environmental stimuli such as noise and vibration, improving monitoring and ventilation as well as considering the timing of postnatal transfer with the ultimate goal to reduce the significant long-term risk of neurodisability.

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Figure Legends

Figure 1. Flowchart of study participants demonstrating inclusions/exclusions and incidence of intraventricular haemorrhage (IVH) for each cohort

Figure 2. Comparison of proportion of severe intraventricular haemorrhage between transported and inborn infants by gestation subgroups

* Denotes significance, $p < 0.05$

Severe IVH, Grade 3 & 4 Intraventricular Haemorrhage

Figure 3. Comparison of proportion of no/mild intraventricular haemorrhage and severe intraventricular haemorrhage in inborn and transported Infants <28 weeks gestation, sub-grouped by antenatal steroid course.

* Denotes significance, $p < 0.05$

IVH, Intraventricular Haemorrhage; No/Mild, none/grade 1 & 2; Severe, grade 3 & 4

Table 1. Comparison of demographic and clinical variables between inborn and transported infants.

Variable	Inborn (n=656)*	Transported (n=391)*	Missing n (%)	p value**
Gestation	28.4 (26.4-29.9)	28.1 (26.4-29.7)	0	p=0.72
Birth weight	1050 (810-1285)	1090 (860-1300)	28 (2.7)	p=0.07
Male	336 (51.2)	226 (57.8)	0	p=0.03
IUGR	81 (12.3)	39 (10)	6 (0.6)	p=0.24
Maternal infection risk	78 (11.9)	72 (18.4)	10 (1)	p=0.003
APH	116 (17.7)	45 (11.5)	6 (0.6)	p=0.008
Antenatal Steroid				
- None/Incomplete	222 (33.8)	196 (50.1)	19 (1.8)	p<0.001
- Complete	423 (64.5)	187 (47.8)		
Mode of delivery				
- NVD	306 (47.0)	194 (49.6)	10 (1)	p=0.16
- Emergency C-S	293 (45.0)	175 (44.8)		
- Elective C-S	36 (5.5)	11 (2.8)		
- Instrumental	16 (2.5)	8 (2.0)		
Intubated first 72hrs	537 (81.9)	341 (87.2)	1 (0.01)	p=0.01
Surfactant	535 (81.6)	342 (87.5)	0	p=0.009
Chest compressions	36 (5.5)	26 (6.6)	0	p=0.43
Adrenaline	10 (1.5)	4 (1)	0	p=0.5
Apgar 1 min	6 (4 – 8)	6 (4 – 8)	148 (14.4)	p=0.36
Apgar 5 min	9 (7 -9)	8 (7 -9)	161 (15.7)	p=0.16
Inotropes	118 (18)	113 (29)	0	p<0.001
Days to first extubation ^a	2 (1 - 4)	3 (1 - 6)	49 (4.7%)	p<0.001
Mortality after day 7	39 (5.9)	27 (6.9)	0	p=0.52

* Data are n (%) or median (interquartile range)

** Categorical data analysed using Chi Squared test; Non-normally distributed continuous data analysed using Mann U Whitney test

^a Extubation without consequent re-intubation within the following 72 hours

IUGR, Intrauterine Growth Restriction; APH, Antepartum Haemorrhage; NVD, Normal Vaginal Delivery; C-S, Caesarean Section

Table 2. Unadjusted and adjusted odds ratios to show the association of transportation with no/mild intraventricular haemorrhage and severe intraventricular haemorrhage for all infants and by gestational subgroups.

GA Group	Outcome Comparison	OR (95% CI)	aOR (95% CI)*
All Infants (n=1047)	No/Mild IVH vs. Severe IVH	1.75 (1.09 – 2.80)	1.69 (1.04 – 2.76)
<28 weeks (n=492)	No/Mild IVH vs. Severe IVH	1.63 (0.94 – 2.82)	1.83 (1.03 – 3.21)
28-32 weeks (n=555)	No/Mild IVH vs. Severe IVH	2.02 (0.77 – 5.35)	1.66 (0.61 – 4.52)

OR, Odds Ratio; aOR, adjusted Odds Ratio; IVH, Intraventricular Haemorrhage; GA Gestational age; Mild, Grade 1 & 2; Severe, Grade 3 & 4. Bold indicates statistical significance $p < 0.05$.

* Adjusted for gender, gestation, birthweight, mode of delivery, intrauterine growth restriction, maternal infection, antepartum haemorrhage, maternal recreational drug use, intubation at birth, surfactant administration, chest compressions at birth, delivery room adrenaline, APGAR scores 1 and 5 and NICU inotropes.

Table 3. Evaluation for the association of transport with severe intraventricular haemorrhage by antenatal steroids status and gestational subgroup.

GA Group	Outcome Variable	OR (95% CI)	aOR (95% CI)*
All Infants (n=1047)	NS & severe IVH	1.45 (0.80 – 2.65)	1.44 (0.76 – 2.72)
	CS & severe IVH	1.70 (0.76 – 3.78)	1.91 (0.82 – 4.41)
< 28 weeks (n=492)	NS & severe IVH	1.12 (0.55 – 2.29)	1.35 (0.64 – 2.84)
	CS & severe IVH	2.13 (0.87 – 5.27)	2.84 (1.08 – 7.47)
28 to 32 weeks (n=555)	NS & severe IVH	2.57 (0.75 – 9.0)	3.19 (0.68 – 15.01)
	CS & severe IVH	0.57 (0.06 – 5.21)	0.47 (0.05 – 4.83)

OR, Odds Ratio; aOR, adjusted Odds Ratio; NS, no/incomplete steroids; CS, complete steroids; IVH intraventricular haemorrhage; Severe IVH, Grade 3 & 4 intraventricular haemorrhage; GA, gestational age. Bold denotes significance $p < 0.05$.

* Adjusted for gender, gestation, birthweight, mode of delivery, intrauterine growth restriction, maternal infection, antepartum haemorrhage, maternal recreational drug use, intubation at birth, surfactant administration, chest compressions at birth, delivery room adrenaline, APGAR scores 1 and 5 and NICU inotropes

Table 4. Incidence of intraventricular haemorrhage on initial and day 7 cranial

		CrUSS day 1-3 ^a n (%)	CrUSS day 7 n (%)	Change (%)
Inborn	None	426 (65%)	391 (59.7%)	-5.3
	Mild IVH	200 (30.5%)	226 (34.5%)	4.0
	Severe IVH	29 (4.4%)	38 (5.8%)	1.4
	Unknown	1	1	
Outborn	None	250 (80.6%)	226 (57.8%)	-22.8
	Mild IVH	53 (17.1%)	127 (32.5%)	15.4
	Severe IVH	7 (2.3%)	38 (9.7%)	7.4
	Unknown	81 ^b	0	

CrUSS, Cranial Ultrasound; IVH, Intraventricular Haemorrhage

^a Cranial Ultrasound scan obtained prior to transport in outborn group

^b Cranial Ultrasound scan obtained after transportation

Figure Legends

Figure S1. Number of infants who received either no/incomplete or complete course of maternal antenatal steroids and developed any intraventricular haemorrhage or severe intraventricular haemorrhage for both transported and inborn groups.

IVH, Intraventricular Haemorrhage; GA, Gestational Age

Figure S2. Comparison of proportion of No/Mild intraventricular haemorrhage and severe intraventricular haemorrhage in inborn and transported Infants 28 to 32 weeks gestation, sub-grouped by antenatal steroid course.

IVH, Intraventricular Haemorrhage; No/mild, none/grade 1 & 2; Severe, grade 3 & 4

Table S1. Day of death of infants who died prior to day 7

	Day of Death (days)	
	Early (0-2)	Late (3-7)
Inborn (n=54)	35	19
Transported (n=11)	4	7

Table S2. Major contributing factors to the cause of death as documented on the death certificate for infants who died prior to day 7. Gestation and birth weight are

Group	Gestation (weeks)	Birth weight (grams)	Prematurity	Respiratory	Sepsis	IVH	Congenital	Other
Inborn (n=54)	26 (24-28)	800 (620-1160)	47	30	22	6	12	23
Transported (n=11)	24 (23-26)	685 (630-930)	9	7	3	4	0	4

median and inter-quartile range.

IVH, Intraventricular Haemorrhage

Table S3. Grades of intraventricular haemorrhage in infants who died prior to day 7

IVH Grade	Inborn (n=54)	Transported (n=11)
No scan	9 (16.7%)	0
No or mild IVH (grade 1 & 2)	38 (70.4%)	8 (72.7%)
Severe IVH (grade 3 & 4)	7 (13%)	3 (27.3%)

IVH, Intraventricular Haemorrhage