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Does Hospital Transfer Predict Mortality in Very Low Birth Weight Infants Requiring Surgery for Necrotizing Enterocolitis?

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Abstract

Background—Necrotizing enterocolitis (NEC) is a leading cause of infant mortality and the most common reason for emergent surgery in very low birth weight (VLBW, <1500g) infants. We investigated whether transfer for higher level of surgical care affects mortality in this population.

Methods—VLBW infants who underwent NEC surgery were retrospectively reviewed from the California Patient Discharge Linked Birth Cohort Database (1999–2007). Transfer for emergent surgery was defined as surgery 2d after transfer. Mortality was analyzed with multivariate logistic regression.

Results—Overall, 1,272 VLBW infants with surgical NEC were identified with a 39% mortality. Transfer for surgery occurred in 406 (32%) infants. Unadjusted mortality was not increased for infants transferred versus not transferred, 37% vs. 40% ($p=0.25$). Adjusted mortality for infants transferred for surgery did not differ from those who received surgery at their primary NICU (OR 0.75, 95% CI 0.42–1.32). Lower birth weight, lack of prenatal care, peritoneal drainage as sole surgical intervention, and pulmonary interstitial emphysema/pulmonary hemorrhage were associated with increased odds of mortality ($p<0.05$).

Conclusions—VLBW infants with surgical NEC do not demonstrate increased risk of mortality when transferred emergently for surgery. Future efforts must engage health professionals caring for this vulnerable population in order to maximize resource allocation and safety.

Introduction

Necrotizing enterocolitis (NEC) is one of the leading causes of infant mortality and the most common reason for emergent surgery in very low birth weight (VLBW, <1500g) infants.^{1, 2} During the past two decades, the number of neonatal intensive care units (NICUs) has

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increased nationwide, particularly the number of NICUs and case complexity cared for in community hospitals.³⁻⁵ However, full surgical capabilities are not available in all NICUs and there is great variability in specialty services provided. Hence, many very sick infants with NEC frequently require transport to a higher level NICU in order to receive appropriate specialized surgical care. Currently, the impact of transport and potential delays in care occurring in this vulnerable population are unknown.

The burden of transfer and consequent increased risk of morbidity and mortality for a critically ill infant is significant.^{6, 7} Lack of trained transport personnel and lack of appropriate resuscitation equipment have been identified as possible causes of the increased mortality seen in transported children.⁸ Others have attributed differences in care between centers as potentially more important than the transport itself in determining the long-term outcome of transported neonates.⁹ However, much of the literature surrounding the risks of neonatal transport is over 10 years old and likely does not reflect recent advances in mobile critical care technology. In addition, research has shown that resource utilization is higher among children who underwent interhospital transfer to intensive care after initial hospitalization, compared with those transferred directly from emergency to intensive care.¹⁰ Neonatal transfer is therefore costly and may contribute a sizeable financial burden in addition to a clinical burden. In order to sufficiently answer the question of whether transport itself confers an additional risk of mortality, an updated analysis of a more uniform patient population that utilizes a significant amount of healthcare resources must be conducted.

To date, no studies examining the effect of transport on VLBW infants with surgical NEC have been conducted in the U.S.¹¹ The goal of this study was to investigate whether transfer for higher level of surgical care affects mortality for VLBW infants with surgical NEC. Utilizing California's hospital discharge dataset linked with maternal records and vital statistics including birth and death records over a nine year period, we hypothesized that children requiring transfer for surgical NEC would have an increased risk of mortality due to inherent delays secondary to transfer of care. These results could then be used to inform health policy makers about the effects of de-regionalization of neonatal care for infants with surgical NEC.

Methods

Data Source

This retrospective cohort study was performed after obtaining IRB approvals from both the University of California, Los Angeles and the California Health and Human Services Agency. Data were obtained from the California Patient Discharge Linked Birth Cohort Database acquired from the California Office of Statewide Health Planning Development (OSHPD).¹² OSHPD collects annual data of all infants and mothers discharged from non-federal hospitals licensed in California. A discharge abstract is reported for each inpatient hospitalization and includes: patient demographics, admission and discharge details, and International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9) diagnosis and procedure codes.¹³ Individual records are flagged and investigated if they contain illogical or erroneous relationships between ICD-9 diagnosis and procedure codes. By means of a unique patient identifier, data are linked for infants and mothers across hospitalizations, including admissions to different hospitals, allowing longitudinal records to be created for each infant over time. Data is then further linked to vital statistics including state birth and death records. Using deterministic and probabilistic record linkages, nearly 100% of maternal and infant hospital admissions are linked to the corresponding infant birth and death certificate.¹⁴⁻¹⁶

Study Cohort

VLBW infants who underwent NEC surgery from 1999–2007 were retrospectively reviewed from the California Patient Discharge Linked Birth Cohort Database. Hospital admissions/transfers from birth to first discharge home were identified. A diagnosis of NEC was identified using ICD-9 codes 777.5–777.53. VLBW was defined as birth weight <1500 grams. Emergent abdominal surgeries were identified using ICD-9 codes representative of major abdominal surgery (ICD-9 45-45.03, 45.1, 45.15, 45.2, 45.26, 45.3-4, 45.40-1, 45.49, 45.5-45.52, 45.6-45.63, 45.7-45.94, 46-46.11, 46.13-4, 46.2-46.79, 54.1-54.2, 54.25, 54.45, 54.51-9, 54.6-54.64, 54.91, 54.93). Transfer for emergent NEC surgery was defined as major abdominal surgery occurring 2d after transfer. Infants were categorized as either transferred for surgery or received surgery at their primary NICU. Infants not transferred for surgery were used as the reference category in the final regression. The primary outcome of interest was one year mortality.

Study Design Measures

Hospital admissions were stratified by NICU levels 2A-3C according to the Levels of Neonatal Care defined by the American Academy of Pediatrics Committee on Fetus and Newborn.¹⁷ The NICU level of the transferring hospital was included in the final regression, with level 3C as the reference. Children who underwent a peritoneal drainage procedure and no other surgical intervention were identified using ICD-9 code 54.91. Surgery occurring < 7 days after birth was identified as a potential proxy for spontaneous intestinal perforation (SIP). Birth weight was measured as a continuous variable on the centigram scale. Maternal age (in years) and infant age at time of surgery (in days) were also measured as continuous variables. If a child received at least one prenatal care visit prior to birth, they were coded as received prenatal care and used as the reference category in the final regression. Insurance was divided into public and private insurance, with private insurance as the referent category. Due to California's State Children's Health Insurance Program (SCHIP), which ensures health insurance coverage for all children in California, children marked as "other" in the dataset were categorized as receiving public insurance. Gender was also included in the final regression with male gender as the referent category.

Major medical comorbidities identified in the infant cohort included intraventricular hemorrhage grade I-IV (ICD-9 772.11-4) and unspecified grade (ICD-9 772.10) with grade IV as the referent category. Significant comorbid diagnoses also included patent ductus arteriosus (PDA, ICD-9 74.70), PDA ligation (ICD-9 38.85), congenital cyanotic heart disease (ICD-9 745.0-3, 746.01-9, 746.1-2, 746.83, 747.41-2), congenital hypoperfusion heart disease (ICD-9 746.3-7, 746.81-4, 747.1, 747.10, 747.22), surgical repair of congenital heart disease (ICD-9 39.0, 35.01, 35.03-4, 35.11, 35.13-4, 35.21-2, 35.25-8, 35.34, 35.41-2, 35.62-3, 35.72-3, 35.81-4, 35.91-6, 37.51, 38.85, 38.45, 39.21-2, 39.54, 39.57-9), acidosis (ICD-9 775.81), sepsis (ICD-9 771.81, 771.83, 038-038.49, 038.8, 022.3, 098.89, 054.5, 036.2, 020.2, 038.9, 790.7), respiratory distress syndrome (RDS, ICD-9 769), pulmonary interstitial emphysema (ICD-9 770.2), pulmonary hemorrhage (ICD-9 770.3) including non-RDS respiratory failure (ICD-9 770.84). The presence of maternal chorioamnionitis (ICD-9 658.40-3) and pregnancy induced hypertension (mild: ICD-9 642.40-4, severe: ICD-9 642.50-4) were also identified.

Statistical Analysis

Descriptive statistics were used to summarize baseline clinical and demographic information to characterize the study population. Unadjusted chi-squared analysis was performed examining infant mortality by transfer status. Finally, infant mortality was analyzed with multivariate logistic regression using a fixed effects model at the level of the hospital that performed surgery in order to adjust for the variance attributed to each individual hospital

(i.e. surgical case volume, teaching status, payer status, etc.). The fixed effects model accounted for the unique case mix of patients seen at each hospital that performed surgery in the cohort. Infants cared for at hospitals with a complete separation of outcomes (i.e. all infants survived or all infants died within a given hospital) were omitted from the final regression analysis (n=50, 3.9%). Only one infant was transferred from a 2A level NICU to a higher level NICU for surgery. This infant was therefore also omitted. Statistical analyses were performed using SAS version 9.2 (SAS Inc., Cary, NC). A p-value < 0.05 was considered significant.

Results

Overall, 1,272 VLBW infants with NEC were identified and underwent abdominal surgery at 70 hospitals throughout California from 1999–2007 (Table 1). The cohort's one year mortality was 39% (n=496). Mean birth weight was 860 ± 260 grams and mean age at time of surgery was 28 ± 29 days. Overall, 406 (32%) infants were transferred for surgical care leaving 866 (68%) who had surgery at their primary NICU. Most children who underwent transfer came from a 3B NICU (n=263, 65%) (Table 2). Few infants (n=89, 3%) had no prenatal care prior to birth. Major comorbidities found in the majority of the cohort included sepsis (n=942, 75%), PDA (n=796, 63%) and RDS (n=1063, 84%). Surgery < 7 days after birth, occurred in 213 (17%) infants, most (n=156, 73%) with a birth weight <1000g. Only 127 infants (10%) underwent peritoneal drainage as the sole surgical intervention. The percent of infants undergoing a drainage procedure after day of life seven did not differ between transferred and non-transferred infants (11% vs. 8%, p-value 0.14). The vast majority of the cohort underwent surgery at either a 3C level NICU (n=795, 63%) or a 3B level NICU (n=462, 36%).

Unadjusted mortality was not increased for infants transferred for surgery versus those not transferred for surgery, 37% vs. 40% (p=0.25). On multivariate analysis, adjusted odds of mortality for infants transferred for surgery did not differ from those who received surgery at their primary NICU (OR 0.75, 95% CI 0.42–1.32) (Table 3). Lack of prenatal care (OR 2.47, 95% CI 1.20–5.11), peritoneal drainage as sole surgical intervention (OR 2.60, 95% CI 1.65–4.08), and pulmonary interstitial emphysema/pulmonary hemorrhage (OR 1.37, 95% CI 1.02–1.84) was associated with increased odds of mortality. Increasing birth weight (OR 0.88, 95% CI 0.83–0.94), RDS (OR 0.60, 95% CI 0.41–0.88) and surgery < 7 days after birth (OR 0.38, 95% CI 0.25–0.56) were associated with decreased odds of mortality. Exclusion of infants with surgery < 7 days after birth on subsequent analysis did not impact the effect of transfer on mortality (results not shown).

Discussion

This study presents the first U.S. report of the impact of transfer for infants with surgical NEC. Most infants with surgical NEC received surgery at a high level NICU (3B or 3C) and a significant proportion were transferred in order to receive a higher level of surgical care. However, transfer did not confer an additional risk of mortality. Birth weight, lack of prenatal care and respiratory compromise more significantly contributed to overall mortality in infants with surgical NEC.

One year mortality was high in this study, but comparable to previously published reports of infants with NEC who require surgical intervention.¹⁸ This study's mortality rate falls within Loh's reported range of 31–50% and builds upon Loh's analysis of the Australian experience which found that infants with NEC transferred for higher level of surgical care did not have increased mortality when compared to infants who received surgery at their primary treatment facility.¹¹ The analysis presented in this study was able to more

specifically isolate the effect of transfer alone by controlling the NICU level of the transferring hospital, as NICU level at birth has been shown to directly affect mortality in VLBW infants.¹⁵ By using a fixed effects regression model, this report also controlled for hospital-level factors at the facility performing the actual surgery. This study was also much larger (n=1272 vs. 124) giving more statistical power to determine risk of mortality after transfer. Finally, this analysis adjusted for major medical comorbidities and many maternal factors known to influence neonatal mortality thereby better isolating the effects of transfer for infants with surgical NEC.

This study also addressed two very important clinical conditions that can confound an analysis of surgical NEC. SIP, defined as isolated intestinal perforation in the neonate, is associated with a lower mortality than NEC. Two populations of infants acquire SIP: Extremely low birth weight infants (<1000g) acquire SIP on average between 7 and 10 days of life after exposure to indomethacin and glucocorticoids, and infants with early SIP (0–3 days) who are significantly less likely to have been exposed to postnatal risk factors and are less premature.¹⁹ However, due to the similarities in clinical presentation, many infants with SIP are identified as having NEC further compounding an analysis relying on ICD-9 coding to identify infants with NEC. We accounted for this potential effect by identifying infants undergoing abdominal surgery <7 days after birth. When SIP is accounted for, NEC is not likely to occur less than seven days after birth.²⁰ In this study, the majority of infants with abdominal surgery < 7 days after birth were <1000g (n=156, 73%). Additionally, surgery < 7 days after birth was independently associated with decreased risk of mortality in the multivariate regression analysis. Both of these findings indicate that our proxy for SIP was likely robust and appropriately adjusted for the presence of infants with SIP who were coded as having NEC in the cohort. Secondly, this analysis also accounted for infants who only underwent a peritoneal drainage procedure and no other major abdominal surgery. Peritoneal drainage in the setting of NEC may be used as a rescue and/or stabilizing measure for VLBW infants with complicated NEC and as an adjunct therapy to exploratory laparotomy.²¹ However, sole peritoneal drainage is used less commonly. In this study, infants with this finding had significantly increased risk of mortality. It is possible that infants who underwent only a peritoneal drainage procedure were not clinically stable enough to tolerate major abdominal surgery and peritoneal drainage was therefore used to stabilize the child, often before care was subsequently withdrawn. Adjusting for this factor enabled the present analysis to more accurately isolate the effect of transfer and identify infants with a severe overall clinical burden.

This study also identified clinical factors known to contribute to overall mortality in neonates. The presence of respiratory compromise in particular, as measured by pulmonary interstitial emphysema and/or pulmonary hemorrhage, was associated with increased odds of mortality. However, RDS, a very prevalent comorbidity in the cohort typically associated with poor outcomes, was associated with decreased odds of mortality in the final regression. This latter finding is likely due to the adverse sequelae of RDS that were also controlled for in the model (i.e. sepsis, pulmonary interstitial emphysema, IVH, etc.). RDS alone does not increase risk of infant mortality. Instead the complications of RDS increase risk of infant death. After controlling for these factors, the odds ratio for RDS represents the independent effect of RDS alone, without subsequent complications. This rationale is further supported by the unadjusted analysis of RDS on mortality. Infants with RDS in this study had higher unadjusted mortality than non-RDS babies (36% vs. 32%). Therefore, adjusting for the sequelae of RDS removed the unadjusted increased risk of mortality that RDS conferred.

The overarching goal of this study was to examine the impact that recent decentralization of neonatal surgical care has had on infants with NEC. Regionalization of neonatal care varies from state to state and California has adopted a model comprised of multiple community

NICU's caring for infants with NEC. If surgical care is needed, infants are then transferred at the discretion of the community NICU which may or may not have surgical capabilities in house. In contrast, the best known model for centralized healthcare delivery is the cancer care model. In this model, medical and surgical cancer care centralized to high volume, academic specialty centers is associated with improved outcomes.^{22,23} The results of this study highlight the efficiency of current regionalization of care and transfer standards for infants with surgical NEC in California. This is in contrast to previous reports using earlier, less extensive versions of the California Linked Birth Cohort Database which found that overall, infants undergoing transfer had increased risk of mortality.^{24, 25} It may be that certain groups of infants are at a significantly increased risk of mortality after transport while current advances in neonatal critical care have made transport sufficiently safe for other groups, such as infants with surgical NEC. In addition, this study reports infant mortality over a nine year period ending in 2007 and is therefore more reflective of current advances in neonatal technology. What this report was unable to quantify was the overall morbidity of infants with surgical NEC, which may be significant, as approximately one third of all transfers of critically ill infants experience an adverse event.²⁶ Long term studies examining the overall disease burden resulting from hospital transfer, including an analysis of physical and developmental delay, is much needed.

It can be assumed that infants who require transfer for surgical care experience a delay in care, and this may indicate that timing of surgery for infants with NEC is less important. However, to answer this question, the time of diagnosis of surgical NEC, the time of transfer and the time of surgery would need to be evaluated. Unfortunately such details are not available in this administrative dataset. Furthermore, this study did not examine infants who required a higher level of surgical care for NEC but died prior to transport. Morbidity and death prior to surgical intervention can be more difficult to identify and quantify using an administrative database but could possibly be better accounted for in longitudinal, multi-institutional studies. Future research must quantify and address the unique needs of neonates with NEC in order to truly improve coordination of care across multiple levels the healthcare system.

Conclusion

VLBW infants with surgical NEC do not demonstrate increased risk of mortality when transferred emergently for higher level of surgical care. It is otherwise uncertain whether lack of surgically capable NICU's contributes to mortality prior to transfer or whether morbidity is affected for infants who survive transport. Future efforts must engage health professionals at all levels caring for this vulnerable population in order to truly maximize resource allocation and safety.

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Abbreviations

NICU	Neonatal Intensive Care Unit
NEC	Necrotizing Enterocolitis
SIP	Spontaneous Intestinal Perforation

VLBW	Very Low Birth Weight
ICD-9	International Classification of Disease, Ninth Revision, Clinical Modification
OSHPD	Office of Statewide Health Planning Development
RDS	Respiratory Distress Syndrome
PDA	Patent Ductus Arteriosus

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Table 1**Cohort Demographics**

Variables	N = 1,272 (%)
Neonatal	
Age at Time of Surgery (days)	28 ± 29
Birth weight (grams)	860 ± 260
Mortality	496 (39)
Gender:	
Male	775 (61)
Female	497 (39)
Insurance Type:	
Public	718 (56)
Private	554 (44)
Peritoneal Drainage Only	127 (10)
Surgery < 7 Days After Birth	213 (17)
Intraventricular Hemorrhage:	
Grade I	107 (8)
Grade II	98 (8)
Grade III	79 (6)
Grade IV	72 (6)
Grade unknown	141 (11)
Acidosis	51 (4)
Sepsis	942 (75)
Patent Ductus Arteriosus	796 (63)
Patent Ductus Arteriosus Repair	365 (29)
Cyanotic Cardiac Disease	24 (2)
Hypoperfusion Cardiac Disease	<10 (<1)
Congenital Cardiac Disease Surgery	13 (1)
Respiratory Distress Syndrome	1,063 (84)
Pulmonary Interstitial Edema and Pulmonary Hemorrhage	372 (29)
Maternal	
Maternal Age (years)	28 ± 7
No Prenatal Care	89 (3)
Chorioamnionitis	226 (18)
Pregnancy-Induced Hypertension	
Mild	19 (1)
Severe	115 (9)

Table 2

Transfer Demographics

Variables	N (%)
Transferred for Surgery	406 (32)
NICU Level Prior to Surgical Transfer (N = 406)	
3C	24 (6)
3B	263 (65)
3A	80 (20)
2B	19 (5)
2A	<10 (<1)
No NICU	19 (5)
NICU Level for Surgery (N = 1,272)	
3C	795 (63)
3B	462 (36)
3A or lower	15 (1)

Table 3**Multivariate Logistic Regression* of Infant Mortality**

Variable	Odds Ratio	P-value	95% Confidence Interval
Transferred for Surgery	0.75	0.315	0.42–1.32
NICU Level Prior to Surgical Transfer:			
No NICU	2.72	0.149	0.87–8.54
2A [†]	-	-	-
2B	1.22	0.687	0.33–4.44
3A	1.70	0.643	0.73–3.98
3B	1.25	0.408	0.66–2.36
3C	1.0	Ref	Ref
Birth weight (centigrams)	0.88	<0.001	0.83–0.94
Insurance Type:			
Public	1.01	0.939	0.74–1.38
Private	1.0	Ref	Ref
No Prenatal Care	2.47	0.014	1.20–5.11
Peritoneal Drainage Only	2.60	<0.001	1.65–4.08
Surgery < 7 Days After Birth	0.38	<0.001	0.25–0.56
Sepsis	0.85	0.299	0.63–1.16
Respiratory Distress Syndrome	0.60	0.008	0.41–0.88
Pulmonary Interstitial Edema and Pulmonary Hemorrhage	1.37	0.036	1.02–1.84
Intraventricular Hemorrhage:			
Grade I	0.88	0.607	0.55–1.41
Grade II	0.62	0.073	0.37–1.04
Grade III	0.85	0.547	0.49–1.46
Grade IV	1.89	0.027	1.08–3.32
Patent Ductus Arteriosus	0.87	0.402	0.63–1.21
Patent Ductus Arteriosus Ligation	0.86	0.380	0.61–1.21
Cyanotic Congenital Heart Disease	2.57	0.116	0.79–8.33
Hypoperfusion Congenital Heart Disease	2.16	0.510	0.22–21.42
Surgical Repair of Congenital Heart Disease	0.54	0.462	0.11–2.78
Acidosis	1.31	0.397	0.70–2.46
Age at Time of Surgery (days)	1.00	0.119	0.99–1.00
Male Gender	1.21	0.166	0.93–1.58
Maternal Age (years)	0.99	0.537	0.98–1.01
Chorioamnionitis	1.20	0.296	0.85–1.70
Pregnancy Induced Hypertension:			
Mild	0.84	0.772	0.26–2.73
Severe	0.88	0.600	0.55–1.41

[†] Too few in category to assess