The Association between Evidence-Based Healthcare Practices and Outcomes among Preterm Births in China

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Keywords

Preterm · Evidence-based healthcare practices · Death · Severe brain injury

Abstract

Introduction: Very preterm infants are at high risk of early death or severe brain injury, with potential for impaired long-term neurodevelopmental function and physical health. There are evidence-based healthcare practices that can reduce the incidence. **Materials and Methods:** Infants born at 24–31⁶ weeks gestational age and admitted within 24 h to NICUs participating in the Chinese Neonatal Network in 2019 were included. We examined the association between 4 evidence-based practices: inborn (born in a tertiary hospital in the Chinese Neonatal Network), ACS (any antenatal corticosteroid), MgSO₄ (prenatal magnesium sulfate), and NT (normothermic temperature [36.0–37.5°C] at admission) and early death and/or severe brain injury in the study pop-

ulation. **Results:** Of 6,035 eligible infants, the incidence of early death and/or severe brain injury was 10.6%. Exposure to ACS only was associated with significant lower incidence of death and/or severe brain injury than none (aOR, 0.71; 95% CI: 0.57–0.88), but not MgSO₄ only (aOR, 0.97; 95% CI: 0.81–1.17), NT only (aOR, 0.91; 95% CI: 0.76–1.08), or inborn only (aOR, 0.91; 95% CI: 0.72–1.15). The association between number of practices and incidence of early death and/or severe brain injury is as follows: none = 23% (31/138), any 1 = 14% (84/592), any 2 = 12% (185/1,538), any 3 = 9% (202/2,285), and all 4 = 9% (140/1,482). **Discussion/Conclusion:** More comprehensive use of evidence-based practices was associated with improved survival without severe brain injury among very preterm infants born at <32 weeks gestational age.

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A complete list of group members appears in the Acknowledgment section.

Introduction

Preterm birth is the leading cause of neonatal mortality and morbidity in the world. According to the WHO, China has a preterm birth rate of 6.9% and the second highest absolute number of preterm births (1.16 million per annum) in the world [1]. Although very preterm infants (VPI) born at <32 weeks gestational age (GA) represent only 2% of all live births or 16% of all preterm births, they have the highest mortality and morbidity, including adverse long-term neurodevelopmental outcomes [2].

During the past decade, several studies have reported that select maternal and newborn practices can improve preterm birth outcomes [3], including delivery in tertiary centers [4, 5], administration of antenatal corticosteroids [6, 7], prenatal MgSO₄ usage [8, 9], and maintenance of normal body temperature [10]. These 4 practices have been shown to be effective in clinical trials and are widely used clinically. However, the efficacy of clinical interventions in the real world is often different from randomized controlled trials since population risks may differ and multiple interventions may coexist. Our objective was to examine the individual and cumulative effects of these 4 evidence-based clinical practices in the VPI population in China and on their subpopulation of extremely preterm infants (EPI) born at 24–27⁶ weeks GA.

Methods

The Chinese Neonatal Network and Database

The Chinese Neonatal Network (CHNN) is a group of multidisciplinary researchers from 57 tertiary-level NICUs in 25 provinces and municipalities that are representative of different geographic regions of China. In 2019, 57 NICUs contributed to the CHNN, which prospectively collects standardized data on demographics, outcomes, selected clinical practices, and resource use on all VPI born at 24⁰–31⁶ weeks GA or with a birth weight <1,500 g and admitted to participating hospitals. This project was approved by the CHNN Executive Committee and the Research Ethics Board at the Children's Hospital of Fudan University, Shanghai, China [11].

Study Population

The population for this study consisted of VPI born at GA of 24⁰–31⁶ weeks and admitted to participating CHNN NICUs within 24 h after birth from January 2019 to December 2019.

Outcome

The primary outcome was early death or severe brain injury. Early death was defined as death within 7 days of age before discharge from the NICU. Severe brain injury was defined as intraventricular hemorrhage grade III or IV according to Papile's classification [2, 12].

Exposure Variables

We used 4 evidence-based practices as exposure variables since they are identified by the literature to be associated with the primary outcome: (1) inborn status, defined as born in a tertiary hospital that participates in the CHNN; (2) ACS, defined as exposure to any antenatal corticosteroids; (3) MgSO₄, defined as administration of magnesium sulfate before delivery for any reason; (4) NT, defined as normal body temperature on NICU admission between 36.0 and 37.5°C.

Statistical Analyses

Descriptive statistical methods were used to summarize the study population. The infant and maternal characteristics were compared between 2 groups: infants with or without the composite of early death or severe brain injury (primary outcome) using the χ^2 test for categorical variables and Student *t* test or Wilcoxon rank-sum test, as appropriate, for continuous variables. To investigate the association between the 4 clinical practices (exposures) and the primary outcome, we used the χ^2 test to compare the 4 practices, individually and cumulatively. We used multivariate logistic regression models to adjust for potential confounders that were identified in the univariate analyses or based on clinical experience, including gestational age, small for gestational age, sex, Apgar score <7 at 5 min, delivery mode, and gestational diabetes. The Generalized Estimating Equation (GEE) approach was used to account for the clustering of infants within NICUs.

To determine the most effective combination group of these 4 practices, we examined the adjusted OR (aOR) of the outcome with different combinations of practices versus no practices using similar models mentioned above. We examined the effect of 2, 3, and 4 practices on the outcome by estimating the percent change in the rate of primary outcome from the observed rate of outcome to the predicted rate of outcome given the exposure of at least 2, 3, and 4 practices based on the multiple logistic regression model adjusted for the potential confounders mentioned above. We also conducted subgroup analyses stratified by GA groups (e.g., 24–27⁶ weeks and 28–31⁶ weeks) using similar methods.

The data management and all statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). Two-sided *p* value of 0.05 was used to determine statistical significance.

Results

During the study period, 10,823 infants were admitted to the 57 CHNN NICUs. Among them, 8,016 infants with GA between 24 and 31⁶ weeks were admitted to the NICUs in CHNN within 24 h in 2019. We excluded 56 infants with major congenital anomalies according to the CHNN data definition manual, 960 infants with missing information on the 4 practices, and 965 infants with missing outcome. The remaining 6,035 eligible infants were included for analyses (Fig. 1).

The incidence of the primary outcome, early death or severe brain injury, was 10.6% in the study cohort. The in-

Table 1. Incidence of early death and/or severe brain injury among preterm infants

Gestational age, weeks	N	Early death, n/N (%)	Severe brain injury, n/N (%) ^a	Early death and/or severe brain injury, n/N (%)
24 ⁺⁰ –27 ⁺⁶	911	80/911 (8.8)	157/870 (18.1)	212/911 (23.3)
28 ⁺⁰ –31 ⁺⁶	5,124	91/5,124 (1.8)	359/5,079 (7.1)	430/5,124 (8.4)
All	6,035	171/6,035 (2.8)	516/5,949 (8.7)	642/6,035 (10.6)

^a 86/6,035 infants missing neuroimaging results due to early death before they would have been screened.

Table 2. Proportion of infants for each individual healthcare practice

Gestational age, weeks	N	Inborn, n (%)	ACS, n (%)	MgSO ₄ , n (%)	NT, n (%)
24 ⁺⁰ –27 ⁺⁶	911	770 (84.5)	695 (76.3)	456 (50.1)	458 (50.3)
28 ⁺⁰ –31 ⁺⁶	5,124	4,269 (83.3)	4,145 (80.9)	2,638 (51.5)	3,020 (58.9)
All	6,035	5,039 (83.5)	4,840 (80.2)	3,094 (51.3)	3,478 (57.6)

Four Evidence-Based Practices: inborn, born in a tertiary hospital within CHNN; ACS, administration of antenatal corticosteroids for any course; MgSO₄, application of magnesium sulfate before delivery for any reason; NT, maintenance of normal body temperature on admission within (36.0–37.5°C). ACS, antenatal corticosteroids; NT, normothermia.

Fig. 1. Flowchart for study population. GA, gestational age.

cidence was much higher among infants born at 24–27⁶ weeks GA compared to those at 28–31⁶ weeks GA (23.3% vs. 8.4%, respectively) (Table 1). Among the 4 evidence-based practices, the incidence of exposure to inborn was 83.5% ($n = 5,039$), ACS was 80.2% ($n = 4,840$), MgSO₄ was 51.3% ($n = 3,094$), and NT was 57.6% ($n = 3,478$) (Table 2).

Comparisons of maternal and infant characteristics are shown in Table 3. Infants who survived without severe

brain injury were significantly ($p < 0.05$) more likely to have maternal diabetes and be born by caesarean section than those who died or had severe brain injury. They also had significantly ($p < 0.05$) higher median GA and mean birth weight and were less likely to be male and have Apgar score <7 at 5 min.

Table 4 shows that exposure to any single practice was not significantly associated with lower incidence of early

Table 3. Characteristics of infants who survived without severe brain injury compared with those who died or developed severe brain injury

Characteristics, <i>n/N (%)</i> ^a	Survival without severe brain injury (<i>N</i> = 5,393)	Early death and/or severe brain injury (<i>N</i> = 642)	<i>p</i> value
Maternal characteristics			
Maternal age, mean (SD), years	31.0 (4.8)	31.1 (4.9)	0.49
Maternal diabetes	989/5,384 (18.4)	80/639 (12.5)	<0.01
Maternal hypertension	1,021/5,386 (19.0)	126/641 (19.7)	0.67
Chorioamnionitis ^b	622/4,136 (15.0)	83/461 (18.0)	0.09
ROM >24 h	1,412/5,304 (26.6)	148/624 (23.7)	0.12
Cesarean section	3,144/5,388 (58.4)	327/639 (51.2)	<0.01
Births, <i>n</i>			
Singleton	3,782/5,393 (70.1)	431/642 (67.1)	0.26
Twins	1,531/5,393 (28.4)	199/642 (31.0)	
Triplets or more	80/5,393 (1.5)	12/642 (1.9)	
Infant characteristics			
Birth weight, mean (SD), g	1,358.1 (308.4)	1,198.9 (332.2)	<0.01
Gestational age, median (IQR), weeks	30.0 (28.7, 31.0)	28.7 (27.1, 30.1)	<0.01
Small for GA, <10th percentile	354/5,393 (6.6)	41/642 (6.4)	0.86
Male	3,012/5,390 (55.9)	390/642 (60.7)	0.02
Apgar score <7 at 5 min	203/5,252 (3.9)	84/621 (13.5)	<0.01

GA, gestational age. ^a All percentages are based on available data. ^b Chorioamnionitis has 24% missing data, while all other variables have less than 3%.

Table 4. The association between the individual practice and the primary outcome of early death or severe brain injury

Exposure	Crude OR (95% CI)		Adjusted OR (95% CI) ^a			
	24 ⁺⁰ –27 ⁺⁶	28 ⁺⁰ –31 ⁺⁶	all	24 ⁺⁰ –27 ⁺⁶	28 ⁺⁰ –31 ⁺⁶	all
Individual practice						
Inborn	0.76 (0.51, 1.14)	0.84 (0.65, 1.08)	0.83 (0.68, 1.03)	0.89 (0.55, 1.44)	0.90 (0.68, 1.18)	0.91 (0.72, 1.15)
ACS	0.50 (0.36, 0.71)	0.70 (0.55, 0.88)	0.61 (0.50, 0.73)	0.58 (0.39, 0.87)	0.77 (0.60, 1.00)	0.71 (0.57, 0.88)
MgSO ₄	0.78 (0.57, 1.06)	0.83 (0.68, 1.01)	0.81 (0.69, 0.95)	1.09 (0.76, 1.57)	0.94 (0.76, 1.16)	0.97 (0.81, 1.17)
NT	0.75 (0.55, 1.02)	0.88 (0.72, 1.07)	0.79 (0.67, 0.93)	0.76 (0.55, 1.07)	0.97 (0.79, 1.19)	0.91 (0.76, 1.08)

ACS, antenatal corticosteroids; NT, normothermia. ^a Adjusted for gestational age, small for gestational age, sex, Apgar score <7 at 5 min, delivery type, and gestational diabetes.

death or severe brain injury (aOR 0.64 [95% CI: 0.38, 1.08]). However, when individual specific practices were considered, ACS was associated with lower incidence of early death or severe brain injury (aOR 0.71 [95% CI: 0.57, 0.88]). Sensitivity analysis using the inversed propensity score weighting (IPSW) method for sensitivity analysis produced similar results (online suppl. Table 1; see www.karger.com/doi/10.1159/000519846 for all online suppl. material). Subgroup analyses were not significant for both the 24⁰–27⁶ weeks GA and 28⁰–31⁶ weeks GA subgroups. Inborn status, MgSO₄, and NT were not indi-

vidually associated with a significantly lower incidence of early death or severe brain injury. Sensitivity analysis excluding births at the lowest gestational ages (online suppl. Table 2) produced similar results.

Among the study cohort, 138 (2.3%) infants received none of the 4 practices, 592 (9.8%) infants received 1 practice, 1,538 (25.5%) infants received 2 practices, 2,285 (37.9%) infants received 3 practices, and 1,482 (24.5%) infants received all 4 practices. Online supplementary Table 3 shows that exposure to 2, 3, or 4 practices was associated with significantly ($p < 0.05$) lower rate of death or

severe brain injury – any 2 practices (aOR 0.55 [95% CI: 0.34, 0.90]), any 3 practices (aOR 0.41 [95% CI: 0.26, 0.67]), all 4 practices (aOR 0.50 [95% CI: 0.30, 0.81]). The lowest incidence of early death or severe brain injury occurred with exposure to ACS + MgSO₄ (aOR 0.38 [95% CI: 0.18, 0.81]) and inborn + ACS + NT (aOR 0.39 [95% CI: 0.23, 0.65]). Sensitivity analysis using the IPSW method produced similar results (online suppl. Table 4). Subgroup analysis showed that combinations of exposures that resulted in a significantly ($p < 0.05$) lower rate of early death or severe brain injury were only detected among infants 28⁰–31⁶ weeks GA but not among infants 24⁰–27⁶ weeks GA. Sensitivity analysis excluding births at the lowest gestational ages (online suppl. Table 5) produced similar results.

Discussion

In this large cohort of 6,035 VPI in China, the incidence of severe brain injury was 8.7%, which is significantly lower than that reported by Kong et al. [13] in China 5 years ago, but still higher than that in other developed countries, such as 7.7% from the Canadian Neonatal Network in 2019 [14] and 6.2% from the EPICE population-based cohort in 2011 [15]. This suggests that although outcomes in Chinese NICUs have improved, there is still room for improvement, and quality-improvement efforts using evidence-based practices may further improve neurodevelopmental and other outcomes.

To our knowledge, this is the first large multicenter study of the association between 4 evidence-based practices and the incidence of early death or severe brain injury among VPI in China. Of the 4 practices examined in this study, the incidence of inborn was the highest, at 83.5%. This compares favorably with reports from developed countries like Canada (73.5% for infants on CNN in 2019) [14] and Australia-New Zealand (88.1% for infants <32 weeks GA in 2017) [16]. There is ample evidence that preterm infants born at tertiary institutions (inborn) where the appropriate level of neonatal care is available have better outcomes, including early death and severe brain injury, than those born elsewhere and then require transportation to tertiary centers for care [4, 5]. While we did not find an association between inborn and early death or severe brain injury, this may be because many of the hospitals in the CHNN are major regional centers with well-developed regionalization and patient referral and transport systems.

The prevalence of exposure to ACS in our cohort was 80.2%, which is significantly increased over the 56% incidence reported by Kong et al. [13] in China in 2013–2014. ACS exposure was lower among infants born at 24–27⁶ weeks GA (76.3%) than those born at 28–31⁶ weeks GA (80.9%). This may be because lower GA infants were more likely to be born by emergency delivery without adequate time for ACS administration. Our finding of an association between any administration of ACS and the rate of early death or severe brain injury is consistent with other reports in the literature [7] and reinforces the need for vigilance in administering ACS to mothers at risk of preterm delivery. Our finding that ACS was significantly ($p < 0.05$) associated with early death or severe brain injury among infants born at 24–27⁶ weeks GA (aOR 0.58 [95% CI: 0.39, 0.87]) but not 28–31⁶ weeks GA (aOR 0.77 [95% CI: 0.60, 1.00]) is consistent with Travers et al. [7]’s report that the benefits of ACS were larger among infants of lower GA.

Although 83.5% of infants in this cohort were inborn in tertiary hospitals, only 57.6% of them were normothermic at NICU admission, suggesting that measures to prevent hypothermia are inadequate. Rodrigo et al. [17] reported that hypothermia is associated with an increased risk of severe intraventricular hemorrhage and mortality. Strategies that have been shown to be successful include the use of plastic bags, wraps, caps, exothermic heat, and mattresses and can be easily adopted in the delivery room and NICU. Of note, in this study, NT was defined as 36.0–37.5°C measured at the first recorded temperature on NICU admission. The lower limit was 36°C [18], not the 36.5°C recommended by the WHO. This may lead to an overestimation of the proportion of NT used compared to other studies.

Brookfield et al. [19] reported that the use of prenatal MgSO₄ for fetal neuroprotection before 32 weeks of pregnancy at standard dose protocol improved neonatal neurological outcomes, but there is currently no evidence that it reduces neonatal mortality. We did not find a lower rate of severe brain injury with administration of MgSO₄, which is consistent with the report of Doyle et al. [8]. In this study, since MgSO₄ was defined as the use of magnesium sulfate before delivery for any reason, and not only neuroprotection, it is possible that this may have diluted the results. However, we also found that use of MgSO₄ in combination with ACS resulted in a lower incidence of early death or severe brain injury than ACS alone, which is consistent with the report of Gentle et al. [20] that the neuroprotective effect of MgSO₄ is enhanced when used in combination with antenatal corticosteroids.

Since 2 of the 4 evidence-based practices in this study are maternal interventions and 2 are neonatal interventions, our study reinforces the need for close collaboration between obstetricians and neonatologists to optimize infant outcomes. Consistent with previous studies [15, 21], our study also shows that exposure to multiple evidence-based practices was associated with a lower risk of early death or severe brain injury than single exposures. Our finding that exposure to 3 practices was just as effective as 4 practices suggests that population or clinical practice differences may lead to real-world variations in efficacy.

Limitations of This Study

Our study had some limitations. Data were unavailable for other evidence-based practices such as use of surfactant within 2 h of birth and early nasal continuous positive airway pressure [22], deferred cord clamping [23], and umbilical cord milking [24]. There were 960 cases with missing information on one of the 4 practices and 965 cases with missing information on the outcome. We did not have information on long-term neurodevelopmental outcomes. We did not examine other perinatal interventions, including those occurring before NICU admission, that may impact outcomes.

Conclusion

Our research shows that the application of evidence-based healthcare practices can improve survival without severe brain injury in very preterm infants who are born at 24–31⁶ weeks GA. Exposure to multiple evidence-based practices was associated with a lower incidence of early death or severe brain injury. Close collaboration between obstetrics and neonatology is critical to improving outcomes.

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Acknowledgment

See online supplementary material.

Statement of Ethics

This study was approved by the Ethics Review Board of Children's Hospital of Fudan University, Approval No. 2018-296. Waiver of consent was granted at all sites.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Hui Wu supervised the study; conceptualized and designed the study; and acquired, analyzed, and interpreted the data. Shoo K. Lee and Yun Cao supervised the study. Di Jin conceptualized and designed the study; drafted the manuscript; and acquired, analyzed, and interpreted the data. Xinyue Gu, Siyuan Jiang, and Yanchen Wang acquired, analyzed, and interpreted the data. Tongling Yang and Yulan Lu administrated and provided technical and material support. All authors critically revised the manuscript for important intellectual content, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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