No Survival or Morbidity Advantage Associated With Cesarean Section in VLBW Infants

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Abstract

This study aimed to determine whether CS was associated with survival and/or morbidity advantage. The infants were assigned to group 1 (n = 5,296) and 2 (n = 3,990) with a survival rate of <50% and ≥50%, respectively, at 23-24 gestational weeks (GW) to reduce skewing of the neonatal outcomes by wide institutional variation in the quality of neonatal intensive care. Each group of infants was further stratified into subgroups according to 23-24, 25-26, 27-28 and 29-34 GW. Mortality and major morbidities were measured. While significantly lower overall mortality and morbidity rates including intraventricular hemorrhage were associated with CS than vaginal delivery in both groups, the gestational age-stratified and adjusted odds ratios for mortality and morbidity were not significantly improved with CS. The mortality rate of group 1 was significantly lower than that of group 2 regardless of delivery mode. CS was not associated with survival or morbidity advantage in VLBWIs. The significantly lower mortality in group 1 than in group 2 regardless of delivery mode suggests that the quality level of neonatal intensive care at each institution rather than the mode of delivery might be a prerequisite for the survival and/or morbidity advantage.

Introduction

Recent progress in perinatal and neonatal intensive care medicine has resulted in a remarkable improvement in survival and morbidity of very low birthweight infants (VLBWIs)[1–3]. However, it is still disputed whether the mode of delivery affects the outcome of VLBWIs[4–9]. Despite the current lack of concrete scientific evidence supporting the benefit of cesarean section (CS) in VLBWIs, there has been an exponential increase in CS rates involving VLBWIs in recent years[1–3, 10–13]. Considering this upsurge in CS rate and potential fetal and maternal complications associated with the operation [14,15], it is important to reassess and establish the optimal mode of delivery for VLBWIs. Nonetheless, as the CS for VLBWIs is the current standard of care for preterm birth[8], conducting new randomized controlled trials to address this issue is not feasible virtually[16,17]. Therefore, analyzing very large data sets from a population-based, comprehensive prospective observational cohort of neonatal networks is the best alternative to RCTs to validate the risk/benefits of CS in VLBWIs.

The Korean Neonatal Network (KNN) is an ongoing nationwide, multicenter, prospective and web-based cohort registry system for VLBWIs[18–20]. We previously reported that the survival rate of peri-viable infants born at 23–24 gestational weeks (GW) reflected the quality of perinatal and neonatal intensive care at each institution's neonatal intensive care unit (NICU)[18], and improved infant survival at 23–24 GW from < 50% to ≥ 50% with significantly improved survival and less morbidity in more mature VLBWIs at 25–34 GW [19, 21–24]. In the present study, we grouped the nationwide population-based KNN cohort data of VLBWIs into group 1 (< 50%) and group 2 (≥ 50%) according to the survival rate of infants at 23–24 GW to reduce skewing of the neonatal outcomes by wide institutional variation in the quality level of neonatal intensive care, and further stratified into 23–24, 25–26, 27–28 and 29–34 GW subgroups according to gestational age (GA) in order to determine the possibility of survival or morbidity advantage associated with CS regardless of GA and quality level of each NICU.

Results

Cesarean section rate

While the overall CS rates were the same 78% in both groups, the CS rates were inversely proportional to GA with the highest CS rate of 84% in the 29–34 GW subgroups, and the lowest CS rates of 61% and 62% rates in 23–24 GW subgroups of groups 1 and 2 (Fig. 1, Table 1).

Demographic and perinatal characteristics

According to the data of the National Statistical Office, the number of VLBW infants born in Korea in 2031 – 2017 was 14,177. In this study 10,399 VLBW infants were registered [25]. Demographic and perinatal characteristics of the VLBWIs according to the delivery mode in each group and subgroup are shown in Table 1. The overall GA, SGA, antenatal steroid use, multiple pregnancies, inborn, and pregnancy-induced hypertension were significantly higher, and chorioamnionitis, length of hospital stay and ventilator days were significantly lower with CS than VD in both groups 1 and 2. GA, birth weight, 1 and 5 min Apgar scores and inborn hypertension were significantly lower, and SGA, multiple pregnancy, chorioamnionitis, length of hospital stay and invasive ventilator days were significantly higher in group 1 than in group 2 with CS.

Mortality and morbidities according to delivery mode

Table 2 lists the mortality and morbidity according to the mode of delivery in each group and GA subgroups. While the overall mortality and morbidity such as BPD, severe IVH, and ROP were lower in CS than in VD involving both groups 1 and 2 (mortality; 12% vs. 16%, BPD; 29% vs. 34%, IVH; 8% vs. 12%, ROP; 8% vs. 12%, respectively), the gestational age-stratified mortality and morbidities were not significantly improved with CS compared with VD in both groups 1 and 2, especially 23–26 GW subgroups. Moreover, the mortality rate was even significantly higher with CS than VD in 25–26 and 27–28 GW subgroups of group 2 (CS 17% vs. VD 15% in 25-26W, CS 38% vs. VD 28% in 27-28W). The mortality rate was significantly higher, and PDA and ROP were lower in group 2 than in group 1 regardless of delivery mode (mortality; 8% vs. 16%, PDA; 33% vs. 29%, ROP; 10% vs. 7%, respectively). Sepsis was significantly higher (group 2 24% vs. group 1 19%) and PVL was lower in group 2 than in group 1 with CS (7% vs. 8%, respectively)

Adjusted ORs for mortality and morbidity

Figure 3 shows the adjusted ORs and 95% CI for mortality and morbidity associated with CS in the total and GA-stratified subgroup. Adjusted variables were GA, Apgar score at 5 minute, SGA, multiple pregnancies, inborn, and PIH. The adjusted ORs for mortality or major morbidities such as BPD, severe IVH, PVL, NEC and ROP were not significantly reduced across all GA subgroups in both groups.

Discussion

We conducted a large nationwide prospective cohort study of VLBWIs with 23–34 GWs in Korea to address the impact of delivery mode on mortality and morbidities such as BPD and IVH. We were unable to locate previous cohort studies large enough to compare the deleterious outcomes of CS vs VD in each of the GA-stratified VLBWI subgroups of 23–24, 25–26, 27–28 and 29–34 GW. Although the 78% overall CS rate indicated that CS is the standard delivery mode for VLBWIs in Korea, the CS rates were inversely proportional to GA showing the lowest 61% in 23–24 GW and the highest 84% in 29–34 GW subgroups, which suggested that the obstetrician's willingness to perform elective CS besides obstetric indications for CS was selection-biased according to the GA-dependent perceived outcomes of VLBWIs[11].

In the present study, while the significantly lower overall mortality and morbidities such as BPD and severe IVH were associated with CS than VD in both groups, the gestational age-stratified and adjusted odds ratios for mortality and morbidities in both groups were not significantly improved with CS. Moreover, the significantly higher mortality rate was associated with CS than VD in 25–26 GW and 27–28 GW subgroups of group 2. The > 15-fold higher mortality in the 23–24 GW than in 29–34 GW subgroup, and > 3-fold higher severe IVH in the 23–24 GW than in 29–34 GW subgroup regardless of delivery mode suggest that the enigmatic overall but not GA-stratified survival and morbidity advantages associated with CS in the present and other studies[6,8,26–28] might be primarily attributable to skewing of the dataset caused by higher absolute proportion of the 29–34 GW subgroup with the highest CS rate and the lowest risk of mortality and morbidity. Consistent with our data, Riskin et al. [9] reported according to their population-based Israel Neonatal Network study that CS was associated with significantly lower mortality than VD. However, in the multivariate analysis, the delivery mode had no effect on mortality in the vertex presenting VLBWIs. Overall, these findings suggest that no survival or morbidity advantage was associated with CS across all GA at 23–34 GW VLBWIs. Therefore, CS cannot be routinely recommended in the absence of other obstetric indications[9,29].

Significantly higher mortality and morbidity in group 2 than in group 1 regardless of delivery mode in our present and previous studies[18–24] suggested that the improved quality of perinatal and neonatal intensive care by experienced and skillful neonatologists including better delivery room management and early admission care as evidenced by improved survival of peri-viable infants at 23–24 GW rather than the delivery mode was a prerequisite not only improving survival but also reducing morbidities of VLBWIs.

The limitations of the present study relate to its uncontrolled observational design. However, in the absence of a recent RCT study, which might not be feasible, we believe that the data obtained from this prospective nationwide large cohort study might be the best alternative to address the issues of association between delivery mode and outcomes in VLBWIs[8,9]. Nonetheless, the study is strengthened by the inclusion of a large dataset enough to facilitate data stratification according to GA and quality of neonatal intensive care. Another limitation of the study relates to the lack of information underlying the rationale for CS. High overall CS rate of 78%, which is well above the known obstetric indications for CS[4–7, 9,29] suggests that CS is the standard delivery mode regardless of its indications for VLBWIs in this study. However, CS being carried out as elective or emergency may have different effect on the neonatal outcome. Emergency CS-carried out mostly due to critical fetal complication-is associated with higher frequency of adverse neonatal outcomes when compared with elective CS, which is most often due to maternal complication. Nevertheless, information on whether the CS was elective or emergency was not available in this study.

The major finding is that CS was not associated with survival or morbidity advantages in VLBWIs. The enigmatic overall but not GA-stratified survival and morbidity advantages associated with CS observed in the present study might merely reflect skewing of the dataset due to the higher absolute proportion of the more mature GA subgroup with the highest CS rate and the lowest risk of mortality and morbidity. Significantly lower mortality in group 1 than in group 2 regardless of delivery mode suggests that the quality of neonatal intensive care at each institution rather than delivery mode might be key to survival or morbidity advantage in VLBWIs.

Methods

Patients

The KNN registry was approved by the institutional review board (IRB) at each participating hospital. Informed written consent to use the data from patients' medical records for research purpose was obtained from the parents at enrollment by the NICUs participating in the KNN. Informed consent was waived by IRB for infants who died in the delivery room or at an early stage in the NICU before informed consent was obtained for chart review. All methods were carried out in accordance with the IRB-approved protocol and in compliance with relevant guidelines and regulations. The current study utilized KNN database, and each patient's identification code was anonymized to protect the individual's privacy. This study was approved by the IRB of Jeonbuk National University Hospital.

The KNN database registry prospectively registered the clinical information of VLBWIs admitted to 67 voluntarily participating NICUs covering > 80% of VLBWIs in Korea [30,31]. Based on the enrolment criteria of KNN, only VLBWIs actively resuscitated in the delivery room and admitted to the NICU were registered in this study. Resuscitating infants at > 24 GW is mandatory by law in Korea, but most Korean tertiary NICUs are currently willing to resuscitate infants up to 23 GW. Trained staff used a standardized operating procedure to collect demographic and clinical information. Out of 10,399 VLBWIs born and registered in the database registry of KNN between January 1, 2013 and December 31 2017, we collected data involving 9,286 infants born at 23^{+0}GW to 34^{+6}GW, and categorized into group 1 based on the survival rate of infants < 50% (n = 5,296 from 25 NICUs) and group 2 as ≥ 50% (n = 3,990 from 33 NICUs) at 23–24 GW to reduce skewing of the neonatal outcomes by wide institutional variations in the quality level of each NICU (Fig. 1, 2).We excluded 1,113 infants including 405 infants with a GA < 23 GW or > 34 GW, 364 ungrouped infants with 25–34 GW due to the absence of a registry of infants at 23–24 GW (9 NICUs) and 344 infants with major congenital anomalies. We further stratified these infants into 23–24, 25–26, 27–28 and 29–34 GW subgroups according to GA. We compared maternal and neonatal variables including GA, birthweight, gender, small for gestational age (SGA), Apgar score at 1 and 5 min, maternal gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), invasive ventilation, noninvasive ventilation, and length of stay between groups 1 and 2 in the 23–24, 25–26, 27–28, and 29–34 GW subgroups depending on CS and vaginal delivery (VD). We compared the mortality rates and various major

morbidities, including bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and neonatal sepsis between the groups 1 and 2 including the 23–24, 25–26, 27–28, and 29–34 GW subgroups according to mode of delivery.

Definitions

We compiled a KNN database operation manual to define the patient characteristics. In the manual, GA was determined using the obstetric history based on the last menstrual period. SGA was defined as < 10 percentile birth weight of estimated GA. Chorioamnionitis was confirmed by placental pathology [32], and premature rupture of membrane (PROM) was defined as the rupture of membranes over 24 hours before the onset of labor. BPD was defined as the use of more than supplemental oxygen at 36 GW, corresponding to moderate-to-severe BPD using the severity-based definition of the National Institutes of Health consensus [33]. Symptomatic PDA was defined by echocardiographic findings of patent ductus with predominant left-to-right shunt plus clinical symptoms of PDA including heart murmur, ventilator dependence, deteriorating respiratory status, increasing recurrent apnea, pulmonary hemorrhage and/or hypotension. IVH was defined as grade ≥ 3 according to the classification of Papile et al [34]. PVL was defined as cystic PVL based on either head ultrasound or cranial magnetic resonance imaging scans performed at ≥ 2 weeks of age. NEC was defined as ≥ stage 2b according to the modified Bell criteria [35]. Early sepsis was defined as a positive blood culture less than 7 days from birth in symptomatic infants suggestive of septicemia and more than 5 days of antibiotic treatment[23]. ROP was defined as any ROP treated with anti-vascular endothelial growth factor and/or laser ablative and/or surgery to prevent visual loss[36].

Statistical analysis

The characteristics of the study participants and their prenatal and neonatal morbidities are described as mean ± standard deviation for continuous variables and as frequency and proportions for binary and categorical variables. Continuous variables were compared using Student's t-test or Wilcoxon rank-sum test. Categorical variables compared using the chi-square or Fisher's exact test. Multiple logistic regression was used to estimate the odds ratio (OR) with 95% confidence interval (CI) adjusted for GA, Apgar score at 5 minutes, SGA, multiple pregnancies, inborn, and PIH. A p-value < 0.05 was considered to be statistically significant. Statistical analyses were performed using STATA version 14.0 (STATA Corp., College, TX, USA).

Declarations

Data availability

Data availability was subjected to the Act on Bioethics and Safety [Law No. 1518, article 18 (Provision of Personal Information)]. Contact for sharing the data or accessing the data can be possible only through the data committee of Korean neonatal network (http://knn.or.kr) and after permitted by the CDC of Korea. Detail contact information was as follows: data access committee: Yun Sil Chang (cys.chang@samsung.com) and ethics committee: Jang Hoon Lee (neopedlee@gmail.com).

Author contributions

JKK and YSC coordinated and supervised data collection, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript.

JHH and MHL designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

WSP conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Conflict of Interest Disclosures

The authors declare no conflict of interest.

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Tables

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Figures

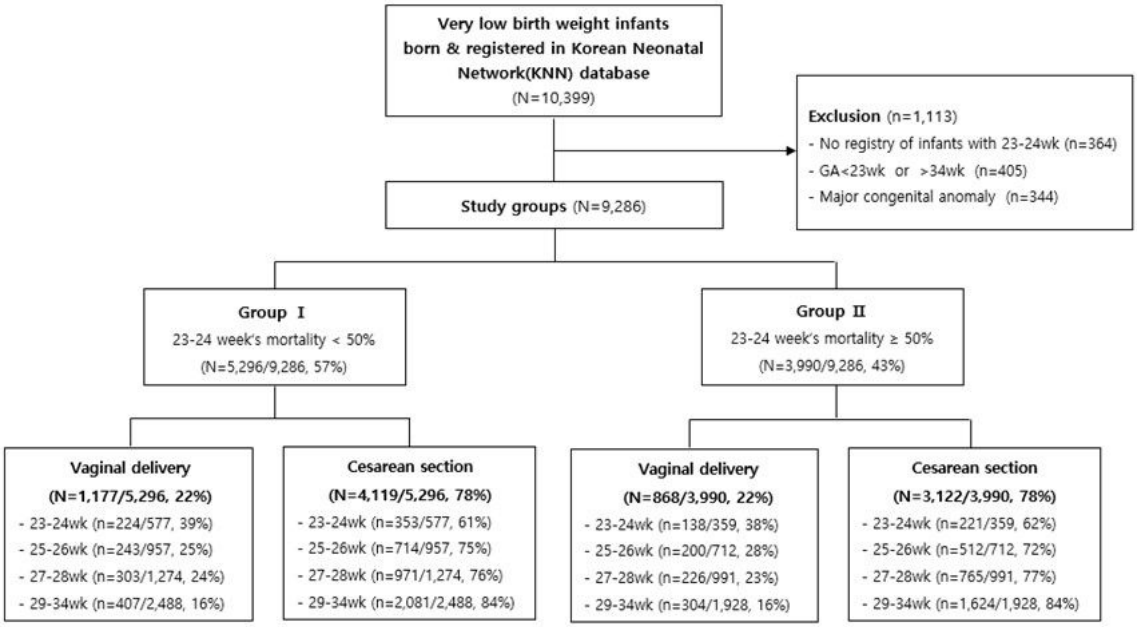

Figure 1

The wide variation in the mortality rates of infants born at 23-24 weeks' gestation from the Korean Neonatal Network included in this study.

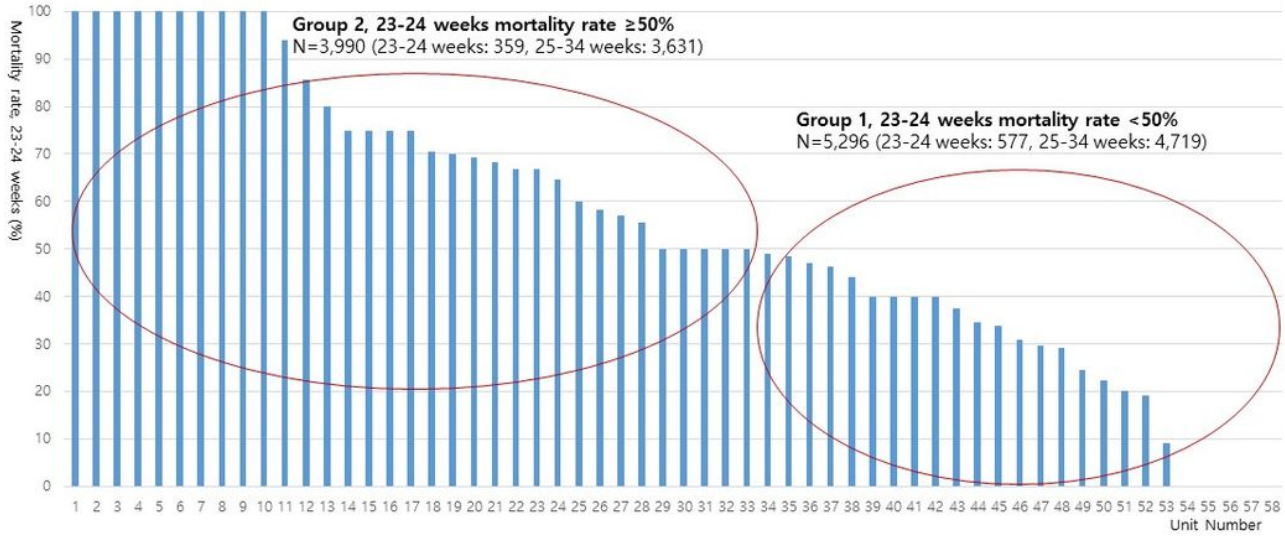

Figure 2

Flowchart shows the study population. This study enrolled 10,399 VLBWIs. We excluded 1,113 infants, and these infants were categorized into 2 groups based on their mortality (< 50% and ≥ 50%) at 23-24 weeks of gestation.

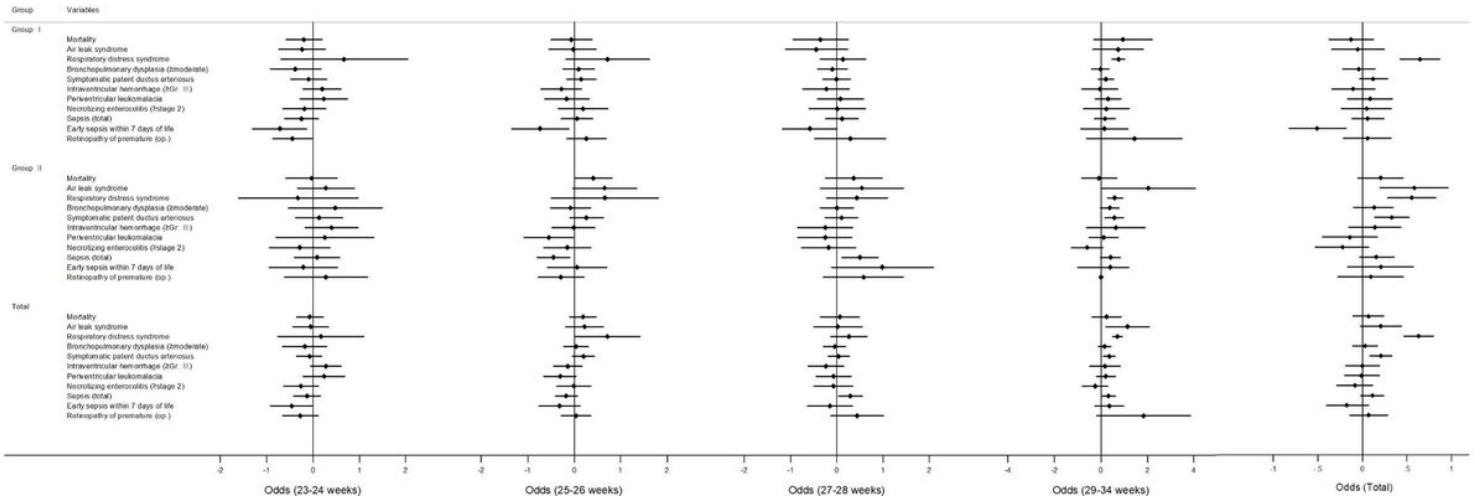

Figure 3

Adjusted odds ratio of mortality and morbidities associated with cesarean section (95% Confidence Interval)

Supplementary Files

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