Original Article

Improved Survival and Survival Without Bronchopulmonary Dysplasia in Very Low Birth Weight Infants after Active Perinatal Care

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ABSTRACT

Background: Perinatal and neonatal care for very low birth weight (VLBW) infants have changed significantly during the past two decades. However, it is unclear how these changes have affected neonatal mortality and morbidity in developing countries. **Objectives:** The aim of this study was to investigate the impact of the advanced neonatal care on short-term outcomes of VLBW infants. **Methods:** A retrospective study was performed to compare the mortality and morbidity of VLBW infants between period I (2007-2011) and period II (2012-2016) in our unit. **Results:** A total of 188 infants in period I and 214 infants in period II were evaluated. The overall in-hospital mortality for VLBW infants dropped from 26.1% in period I to 13.1% in period II. The incidence of birth asphyxia decreased significantly during period II (10.1% [period I] vs 3.7% [period II]). The rate of nasal continuous positive airway pressure (NCPAP) use (69.8% vs 87.1%) and the duration of NCPAP therapy (median: 3 days [period I] vs 5 days [period II]) increased significantly, while the proportion of infants treated with mechanical ventilation and the duration of mechanical ventilation significantly decreased. There was a significant increase in the proportion of survivors without major neonatal morbidity, mainly due to a significant increase in the incidence of survival without bronchopulmonary dysplasia (BPD) (72.7% vs 82.8%). In contrast, the incidence of late-onset sepsis increased significantly during period II (7.9% vs 19.4%). **Conclusions:** Active perinatal care is associated with improvements in survival and survival free of BPD for VLBW infants. However, late-onset sepsis is still a major concern.

KEYWORDS: *Morbidity, mortality, perinatal care, prematurity, sepsis, very low birth weight*

INTRODUCTION

Premature birth is the leading cause of infant mortality worldwide. It is estimated that 28% of neonatal deaths globally are directly attributable to preterm birth.[1] Although premature infants with very low birth weight (VLBW; <1500 g) account for only 1.5% of all live births, they continue to contribute disproportionately to perinatal mortality and morbidity.[2] With the development of antenatal and neonatal intensive care during the past two decades, the survival of this high-risk population has significantly improved. Recent data from developed nations indicate that mortality for infants weighing 501 to 1500 g decreased from 14.3% to 12.4% in the United States between 2000 and 2009, from 10.8% to 8.7% in Japan between 2003 and 2008.[3,4] Whereas data on mortality and morbidity for VLBW infants in developing countries are relatively sparse. The mortality for VLBW infants ranges from 11.0% to 64.4% in these countries,[5-7] suggesting that the survival of these infants still far lags behind that of developed countries and there is great room for improvement.

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As the largest developing country in the world, China bears 10% of the global burden of neonatal mortality due to its large population despite relatively low neonatal mortality rate (NMR) compared with other developing countries.[8] China ranked second among the 10 countries with the highest numbers of preterm births.[9] With the rapid economic development and increased supports from the government over the past decades, there has been a dramatic growth in the perinatal and neonatal care system at provincial and sub-provincial tertiary centers in China.[10] However, there have been no published reports regarding the impact of the advanced perinatal and neonatal care [such as administration of antenatal steroids, surfactant replacement therapy and introduction of early continuous positive airway pressure (CPAP), and mechanical ventilation] on trends in mortality and morbidity among VLBW infants.

In the present study, we sought to examine the impact of changes in perinatal-neonatal care on the early outcomes of VLBW infants born between 2007 and 2016 in a tertiary neonatal intensive care unit (NICU) at a university hospital in China.

Subjects and Methods

NICU in a university hospital

This study was conducted in the NICU of First Affiliated Hospital, Sun Yat-sen University in Guangzhou, a developed region located in the south of China. The hospital is one of the largest tertiary university hospitals in the country, which serves patients from the densely populated Guangdong province. The maternity unit at this hospital is a referral center for high-risk pregnancies. In recent years, there are approximately 3500 deliveries in this hospital annually and about 1400 neonates, mostly inborn, are admitted to the NICU. The preterm low birth weight infants account for about 30% of these total admissions.

Recent changes in care practices in the unit

With the dramatic changes in perinatology and neonatology in this country during period II, new evidence-based strategies and therapies have been introduced in this NICU. Significant practice changes in our early management of VLBW infants included (1) administration of antenatal steroids for the acceleration of fetal lung maturity to women at risk for preterm delivery as standard therapy; (2) changing to a respiratory strategy of early initiation of CPAP after birth in infants at risk for respiratory distress syndrome (RDS), and surfactant administration using intubate-surfactant-extubate (INSURE) to CPAPtechnique early in the course of RDS, instead of mechanical ventilation after surfactant administration; (3) lowering target for oxygen saturation from >95% to 90% to 94% in infants receiving supplemental oxygen; (4) a strategy of permissive hypercarbia, maintaining blood partial pressure of carbon dioxide (PaCO2) between 50 and 55 mmHg while on mechanical ventilation; (5) initiating early parenteral amino acid supplementation with 1.5-2.0 g/kg/day on the first day of life advancing over 3 days to 3.5 g/kg/day, rather than starting with 0.5 g/kg/day on the second day of life and increasing by 0.5 g/kg/day until reaching 3 g/kg/day; (6) making great effort to decrease neonatal asphyxia through strengthening neonatal resuscitation training; (7) stressing basic infection control protocol of hand hygiene.

Study population

The study population consisted of all preterm infants weighing less than 1500 g at birth, admitted to this NICU during a period of 10 years from 2007 to 2011 (Period I) and from 2012 to 2016 (Period II). Exclusion criteria included the presence of major congenital malformations and/or chromosomal anomalies, as well as death in the delivery room. The study was approved by the Ethics Committee of First Affiliated Hospital, Sun Yat-sen University.

Data abstraction

Patient information was obtained from the infants' medical records. The data were collected retrospectively on precoded forms with predefined diagnostic criteria and included antenatal history, perinatal and neonatal variables, medical treatment or procedures, complications during hospitalization, neonatal mortality, and timing and cause of death.

Definitions

Patent ductus arteriosus (PDA) was diagnosed through clinical means and echocardiography and ibuprofen therapy was used to treat symptomatic PDA. Intraventricular hemorrhage (IVH) was diagnosed by cranial ultrasound based on Papile criteria.[11] Severe IVH was defined as grades 3 and 4. Periventricular leukomalacia (PVL) was defined in accordance with the classification of de Vries *et al*.[12] Necrotizing enterocolitis (NEC) was based on modified Bell's classification stage IIA or greater.[13] The diagnosis and staging of retinopathy of prematurity (ROP) were based on the international classification, and severe ROP was defined as stages 3 to 5.[14] Sepsis was diagnosed either by positive blood culture or an abnormal white blood cell count and differential in the presence of obvious clinical signs of systemic infection. Late-onset sepsis was defined as sepsis occurring after 72 h of life. Bronchopulmonary dysplasia (BPD) was defined as receiving supplemental oxygen at 36 weeks of corrected

age (postmenstrual plus postnatal age in weeks).[15] Birth asphyxia was defined as failure to initiate spontaneous respirations and/or 5 min Apgar score <5.[16] Small for gestational age (SGA) was defined as birth weight <10th percentile for GA according to intrauterine growth charts of Chinese references.[17] Infants were classified as having major neonatal morbidity if they had ≥1 of the following conditions before discharge: BPD, NEC, severe IVH, PVL, or severe ROP.[18]

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences Version 15.0 (SPSS, Chicago, IL, USA). Unpaired t-test or Mann–Whitney U test was used to compare differences between means or medians of two groups. Categorical variables were analyzed with Chi-square statistics or Fisher's exact test. A *P* value <0.05 was considered statistically significant.

Results

Subjects

A total of 402 preterm live-born infants with birth weight <1500 g and GA ≤34 weeks were admitted to this NICU between January 2007 and December 2016. The 10-year study time was divided into two 5-year periods: Period I (2007-2011) and Period II (2012-2016). For Period I, 188 infants were included, of whom 139 survived until discharge. For Period II, 214 infants were included, of whom 186 survived until discharge.

Perinatal characteristics

A comparison of perinatal characteristics of VLBW infants in Period I and Period II cohorts is shown in Table 1. The rate of multiple births increased significantly in the total group during Period II. Of note, antenatal administration of corticosteroids occurred more often either in the total group or in the two birth weight subgroups during Period II. Moreover, the rate of birth asphyxia, as evidenced by Apgar scores of <5 at 5 min, decreased significantly during period II.

In-hospital mortality

A comparison of in-hospital mortality for VLBW infants by birth weight category between the two periods is presented in Table 2. The mortality rate in the total cohort was 26.1% and 13.1% in Period I and Period II, respectively. The decrease from Period I to Period II was statistically significant. The most significant improvement in mortality was observed in the extremely low birth weight infants from 47.6% in Period I to 20.7% in Period II ($P < 0.01$). This reduction was mainly due to the decreased mortality in infants with birth weight between 750 and 999 g from 47.2% to 20.8% [Table 3]. When mortality for VLBW infants was compared by GA category, the reduction in mortality was most striking in neonates with a GA of 28 weeks or more, as shown in Table 2.

Cause of mortality and age at death

The cause of mortality in Period I and Period II cohorts is shown in Table 4. The primary cause of death was

Table 1: Comparison of perinatal characteristics of VLBW infants between Period I and Period II

Characteristics	BW <1000 g		BW 1000-1499 g		Total	
	Period I (*n*=42)	Period II (*n*=58)	Period I (*n*=146)	Period II (*n*=156)	Period I (*n*=188)	Period II (*n*=214)
Maternal characteristics						
Maternal age, y	31.8±4.7	30.7±4.7	30.3±4.8	30.0±4.3	30.6±4.8	30.2±4.4
Cesarean section	29 (69.0)	41 (70.7)	110 (75.3)	123 (78.8)	139 (73.9)	164 (76.6)
PIH	15 (35.7)	15 (25.9)	37 (25.3)	37 (23.7)	52 (27.7)	52 (24.3)
GDM	8 (19.0)	13 (22.4)	17 (11.6)	31 (19.9)	25 (13.3)	44 (20.6)
PROM >24 h	5 (11.9)	7 (12.1)	27 (18.5)	26 (16.7)	32 (17.0)	33 (15.4)
Multiple birth	24 (57.1)	41 (70.7)	83 (56.8)	102 (65.4)	107 (56.9)	143 (66.8)*
In vitro fertilization	10 (23.8)	18 (31.0)	34 (23.3)	45 (28.8)	44 (23.4)	63 (29.4)
Antenatal steroids	22 (52.4)	47 (81.0)**	98 (67.1)	122 (78.2)*	120 (63.8)	169 (79.0)**
Neonatal characteristics						
Male gender	24 (57.1)	29 (50.0)	69 (47.3)	72 (46.2)	93 (49.5)	101 (47.2)
SGA	30 (71.4)	33 (56.9)	63 (43.2)	62 (39.7)	93 (49.5)	95 (44.4)
GA, wk	29.0±2.3	29.1±2.3	30.8±2.0	30.7±2.0	30.4±2.2	30.3±2.2
Birth weight, g	898±121	914±110	1306±123	1283±120	1214±210	1183±202
Apgar scores						
<5 at 1 min	16 (38.1)	12 (20.7)	23 (15.8)	12 (7.7)*	39 (20.7)	24 (11.2)**
<5 at 5 min	8 (19.0)	4 (6.9)	11 (7.5)	4 (2.6)*	19 (10.1)	8 (3.7)*

Note: Data are expressed as mean±SD or number of infants (percentage). Comparison between period I and period II: *P<0.05, **P<0.01. VLBW: very low birth weight; PIH, pregnancy-induced hypertension; GDM: gestational diabetes mellitus; GA: gestational age; PROM: prolonged rupture of membranes; SGA: small for gestational age

Table 2: Comparison of in-hospital mortality of VLBW infants according to birth weight and gestational age between Period I and Period II

	Period I		Period II		χ^2	*P*
	No.	Death *n* (%)	No.	Death *n* (%)		
BW (g)						
<1000	42	20 (47.6%)	58	12 (20.7%)	8.118	0.004**
1000-1499	146	29 (19.9%)	156	16 (10.3%)	5.489	0.019*
GA (wk)						
24-27	13	7 (53.8%)	19	5 (26.3%)	2.496	0.114
28-31	118	31 (26.3%)	135	19 (14.1%)	5.907	0.015*
32-34	57	11 (19.3%)	60	4 (6.7%)	4.173	0.041*
Total	188	49 (26.1%)	214	28 (13.1%)	10.888	0.001**

Note: Comparison between period I and period II: *P<0.05, **P<0.01. VLBW: very low birth weight; BW: birth weight; GA: gestational age

Table 3: Comparison of in-hospital mortality of extremely low gestational age and extremely low birth weight infants between Period I and Period II

	Period I		Period II		*P*
	No.	Death *n* (%)	No.	Death *n* (%)	
BW (g)					
<500	0	-	0	-	-
500-749	6	3 (50%)	5	1 (20%)	0.689
750-999	36	17 (47.2%)	53	11 (20.8%)	0.008**
GA (wk)					
24	1	1 (100%)	0	-	-
25	0	-	1	0 (0%)	-
26	4	4 (100%)	3	2 (66.7%)	0.876
27	8	2 (25%)	15	3 (20%)	1.000

Note: Comparison between period I and period II: **P<0.01. BW: birth weight; GA: gestational age

Table 4: Comparison of cause of mortality in VLBW infants between Period I and Period II

	Period I (*n*=49)	Period II (*n*=28)	χ^2	*P*
RDS	19 (38.8%)	6 (21.4%)	2.445	0.118
Pulmonary hemorrhage	7 (14.3%)	5 (17.9%)	0.173	0.678
Birth asphyxia	14 (28.6%)	2 (7.1%)	4.970	0.026*
Sepsis	5 (10.2%)	12 (42.9%)	11.043	0.001**

Note: Comparison between period I and period II: *P<0.05, **P<0.01. VLBW: very low birth weight; RDS: respiratory distress syndrome

determined on the basis of clinical assessments (autopsy was not approved by the parents). The most common cause of death was respiratory distress syndrome in Period I cohort. However, sepsis is the leading cause of death in Period II cohort. It should be noted that the percentage of deaths attributable to birth asphyxia decreased significantly in Period II, in comparison to Period I ($P < 0.05$), while the percentage of deaths caused by sepsis increased significantly ($P < 0.01$). Although the percentage of infants who died of RDS did not differ between the two periods, mortality from RDS as a function of the number of infants who had RDS, decreased significantly (Period I: 14.2%, 19/134 vs Period II: 4.3%, 6/138, $P < 0.01$). Treatment was withdrawn due to medical futility or poor neurologic prognosis in 49.0% (24 of 49) of the deaths in Period I and in 35.7% (10 of 28) of the deaths in Period II ($P > 0.05$). The median age at death was 4 days for Period I cohort and 8.5 days for Period II cohort ($P < 0.05$).

Neonatal morbidity and interventions in survivors

A comparison of neonatal morbidities and interventions of surviving VLBW infants between Period I and Period II is shown in Table 5. The rate of BPD decreased significantly in Period II, mainly due to a decline in the 1000 to 1499 g birth weight subgroup. In contrast, the rate of late-onset sepsis increased because of an increase in the 1000 to 1499 g birth weight subgroup. There were no significant differences in the rates of other morbidities between the two periods.

Major changes were also observed in the therapeutic interventions used after birth. From Period I to Period II, there was a trend towards a greater percentage of infants treated with surfactant, although the difference was not statistically significant. Of note, the rate of NCPAP use and the duration of NCPAP therapy increased significantly, while the proportion of infants treated with mechanical ventilation and postnatal steroids, the duration of mechanical ventilation and treatment with supplemental oxygen significantly decreased. Furthermore, significant increased use of a peripherally inserted central venous catheter (PICC) and longer catheter dwell times were noted in Period II.

Survival without major neonatal morbidity

Of the survivors, the proportion of infants who were discharged home without any major morbidity increased significantly, from 69.1% (96 of 139) in Period I to 78.5% (146 of 186) in Period II ($P < 0.05$). This was mainly due to a significant increase in the incidence

Table 5: Comparison of neonatal morbidities and interventions of surviving VLBW infants between Period I and Period II

	BW <1000 g		BW 1000-1499 g		Total	
	Period I (*n*=22)	Period II (*n*=46)	Period I (*n*=117)	Period II (*n*=140)	Period I (*n*=139)	Period II (*n*=186)
Morbidity						
RDS	18 (81.8)	34 (73.9)	82 (70.1)	85 (60.7)	100 (71.9)	119 (64.0)
BPD	13 (59.1)	19 (41.3)	25 (21.4)	13 (9.3)**	38 (27.3)	32 (17.2)*
Pneumothorax	2 (9.1)	1 (2.2)	1 (0.9)	2 (1.4)	3 (2.2)	3 (1.6)
IVH grade 3 and 4	0 (0)	4 (8.7)	3 (2.6)	1 (0.7)	3 (2.2)	5 (2.7)
PVL	1 (4.5)	3 (6.5)	0 (0)	1 (0.7)	1 (0.7)	4 (2.2)
Late-onset sepsis	3 (13.6)	9 (19.6)	8 (6.8)	27 (19.3)**	11 (7.9)	36 (19.4)**
NEC	2 (9.1)	3 (4.3)	3 (2.6)	2 (1.4)	5 (3.6)	4 (2.2)
PDA	6 (27.3)	15 (32.6)	21 (17.9)	23 (16.4)	27 (19.4)	38 (20.4)
ROP stage ≥3	2 (9.1)	5 (10.9)	4 (3.4)	6 (4.3)	6 (4.3)	11 (5.9)
Interventions						
Surfactant therapy	20 (90.9)	43 (93.5)	91 (77.8)	114 (81.4)	111 (79.9)	157 (84.4)
Postnatal steroids	12 (54.5)	15 (32.6)	18 (15.8)	9 (6.5)*	30 (22.1)	24 (13.0)*
NCPAP	19 (86.4)	42 (91.3)	78 (66.7)	120 (85.7)**	97 (69.8)	162 (87.1)**
Mechanical ventilation	20 (90.9)	38 (82.6)	63 (53.8)	52 (37.1)**	83 (59.7)	90 (48.4) *
Days on NCPAP	5 (2-12)	8 (3-12)	2 (0-5)	4 (2-8)**	3 (0-5)	5 (2-10)**
Days on mechanical ventilation	17 (9-23)	7 (4-18)	1 (0-11)	0 (0-2)**	3 (0-15)	0 (0-6)**
Mechanical ventilation >3 days	20 (90.9)	35 (76.1)	45 (38.5)	30 (21.4) **	65 (46.8)	65 (34.9) *
PICC	21 (95.5)	45 (97.8)	91 (77.8)	127 (90.7)**	112 (80.6)	172 (92.5) **
Duration of PICC (d)	32.1±21.1	41.5±18.7	18.1±14.3	27.0±5.1**	20.3±16.3	30.6±17.2**
Duration of oxygen therapy (d)	48 (29-71)	36 (26-64)	27 (19-37)	18 (10-27)**	28 (21-43)	21 (12-32)**
Length of stay (d)	64.2±22.5	57.2±22.8	42.4±15.4	35.8±13.3**	45.8±18.4	41.1±18.6*

Note: Data are expressed as mean±SD or number of infants (percentage). Days on NCPAP, days on mechanical ventilation, duration of oxygen therapy are expressed as median (quartile). Comparison between period I and period II: *P<0.05, **P<0.01. VLBW: very low birth weight; RDS: respiratory distress syndrome; BPD: bronchopulmonary dysplasia; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; ROP: retinopathy of prematurity; NCPAP: nasal continuous positive airway pressure; PICC: peripherally inserted central venous catheter

of survival without BPD (Period I: 72.7%, 101/139 vs Period II: 82.8%, 154/186, P < 0.05).

Discussion

This study investigated the impact of advanced neonatal care on short-term outcomes of VLBW infants in a tertiary NICU in China. The overall mortality rate for VLBW infants born at our center decreased significantly from 26.1% in Period I (between 2007 and 2011) to 13.1% in Period II (between 2012 and 2016). The most significant improvement in mortality was observed in the extremely low birth weight infants from 47.6% to 20.7%. This reduction was mainly due to the decreased mortality in infants weighing 750 g to 999 g from 47.2% in Period I to 20.8% in Period II. Such an improvement is attributable to a more active perinatal approach and better NICU. Our neonatal survival rate (86.9%) for VLBW infants in Period II was higher than those of recent reports from developing countries, ranging from 35.6% to 70.5%.[6,7,19] Moreover, the survival rate (79.3%) for ELBW infants in Period II is compared favorably with those of other developing countries, ranging from 34.9% to 56.1%.[19,20] But the survival of extremely low GA infants, especially at lower GA (≤26 week) in the present study is substantially below that of developed countries.[21,22] The quality of antenatal or neonatal care is the most important factor influencing the survival of this group of infants. Effective measures are needed for further improvements in neonatal outcomes of extremely preterm infants.

In this study, the reduced mortality was associated with major changes in obstetric care. There was a significant increase in the percentage of mothers treated with antenatal steroids from Period I to Period II. During Period II, the administration of antenatal steroids for the acceleration of fetal lung maturity to women who were expected to deliver between 24 and 34 weeks' gestation became standard therapy. Prenatal steroid use is offered to women in imminent premature labor, unless the mothers present late in labor or an emergency caesarean section has to be performed due to fetal distress. Our finding is in consistent with previous reports from developed countries that have shown that antenatal steroids reduce neonatal mortality and morbidity in

premature infants.[23,24] Therefore, the use of antenatal steroid treatment should be given a high priority to be implemented in developing countries, where resources are scarce and it is often difficult to provide expensive neonatal care.

Another noticeable improvement in perinatal care was that the incidence of birth asphyxia, as evidenced by Apgar scores of <5 at 5 min, decreased significantly during Period II. This substantial improvement is associated with the implementation of updated guidelines on neonatal resuscitation. A nationwide neonatal resuscitation program has been introduced to improve the knowledge and skills of hospital delivery room personnels in China in recent years.[25] As the low Apgar score is strongly associated with poor prognosis,[26] the significant improved Apgar scores at both 1 and 5 minutes may contribute in improving the outcomes of VLBW infants in this study.

Surfactant replacement therapy (SRT) is now the most effective and standard treatment for RDS in preterm neonates in developed countries. Randomized clinical trials have established its efficacy in reducing mortality and morbidity in RDS.[27,28] However, only a few developing countries use surfactant routinely due to the high cost, and the published data on SRT and its impact from the developing world are still limited.[29] Available evidence suggests that SRT is effective and safe in level-3 neonatal units and has the potential to reduce neonatal mortality and air leaks in low-resource settings.[30] In this study, the improved outcome of preterm infants with RDS in Period II was reflected by the decreased mortality from RDS and the reduced need and duration of mechanical ventilation. These are associated with early timing in surfactant use, and better surfactant treatment strategies (INSURE technique) in conjunction with the increased use of antenatal steroids and CPAP therapy.

Although the improvements in perinatal and neonatal care have contributed to a reduction in the overall mortality of VLBW infants in this study, no significant change in survival for extremely preterm infants (<28 weeks' gestation) was observed between the two periods. There are several possible reasons for the unfavorable survival rate for these infants. The quality of antenatal or neonatal care is the most important factor influencing the survival of extremely preterm infants. Although the administration of antenatal steroids, delivery by cesarean section, attendance of trained staff at delivery, intubation at birth and use of surfactant were frequent in our center in Period II, reflecting the attitudes toward active treatment of these smallest infants, deficiencies in other aspects of neonatal care including insufficient infection control policy associated with overcrowded NICU and low nursing staff-to-patient ratio, inappropriate use of some interventions by inexperienced personnel, may have resulted in adverse outcomes. Also, parental desires are still to be regarded as most important in the decision-making process to life support for the smallest infants. The parents make a decision to withdraw intensive care due to medical futility or anticipation of a poor long-term prognosis.

Improved survival of the VLBW infants has been reported to be accompanied by increased or similar major neonatal morbidity.[31-33] In contrast, we found a significant decrease in the proportion of survivors with major neonatal morbidity during the two periods (from 30.9% to 21.5%), mainly due to the lowered incidence of survival with BPD (from 27.3% to 17.2%). The BPD rate (17.2%) in Period II was comparable to that reported from Swiss Neonatal Network in 2008 (14.7%).[34] During Period II, there were several changes in respiratory support of preterm neonates, including more frequent use of NCPAP, early INSURE method rather than endotracheal-assisted ventilation and lower target for oxygen saturation of 90% to 94% in infants receiving supplemental oxygen. These strategies are supported by the evidences that mechanical ventilation and oxidative injury have been implicated as significant risk factors for BPD,[35,36] and early NCPAP, as a means of avoiding endotracheal intubation and mechanical ventilation, has been shown to reduce the incidence of BPD in premature infants with RDS.[37] Available evidence from low- and middle-income countries suggests that CPAP is a safe and effective mode of therapy in preterm neonates with respiratory distress. It reduces in-hospital mortality and the need for ventilation.[38] Therefore, CPAP should be the first option in the management of neonatal RDS, particularly in developing countries with limited resources.

Although the reduced need for mechanical ventilation or days on a ventilator may lower the incidence of ventilator-related infection,[39] we found more frequent late-onset sepsis in survivors in Period II, indicating that late-onset sepsis remains a major concern. This may be associated with the increased use of PICC lines for total parenteral nutrition or intravenous access, and longer catheter dwell times because of the improved survival rate and mortality at later points. This notion was supported by a recent report, which showed that prolonged catheter dwell time is an important risk factor for PICC-associated bloodstream infection in neonates.[40] Other relevant factors may include a low threshold for the empirical use of antimicrobial agents, insufficient infection control policy associated with overcrowding,

and inadequate nursing care, even though monitoring of compliance with hand hygiene has been stressed. Hence, effective strategies to reduce nosocomial infections are urgently required.

Conclusions

More active perinatal and neonatal care, in particular, the increased use of antenatal steroids, NCPAP and INSURE technique were associated with marked improvements in survival and survival without BPD of VLBW infants. However, late-onset sepsis is still a major concern. Further studies for developing better clinical practice to improve outcomes of VLBW infants are desperately needed.

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Conflicts of interest

There are no conflicts of interest.

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