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Prognosis of Very Preterm Infants with Severe Respiratory Distress Syndrome Receiving Mechanical Ventilation

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Abstract
Objective To evaluate the prognosis of very preterm infants with severe respiratory distress syndrome (RDS) receiving mechanical ventilation.
Methods A total of 288 preterm infants mechanically ventilated for severe RDS and completed follow-up till 18 months of corrected age comprised these study subjects. The associations of prenatal and postnatal factors, mode and duration of conventional mechanical ventilation (CMV), medication and treatment, and complications with cerebral palsy or mental developmental index (MDI) < 70 at 18 months of age were analyzed.
Results The incidences of CP among study subjects were 17, 5, and 2 % in infants less than 28, 28–30, and 30–32 weeks, respectively. The incidences of MDI < 70 were 49, 24, and 13 % in infants less than 28 weeks, 28–30 weeks, and 30–32 weeks, respectively. Antenatal corticosteroids, preeclampsia, fetal distress, early and late bacteremia, and decreased weight gain were associated with CP and an MDI < 70. In the CP and MDI < 70 groups, the number of infants on CMV was significantly higher than on high-frequency oscillatory ventilation (HFOV). Longer duration of mechanical ventilation and blood transfusions were associated with an increased risk of having an MDI < 70 or CP. The complications in study subjects associated with an MDI < 70 or CP were BPD, NEC, and IVH grade III–IV.
Conclusion The prognosis of very preterm infants with severe RDS may be influenced by several prenatal and postnatal factors. HFOV although decreased the duration of mechanical ventilation, whether it will decrease the incidence of neurodevelopmental disability, needs to be explored further.

Keywords Prognosis · Mechanical ventilation · Preterm infants · Respiratory distress syndrome

Abbreviations

NDI	Neurodevelopmental impairment
GA	Gestational age
BW	Birth weight
BPD	Bronchopulmonary dysplasia
CDP	Continuous distending pressure
PS	Pulmonary surfactant
MV	Mechanical ventilation

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CMV	Conventional mechanical ventilation
FIO_2	Fraction of inspiration oxygen
HFOV	High-frequency oscillatory ventilation
IVH	Intraventricular hemorrhage
MAP	Mean airway pressure
MDI	Mental developmental index
nCPAP	Nasopharyngeal continuous positive airway pressure
ENCPAP	Early nasal continuous positive airway pressure
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care units
OI	Oxygenation index
PaO_2	Partial arterial oxygen pressure
PEEP	Positive expiratory end pressure
PIP	Peak inspiratory pressure
PMA	Post-menstrual age
RDS	Respiratory distress syndrome
SIMV	Synchronized intermittent mandatory ventilation
ELBW	Extremely low birth weight

Introduction

Advances in neonatal-perinatal medicine have resulted in increased survival rates of premature infants [1]. There have been concerns that some of those survivors are at increased risk for neurodevelopmental disability [1]. Gestational age, birth weight, gender, multiple births, antenatal corticosteroids, neonatal infection, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and major brain lesions such as periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH) have been shown to influence both short- and long-term outcomes [2–4]. Respiratory distress syndrome (RDS) is common in preterm infants born before 32 weeks of gestation [5–7] for which conventional mechanical ventilation (CMV) has been the standard treatment [8]. Since the development of high-frequency oscillatory ventilation (HFOV) during the late 1970s, its use in sicker and smaller infants with more compromised respiratory systems has been steadily increasing every year. Thus far, no studies have confirmed that HFOV is better than conventional ventilation for the prevention of BPD or neurodevelopmental impairment [9]. Severe BPD is associated with neonatal death, prolonged neonatal intensive care stay, and impaired neurodevelopment [10]. Longer periods of CMV increased risk of BPD [11], and associated with cerebral palsy (CP) or neurodevelopmental delay (NDD), have been reported [3]. However, the long-term neurodevelopmental outcomes associated with the modes of mechanical ventilation with severe RDS are not well known. The purpose of this study was to evaluate the effect of early intervention on the neurodevelopmental outcome of preterm infants with severe RDS and to investigate the relationship between CMV and neurodevelopmental impairment (NDI).

Methods

Patient Population

Preterm infants with gestational age $\leq$32 weeks, birth weight <1,500 g, and less than 24 h of life who developed RDS requiring mechanical ventilation were included in the study if they met following criteria: a partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FIO_2) ratio <200 (determined when patients were receiving nasopharyngeal continuous positive airway pressure or CMV); and chest radiograph criteria satisfying severe RDS, classified as Stage III, or IV using Bomsel's classification [12]. Cranial ultrasonographies (USG) were being routinely obtained to screen the probable IVH/other intracranial lesions on day one after birth and subsequently at the discretion of the treating clinician. This retrospective cohort study was performed between January 2006 and December 2010 in the Zhengzhou Children's Hospital of Henan Province, China.

Preterm infants with spontaneous breathing and RDS were initially put on nasopharyngeal continuous positive airway pressure (nCPAP). If the infants had clinical symptoms of worsening respiratory distress or hypoxemia, as well as recurrent apnea and bradycardia episodes, they were intubated and positive pressure ventilation was provided through a T-piece (Neopuff, Fisher & Paykel Healthcare, Auckland, New Zealand). Infants with genetic or metabolic diseases, congenital abnormalities, and pneumothorax were excluded from the study. The study was approved by the Life Science Ethics Committee of Zhengzhou University in accordance with the Helsinki Declaration.

Ventilators

An SLE5000 infant ventilator (SLE Ltd, South Croydon, Surrey, UK) was used for high-frequency ventilation, and a Servo-i-Maquet (Maquet Critical Care AB, Solna, Sweden) was used for the CMV. The ventilation strategies were emphasized on using the lung protective strategy while avoiding atelectasis and over-distention. The optimal lung volume was determined as the lung expansion to the 8th to 9.5th ribs for most of the infants, and the 7th to 8th ribs for infants with air leakages [13, 14]. Oxygenation was used as an indirect marker of lung volume. After 2 h ventilation, if PaO_2/FIO_2 was <200, patients were given rescue surfactant

therapy (Curosurf, 200 mg/kg). A subsequent dose (100 mg/kg) was administered 12 h after the previous dose if PaO_2/FIO_2 remained <200 [15]. The infants were changed from CV to HFOV after 2 h of the second dose surfactant if PaO_2/FIO_2 still remained <200. The protocol dictated maintenance of arterial oxygen saturation, as measured by pulse oximetry, between 88 and 96 %, an arterial pH of at least 7.20, and moderate permissive hypercapnia with a partial pressure of carbon dioxide (pCO_2) up to 55 mmHg. For infants with chronic lung disease, air-leak syndromes, or persistent lung hyperinflation, the target pCO_2 of 45–65 mmHg was considered [13]. The infants were extubated from HFOV or SIMV onto nCPAP (Infant Flow, Electro Medical Equipment), weaned to a nasal cannula, and then to room air.

Data Collection

We collected the following prenatal and postnatal data: use of antenatal corticosteroids, maternal hypertension and/or preeclampsia, premature rupture of membranes, presence of fetal distress, intrauterine growth retardation, mode of delivery, gender of the infant, whether the infants were singletons, twins, or triplets, early (<3 days) or late (>3 days) bacteremia, and weight gain in grams from birth through the sixth week of life (defined as the baby's weight measured at completion of 6 weeks minus the BW). The mode and duration of mechanical ventilation, medications and other treatments, and complications including pneumothorax, pulmonary hemorrhage, NEC, patent ductus arteriosus (PDA), IVH grade III–IV, and BPD were also collected for analysis. BPD was determined by an oxygen reduction test at 36 weeks post-menstrual age (PMA) and further classified according to criteria adapted from the National Institute of Child Health and Human Development [16]. Mild BPD was defined as the need for supplemental oxygen for ≤28 days. Moderate BPD was defined as the need for supplemental oxygen at a PMA of 36 weeks without positive pressure support, and severe BPD was defined as the need for positive pressure support.

These infants were followed up at the Department of Child Healthcare. Upon completion of follow-up at 18 months of corrected age, we examined the long-term outcomes, and the occurrence of moderate or severe disability at 18 months of corrected age that included severe hearing loss, blindness, CP, and an MDI < 70 (on the Bayley Scales of Infant Development, Second Edition). CP was defined as a nonprogressive central nervous system disorder characterized by abnormal muscle tone in at least one extremity and abnormal control of movement or posture. Children who were not ambulatory or who required an assistive device for ambulation were considered to have moderate to severe CP [17].

Statistical Analyses

All analyses were performed using SPSS 17.0 (SPSS Chicago, IL, U.S). Quantitative data are expressed as mean ± standard deviation (SD). Entry data and outcome differences were compared using the t -test and Fisher's exact tests. Variables especially gestational age, birth weight, preeclampsia, fetal distress, early bacteremia, late bacteremia, mechanical ventilation, CV, HFOV, surfactant usage, NEC, IVH grade III–IV, and BPD were considered for logistic regression. Based on the significance of these factors after univariate analysis, they were further subjected to multivariate logistic regression analysis. The level of statistical significance was set at $P < 0.05$.

Results

Outcomes

A total of 812 preterm infants weighing less than 1,500 g were admitted to the NICU during the study period, and 560 infants had RDS. Of 560 infants, 272 were excluded for the following reasons: 135 did not require MV, 97 had moderate RDS, five had congenital anomalies, four had grade III–IV IVH, two had genetic diseases, 20 were lost to follow-up, and nine infants died. Finally, 288 infants were studied. Of these, 19 infants developed CP, 74 had an MDI < 70, and 195 were normal (Fig. 1).

The incidence of CP and MDI < 70 among the infants decreased with increasing gestational age and birth weight. For CP, the incidence was 17 % (12/70) in infants <28 weeks, 5 % (5/98) in infants 28–30 weeks, and 2 % (2/120) in infants 30–32 weeks. For an MDI < 70, the incidence was 49 % (34/70) in infants <28 weeks, 24 % (24/98) in infants 28–30 weeks, and 13 % (16/120) in infants 30–32 weeks. (Table 1). Preeclampsia, fetal

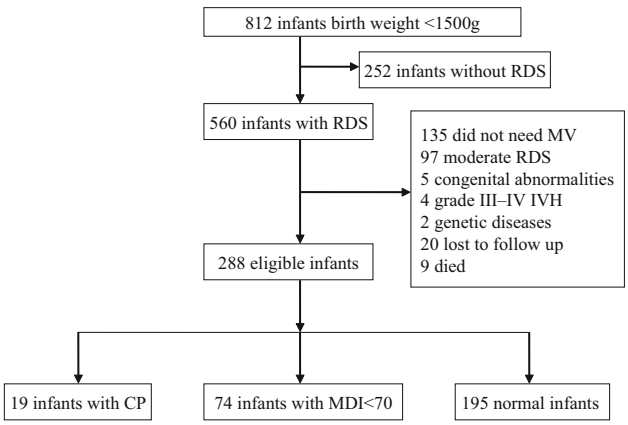

Fig. 1 Overview of study neonates

distress, early bacteremia, late bacteremia, and low weight gain were significantly associated with cerebral palsy or an MDI < 70 ($P < 0.05$) (Table 2). Within the CP groups, more infants were on CMV than on HFOV ($P < 0.05$). In infants with CP or an MDI < 70, the duration of mechanical ventilation was longer than infants without neurodevelopmental disabilities ($P < 0.001$) (Table 3). Less pulmonary surfactant (PS), less methylxanthine, and higher blood transfusions were used on infants that developed CP or an MDI < 70 than on other infants ($P < 0.05$) (Table 3). Co-morbidities associated with CP at 18 months of corrected age were BPD, PVL, seizure, NEC, and IVH grade III–IV ($P < 0.05$), and for the co-morbidities associated with MDI < 70 were IVH grade III–IV, PVL, and BPD (Table 4).

Table 1 Incidence of CP and lower MDI among infants with different gestational ages and birth weights

	Total number	MDI < 70, *n* (%)	CP, *n* (%)
Gestational age			
<28 weeks	70	34 (49)	12 (17)
~30 weeks	98	24 (24)	5 (5)
~32 weeks	120	16 (13)	2 (2)
P value		<0.001	<0.001
Birth weight			
<1000 g	65	30 (46)	10 (15)
~1250 g	105	29 (28)	6 (6)
~1500 g	128	15 (12)	3 (2)
P value		<0.001	0.002

For MDI < 70, the variables gestational age, birth weight, antenatal corticosteroid use, preeclampsia, fetal distress, bacteremia, mechanical ventilation mode (CV/HFOV), surfactant use, BPD, NEC, and IVH grade III–IV were found to be having significant association (Table 5). These variables were further subjected to multiple logistic regression models, and six of them found to have significant risk factors for MDI < 70 (Table 6).

Discussion

In recent decades, use of a relatively new type of ventilation technique, HFOV, has been steadily increasing in the NICUs, particularly for sicker, smaller infants with greater degrees of respiratory compromise. Studies were yet to confirm whether this ventilation technique is better than conventional ventilation especially for the prevention of subsequent neurodevelopmental impairment [16]. The current study performed on preterm Chinese infants showed HFOV to be associated with significantly lower rates of infant mortality and of BPD, indicating its beneficial effect on premature infants. BPD has been associated with poor neurodevelopmental outcome and was the strongest predictor of poor neurodevelopmental outcome in extremely preterm neonates receiving prolonged positive pressure support and having grade III–IV IVH [18] .

The results of the present study also indicated that longer periods of mechanical ventilation are strongly associated with neurodevelopmental impairment in preterm infants with severe RDS. The correlation of duration of

Table 2 Prenatal and postnatal factors associated with lower MDI or CP at a corrected age of 18 months

	Non-CP, $N = 269$	CP, $N = 19$	*P* value	MDI > 70, $N = 214$	MDI < 70, $N = 74$	*P* value
Twins and triplets	73 (27)	8 (42)	0.19	55 (26)	26 (35)	0.13
Cesarean delivery	113 (42)	9 (47)	0.64	88 (41)	34 (45)	0.50
Antenatal corticosteroid	201 (75)	13 (68)	0.001	164 (77)	50 (68)	0.13
Maternal hypertension	78 (29)	7 (37)	0.45	59 (28)	26 (35)	0.24
Preeclampsia	14 (5)	4 (21)	0.02	8 (4)	10 (14)	0.009
Premature rupture of membranes	75 (28)	6 (32)	0.79	57 (27)	24 (32)	0.37
Fetal distress	59 (22)	7 (37)	0.16	41 (19)	25 (34)	0.02
Intrauterine growth retardation	15 (6)	2 (10)	0.31	10 (5)	7 (9)	0.15
Early bacteremia, day 3						
Presumed	20 (7)	3 (16)	0.19	14 (7)	9 (12)	0.14
Definite	7 (3)	4 (21)	0.003	5 (2)	6 (8)	0.04
Late bacteremia, day >3						
Presumed	32 (12)	8 (42)	0.002	24 (11)	16 (22)	0.03
Definite	11 (4)	6 (32)	<0.001	6 (3)	11 (15)	0.001
Weight gain (g)	501 ± 392	367 ± 126	<0.001	542 ± 484	404 ± 231	0.001

Data are expressed as number (%). For weight gain, mean ± SD is mentioned, *t* -test was used

Table 3 Medications and treatment modalities associated with MDI or CP at a corrected age of 18 months

	Non-CP, $N = 269$	CP, $N = 19$	P value	MDI > 70, $N = 214$	MDI < 70, $N = 74$	P value
Mechanical ventilation (days) CMV (%)	3.4 ± 3.0	15.5 ± 11.5	<0.001	3.4 ± 3.1	7.5 ± 7.7	<0.001
	129 (48)	14 (74)	0.03	96 (45)	47 (64)	0.01
HFOV (%)	140 (52)	5 (26)	0.03	109 (51)	40 (49)	0.69
Surfactant (%)	139 (52)	7 (37)	0.24	116 (54)	30 (41)	0.04
Ibuprofen (%)	16 (6)	2 (10)	0.34	13 (6)	5 (7)	0.79
Methylxanthine (%)	174 (65)	8 (42)	0.08	142 (66)	32 (43)	0.001
Blood transfusion (%)	94 (35)	12 (63)	0.02	70 (33)	36 (49)	0.02

Table 4 The co-morbidities associated with MDI or CP at a corrected age of 18 months

	Non-CP, $N = 269$	CP, $N = 19$	P value	MDI > 70, $N = 214$	MDI < 70, $N = 74$	P value
IVH grade III-IV (%)	51 (19)	8 (42)	0.03	36 (17)	23 (31)	0.01
PVL	20 (7)	6 (32)	0.004	14 (7)	12 (16)	0.02
Seizure	2 (1)	3 (16)	0.002	2 (1)	3 (4)	0.11
BPD (%)	49 (18)	8 (42)	0.03	32 (15)	25 (34)	0.001
Necrotizing enterocolitis (%)	10 (6)	3 (14)	0.046	7 (3)	6 (8)	0.10

IVH intracranial hemorrhage, *PVL* periventricular leukomalacia, *BPD* bronchopulmonary dysplasia

Table 5 Relationship of selected Factors with MDI < 70 by univariate logistic regression analysis

	OR	95 % CI	P value
Gestational age	1.38	1.08–1.87	0.038
Birth weight	1.00	1.00–1.01	<0.001
Antenatal corticosteroid	0.60	0.30–1.21	0.152
Preeclampsia	1.09	0.43–5.90	0.487
Fetal distress	0.71	0.35–1.43	0.338
Bacteremia	0.42	0.18–0.96	0.039
Mode of ventilation (CMV/HFOV)	2.14	1.09–4.19	0.027
Mechanical ventilation days	0.89	0.79–0.99	0.033
Surfactant	1.46	0.67–3.08	0.350
BPD	1.87	0.72–4.88	0.201
Necrotizing enterocolitis	2.70	0.92–8.28	0.070
IVH grade III–IV	1.51	0.71–3.21	0.282

Table 6 Multivariate logistic regression analysis of potential risk factors associated with MDI < 70

	OR	95 % CI	P value
Gestational age	1.51	1.14–2.00	0.005
Birth weight	1.01	1.00–1.01	<0.001
Bacteremia	0.39	0.17–0.90	0.027
Mode of ventilation (CMV/HFOV)	2.40	1.27–4.53	0.007
Mechanical ventilation days	0.89	0.80–0.99	0.032
Necrotizing enterocolitis	3.21	1.17–8.79	0.023

mechanical ventilation and neurodevelopmental impairment is probably due to several effects. Mechanical ventilation inducing positive intrathoracic pressure can impede venous return which in turn decreases cardiac preload. Subsequently, cardiac output is compromised and cerebral blood flow fluctuates. Fluctuating cerebral blood flow may have future adverse consequences [3]. In addition, the exchange of carbon dioxide (CO_2) in infants supported by mechanical ventilation is typically manipulated by the managing team using predetermined parameters. However, the impact of overriding an infant's ability to control arterial pressure of CO_2 ($PaCO_2$) on cerebral blood flow has not been studied. The mechanical ventilation was also known to induce lung inflammation [3]. This type of inflammation may trigger a systemic response that can injure the brain and other organs [19]. The sedatives used in these ELBW infants during mechanical ventilation may also have a role in compromised brain development. Premature infants managed with mechanical ventilation suffer from frequent sleep interruptions as well as pain and discomfort during routine procedures such as tracheal suctioning, heel sticks, and blood sampling [3]. The current ventilator alarms are said to significantly exceed the recommended noise level in the NICU and can be hazardous to the developing brain [20]. Other developmental risks related to mechanical ventilation in premature infants

include loss of self-regulatory behaviors to control stress, a delay in oral readiness for feeding, and maternal deprivation caused by the physical limitations of mechanical ventilation. Conversely, individualized strategy and developmentally oriented care premature infants led to a shorter duration of mechanical ventilation, a reduced use of opiates, and earlier discharge from the hospital [21]. Early HFOV may be a feasible strategy for sick infants with greater degrees of respiratory compromise.

This study has some limitations resulting from its retrospective structure. First, the patient inclusion was based on severe RDS need mechanical ventilation and not on all RDS need for invasive mechanical ventilation. This means that not all mechanically ventilated infants were included in the patient cohort. Second, this study was single-center study and was representative of Chinese preterm neonatal population at small. In our study, the duration of mechanical ventilation was shorter in the HFOV group than in CMV group. It may be that changes in the concepts of management will lead to a significant decrease in the number of intubation procedures, and that an even more aggressive approach to earlier extubation will shorten the duration of mechanical ventilation.

In summary, the prognosis of very preterm infants with severe RDS may be influenced by several prenatal and postnatal factors. Longer duration of mechanical ventilation was found to be strongly associated with an increased risk of neurodevelopmental impairment and HFOV mode resulted in decreased days on ventilation. It is worth exploring further whether HFOV decreases the incidence of neurodevelopmental disability. For preterm infants with severe RDS, earlier surfactant administration, optimized ventilation mode, earlier termination of mechanical ventilation, physiotherapy, and music are warranted in order to limit or avoid future neurodevelopmental disability.

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Conflict of interest There is no conflict of interest (COI) statement in this study.

References

1. Moore T, Hennessy EM, Myles J et al (2012) Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. BMJ 345:e7961
2. Koo KY, Kim JE, Lee SM et al (2010) Effect of severe neonatal morbidities on long term outcome in extremely low birthweight infants. Korean J Pediatr 53(6):694–700
3. Ehrenkranz RA, Dusick AM, Vohr BR et al (2006) Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics 117(4):1253–1261
4. Stephens BE, Vohr BR (2009) Neurodevelopmental outcome of the premature infant. Pediatr Clin N Am 56(3):631–646 (Table of contents)
5. Stephens BE, Liu J, Lester B et al (2010) Neurobehavioral assessment predicts motor outcome in preterm infants. J Pediatr 156(3):366–371
6. Kanmaz HG, Erdeve O, Canpolat FE et al (2013) Surfactant administration via thin catheter during spontaneous breathing: randomized controlled trial. Pediatrics 131(2):e502–e509
7. Valcamonico A, Accorsi P, Sanzeni C et al (2007) Mid- and long-term outcome of extremely low birth weight (ELBW) infants: an analysis of prognostic factors. J Matern Fetal Neonatal Med 20(6):465–471
8. Bahadue FL, Soll R (2012) Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database Syst Rev, 11:CD001456
9. Rademaker KJ, de Vries WB (2009) Long-term effects of neonatal hydrocortisone treatment for chronic lung disease on the developing brain and heart. Semin Fetal Neonatal Med 14(3): 171–177
10. Doyle LW, Faber B, Callanan C et al (2006) Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. Pediatrics 118(1):108–113
11. Van Marter LJ, Dammann O, Allred EN et al (2002) Chorioamnionitis, mechanical ventilation, and postnatal sepsis as modulators of chronic lung disease in preterm infants. J Pediatr 140(2):171–176
12. Bae CW, Hahn WH (2009) Surfactant therapy for neonatal respiratory distress syndrome: a review of Korean experiences over 17 years. J Korean Med Sci 24(6):1110–1118
13. Courtney SE, Durand DJ, Asselin JM et al (2002) High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. N Engl J Med 347(9):643–652
14. Miedema M, de Jongh FH, Frerichs I et al (2011) Changes in lung volume and ventilation during lung recruitment in high-frequency ventilated preterm infants with respiratory distress syndrome. J Pediatr 159(2):199–205 (e192)
15. Moriette G, Paris-Llado J, Walti H et al (2001) Prospective randomized multicenter comparison of high-frequency oscillatory ventilation and conventional ventilation in preterm infants of less than 30 weeks with respiratory distress syndrome. Pediatrics 107(2):363–372
16. Ehrenkranz RA, Walsh MC, Vohr BR et al (2005) Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics 116(6):1353–1360
17. Schlapbach LJ, Aebischer M, Adams M et al (2011) Impact of sepsis on neurodevelopmental outcome in a Swiss National Cohort of extremely premature infants. Pediatrics 128(2):e348–e357
18. Trittmann JK, Nelin LD, Klebanoff MA (2013) Bronchopulmonary dysplasia and neurodevelopmental outcome in extremely preterm neonates. Eur J Pediatr 172(9):1173–1180
19. Zwiener U, Walter B, Kratzsch B et al (2003) Marked reduction of brainstem blood flow in artificially ventilated newborn piglets during normoxia and normocapnic hypoxia. Intensive Care Med 29(12):2277–2284
20. Elserafy FA, Alsaedi SA, Louwrens J et al (2009) Oral sucrose and a pacifier for pain relief during simple procedures in preterm infants: a randomized controlled trial. Ann Saudi Med 29(3):184–188
21. Hassanein SM, El Raggal NM, Shalaby AA (2013) Neonatal nursery noise: practice-based learning and improvement. J Matern Fetal Neonatal Med 26(4):392–395