Duration of Mechanical Ventilation and Extubation Success among Extremely Premature Infants

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Research Article

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Short Title: ***Mechanical ventilation duration and extubation success***

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Abstract

Objective: To examine the duration of mechanical ventilation (MV) in days until the first successful extubation and the cumulative duration of MV until discharge of infants with gestational age (GA) < 26 weeks. We also aimed to explore associations between early clinical variables and the cumulative duration of MV.

Design and setting: This population-based study analysed data reported to the Norwegian Neonatal Network on extremely premature infants admitted between 1 January 2013 and 31 December 2018.

Results: A total of 406 infants were included, of which 293 (72%) survived to discharge. The proportion successfully extubated on their first attempt was 34% of infants born at GA 22-23 weeks, 50% at GA 24 weeks, and 70% at GA 25 weeks. Median postmenstrual age (PMA) at the first successful extubation was 27 weeks. The median duration of MV was 35, 24 and 12 days for infants born at GA 22-23, 24 and 25, respectively. Male sex and low 5-minute Apgar score were independent early predictors for prolonged MV duration adjusted for GA in regression analyses.

Conclusions: Most of the infants born at GA 25 were successfully extubated on the first attempt. However, half of the infants born < 26 weeks experienced unsuccessful extubations, indicating a lack of useful clinical predictors of successful extubation. The median duration of MV in survivors was four weeks longer for infants at GA 22-23 compared to infants born at GA 25, while the difference in median PMA at the first successful extubation was two weeks.

Introduction

Mechanical ventilation (MV) is inevitable for most extremely premature (EP) infants with respiratory distress after birth [1,2]. Among infants with gestational age (GA) below 26 weeks in Norway, 93% received MV within the first 72 hours after birth, and 98% received MV at some point during the entire hospital stay [1]. Prolonged MV in premature infants has been associated with adverse outcomes including infection, bronchopulmonary dysplasia (BPD), death and neurodevelopmental impairment at 12-22 months of age has [3,4,5]. Hence, clinicians strive for early weaning from MV to reduce the risk of adverse outcomes. Although variations exist in ventilation practices among Norwegian Neonatal Intensive Care Units (NICU), there is a shared approach to minimise and deliver gentle MV with volume targets of 5-7 ml/kg and oxygen saturation targets of 90- 94%. Non-invasive ventilation modes are preferred both early after birth and after extubation if the infant is considered ready [6,7]. To minimise duration of MV it is important to identify the optimal time for extubation. However, extubation failure and re-initiation of MV in premature infants is common [8]. Lower GA, lower birth weight (BW) and male sex are factors associated with longer cumulative duration of MV (cMV) and a higher number of ventilator courses [9].

The aim of our study was to examine duration of MV in days until the first successful extubation, and the cMV until discharge home. We also aimed to explore associations between cMV and early clinical variables, such as GA, growth restriction at birth, illness severity score at birth (Critical Risk Index for Babies, CRIB II) and Apgar score.

Methods

This population-based study examined data reported to the Norwegian Neonatal Network (NNN) on EP infants born between 1 January 2013 and to 31 December 2018. Data on all patients admitted to any Norwegian NICU (n = 20) are collected daily by trained staff and entered into NNN`s electronic registration platform. NNN contains anthropometric and demographic data, detailed data on

resuscitation, treatment modalities, treatment procedures, diagnoses, outcome parameters and status at discharge.

Participants

Register records of infants with GA < 26 weeks were screened for eligibility. Infants alive at 12 hours of age, who received MV at any time during their NICU stay were included. All subjects were followed from birth until death or discharge home.

Explanatory variables and definitions

Only variables available in the NNN were retrieved and analysed. Perinatal variables included antenatal steroids, delivery method and single/multiple births. Antenatal corticosteroids were defined as a complete course if the mothers had received at least 2 doses and 24 hours had passed since the first dose [10]. Anthropometric and demographic variables included GA, BW and sex. For most infants, GA was calculated based on ultrasound. If no foetal ultrasound before 20 weeks' gestation was available, GA was based on the last menstrual period. Small for gestational age (SGA) was defined as birth weight below the 10^{th} centile [11]. Variables for illness severity scores included the clinical risk index for babies (CRIB II) score and 5-minute Apgar score.

Variables related to treatment in the delivery room and in the NICU included endotracheal intubation, administration of surfactant through the endotracheal tube or by less-invasive surfactant administration (LISA), postnatal corticosteroids, and surgical or medical treatment of patient ductus arteriosus (PDA). Variables relevant to intubation and extubation included postnatal age (PNA) and postmenstrual age (PMA) at extubation attempt. An intubation event was defined if nasal or oral intubation was registered in combination with conventional or high frequency ventilation at the same treatment day. LISA was not considered as an intubation event. Successful extubation was defined as not being reintubated within 72 hours. The cMV was counted as each registered hour the infant received respiratory support through an endotracheal tube.

Statistical Analysis

Statistical analysis was performed using SPSS 26.0 software (SPSS Inc., Chicago, IL, USA). Demographic data were expressed as numbers with proportions (%), means with standard deviation (SD) or medians with 25^{th} and 75^{th} percentiles (interquartile range (IQR)). The included infants were

categorised into three groups based on GA at birth. Group 1: GA 22^0-23^6, group 2: GA 24^0-24^6 and group 3: GA 25^0-25^6. Age at successful extubation and cMV were explored for these three groups.

Only infants who survived until discharge from the NICU were included in the analyses of duration of MV and extubation outcome. Infants registered with tracheostomy were excluded from the analysis of the cMV to ensure data quality to describe MV vs. Continuous Positive Airway Pressure. When exploring age at successful extubation, infants who were never successfully extubated were excluded.

Independent t-test was used to examine differences between subgroups. Infants were categorised into subgroups according to illness severity scores at birth. Infants with CRIB II score ≥ 14 were compared to infants with CRIB II score < 14. Infants with 5-minute Apgar score ≥ 5 were compared to infants with 5-minute Apgar score < 5. Linear regression was used to identify explanatory variables with *p*-values < .20 to be included in a multiple linear regression model with cMV as the dependent variable. Kaplan-Maier-curves with log rank tests were used to compare time-to-event variables such as age at the first successful extubation. P-values < .05 were considered statistically significant.

Results

Patient characteristics

Of 482 infants admitted to a NICU, 449 met the eligibility criteria. However, 43 (9.6%) were excluded as mother's address could not be verified or the mothers chose to opt out (Fig. 1). There were no statistically significant differences in GA, BW or mortality before discharge in included infants compared to those not included (data not shown).

The characteristics of the 406 subjects and details of peri- and postnatal interventions are displayed in Table 1. Characteristics of surviving and non-surviving infants are provided in supplementary Table 1. Of included infants, 72% survived until discharged home. Median GA was 24.4 weeks (IQR, 23.6-25.2) and there was no difference in GA between survivors and non-survivors in either of the three groups. Most infants received antenatal steroids, whereas only 58% received a complete course. Practically all infants (98%) received surfactant before 30 minutes of age, with no differences between gestational weeks or survivors and non-survivors. LISA was applied more commonly among survivors at GA 24 and 25 compared to infants at GA 22-23. Systemic postnatal corticosteroid treatment for BPD was administered to 61 of 67 (91%) infants at GA 22-23 who survived to discharge and to 78 of 97 (80%) and 65 of 129 (50%) of infants at GA 24 and 25, respectively. A tracheostomy was performed on 8 (3%) of the surviving infants. Two infants were discharged home with a

tracheostomy and were never successfully extubated. Neonatal morbidity rates are displayed in supplementary table 1.

Duration of mechanical ventilation and extubation outcome

Median duration of MV among surviving infants was 4 weeks longer for the most immature infants compared to infants born at GA 25. For infants successfully extubated (n=291), age at intubation and extubation events, and total number of extubation attempts and MV courses are presented in Table 2. The first extubation attempt was at a higher PNA for the most immature infants, compared to infants born at GA 24 and 25. PNA in weeks at the first successful extubation for infants at GA 22-23, 24 and 25 were 5 (95% CI: 4.1-5.4), 3 (95% CI: 2.5-3.2) and 1 (95% CI: 0.5-1.2) respectively (Fig. 2a). The median PMA at the first successful extubation for infants born at GA 22-23 (28 weeks, 95% CI: 27.3-28.7) was 2 weeks longer than the median for those born at GA 25 (26 weeks, 95% CI: 25.9-26.7) (Fig. 3a). When successful extubation was defined as 72 hours without reintubation, 34% of infants at GA 22-23 were successfully extubated on their first attempt compared to 50% and 70% for those born at GA 24 and 25, respectively. We also performed analyses for 7 days without reintubation (Fig. 2b and 3b). Comparing the 72-hour and 7-day time frames, PNA at the first successful extubation was equal in 88%, 80% and 82% of infants born at GA 22-23, 24 and 25, respectively.

Male infants, SGA infants, infants with CRIB II score > 14 and infants with 5-minute Apgar score < 5 had significantly longer cMV compared to their counterparts. When corrected for GA in multiple regression analyses, male sex and low 5-minute Apgar scores remained strongly associated with prolonged MV (Table 3).

Discussion

In this study, the proportion successfully extubated on their first attempt was 34% of infants born at GA 22-23 weeks, 50% at GA 24 weeks, and 70% at GA 25. Previously, Chawla et al. demonstrated extubation without the need for reintubation within 5 days in 58% of premature infants < 28 weeks GA [8], while Gupta et al. reported a success rate of 73% in infants with birth weights ≤ 1250 g, with a similar 5-day extubation failure criterion [12]. However, heterogeneity when defining successful extubation in EP infants makes comparisons with previous results challenging [13]. We defined successful extubation as 72 hours without reintubation to prevent inclusion of extubations that failed for non-respiratory reasons. Moreover, we performed analyses comparing different observation windows as a recent study reported that most respiratory-related reintubations occurred within 7 days of extubation [14]. Age at first successful extubation was identical for 80% of the infants regardless of the used definition (72 hours vs. 7days).

Our findings raise questions about the role of timing of the first extubation and respiratory outcomes. Infants born at GA 25 were generally extubated successfully upon their first attempt during the first week of life. In contrast, the smallest infants were kept longer on MV before clinicians decided to extubate, and they usually had at least one failing attempt prior to successful extubation. These findings might suggest that both prolonged MV and need for reintubation independently affect respiratory outcomes, and that clinicians might hesitate too long prior to the first extubation attempt among the smallest infants.

Most infants in this study were intubated immediately after birth for surfactant administration. European consensus guidelines recommend surfactant given early in the course of the disease and LISA as the preferred mode of administration for spontaneously breathing EP infants <28 weeks who are stable on CPAP [15]. The relatively low proportion with LISA in our study may reflect that the most immature infants are less likely to be spontaneously breathing immediately after birth, or clinicians consider primary intubation a safer approach.

Similar to other investigators, we found that cMV was negatively associated with lower GA, male sex and low 5-minute Apgar scores [8,9,16]. Moreover, the most premature infants (GA 22-23 weeks) needed MV to a higher PMA compared to infants born at GA 25 weeks, suggesting that other factors than immaturity per se may have significant impact on the duration of MV. Lower GA is strongly associated with severe neonatal morbidities, implying a risk of increased exposure to invasive procedures and intensive care, which in turn, is likely to negatively affect lung maturation and extubation readiness [2,17]. Additionally, rates of surgical or medical treatment for a PDA were higher among infants born at GA 22-23 and 24 weeks compared to infants born at GA 25 weeks. Whether presence of a hemodynamically significant PDA could explain delayed extubation attempts in the more immature infants is not possible to answer based on the available data in our study. Presumably, several postnatal factors such as reintubation and neonatal morbidities, independently influence the respiratory outcome and require further investigation.

The duration of MV among infants in the present study was notably lower than the duration reported for comparable infants in a retrospective population-based study by Wilson et al., which is the only study we have found that provides GA-specific duration of MV [18]. However, the Wilson study was completed during the 1990s when treatment strategies for EP infants were different. Practices of MV is constantly evolving and our results must be interpreted according to the time period the study was performed.

Our study has certain limitations. Firstly, we were not able to distinguish between planned and unplanned extubations. Self-extubations are common in the NICU, and the length of time intubated

is reported as an independent predictor of such events [19]. Self-extubations may more often lead to reintubations, which could have contributed to more reintubations among the smallest infants in our study. Secondly, we were not able to provide information directly related to the infants' clinical condition surrounding the extubation events, as this study was based solely on register data. Future studies including detailed clinical pre-, and post extubation variables are warranted in order to improve prediction of successful extubations in EP infants. Nevertheless, this population-based study provides a valuable description of a large sample size, representing all NICUs in Norway. Although some infants were not included because of the opt-out provision or inability to find an address, the inclusion rate exceeded 90%, and the analyses showed no significant difference between excluded and included infants. This indicate that studying the total population would not have altered the results.

Conclusion

Our study reports age at the time of successful extubation among EP infants < 26 weeks GA. Infants born at the lowest GA received MV to a higher PMA, compared to infants born at GA 25. Additional research is needed to increase the ability to predict when a preterm infant can be considered ready for extubation with the highest chance of success. To strengthen the clinical assessment regarding extubation readiness among the most premature infants, it is crucial to understand the what predicts success and failure regarding extubation of EP infants.

Acknowledgement

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Statement of Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (REC north) with reference number: 2018/1346. An information letter describing the purpose of the study was distributed to the infants' mothers, with an opt-out alternative. An infant was automatically enrolled in the study if the mother did not respond to the letter within four weeks to decline participation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

MOO conceptualised and designed the study; contributed to the data acquisition, database preparation, statistical analyses and interpretation of the results; and wrote the initial and subsequent drafts of the manuscript. HJS contributed to study design, data acquisition, statistical analyses, interpretation of the results and drafting of the manuscript. CRT contributed to study design, statistical analyses, interpretation of the results and critical revision of the manuscript. AER conceptualised, designed and supervised the study; contributed to data acquisition, statistical analyses, and interpretation of the results; and drafting of the manuscript; all approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Figure Legends

Fig. 1. Flow diagram of participant inclusion in the study

Fig. 2a. Postnatal age in weeks at the first successful extubation with extubation success defined as 72 hours without reintubation. Kaplan-Maier survival curve shows the proportion of infants still mechanically ventilated in the three GA groups (LogRank, p=<.001).

Fig.2b. Postnatal age in weeks at the first successful extubation with extubation success defined as 7 days without reintubation. Kaplan-Maier survival curve shows the proportion of infants still mechanically ventilated in the three GA groups (LogRank, p=<.001)

Fig. 3a. Postmenstrual age at the first successful extubation with extubation success defined as 72 hours without reintubation. Kaplan-Maier survival curves show the proportion of infants still mechanically ventilated in the three GA groups (LogRank, p=.054)

Fig. 3b. Postmenstrual age at the first successful extubation with extubation success defined as 7 days without reintubation. Kaplan-Maier survival curves show the proportion of infants still mechanically ventilated in the three GA groups (LogRank, p=.338)

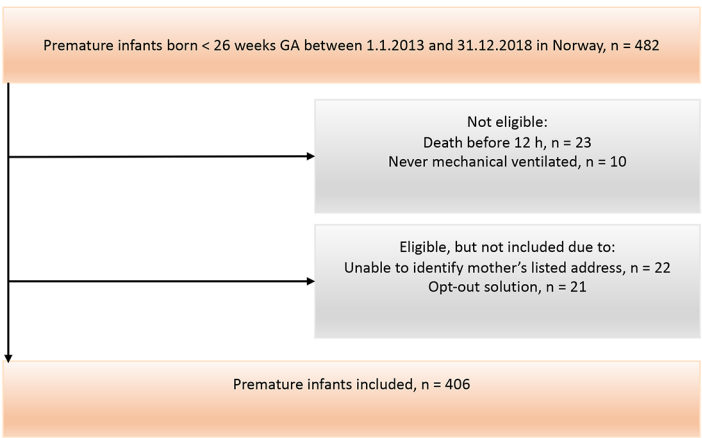
Premature infants born < 26 weeks GA between 1.1.2013 and 31.12.2018 in Norway, n = 482
Not eligible:
Death before 12 h, n = 23
Never mechanical ventilated, n = 10
Eligible, but not included due to:
Unable to identify mother's listed address, n = 22
Opt-out solution, n = 21
Premature infants included, n = 406

Table 1: Demographics of live-born infants at gestational age 22^0-25^6 with characteristics of peri- and postnatal interventions

Characteristics	**GA 22^0-23^6 (n=111)**	**GA 24^0-24^6 (n= 143)**	**GA 25^0-25^6 (n=152)**	**Total (n= 406)**
Birthweight, mean gram (SD)	556 (70)	658 (91)	743 (147)	658 (133)
Male, n (%)	63 (57)	76 (53)	77 (51)	216 (53)
Singleton, n (%)	71 (64)	106 (74)	116 (76)	293 (72)
AGA, n (%)	90 (81)	117 (82)	125 (82)	332 (82)
SGA, n (%)	21 (19)	26 (18)	27 (18)	74 (18)
Caesarean delivery, n (%)	15 (14)	40 (28)	67 (44)	122 (30)
ANS any exposure (both partial and complete), n (%)	95 (86)	137 (96)	146 (96)	378 (93)
ANS complete course, n (%)[1]	55/105 (52)	75/139 (66)	94/143 (66)	224/387 (58)
CRIB II score, mean (SD)	16 (1)	14 (1)	13 (2)	14 (2)
Apgar score at 5 min, median (% below 5)	6 (25)	6 (23)	7 (16)	6 (21)
Infants dead prior discharge from the NICU, n (%)	44 (40)	46 (32)	23 (15)	113 (28)
Treatment in the delivery room/NICU				
Surfactant administered before 30 minutes of age, n (%)[2]	106/109 (97)	139 (97)	151/151 (100)	396/403 (98)
LISA, n (%)[3]	3 (3)	8 (6)	26 (17)	37 (9)
Surfactant after delivery room, n (%)[2]	42 (38)	73 (51)	61 (40)	176 (43)
Postnatal corticosteroids for BPD, n (%)	70 (63)	89 (62)	68 (45)	227 (56)
Surgical ligation of PDA, n (%)	7 (6)	12 (8)	4 (3)	23 (6)
Indomethacin or ibuprofen for PDA, n (%)	55 (50)	74 (52)	55 (36)	184 (45)
Tracheostomy, n (%)	6 (5)	4 (3)	2 (1)	12 (3)
cMV, median days (IQR)[4]	35 (28-50)	24 (16-36)	12 (5-25)	23 (10-35)

GA, Gestational Age; SD, standard deviation; AGA, appropriate for gestational age; SGA, small for gestational age; ANS, antenatal steroids; CRIB, Clinical Risk Index for Babies; NICU, Neonatal Intensive Care Unit; BPD, Bronchopulmonary dysplasia; PDA, patient ductus arteriosus; IQR, interquartile range

[1] ANS complete course: defined when the first dose was administered at least 24 h before birth. Time of first dose was not registered in 19 (4.7%) infants.

[2]Time of surfactant administration was not registered in 3 (0.7%) infants.

[3]Administration of surfactant in the delivery room with use of less invasive teqnique.

[4]Infants dead prior discharge from the neonatal intensive care unit, and infants registered with tracheostomy were excluded from the analysis.

Table 2: Age at intubation and extubation events, number of extubation attempts and total mechanical ventilation courses among surviving infants

Characteristics[1]	**GA 22^0-23^6 n= 67**	**GA 24^0-24^6 n= 95**	**GA 25^0-25^6 n= 129**
Infants intubated first day of life, n (%)	65 (97)	84 (87)	104 (81)
PNA at intubation, median minutes (IQR)[2]	5 (3-9)	5 (3-10)	5 (0-9)
PNA at first extubation attempt, median days (IQR)	20 (10-32)	7 (3-20)	5 (1-10)
Number of extubation attempts prior first successful extubation, median attempts (IQR)	1 (0-2)	0 (0-1)	0 (0-1)
Total MV runs, median number (IQR)	3 (2-4)	2 (2-4)	2 (2-3)
PNA at first successful extubation, median days (IQR)	33 (23-43)	21 (7-32)	7 (2-19)
PMA at first successful extubation, median weeks (IQR)	28 (27-29)	27 (25-29)	26 (26-28)

PNA, postnatal age; IQR, interquartile range; PMA, postmenstrual age; MV, mechanical ventilation.
[1]Infants never identified as successfully extubated were excluded from the analyses (n=2, 0.7%)
[2]Registered time for intubation of infants intubated in the delivery room

Table 3: Duration of mechanical ventilation and characteristics of infants who survived to discharge[1]

Characteristics		Regression analysis Unadjusted			Regression analysis Adjusted[2]		
		Cumulative duration MV, mean days	Regression coefficient (CI)	*p*-value	Cumulative duration MV, estimated mean days	Regression coefficient (CI)	*p*-value
Gender	Male	27.9			34.2		
	Female	21.4	6.5 (2.6,10.4)	.001	27.7	5.8 (6.1,15.4)	< .001
Growth at birth	SGA	29.5			32.0		
	AGA	23.4	6.1 (1.0, 11.1)	.018	29.9	2.7 (-1.6,6.9)	.332
CRIB	CRIB >=14	30.5			30.7		
	CRIB <14	17.6	13.1 (9.3,16.9)	< .001	31.2	-1.1 (-5.8,3.6)	.840
Apgar	Apgar >=5	22.7			26.4		
	Apgar <5	33.2	-10.4 (-15.5,-5.4)	< .001	35.5	-9.5 (-13.7,-5.2)	< .001
ANS	No ANS treatment	26.8			32.1		
	ANS treatment	22.7	-4.1 (-8.1,-.05)	.048	30.5	-1.6 (-5.0,1.8)	.369

SGA, small for gestational age; AGA, appropriate for gestational age; CRIB, Clinical Risk Index for Babies; ANS, antenatal steroids

[1] Infants registered with tracheostomy during admission in the NICU were excluded from the analyses (n = 8).

[2]Corrected for gestational age.

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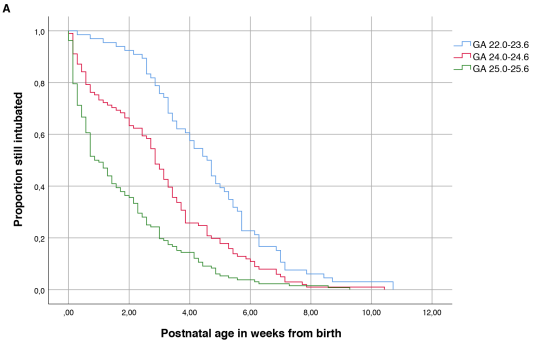
Proportion still intubated
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0,8
0,6
0,4
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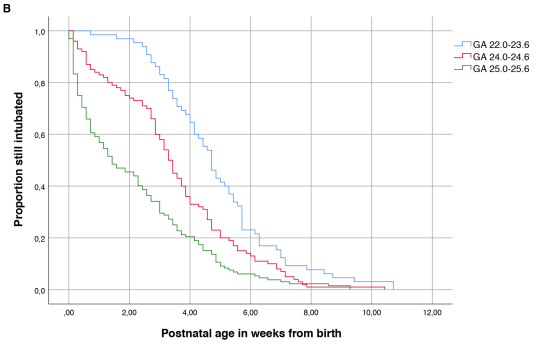
0,0
,00
2,00
4,00
6,00
8,00
10,00
12,00
Postnatal age in weeks from birth
GA 22.0-23.6
GA 24.0-24.6
GA 25.0-25.6

B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0,8
0,6
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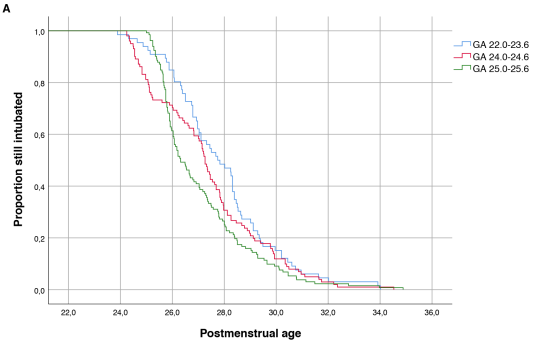
6,00
8,00
10,00
12,00
Postnatal age in weeks from birth
GA 22.0-23.6
GA 24.0-24.6
GA 25.0-25.6

A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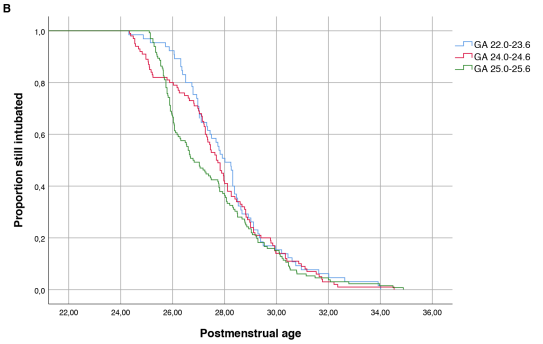
0,6
0,4
0,2
0,0
22,0
24,0
26,0
28,0
30,0
32,0
34,0
36,0
Postmenstrual age
GA 22.0-23.6
GA 24.0-24.6
GA 25.0-25.6

B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0,2
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22,00
24,00
26,00
28,00
30,00
32,00
34,00
36,00
Postmenstrual age
GA 22.0-23.6
GA 24.0-24.6
GA 25.0-25.6

Supplementary table 1: Demographics of live-born infants at gestational age 22^0-25^6 with characteristics of peri- and postnatal interventions

Characteristics	GA 22^0-23^6 (n=111)		GA 24^0-24^6 (n= 143)		GA 25^0-25^6 (n=152)		Total (n= 406)	
	Survivors (n=67)	Non-survivors (n=44)	Survivors (n=97)	Non-survivors (n=46)	Survivors (n=129)	Non-survivors (n=23)	Survivors (n = 293)	Non-survivors (n = 113)
Birthweight, mean gram (SD)	551 (75)	565 (61)	645 (79)	685 (109)	752 (138)	690 (182)	671 (135)	639 (128)
Male, n (%)	34 (51)	29 (66)	50 (52)	26 (57)	62 (48)	15(65)	146 (50)	70 (62)
Singleton, n (%)	45 (67)	26 (59)	73 (75)	33 (72)	101(78)	15 (65)	219 (75)	74 (66)
AGA, n (%)	52 (78)	38 (86)	77 (79)	40 (87)	109 (85)	16 (70)	238 (81)	94 (83)
SGA, n (%)	15 (22)	6 (14)	20 (21)	6 (13)	20 (16)	7 (30)	55 (19)	19 (17)
Caesarean delivery, n (%)	10 (15)	5 (11)	23 (24)	17 (37)	58 (45)	9 (39)	91 (31)	31 (27)
ANS any exposure (both partial and complete), n (%)	59 (88)	36 (82)	96 (99)	41(89)	123 (95)	23 (100)	278 (95)	100 (89)
ANS complete course, n (%)[1]	33/63 (52)	22/42 (52)	54/93 (58)	21(46)	80/121 (66)	14/22 (64)	167/278 (60)	57/109 (52)
CRIB II score, mean (SD)	16 (1)	16 (2)	14 (1)	14 (2)	13 (2)	14 (2)	14 (3)	15 (2)
Apgar score at 5 min, median (% below 5)	6 (24)	6 (27)	6 (19)	6 (33)	7 (14)	6 (30)	7 (18)	6 (30)
Postnatal age death, median days (IQR)	N.A.	8 (2-16)	N.A.	8 (2-26)	N.A.	9 (3-33)	N.A.	8 (2-21)
Treatment in the delivery room/NICU								
Surfactant administered before 30 minutes of age, n (%)[2]	65/66 (97)	41/43 (93)	95 (98)	44 (96)	128/128 (100)	23 (100)	288/291 (99)	108/112 (96)
LISA, n (%)[3]	1(2)	2(5)	7(7)	1(2)	25(19)	1(4)	33(11)	4(4)
Surfactant after delivery room, n (%)[2]	21 (31)	21(48)	46 (47)	27 (59)	54(41)	7 (30)	121 (41)	55 (49)
Postnatal corticosteroids for BPD, n (%)	61 (91)	9 (21)	78 (80)	11 (24)	65 (50)	3 (13)	204 (70)	23 (20)
Surgical ligation of PDA, n (%)	7 (10)	0 (0)	10 (10)	2 (4)	4 (3)	0 (0)	21 (7)	2 (2)
Indomethacin or ibuprofen for PDA, n (%)	42 (63)	13 (30)	61 (63)	13 (28)	50 (39)	5 (22)	153 (52)	31 (27)
Tracheostomy, n (%)	3 (5)	3 (7)	3 (3)	1 (2)	2 (2)	0 (0)	8 (3)	4 (4)
cMV, median days (IQR)[4]	35 (28-50)	7 (2-12)	24 (16-36)	7 (2-17)	12 (5-25)	4 (2-11)	23 (10-35)	6 (2-14)

GA, Gestational Age; SD, standard deviation; AGA, appropriate for gestational age; SGA, small for gestational age; ANS, antenatal steroids; CRIB, Clinical Risk Index for Babies; IQR, interquartile range; ETT, endotracheal tube; BPD, Bronchopulmonary dysplasia; PDA, patient ductus arteriosus

[1] ANS complete course: defined when the first dose was administered at least 24 h before birth. Time of first dose was not registered in 19 (4.7%) infants.

[2]Time of surfactant administration was not registered in 3 (0.7%) infants.

[3]Administration of surfactant in the delivery room with use of less invasive teqnique

[4]Infants registered with tracheostomy were excluded from the analysis.

Supplementary table 2: Frequency distribution of neonatal morbidities among live-born infants at gestational age 22^0-25^6

Neonatal morbidities	GA 22^0-23^6 (n=111)		GA 24^0-24^6 (n= 143)		GA 25^0-25^6 (n=152)		Total (n= 406)	
	Survivors (n=67)	Non-survivors (n=44)	Survivors (n=97)	Non-survivors (n=46)	Survivors (n=129)	Non-survivors (n=23)	Survivors (n = 293)	Non-survivors (n = 113)
Intraventricular haemorrhage[1], any bleed, n (%)	35 (52)	29 (66)	40 (41)	25 (54)	45 (35)	10 (44)	120 (41)	64 (57)
Severe intraventricular haemorrhage[1], Papile grade 3-4, n (%)	5 (8)	21 (48)	12 (12)	16 (35)	9 (7)	4 (17)	26 (9)	41 (36)
Bronchopulmonary dysplasia[2], n (%)	58 (87)	3 (7)	72 (74)	3 (7)	77 (60)	1 (4)	207 (71)	7 (6)
Necrotizing enterocolitis[3], Bell stage 2-3, n (%)	13 (19)	4 (9)	8 (8)	6 (13)	8 (6)	4 (17)	29 (10)	14 (12)
Microbiologically verified sepsis[4], n (%)	35 (52)	11(25)	38 (39)	12 (26)	43 (33)	5 (22)	116 (40)	28 (25)
Retinopathy of prematurity[5], grade 3-5, n (%)	20 (30)	1 (2)	29 (30)	2 (4)	21 (16)	1 (4)	70 (24)	4 (4)

GA, Gestational Age

[1]Intraventricular haemorrhage (IVH) was defined according to Papile et al. as the most severe cranial ultrasonogram registered before hospital discharge or death, with severe IVH defined as grade 3-4 (Papile et al., 1978)

[2]Bronchopulmonary dysplasia (BPD) was defined as the need for supplemental oxygen or respiratory support at PMA 36 weeks, corresponding to moderate-to-severe BPD(Jobe & Bancalari, 2001)

[3]Necrotizing enterocolitis (NEC) was defined according to Bell stage 2 or 3 (Bell et al., 1978)

[4] Sepsis was diagnosed as the growth of bacteria in blood culture. Cases with a growth of coagulase-negative staphylococci additionally required a C-reactive protein ≥ 10 mg/L during treatment for at least 5 days

[5] Severe retinopathy of prematurity (ROP) was defined as stage 3 to 5 according to the International Committee for the Classification of Retinopathy of Prematurity (International Committee for the Classification of Retinopathy of Prematurity, 2005)