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REGULAR ARTICLE

Premature infants born at <25 weeks of gestation may be compromised by currently recommended resuscitation techniques

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ABSTRACT

Aim: Standard resuscitation guidelines are based on data from a range of gestational ages. We sought to evaluate the effectiveness of our delivery room resuscitation protocol across a range of gestational ages in preterm infants born at <29 weeks.

Methods: We performed an observational study of prospectively collected video recordings of 73 preterm infants. The percentage of bradycardic patients, time to reach target oxygen saturation and the extent of all interventions were compared between three gestational age groups: 22–24 weeks (n = 22), 25–26 weeks (n = 27) and 27–28 weeks (n = 24).

Results: Although the same resuscitation protocol was followed for all infants, bradycardic infants born <25 weeks responded poorly and required significantly longer to reach oxygen saturation targets of >70%, >80% and >90% ($p < 0.03$). They required significantly more interventions and had higher rate of death ($p < 0.05$) and severe intraventricular haemorrhage ($p < 0.03$). Significantly lower heart rate and oxygen saturation values were found in infants with intraventricular haemorrhage.

Conclusion: Current recommendations for resuscitation may fail to achieve timely lung aeration in infants born at the borderline of viability, leading to higher mortality and morbidity. Sustained inflation and delayed cord clamping may be effective alternatives.

INTRODUCTION

Most very premature infants with spontaneous breathing activity can be stabilised effectively by continuous positive airway pressure (CPAP) support without the need for intubation or surfactant therapy. However, immaturity of the respiratory system, weakness of the breathing muscles and concomitant foetal inflammation or hypoxia may compromise spontaneous aeration of lungs and lead to a need for positive pressure ventilation (PPV) or endotracheal intubation (1). The extent of these interventions is inversely related to gestational age (2). However, previous studies have indicated that reception of delivery room resuscitation was associated with a higher incidence of intraventricular haemorrhage (IVH) (3,4) and chest compressions and epinephrine administration were prognostic markers for higher mortality and neurodevelopmental impairment in extremely low gestational age newborns (ELGANs) (5).

A later study (6) showed that the premature infants requiring intubation or bag-mask resuscitation had disturbances in cerebral energy substrate delivery and oxidative metabolism. Seemingly, the avoidance of these interventions may be the key for reduction of morbidity and mortality. However, the resuscitation protocol was not described precisely and detailed information about the effectiveness of provided interventions was lacking in these studies. Without this information, we are not able to understand the impact the ineffectiveness of resuscitative interventions on morbidity and mortality in fragile ELGANs who require these interventions in the delivery room. After the introduction of evidence-based delivery room guidelines, the quality of delivery room resuscitation improved in very preterm infants (7) even though the last International Liaison Committee on Resuscitation (ILCOR) recommendations (8) were less clearly elucidated for this group of infants and evaluation of their effectiveness has been lacking, especially in very tiny extremely preterm infants. It has been observed that the suggested timing for some interventions seems to be too short (9) and neonatal

Key notes

- This study compared the effectiveness of conventional resuscitation guidelines in 73 infants below 29 weeks of gestational age.
- Oxygen saturation (SpO_2) was effectively achieved in infants of at least 25 weeks, but younger infants took longer to reach the target heart rate and SpO_2 values were associated with higher mortality and intraventricular haemorrhage.
- New approaches using initial prolonged inflation and delayed cord clamping following lung aeration should be investigated.

caregivers often deviate from these resuscitation guidelines (10). Although the consensus to keep the heart rate (HR) and oxygen saturation (SpO_2) values between the 10th and 90th percentiles is now widely accepted, our practice and skills using current techniques and instruments may not be always effective enough to achieve safe oxygenation in a timely manner, especially in ELGANs. We conducted an observational study of prospectively collected data to compare the effectiveness of delivery room interventions performed according to the same resuscitation protocol in three gestational age groups of ELGANs, including a group of infants delivered at 22–24 weeks of gestation.

METHODS

The study was conducted at the tertiary perinatal centre of the General Faculty Hospital in Prague. Approximately 4500 infants are born, and more than 120 infants <1500 g are admitted into the neonatal intensive care unit annually. The data were prospectively collected from January 2011 to June 2012. All the inborn ELGANs <29 weeks, except those born precipitously, were placed immediately after delivery into a specially modified mobile resuscitation warmer bed (ALFAMEDIC sro, Lisov, Czech Republic) with two cameras attached to the frame. In the case of multiple births, only one infant was recorded. We follow an internal standardised protocol for resuscitation of ELGANs, created on the background of current knowledge and evidence and principally based on the last ILCOR recommendations (8). The resuscitation procedure was provided by a clinical team, which usually included a neonatal specialist, a fellow and at least two neonatal nurses. The percentages of bradycardic infants at each time point and the times to reach the target SpO_2 values were recorded as variables reflecting the effectiveness of resuscitation. The extent of delivery room interventions, death and rates of severe morbidity were also noted and compared between three gestational age groups of ELGANs: 22 + 0–24 + 6 weeks, 25 + 0–26 + 6 weeks and 27 + 0–28 + 6 weeks. Information concerning the study and the proactive approach in infants at 22–24 weeks of gestation was provided, and a written informed consent was signed by the mother.

Resuscitation procedure

The infants were covered with a plastic wrap (NeoWrap; Fischer Paykel Ltd., Oakland, New Zealand) and placed into the resuscitation bed. A pulse oximeter sensor was placed on the right wrist as soon as possible and connected to a Massimo pulse oximeter with set at a two second averaging interval (Massimo Radical-7®; Massimo Corporation, Irvine, CA, USA). Auscultation of HR was the first method to identify a bradycardic patient and was repeated every 30 seconds until a valid pulse oximetry signal with a good plethysmographic curve appeared. Ventilatory support was provided exclusively by a Neopuff Infant T-piece Resuscitator (Neopuff™; Fischer Paykel Ltd.). Primary settings for the T-piece were as follows: gas flow of 10 L/minute, positive inflation pressure (PIP) of 25 cm H_2O and positive end-expiratory pressure (PEEP) of 6 cm H_2O. The recommended frequency of PPV was 40–60/minute, sustained inflation was not routinely used with the initiation of PPV, and CPAP and PPV with PEEP were provided either via a soft silicone face mask size 00 (Laerdal Medical, Stavager, Norway) or via an Argyle CPAP rubber bi-nasal cannula of X-small or small size (Argyle CPAP Nasal Cannula, Mansfield, Covidien) (11). To minimise leaks during nasal support, the nasal cannula leafs were fixated on the upper jaw by the thumb and the second finger and the mouth was closed by a lower jaw thrust using the other fingers of the left hand. All infants received CPAP initially. PPV with PEEP was only initiated if: bradycardia <100 beats per minute (bpm) continued more than 60 seconds after cord clamping while CPAP was being administrated and spontaneous breathing was stimulated. Intubation was indicated if: (i) bradycardia without any fluctuations above 100 bpm persisted despite more than 90 seconds of PPV with PEEP, (ii) poor spontaneous breathing activity requiring PPV with PEEP was not sufficient to achieve a target range of SpO_2 after six minutes of life, and (iii) external cardiac compressions were needed. Surfactant, 100–200 mg/kg of Curosurf® (Chiesi Farmaceutici S.p.A.), was administered to all infants intubated in the delivery room. Fraction of inspired oxygen (FiO_2) was commenced at 0.30 and subsequently titrated in 0.10–0.20 increments every 30–60 seconds if (i) the preductal SpO_2 value was outside the defined time-related range (an increasing trend between 60 and 85% at two to six minutes, then between 80 and 93%), or (ii) if HR <100/minutes persisted for more than a minute after the initiation of PPV. If bradycardia <60/minutes lasted for more than 30 seconds a switch to the use of FiO_2 1.0 was suggested. Infants stabilised with CPAP and infants extubated in the delivery room were connected to an Infant Flow® generator (CareFusion Corporation, San Diego, CA, USA) with flow of 10–12 L/minutes and transferred to the neonatal intensive care unit (NICU).

Primary and secondary outcomes

The primary outcomes were the percentage of bradycardic infants at each minute of life and the times to reach the defined target values of oxygen of 70%, 80% and 90%, without subsequent deterioration or large fluctuation. Bradycardia was defined as HR <100 bpm. The secondary outcomes included need for PPV, intubation, repeated intubation, duration of intubation, reception of 100% oxygen and maximum FiO_2, early nasal CPAP (within 30 minutes of life), duration of endotracheal intubation attempt, IVH, oxygen supplementation at 36 weeks of postmenstrual age, retinopathy of prematurity >stage 2 (ROP), laparotomy due to necrotising enterocolitis (NEC) or spontaneous intestinal perforation (SIP) or death prior to discharge.

Data collection and statistical analysis

One camera recorded all interventions that the patient was receiving on the resuscitation bed while the second camera

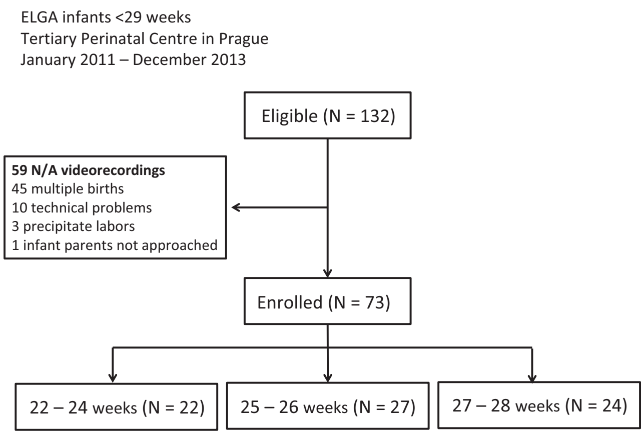

Figure 1 Derivation of the study cohort.

recorded the actual time, pulse oximetry values, FiO_2, PIP and PEEP levels. Using the TRAL software (12), sequence analysis made it possible to concurrently evaluate both of the recorded sequences on one screen. All interventions such as CPAP administration, PPV, intubation and surfactant administration as well as FiO_2 settings, HR and SpO_2 values were assessed and tabulated in 15-second intervals from the collected video recordings of each patient by a single unbiased independent physician not involved in the actual resuscitations. The time-related data were calculated from actual precise values of HR and SpO_2 of each patient evaluated as stable without further deterioration. Prior to availability of valid pulse oximetry readings, bradycardia was evaluated by auscultation. Heart beats were counted in six-second intervals and multiplied by 10. The percentage of bradycardic patients and the times to reach SpO_2 targets of >70%, >80% and >90% were compared with the published data reported by Dawson et al. (13,14) in preterm infants who required no oxygen or ventilatory support. The categorical demographic and resuscitation intervention data are expressed as numbers and percentages and were compared using the Pearson χ^2 test or the Fisher's exact test between the groups of ELGANs. Normally distributed noncategorical data are expressed as means with standard deviation (SD) and skewed distributed data as median with interquartile range. A nonparametric one-way analysis of variance and a two-tailed Mann–Whitney *U*-test were used to compare the groups.

RESULTS

A total of 132 eligible infants were born during the study period. Video recordings were not available in 59 infants, 45 for twin births (only twin A could be recorded), 10 video recordings were dismissed due to poor technical quality, and the bed was not available in three cases of precipitous labour. In one case, the mother refused a proactive approach in 22 + 6 week old infant. Finally, 73 ELGAN were enrolled, 22 in the 22- to 24-week group, 27 in the 25- to 26-week group and 24 in the 27- to 28-week group (Fig. 1). The demographic characteristics of the three groups are introduced in Table 1. A trend of higher rate of Caesarean sections and a higher Apgar score at five minutes were likely related to the increasing gestational age of the groups.

Primary outcome

A clear plethysmographic curve with valid HR values was displayed in more than 80% of infants at two minutes, 92% at three minutes and in all infants from the fourth minute in all groups. The time-related percentage of bradycardic infants negatively correlated with the gestational age of the groups (Fig. 2). Forty-two (58%) of all ELGANs were bradycardic by auscultation during the first minute, 14

Table 1 Basic characteristics in the three groups of ELGA infants

	Group 1 22–24 weeks N = 22	Group 2 25–26 weeks N = 27	Group 3 27–28 weeks N = 24	p*	p**	p***
Gestational age (weeks), mean (SD)	23.9 (0.7)	26.1 (0.58)	28.0 (0.5)	0.000	0.000	0.001
Birthweight (g), mean (SD)	633 (85.8)	800 (146.8)	971 (228)	0.000	0.000	0.000
Male, n (%)	12 (54)	11 (41)	12 (50)	0.336	0.757	0.579
Any antenatal steroids, n (%)	17 (77)	21 (78)	24 (100)	0.966	**0.013**	**0.024**
Antepartum haemorrhage, n (%)	4 (18)	10 (37)	3 (12.5)	0.146	0.592	0.058
Caesarean section, n (%)	12 (57)	20 (74)	22 (92)	0.153	**0.004**	0.099
Breech position, n (%)	6 (27)	4 (15)	8 (33)	0.311	0.525	0.119
Apgar score 5 minutes, median (IQR)	6 (5–7)	7 (5–8)	8.5 (7.2–9.2)	**0.048**	**0.000**	**0.001**
Cord pH, mean (SD)	7.32 (0.11)	7.30 (0.11)	7.30 (0.05)	0.401	0.545	0.320
Cord milking, n (%)	19 (86)	15 (56)	15 (63)	**0.012**	0.065	0.614

*Statistical significance between groups 1 and 2.
**Statistical significance between groups 1 and 3.
***Statistical significance between groups 2 and 3.
The bold values are statistical significant.

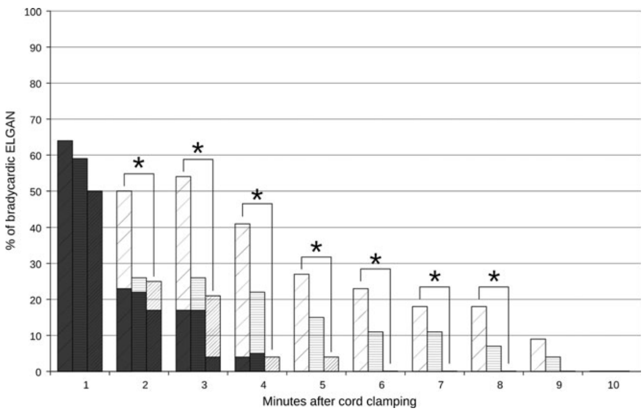

Figure 2 Comparison of the percentages of bradycardic ELGA infants (HR < 100 bpm) in the three groups during the first 10 minutes after birth. Wide diagonal hatched bars – group one, horizontal hatched bars – group two, narrow diagonal hatched bars – group three. The dark proportion of bars shows the percentage of bradycardia evaluated by auscultation after cord clamping in all infants. The percentage of bradycardic infants differs between all groups during the first 10 minutes, and the differences between groups one and three were significant from the third minute until the eighth minute: three minutes *p = 0.018, four minutes *p = 0.004, five minutes *p = 0.043, six minutes *p = 0.019, seven minutes *p = 0.045, eight minutes *p = 0.045.

(64%) in group one, 16 (59%) in group two and 12 (50%) in group three. At two minutes after cord clamping the percentage of bradycardic ELGANs in all groups decreased, but only in groups two and three significantly ($p < 0.03$). At three minutes, the percentage of bradycardic patients slightly increased in group one while stayed similar in the other two groups, then decreased incrementally each minute proportionally to the gestational age of the groups. The percentage of bradycardic infants differed among all groups during the first 10 minutes; the differences between group one and three were significant between the third and eighth minute ($p < 0.05$). The median times (IQR) in seconds to reach target values of SpO_2 >70%, >80% and >90% were also significantly different between all groups (Table 2).

Secondary outcomes

Positive pressure ventilation with PEEP was started in 25 of 73 ELGANs (34%), 11 of 22 (50%) in group one, eight of 27 (26%) in group two and six of 24 (25%) in group three, because of bradycardia in combination with poor spontaneous respiratory effort on CPAP support one minute after cord clamping. Of the 73 ELGANS, 48 (66%) remained on CPAP and 24 (33%) subsequently required PPV because of bradycardia or unstable heart rate during the second and third minutes of life. Ultimately PPV was required in 49 of 73 (67%) of infant, and its requirement was negatively correlated with the gestational age of the three groups (20/22 [91%] versus 19/27 [70%] versus 10/24 [42%]). The difference was significant between group one and group three ($p < 0.001$). The median time (IQR) in seconds from cord clamping to PPV commencement was significantly shorter in group one (72 [67–107] versus 120 [96–146] versus 145 [92–161], $p < 0.05$). The need for endotracheal intubation in the delivery room showed significant negative correlation to the gestational age of the three groups (16/22 [73%] versus 9/27 [33%] versus 2/24 [8%], $p < 0.05$). Repeated intubation and reception of 100% oxygen as well as maximum FiO_2 in the DR were significantly higher in group one ($p < 0.05$), and the infants in this group also significantly less frequently managed with early nasal CPAP, requiring more mechanical ventilation on the third day of life ($p < 0.01$). The most immature infants in group one had a significantly higher rate of death (8/22 [36%] versus 3/27 [11%] versus 1/24 [4%], $p < 0.04$), severe IVH (8/22 [36%] versus 2/27 [7%] versus 1/24 [4%], $p < 0.02$) and the need for oxygen therapy at 36 weeks postmenstrual age (8/22 [36%] versus 1/27 [4%] versus 1/24 [4%], $p < 0.01$). All ELGANs with severe IVH died (Table 3).

Post hoc analysis

A significantly higher rate of severe IVH along with more bradycardia lasting for longer periods of time and slow attainment of the target SpO_2 in group one prompted the post hoc analysis. We hypothesised that IVH may be associated with delayed lung aeration caused by ineffective delivery room interventions resulting in a hypoxic–ischaemic insult; therefore, we compared infants with IVH and those without IVH in group one.

Eleven infants in group one had severe IVH; eight had grade 3–4 IVH; and three had grade 2 IVH. Basic characteristics and resuscitation interventions of infants with and without IVH are listed in Table 4. Infants with IVH were delivered by Caesarean section less frequently, required more intubation in the delivery room, their median values

Table 2 Times for groups of ELGA infants to reach target values SpO_2

	Group 1 23–24 weeks N = 22	Group 2 25–26 weeks N = 27	Group 3 27–28 weeks N = 24	p Value**	Reference times†
Time to reach SpO_2 > 70%, seconds, median (IQR)	503 (427–757)	250 (199–528)	210 (158–307)	<0.03	372 (216–540)
Time to reach SpO_2 > 80%, seconds, median (IQR)	578 (440–769)	415 (301–585)	236 (203–387)	<0.00	438 (276–600)
Time to reach SpO_2 > 90%, seconds, median (IQR)	602 (494–769)	477 (390–536)	290 (233–415)*	<0.03	486 (402–630)

*No statistically significant difference between groups one versus two and two versus three.
**Mann–Whitney *U*-test.
†Dawson et al. (14), medians (IQR) are converted from minutes to seconds.

Table 3 Secondary outcomes. Delivery room interventions, time variables and short-term outcomes in three groups of ELGA infants

	Group 1 23–24 weeks N = 22	Group 2 25–26 weeks N = 27	Group 3 27–28 weeks N = 24	p*	p**	p***
Positive pressure ventilation (PPV) in the delivery room (DR), n (%)	20 (91)	19 (70)	10 (42)	0.076	**0.000**	**0.038**
Sustained inflation manoeuvre, n (%)	5 (22)	0	0	**0.009**	**0.013**	1.000
Maximum FiO_2, median (IQR)	0.8 (0.53–1.0)	0.5 (0.4–0.65)	0.43 (0.3–0.63)	**0.015**	**0.000**	0.199
Received 100% oxygen in the DR, n (%)	10 (45)	0	1 (4)	**0.000**	**0.001**	0.284
Intubation in the DR, n (%)	16 (73)	9 (33)	2 (8)	**0.006**	**0.000**	**0.030**
Repeated intubation in the DR	8 (36)	3 (11)	0	**0.046**	**0.001**	0.092
Surfactant administered in the DR, n (%)	16 (73)	9 (33)	2 (8)	**0.006**	**0.000**	**0.030**
Early NCPAP, n (%)	13 (59)	25 (92)	24 (100)	**0.009**	**0.000**	0.173
Time to first PO data, seconds, median (IQR)	71 (65–96)	85 (71–127)	87 (56–118)	0.099	0.258	0.525
Time of PPV commencement, seconds, median (IQR)	72 (67–107)	120 (98–146)	145 (92–161)	**0.046**	**0.031**	0.673
Time of DR intubation, seconds, median (IQR)	400 (280–534)	339 (278–387)	222 (170–274)	0.587	0.258	0.365
Duration of endotracheal intubation attempt, seconds, median (IQR)	124 (42–235)	64 (55–99)	22 (17–27)	0.529	**0.036**	0.218
Surfactant treatment, n (%)	20 (91)	18 (67)	13 (54)	**0.043**	**0.006**	0.361
Subsequent surfactant, n (%)	6 (27)	2 (7)	7 (29)	0.061	0.745	**0.041**
Mechanical ventilation on day 3, n (%)	11 (50)	4 (15)	5 (21)	**0.000**	**0.038**	0.573
Died before discharge, n (%)	8 (36)	3 (11)	1 (4)	**0.035**	**0.006**	0.357
Intraventricular haemorrhage grade 3 or 4, n (%)	8 (36)	2 (7)	1 (4)	**0.012**	**0.006**	0.623
Retinopathy of prematurity stage 3 or 4, n (%)	2 (9)	1 (4)	0	0.433	0.130	0.341
Oxygen therapy at 36 weeks, n (%)	8 (36)	1 (4)	1 (4)	**0.003**	**0.006**	0.932
Laparotomy, n (%)	4 (18)	1 (4)	0	0.095	**0.028**	0.341

*Statistical significance between groups 1 and 2.
**Statistical significance between groups 1 and 3.
***Statistical significance between groups 2 and 3.
The bold values are statistical significant.

of HR were below the 10th percentile, and the median values of SpO_2 were below the 3rd percentile of Dawson's nomograms (13,14) during the first 10 minutes after cord clamping (Figs 3 and 4). When the 15 second interval values of HR and SpO_2 recorded during the first 10 minutes of life were compared between the infants with and without IVH (Mann–Whitney test), the values of HR and SpO_2 were lower in the infants with severe IVH, reaching statistical significance at several postnatal times (Figs 3 and 4).

DISCUSSION

In this observational study using a standard protocol for resuscitation, the percentages of bradycardic infants, the times to reach defined targets of SpO_2 as well as delivery room interventions showed a negative correlation with the gestational age of the groups, as would be expected. At two minutes after cord clamping, the percentage of bradycardic ELGANs ≥25 weeks correlated very well with the percentage of bradycardic more mature infants not receiving interventions in the delivery room published by Dawson (13). The cord pH of most of our ELGANs was in the normal range, and a significant number of our ELGANs ≥25 weeks increased their HR >100 bpm during the next minute similar to Dawson's cohort (13). Vagal stimulation is one of the main causes of bradycardia if the cord is cut before spontaneous breathing. Although from the second minute of life during the subsequent period of PPV the number of bradycardic patients decreased, the decrease was delayed by one minute in group three and further prolonged in group two in comparison with Dawson's cohort (13). In the study of Yam et al. (15), it took more than one minute of PPV for infants <30 weeks of gestation to rise their HR >100 bpm. That means that six infants from group two and only one from group three did not aerate their lung by means of PPV sufficiently and so their HR stabilisation was delayed. Finally, only a few ELGANs born at ≥25 weeks (4/51, 8%) were bradycardic after five minutes of life, three in group two and one in group three. Their previous lung inflations were not effective enough to increase left heart filling with oxygenated blood, and consequently, hypoxia might have contributed to prolonged bradycardia. These few bradycardic infants were rescue intubated. The times to reach the target values of SpO_2 were compared with the reference times described in spontaneously breathing preterm infants <37 weeks without any ventilatory support or supplemental oxygen published by Dawson (14) (median time (IQR) in seconds to reach SpO_2 >70% = 372 [216–540]; >80% = 438 [276–600]; >90% = 486 [402–630]). Our ELGANs from 25 to 26 weeks of gestation achieved the median time of target value of SpO_2 >70% even faster, and the median times of target values of SpO_2 >80% and >90% were the same. Six of these infants (22%) were intubated because their target values of SpO_2 could not be stabilised in the predefined target range of SpO_2. The ELGANs born at 27–28 weeks of gestation reached all the target values of SpO_2 more rapidly. Only two of them were intubated in the DR with surfactant administration, one because bradycar-

Table 4 Basic characteristics and delivery room interventions in 22- to 24-week gestation ELGANs with and without grade 2–4 intraventricular haemorrhage (IVH)

	With IVH N = 11	Without IVH N = 11	p
Gestational age (weeks), mean (SD)	23.9 (0.8)	24.0 (0.7)	0.581
Birthweight (g), mean (SD)	615 (88.31)	651 (87.81)	0.358
Male, n (%)	4 (57)	8 (73)	0.198
Any antenatal steroids, n (%)	10 (91)	7 (64)	0.127
Antepartum haemorrhage, n (%)	3 (27)	1 (9)	0.586
Caesarean section, n (%)	5 (45)	7 (64)	0.669
Breech position, n (%)	3 (27)	3 (27)	1.0
Apgar score 5 minutes, median IQR	6 (5–7)	6 (5–7)	0.870
Cord pH, mean (SD)	7.31 (0.16)	7.34 (0.08)	0.734
Milking, n (%)	10 (91)	9 (82)	0.534
Temperature on admission to NICU, mean (SD)	36.4 (0.45)	36.1 (0.93)	0.358
Positive pressure ventilation in the delivery room (DR), n (%)	11 (100)	10 (91)	0.336
Sustained inflation manoeuvre, n (%)	4 (36)	1 (9)	0.310
Maximum FiO_2, median (IQR)	0.8 (0.65–1.0)	0.7 (0.4–0.9)	0.253
Received 100% oxygen in the DR, n (%)	5 (45)	5 (45)	1.0
Intubation in the DR, n (%)	10 (91)	6 (55)	0.148
Repeated intubation in the DR	4 (36)	4 (36)	1.0
Surfactant administered in the DR, n (%)	10 (91)	6 (55)	0.148
Early NCPAP, n (%)	5 (45)	8 (72)	0.387

*Pearson chi-square test and Fisher exact test for categorical data, Mann–Whitney for numerical data

dia persisted and one because PPV with higher FiO_2 could not stabilise the SpO_2 in the target range. Both were extubated to nasal CPAP after surfactant administration in the delivery room. In total, 92% of infants in group two and all infants in group three were supported by primary nasal CPAP in NICU. Their mortality and early neonatal morbidity rates were even lower than the rates of the same gestational age cohorts in the studies where mortality and morbidities were evaluated as the primary outcomes (16,17). Although some of our 25- to 28-week ELGANs required PPV and intubation and/or oxygen supplementation, the transition from placental support to air breathing was appropriate in the majority of cases when managed according to our resuscitation protocol, enabling them to achieve the target reference range of the SpO_2 nomograms. Furthermore, the rapid achievement of SpO_2 targets in some infants alerted us to be more careful in increasing of FiO_2 especially in those ELGANs who are on CPAP with good spontaneous breathing effort (18,19). A more rapid attainment of oxygen saturation than the reference range was also described in the observational study of Vento et al. (1), where only well-adapted preterm infants ≤32 weeks of gestation aided by a face mask CPAP with air were included.

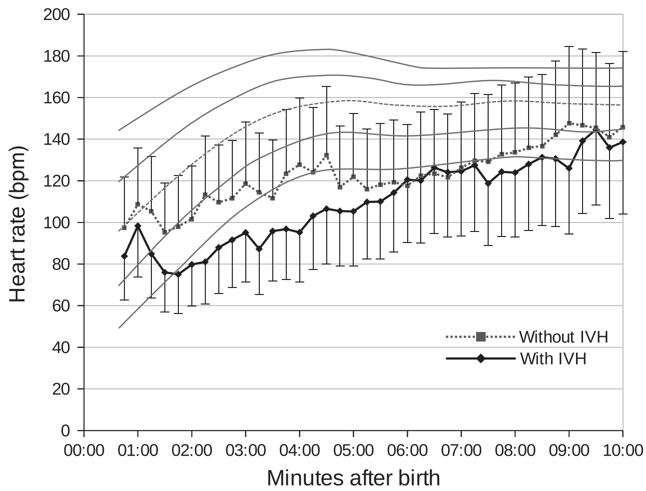

Figure 3 Heart rate (HR) values in 15-second intervals during the first 10 minutes after birth in 22- to 24-week ELGANs with and without intraventricular haemorrhage (IVH). The values are medians with IQR. ELGANs with IVH had significantly lower values in the following time points: 2:45, p = 0.006; 4:15, p = 0.043; 4:30, p = 0.024; 5:00, p = 0.043. The median HR values of ELGAN with IVH remain below 10th percentile of Dawson's percentile nomogram (background) between two and nine minutes after birth.

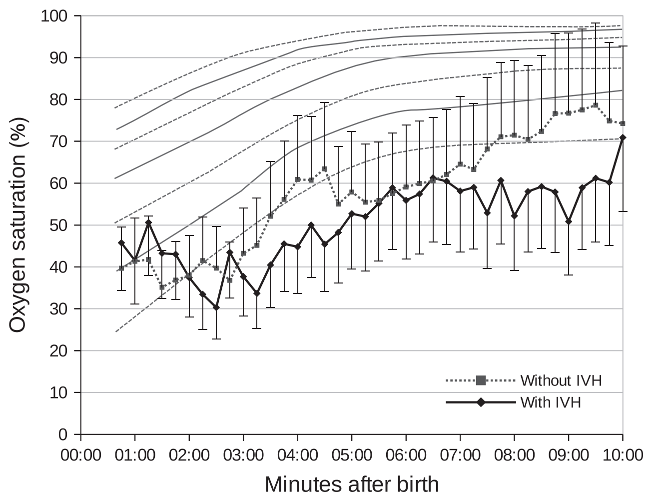

Figure 4 Pulse oximeter displayed oxygen saturation (SpO_2) values in 15-second intervals during the first 10 minutes after birth in ELGANs with and without intraventricular haemorrhage (IVH) born in 22- to 24-week gestation. The values are medians with IQR. ELGANs with IVH had significantly lower values in the following time points: 5:00, p = 0.047; 8:30, p = 0.041; 9:30, p = 0.013; 9:45, p = 0.049. The median SpO_2 values of ELGANs with IVH are far below 3rd percentile of Dawson's percentile nomogram (background) between two and 10 minutes, while the median values of SpO_2 of ELGAN without IVH fluctuated around the lower end of the range.

In contrast, when we used the same strategy and parameters of ventilatory support in ELGANs born at <25 weeks of gestation, the initial percentage of bradycardic patients decreased minimally with PPV and even slightly increased at three minutes, a time when all of these infants had received PPV for at least one minute. If we accept that increasing HR reflects adequate lung aeration, then a significant number of our infants born <25 weeks were inflated ineffectively for some time. The prolonged inadequate aeration of lungs resulted in more than two minutes longer median times to reach all the target values of SpO_2 than the reference values published by Dawson (14). These infants of group one required more delivery room interventions with more supplemental oxygen, and their mortality and morbidity rates were higher than in the more mature groups two and three. Finally, 16 patients (73%) in group one required intubation, five of them (31%) due to persistent bradycardia and 11 (69%) due to low SpO_2 values during PPV. More repeated intubations were required and the achievement of success took more time. The intubation of very tiny infants is a difficult skill with a low success rate per attempt and is usually accompanied by deterioration of HR and SpO_2 (20). Although the association between delivery room intubation and severe forms of IVH has been published, it is not clear whether the hypoxic insult is the result of this stressful procedure itself or to previous poor aeration of the lungs caused by ineffective PPV and delayed intubation (4). In our post hoc analysis, we observed significantly lower HR values during the first five minutes of life and significantly lower values of SpO_2 during the next five minutes in several measured time points in the <25 week infants with IVH. That indicates that the pattern of positive pressure inflations using a peak pressure of 25 cm H_2O with inflation time of one to two seconds and PEEP of 6 cm H_2O did not aerate the lungs sufficiently to initiate gas exchange and deliver sufficient oxygen in these infants who later developed IVH. The inflation pressures of 20–25 cm H_2O are generally recommended initially in preterm infants (21). However, we found that pressures of 25 cm H_2O with inflation time of one to two seconds were not effective enough in a significant proportion of our ELGANs born at <25 weeks. Either the low inflation pressure or the short inflation time, or both may be insufficient for adequate time-related aeration of the respiratory system in these tiny babies. At birth, the lungs are fluid-filled and the lung fluid has much higher viscosity than air, and thus, substantially longer time constants would be predicted. The tiny airways also lead to high airway resistance and surfactant deficiency results in poor lung compliance. Both an increase in inflation pressure and prolongation of inflation time may help to overcome these problems and aerate the stiff lung more effectively. Neither was practiced routinely in this study. A more aggressive approach using higher inflation pressure and earlier intubation may be harmful and may cause lung injury (22). Prolongation of inflation time, such as sustained lung inflation, can improve the establishment of a functional residual capacity and increase HR and SpO_2 rapidly, albeit with some delay in infants without respiratory activity (23). Preterm infants treated with sustained inflations in an earlier randomised trial (24) required intubation less often within the first 72 hours of life and bronchopulmonary dysplasia developed less frequently. However, sustained lung inflation, not being the routine practice, was used only in five infants in group one; severe IVH developed in four of them. In contrast, a group of German investigators (25) published better outcomes after the introduction of a revised delivery room management protocol for infants <26 weeks of gestation. Aiming to avoid mechanical ventilation, a gradual increase of CPAP pressure (8–10 cm H_2O) via face mask with a variable flow CPAP device was initiated and followed by a 30 second sustained inflation of 25 cm H_2O, which could be repeated up to three times if HR <100 bpm persisted. The principle of this gradual and less aggressive approach is the use of higher CPAP pressures and sustained inflations for a longer time to better overcome the obstructions and leaks commonly and most frequently present in these very tiny infants. The rate of intubation in the DR was low (24%) and the severe forms of IVH developed only in 6% of infants born at 23 and 24 weeks of gestation. Although the precise time of intubation was not reported, intubation was indicated if HR <100 persisted for more than 270 seconds after delivery. More than 25% of our patients born at the same gestational age were bradycardic for a longer time and were intubated later and more frequently. This suggests that standard respiratory support using positive pressure inflations with peak pressures of 25 cm H_2O with a short inflation time of one to two seconds is less effective than the approach provided by the German investigators (25). The second reason for a lower rate of delivery room intubation in the German study may be the simultaneous initiation of ventilatory support and placental transfusion, which may reduce the number of bradycardic infants (26). Furthermore, using this method the amount of placental blood transfused to the infant might be bigger in comparison with the milking procedure we use. Additionally, initial bradycardia might occur less frequently because the venous return was not interrupted immediately, possibly contributing to the lower risk of IVH (27).

We are aware of the several obvious limitations of this study. Firstly, we were unable to analyse all eligible ELGANs mainly those from multiple pregnancies because only one specially modified mobile resuscitation warmer bed was available; consequently, our cohort does not represent all ELGANs resuscitated during the investigational period. We were limited in the accurate determination of the HR during the first few minutes of life because only auscultation could be used until valid HR values were displayed on the screen of the pulse oximetry. However, our initial percentage of bradycardic patients correlates very well with Dawson's percentage of bradycardia in more mature and healthier infants (13). It can be argued that in spite of the earlier initiation of PPV in group one, PPV might be inappropriately delayed. In agreement with McCarthy's study (9), we think that the ILCOR recommendation of intervening within 30 seconds in apnoeic and bradycardic infants seems to be unrealistic and inappropriate for most of the preterm infants who are not primarily asphyxiated and who are being assessed, stimulated and supported by CPAP to avoid unnecessary intervention. Secondly, we did not measure leak and airway obstruction and so we can only speculate whether it is the tiny upper airways causing the obstruction, or the inadequate fit between the face anatomy of tiny infants and the smallest size of the interface contributing to a face mask leak that compromises ventilatory support. Thirdly, the resuscitation protocol was not strictly followed in some infants who responded poorly to PPV, because the median time of initiation of intubation was delayed even though bradycardia had persisted longer than 180 seconds after cord clamping. A possible explanation of this violation could be misinterpretation of the labile heart rate fluctuating around 100 bpm as a hopeful sign for a further increase in HR, and consequently, PPV via the interface was continued instead of immediate intubation. We can only speculate if earlier intubation of some infants born on the threshold of viability might improve their results.

The conventional way of ventilatory support in the delivery room was effective in achieving the reference range of oxygen saturation in the cohort of ELGA infants ≥25 weeks of gestation. However, infants <25 weeks of gestation responded poorly to this kind of intervention and ultimately most of them required intubation in the DR. Their mortality and early neonatal morbidity were inappropriately higher. We found an association between a lower HR and time-related SpO_2 values and IVH which developed within 72 hours of life.

Using the current recommendations for resuscitation without the standard use of initial sustained inflation, adequate lung aeration may be inappropriately delayed in infants delivered at the threshold of viability. Consequently, the very early hypoxic–ischaemic insult followed by reperfusion may contribute to their immaturity-related high rate of intraventricular haemorrhage (28). Ventilatory support should be more individualised and new approaches and innovative techniques should be investigated in this fragile and unique group of infants.

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