ARTICLE

Stabilization, respiratory care and survival of extremely low birth weight infants transferred on the first day of life

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OBJECTIVE: To assess stabilization, respiratory care and survival of extremely low birth weight (ELBW, <1000 g at birth) infants requiring emergency transfer to tertiary NICUs on the first day of life.
STUDY DESIGN: Retrospective cohort study of 55 ELBW infants transported by a dedicated neonatal transport service over a 65-month period. Ventilator data were downloaded computationally.
RESULTS: 95% of infants were intubated and received surfactant prior to transfer. Median expired tidal volume was 5.0 mL/kg (interquartile range: 4.6–6.2 mL/kg). Infants ventilated with SIPPV had significantly higher mean airway pressure and minute ventilation, but similar FiO_2 compared to babies on SIMV. Blood gases showed significant improvement during transport. 55% of infants survived to discharge from NICU.
CONCLUSION: Most ELBW infants transferred on the first day of life require mechanical ventilation and can be ventilated with 5 mL/kg tidal volume.

Journal of Perinatology; https://doi.org/10.1038/s41372-024-02043-w

INTRODUCTION

Despite advances in modern neonatal intensive care and improving mortality and morbidity rates, preterm birth remains a major healthcare problem, putting a significant burden on patients, families, and communities [1, 2]. Of all infants admitted to neonatal intensive care units (NICUs), babies born with a birth weight of less than 1000 grams, also known as extremely low birth weight (ELBW) infants, are at highest risk of death and short- or long-term morbidities including chronic respiratory problems and neurodevelopmental disability [3, 4].

Mothers who are at risk of delivering ELBW infants are frequently transferred to hospitals equipped with level 3 NICUs where definitive neonatal intensive care can be provided [5, 6]. However, a significant proportion of them are born in hospitals without a tertiary NICU, because precipitous labor or fetal or maternal concerns make an in utero transfer unsafe or infeasible. These infants are usually transferred ex utero, after initial stabilization, via a dedicated neonatal transport team. Early postnatal transfer of them is particularly challenging due to their clinical instability and particular vulnerability to heat loss, dehydration, and trauma associated with the movement and acceleration of the ambulance vehicle [7]. It has been reported that exposure to vibration may be particularly relevant when transporting extremely low birth weight neonates [8]. In most NICUs, out-born infants have worse outcomes than inborn babies, including the higher prevalence of intraventricular hemorrhage (IVH), although it is uncertain whether this is due to transport itself or better initial care in hospitals with tertiary NICUs [5, 9].

Respiratory care of ELBW infants transferred during the acute phase of respiratory distress syndrome (RDS) is frequently challenging. The equipment providing respiratory support during transport is likely to be different from the one used on the referring unit; the same settings on the transport ventilator may result in different gas exchange. Many transport services do not use synchronized ventilation and most of them use pressure controlled, rather than volume targeted ventilation [10]. Occurrence of large tidal volumes has been reported in infants transferred on pressure-controlled ventilation [11]. The first report on volume targeted ventilation during neonatal transport has been published only recently [12]. There have been no reports specifically on the respiratory management of ELBW infants during transport.

In this study, we investigated pre-transport stabilization and respiratory care ELBW infants received during transfer to tertiary NICUs on the first day of their life. We analyzed what expired tidal volumes they received during transfer and how their blood gas values changed. We compared ventilator parameters during synchronized intermittent positive pressure ventilation (SIPPV, also known as assist-control ventilation, AC or patient triggered ventilation, PTV) and synchronized intermittent mandatory ventilation (SIMV). We also report their survival to discharge from tertiary NICU.

SUBJECTS AND METHODS

Patients and clinical care

Clinical and ventilator data were collected from infants transferred by the Neonatal Emergency and Transport Service of the Peter Cerny Foundation

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Received: 2 February 2024 Revised: 21 June 2024 Accepted: 25 June 2024
Published online: 06 July 2024

(NETS-PCA, Budapest, Hungary) over a 65-month period (between 20/03/2017 and 20/08/2022) who received invasive or noninvasive respiratory support during inter-hospital transport.

NETS-PCA is a dedicated neonatal transport service operating since 1989 that covers a geographical area in central Hungary which includes Budapest and has a total population of ~5 million. The transport team included a fully trained neonatologist with experience in neonatal transport, an experienced neonatal transport nurse practitioner and a professional driver with experience in driving neonatal ambulances. All emergency transfers were completed using blue lights, siren, and ambulance priority.

Respiratory support was provided using fabian™ + ncpap evolution or fabian™ HFO neonatal ventilators (Vyaire Medical, Mettawa, IL, US). Respiratory management including the choice of respiratory support and ventilation settings was at the discretion of the transport team without an explicit guideline.

For this study, infants were considered if their birth weight was <1000 g and they were transferred during the first day of life to a tertiary NICU. Transfers between tertiary NICUs or shorter than 10 min and infants with major congenital malformations have been excluded. The study was approved by the Scientific and Medical Research Council Ethics Committee of Hungary (reference number: 40158/2018/EKU).

Data retrieval

Ventilator data were recorded by a data logger developed by Vyaire for research purposes. The software downloaded airway pressure, flow, and volume data at 125 Hz frequency. It also downloaded ventilator parameters (e.g., peak inflating pressure, tidal volume, ventilator rate, minute ventilation, fraction of inspired oxygen, etc.) with a 0.5 Hz sampling rate. Ventilator settings and their changes were also recorded. The 0.5 Hz peak inflating pressure and tidal volume data correspond to the last inflation that occurred before the time stamp. Minute ventilation is calculated as a rolling mean over 30 s, and it includes both ventilator inflations and spontaneous breaths, if present. Data were retrieved with millisecond time stamps and exported as text files.

Clinical data were collected from electronic health care records. Blood gases were obtained via capillary sampling using heel pricks in all cases, as babies did not have arterial catheters.

Data analysis

Data were analyzed using Python (version 3.9.182, https://www.python.org) and its data science packages. Programming was done using Jupyter Notebook (version 8.15.0, http://ipython.org/notebook.html). Data were processed and analyzed using NumPy (version 1.24.3, http://www.numpy.org) and pandas (version 2.1.4, http://pandas.pydata.org). Statistical analysis was performed using SciPy (version 1.9.3, www.scipy.org). Visualization was done using matplotlib (version 3.8.0, http://matplotlib.org). All software is open source and freely available. The Jupyter notebooks containing and explaining all steps of data processing and analysis can be viewed on GitHub code repository at https://github.com/belteki/transport_ELBW.

To exclude artefacts, ventilator inflations were excluded if PIP was lower than PEEP, as this cannot normally occur during positive pressure ventilation (0.08%). Ventilator inflations when VTe was >25 mL/kg (0.005%), or periods with a ventilator rate >130/min (0.003%) or with minute ventilation >1 L/min/kg (0.3%) were also excluded. These events do not normally occur during conventional mechanical ventilation, and they probably represent artefacts, e.g., when the ventilator circuit was open or when condensed water in the ventilator's circuit caused auto-triggering. In total, 573 data points (0.37%) were excluded.

For ventilator parameters showing normal distribution within the recordings, arithmetic mean and standard deviation (SD), for parameters with non-parametric distribution, median and interquartile range were calculated. As these aggregate values were not normally distributed, groups were compared using non-parametric Mann–Whitney U-tests.

When comparing different ventilator modes (SIPPV, SIMV, with VG, without VG), only cases where the given mode was used for >95% of the time were considered; parts of these recordings with other mode(s) were excluded. For SIMV, only recordings or recording parts without additional pressure support were included. During SIMV, the mean tidal volume of spontaneous breaths was calculated separately from the tidal volume of the ventilator inflations. Spontaneous breaths were included when calculating the minute ventilation during SIMV.

RESULTS

Of the 1450 infants from whom ventilator data were available, 180 had a birth weight of <1000 g, and of them, 62 were transferred on the first day of life. We excluded two infants who were transferred between tertiary NICUs for capacity reasons, two babies who had major congenital malformations, and two cases where transport itself lasted for <10 min. Detailed clinical data were not available for 1 infant. Therefore, our final dataset included 55 cases (Supplementary Fig. 1). Basic demographic details of the infants as well as data on pregnancy and delivery are shown in Table 1.

Only 15 mothers (27%) were documented to receive a complete or incomplete course of prenatal steroids. 28 infants (51%) were born by Caesarean section; 7 (13%) were born outside healthcare facilities. More than half of them were hypothermic at the arrival of the transport service (Fig. 1A). All except three (95%) were intubated and received surfactant prior to transfer. The median age at surfactant administration was 55 min but it ranged between 9 min and 3.5 h (Fig. 1B). In addition, a significant proportion of them received chest compressions or adrenaline

Table 1. Demographic and basic clinical details of the patients included in the study.

Number of cases	**55**
Demographic details	
Gestational age, completed weeks, median (range)	25 (21–31)
Birth weight, grams, median (range)	750 (300–990)
Gender (male/female)	32/23
Twin/singleton	10/45
Antenatal care and delivery	
Maternal problems	
Bleeding	20
Infection	4
Pre-eclampsia/hypertension	5
Other[a]	6
No data	20
Antenatal steroids (full course/incomplete course/none/no data)	10/5/33/7
Mode of delivery (vaginal/Caesarean section)	27/28
Born outside hospital (yes/no)	7/48
Care after delivery	
Initial care provider	
Parent/paramedic	7
Local pediatrician	31
Neonatal transport service	17
Intubation (yes/no)	52/3
Surfactant before transfer (yes/no)	52/3
Chest compressions (yes/no)	9/46
Adrenaline bolus (yes/no)	7/48
Care before and during transport	
Respiratory support (mechanical ventilation/nasal CPAP)	52/3
Sedation (yes/no)	12/43
Fluid bolus (yes/no)	18/37
Inotropic support (yes/no)	6/49

[a]Includes umbilical cord complications.

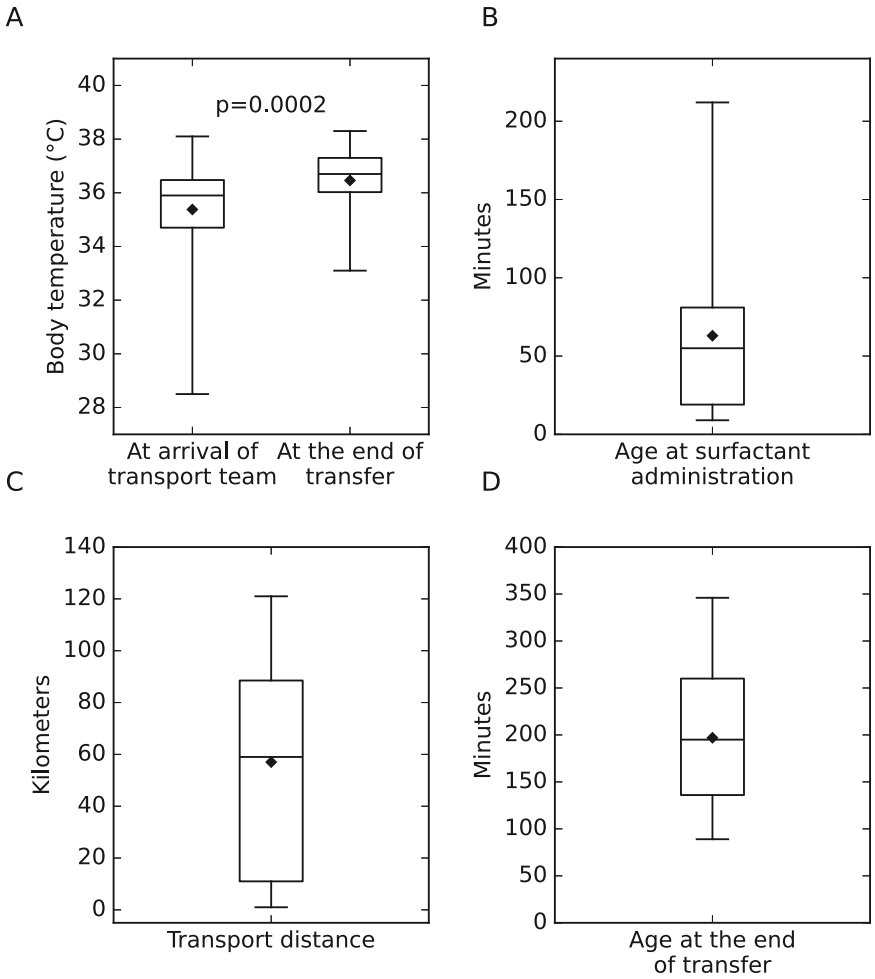

Fig. 1 Clinical and transport characteristics of ELBW infants transferred on the first day of life. A Core body temperature of the infants at the arrival of the transport team to the place of delivery and at the handover to tertiary NICU. **B** Age at the time of surfactant administration. **C** The distance travelled from the place of delivery to tertiary NICU. **D** Postnatal age at the end of transfer. On all boxplots, medians are shown as horizontal lines, boxes represent interquartile ranges, whiskers represent the full range of data. Means are shown as black diamonds.

bolus after birth, as well as fluids boluses, inotropic agents or sedation before and during the transport (Table 1).

The median distance of transfer was 59 kilometers (range: 1–121 kilometers, Fig. 1C) and the median age at the time of arrival to the tertiary NICU was 3 h 15 min (range: 1 h 29 min–5 h 46 min, Fig. 1D). The infants' body temperature has improved significantly during the transfer (Fig. 1A).

All infants intubated after birth were transferred on invasive mechanical ventilation; 3 infants were transferred on nasal CPAP provided by the ventilator. Statistics on ventilator parameters are shown in Table 2. The median expired tidal volume was 5.0 mL/kg (interquartile range: 4.6–6.2 mL/kg). Blood gases showed significant improvement during the transport (Fig. 2).

Infants were ventilated with SIPPV mode in 29 cases, with SIMV in 13 cases and with SIMV-PS in 2 cases; 8 infants were ventilated with multiple modes (7 babies with SIPPV and SIMV, 1 infant with SIMV and SIMV-PS). There were no differences in the clinical characteristics of the infants receiving different ventilation modes (Supplementary Table 1). Infants ventilated with SIPPV had significantly higher mean airway pressure, positive end-expiratory pressure, ventilator rate and minute ventilation than babies ventilated with SIMV (Table 2). Nonetheless, spontaneous breaths between ventilator inflations constituted on average <15% of minute ventilation in infants ventilated with SIMV. There was no significant difference between the groups in the median FiO_2 during the journey. The blood gases at the end of the transfer were also not different, although before the transfer infants ventilated with SIPPV had significantly lower pH (Table 2). There was no significant difference in the ventilator parameters of the 7 infants who received both SIPPV and SIMV during their transfer, (Supplementary Table 2).

VG was used in 41 cases and was not used in 6 cases; 5 infants were ventilated both with and without VG during their transport. The leak around the endotracheal tube was significantly ($p = 0.002$) higher in infants ventilated without VG (median: 11%, IQR: 0–64%), than in infants ventilated with VG (median 0%, IQR: 0–15%).

Survival to discharge from tertiary NICU is shown in Table 3, separately for each gestational week. Overall, at least 55% of the group (30 out of 55 infants) survived, which was below the national survival of inborn ELBW infants during an overlapping period (975 out of 1290 infants, 76%), over a 3-year period between 2019 and 2021 (source: Annual Report of the National In Vitro Fertilization, Obstetric and Neonatal Registry of Hungary, unpublished), albeit without statistical significance ($p = 0.18$, Fisher's exact test). However, there were no survivors among infants born below 24 weeks of gestation, while the national survival of them was 22% (25 out of 113 infants). Of the survivors, 7 infants (23%) had severe (grade 3–4) intraventricular hemorrhage or posthaemorrhagic hydrocephalus requiring neurosurgical intervention.

Table 2. Statistics on ventilator parameters used during transport and on blood gases before and after transfer.

Ventilator parameters	All ventilated cases ($n = 52$)	SIPPV ($n = 29$)	SIMV ($n = 13$)	p-value[b] (SIPPV vs SIMV)
PIP (cmH_2O)	20.0 (15.9–23.8)	20.6 (16–25.9)	18.2 (17.2–22.5)	NS
MAP (cmH_2O)	9.5 (8.1–10.8)	10.4 (9.2–11.4)	8.2 (7.8–9.3)	<0.001
PEEP (cmH_2O)	6.1 (5.8–6.2)	6.1 (6.0–6.3)	5.9 (5.2–6.1)	0.002
VTe (mL/kg)[a]	5.0 (4.6–6.2)	5.3 (4.8–6.2)	4.9 (4.6–5.5)	NS
VTespon (mL/kg)	n/a	n/a	1.9 (1.6–2.3)	n/a
RR (1/min)[a]	49 (39–59)	57 (50–63)	38 (35–40)	<0.0001
MV (L/min/kg)	0.30 (0.24–0.34)	0.32 (0.27–0.35)	0.26 (0.23–0.30)	0.02
Mvspon (%)	n/a	n/a	14.8 (10.5–22.5)	n/a
FiO_2 (%)	25 (21–34)	25 (23–40)	28 (21–30)	NS
Leak (%)	0 (0–15)	0 (0–11)	0 (0–17)	NS
Blood gas at the beginning of transport				
Blood gas available (n)[c]	47	24	11	
pH	7.19 (7.10–7.24)	7.14 (7.09–7.22)	7.24 (7.18–7.28)	0.04
pCO_2 (mmHg)	51.7 (46.7–64.2)	56.1 (51.1–68.4)	49.0 (45.9–52.7)	NS
BD (mmol/L)	7.7 (5.0–11.9)	8.8 (6.0–12.2)	5.3 (4.3–6.8)	NS
Blood gas at the end of transport				
Blood gas available (n)[c]	50	26	12	
pH	7.27 (7.20–7.32)	7.29 (7.24–7.32)	7.29 (7.21–7.34)	NS
pCO_2 (mmHg)	48.7 (40.8–56.2)	48.8 (41.1–57.7)	49.9 (40.1–62.3)	NS
BD (mmol/L)	3.6 (1.0–7.3)	3.5 (1.4–6.8)	2.4 (0.8–4.5)	NS

For each infant the mean (PIP, MAP, PEEP, VTe, RR, MV) or median (FiO_2 and leak) of the parameter has been calculated. Data shown are group medians and interquartile ranges. Infants receiving SIPPV or SIMV were compared. For blood gases, group medians and interquartile ranges are shown for pH, pCO_2 and base deficit in samples taken prior to transfer and at the end of transfer.

SIPPV synchronized intermittent positive pressure ventilation, *SIMV* synchronized intermittent mandatory ventilation, *PIP* peak inspiratory pressure, *MAP* mean airway pressure, *PEEP* positive end-expiratory pressure, *VTe* expired tidal volume of ventilator inflations, *VTespon* expired tidal volume of spontaneous breaths, *RR* ventilator rate, *MV* minute ventilation, *MVspon* contribution of spontaneous breaths to minute ventilation, *FiO_2* fraction of inspired oxygen, *BD* base deficit, *IQR* interquartile range, *NS* not significant, *n/a* not applicable.

[a]Only includes ventilator inflations. Spontaneous breaths during SIMV have been excluded.

[b]Mann–Whitney U-test.

[c]All blood gases were capillary camples.

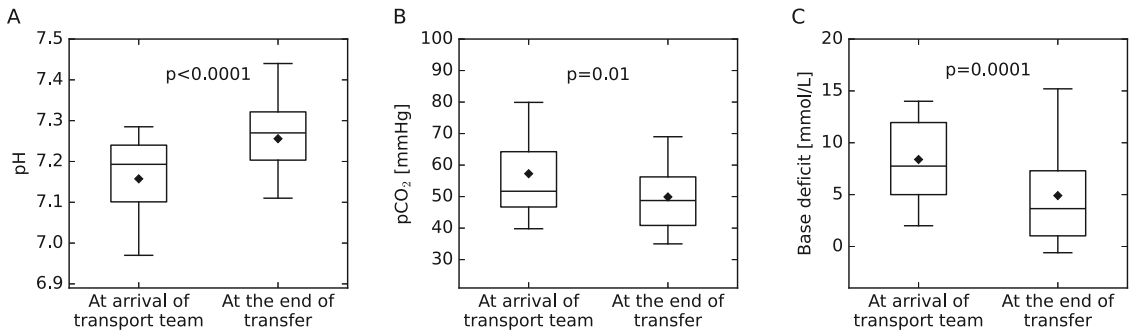

Fig. 2 Blood gases performed before and after the transport of ELBW infants. pH (**A**), pCO_2 (**B**) and base excess (**C**) are shown. All gases were capillary samples. On all boxplots, medians are shown as horizontal lines, boxes represent interquartile ranges, whiskers represent 5th and 95th percentiles, and outliers are not shown. Means are shown as black diamonds.

DISCUSSION

With the improvement of in utero transfer, early postnatal transport of ELBW infants has become rare: in our dataset, it represented only 4.3% (62 out of 1450) of the transfers by the regional transport service on respiratory support. However, these infants are highly vulnerable due to their immaturity, critical illness, and the risk of acute complications such as IVH.

In this paper, we provide the first analysis of the respiratory management of ELBW infants transferred to tertiary NICUs on the first day of life. Non-invasive respiratory support has been increasingly used in the management of RDS in ELBW infants [13, 14]. In our cohort, >90% of ELBW infants were intubated before transfer and were transported on mechanical ventilation, similar to the findings of Massirio et al., who also reported a > 90% intubation rate for infants born at <30 weeks of gestation who required early postnatal transfer [15]. This may have been due to the poor condition and more severe RDS of the infants, caused by precipitous labor and preventing in utero transport and prenatal steroid use and, in some cases, delivery outside the hospital. Ensuring safe transport may also have been a consideration because the journeys were longer than ~60 kilometers in half of the cases.

Table 3. Survival to discharge and intraventricular hemorrhage in ELBW infants transferred on the first day of life.

Survival to discharge from tertiary NICU				
Gestation at birth	**Number of cases**	**Survived**	**Did not survive**	**Data not available**
<23	3	0	3	0
23	7	0	6	1
24	10	5	5	0
25	11	7	3	1
26	11	6	4	1
27	6	5	1	0
28	4	4	0	0
>28	3	3	0	0
Total	55	30	22	3
Intraventricular hemorrhage among survivors				
No IVH	14			
IVH grade 1-2[a]	7			
IVH grade 3-4[a]	4			
Posthaemorrhagic hydrocephalus[b]	3			
Data not available	2			

[a]Intraventricular hemorrhage, Papille grading.
[b]Requiring neurosurgical intervention.

We found that almost all infants were ventilated with expired tidal volumes between 4–6 mL/kg (group median 5 mL/kg), and their carbon dioxide levels at arrival to the NICU were normal. In a recent study using volumetric capnography to estimate dead space in extremely preterm infants, physiologic dead space volumes of 5.7 mL/kg were found for ELBW babies on the first days of life, suggesting the need for using tidal volumes >6 mL/kg in these babies [16]. However, our findings align more with the results of Keszler et al., who reported that babies <800 g can be ventilated with ~5 mL/kg tidal volume, even though it is less than even their anatomic dead space [17, 18]. Together these results suggest that gas exchange mechanisms other than tidal ventilation operate even at respiratory rates used during conventional ventilation [19].

Volume targeted ventilation was used in most (46 out of 52) patients which is reassuring as it has been shown to improve clinical outcomes in this patient group [20]. Infants ventilated without VG had significantly larger leak around their tube; it is conceivable that the larger leak was the reason for not using VG in some of these cases.

SIPPV is associated with lower work of breathing and shorter duration of mechanical ventilation than SIMV [21, 22] and is widely used in this patient population. In our study, babies receiving SIPPV had higher ventilator rates and minute ventilation than babies receiving SIMV. Their mean airway pressure was also higher, in part due to the higher PEEP setting. Their blood gases on arrival to NICU were not different from those of infants transferred on SIMV, although their initial blood gases had shown more severe acidosis, suggesting worse initial clinical condition, which improved during transport. Of note, during SIMV, only a small proportion of MV was provided by spontaneous breaths, despite the relatively low set ventilator rate (median 38/min). This may be due to the weak respiratory effort of these patients, or the sedation used during the transport in some of them. When comparing these ventilator parameters in the patients who were ventilated using both modes during their transfer, they were not different; however, their small number ($n = 7$) limited the statistical power to identify such differences.

Survival of the cohort was not significantly worse than national survival of infants born in hospitals with tertiary NICUs, but we may have lacked the statistical power to detect a difference. However, there were no survivors among babies born before 24 weeks. Several factors may have contributed to this. Rapid labor or the need for emergency delivery may have prevented the completion of a prenatal steroid course. The experience of the local clinical teams in stabilizing ELBW infants may have been less than in hospitals with tertiary neonatal services, although the neonatal transport team has actively participated in the initial care of a significant proportion of cases. Some infants were born outside healthcare facilities, where circumstances were suboptimal and initial care was sometimes provided by adult ambulance services. Finally, despite the dedicated ambulance and experienced drivers, physical forces during ground transport over considerable distances may have had a significant impact [23].

Our study has several limitations. Although ventilator data were collected computationally with high sampling rate, patient monitor parameters were not collected; therefore, we had no detailed minute-to-minute information about the infants' condition during transport. Blood gases were capillary samples, because the clinical team did not routinely insert arterial lines in these infants prior to transfer. The pre-transport period in the referring hospitals was short in most cases; therefore, we could not compare respiratory management before and during transport. Finally, we were only able to follow cases up to their discharge from tertiary NICUs and cannot present long term outcome data.

In summary, most ELBW infants transferred ex utero on the first day of life require mechanical ventilation during transfer and can be ventilated with ~5 mL/kg tidal volumes despite their relatively larger dead space.

DATA AVAILABILITY

Datasets generated during the current study are available from the corresponding author on reasonable request. Analysis steps can be accessed via GitHub code repository at https://github.com/belteki/transport_ELBW.

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ACKNOWLEDGEMENTS

We thank to Rainer Kühner (Vyaire) for help with exporting data from the fabian +nCPAP evolution™ and fabian HFO ventilators. We thank to Miklos Szabo (Semmelweis University, Budapest, Hungary) for sharing national statistics on ELBW infants.

AUTHOR CONTRIBUTIONS

VB participated in the conception of the study, collected clinical information, participated in interpretation of results, and edited the manuscript. LL participated in acquisition and interpretation of clinical data and revising the article. AV participated in interpretation of clinical data. AJ participated in interpretation of clinical data and revising the article. ZsS participated ins interpretation of clinical data and revising the article. GB was responsible for the conception of the study, the outline of statistical analysis and interpretation of data, and wrote the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

GB is a consultant to Vyaire Medical (Mettawa, IL, US) and Dräger Medical (Lübeck, Germany). Vyaire Medical did not participate in this research and did not provide any payment for it. The other authors declare no conflict of interest.

ETHICS APPROVAL

The study was approved by the Scientific and Medical Research Council Ethics Committee of Hungary (reference: 40158-2/2018/EKU). Parental consent was waived. The study was performed in accordance with the Declaration of Helsinki.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41372-024-02043-w.

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