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Original article

Delivery room management of infants with less than 27 weeks of gestational age

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Abstract

Background: The medical management of a preterm birth is a challenge, and there is not a definite consensus on how to deal with this situation. The aim of this study was to evaluate the effect of delivery room (DR) management on clinical condition (temperature, peripheral oxygen saturation, blood glucose level, hemoglobin level, mean blood pressure and pH) on the Neonatal Intensive Care Unit (NICU) admission of preterm infants born before 27^{+0} weeks of gestational age (GA).

Methods: This study was performed among all preterm infants with a GA between 23^{+0} and 26^{+6} weeks admitted to the Level III NICU of Centro Hospitalar Universitário de São João (Porto, Portugal) between 1st January 2005 and 31st December 2018. Maternal demographics, gestation information, infants' characteristics, DR and NICU data were evaluated.

Results: A total of 65 preterm neonates were included in this study. The admission pH was associated to the administration of epinephrine in DR (B = -0.786; p = 0.003; 95%CI [-1.282; -0.290]); blood glucose level to body weight at birth (B = 0.253; p = 0.006; 95%CI [0.078; 0.428]) and epinephrine in DR (B = 72.719; p = 0.02; 95%CI [12.530; 132.908]); body temperature to epinephrine administrated in DR (B = -1.703; p = 0.001; 95%CI [-2.692; -0.714]); and hemoglobin level to early continuous positive airway pressure (CPAP) in DR (B = 6.008; p = 0.013; 95%CI [1.356; 10.660]).

Conclusion: DR procedures can have negative or positive effects on early outcomes of preterm newborns. It is crucial to research more about their impact to optimize the NICU management of this particular and challenging neonatal group and support the neonatologists' clinical decisions.

Keywords

Preterm birth, extremely low gestational age, delivery room management, Neonatal Intensive Care Unit, neonatal mortality, neonatal resuscitation.

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Introduction

The World Health Organization states that a preterm birth occurs before 37 completed weeks of gestation or less than 259 days from the first date of a woman's last menstrual period [1]. Prematurity accounts for 5% to 18% of worldwide births and is one of the leading causes of death in children under 5 years old [1]. In fact, it is one of the main causes of neonatal mortality [2, 3] and is related to many neurodevelopmental disturbances, severe impairment, and chronic diseases later in life [4, 5]. Among preterm infants, the risk of abnormalities and mortality are uncertain in the extremely low gestational age newborns (ELGANs), born with less than 28 weeks [2].

The management of a preterm birth is delicate and complex, since it implicates medical, social and ethical issues and challenges [6]. As for this, there is no definite consensus in developed countries on how to approach these cases [7].

Delivery room (DR) procedures in the first minutes of life may have a significant impact on the short- and long-term outcomes of preterm infants. This period is referred to as the "Golden Hour", a term which is also applied in emergency medicine [8]. The management of preterm infants in this critical hour aims for a better neonatal outcome, especially in ELGANs. It should be held by specialized professionals and is structured by many components such as antenatal counselling and team briefing, resuscitation, temperature maintenance, support of the cardiorespiratory system, early nutritional care, hypoglycaemia and infection prevention, initiation of breastfeeding, monitoring and communication with family [9].

The aim of this study was to evaluate the effect of DR management on clinical conditions (pH, hemoglobin level, blood glucose level, peripheral oxygen saturation, mean blood pressure [BP] and body temperature) on Neonatal Intensive Care Unit (NICU) admission of preterm infants born before 27^{+0} weeks of gestational age (GA).

Materials and methods

This retrospective observational study was performed among all preterm infants with a GA between 23^{+0} and 26^{+6} weeks admitted to Level III NICU of Centro Hospitalar Universitário de São João (Porto, Portugal), over 14 years (1st January 2005 until 31st December 2018), with an average of 450 admissions per year, including about 45 very low birth weight (VLBW) infants [10].

After the approval of the institutional Ethics Committee, clinical records were reviewed and the data was collected. We excluded pregnancies with complications such as major congenital or chromosomal anomalies, TORCH (Toxoplasmosis; Others – such as syphilis, parvovirus B19 or varicella-zoster; Rubella; Cytomegalovirus; and Herpes) infection and fetal hydropsis. Outborn infants and those transferred to other healthcare units in the first 24 hours of life were excluded, too.

We did a demographic and perinatal characterization of the mother: age; GA (recorded as complete weeks) – assessment was based on menstrual age (in women with regular menstrual cycles), ultrasound examination (when a discrepancy of two or more weeks existed between the age derived by menstrual dating and the one derived sonographically, or in the absence of a menstrual date) [11] or the New Ballard Score (in the absence of obstetrical indexes) [12]; previous pregnancies; singleton or multiple gestation; assisted reproductive technology; smoking habits; usual medication, alcohol or drug consumption; complete cycles of antenatal corticosteroid (ACS) therapy;

administration of magnesium sulfate; disorders associated with pregnancy such as: gestational diabetes, renal failure, hypertensive disease (defined as maternal BP > 140 mmHg systolic and > 90 mmHg diastolic), preeclampsia (defined as hypertension accompanied with proteinuria), low platelets (HELLP syndrome), feto-fetal transfusion syndrome; clinical chorioamniotitis; placental abruption; placenta previa; fetal growth restriction (defined as estimated fetal weight < 10th centile for GA in Fenton's growth charts [13]); and abnormal umbilical flow.

Due to protocol changes in our centre, the ACS administrated to women before February 2014 was betamethasone, followed by the use of dexamethasone since March 2014. A course consisted of 2 doses of 12 mg of intramuscular betamethasone with 24-hour interval or 4 doses of 6 mg intramuscular dexamethasone every 12 hours.

Data from the peripartum period and labour were also studied. This information included preterm premature rupture of membranes (defined as membrane ruptured > 18 hours before delivery), infant's gender and birth weight, type of delivery, abnormal amniotic fluid, fetal presentation, and Apgar score at 1st and 5th minutes < 5 or < 7, respectively.

DR procedures such as oxygen administration, neonatal resuscitation (endotracheal intubation, chest compressions, epinephrine), ventilation equipments (invasive mechanical ventilation [MV], early continuous positive airway pressure [CPAP]), surfactant administration, and umbilical cord pH level (arterial and venous) were included as well.

Neonates' hemoglobin level (g/dL), platelets (10^3/μL), blood glucose level (mg/dL), peripheral oxygen saturation (SpO_2%), respiratory (cycles per minute) and heart (beats per minute) rates, systolic, diastolic and mean BP (mmHg), temperature (degrees Celsius, ºC) and pH level were evaluated on the newborn admission to the NICU. Neonatal death was also considered.

Regarding clinical condition at NICU admission, we considered: anemia if hemoglobin level < 12 g/dL [14]; hypoglycaemia if blood glucose level < 40 mg/dL; hypoxia if SpO_2 < 94%; hypotension when mean BP < GA [15]; hypothermia if temperature < 36.5ºC [15]; and acidosis if blood pH < 7.25.

The sample was divided into two major groups for the analysis: 24 or 25 weeks of GA and 26 weeks of GA. The preterms born at 23 weeks of GA were only 5, so we decided not to include them in the analysis and show their data separately.

Statistical analysis

Statistical analysis was performed using SPSS®, version 25. Categorical variables were analyzed by absolute and relative frequencies, and continuous variables were analyzed according to their distribution by mean (± standard deviation) for symmetric distribution or median (minimum-maximum) for asymmetric distribution. Categorical variables were evaluated by Chi-squared or Fisher's exact test and continuous variables by Independent t-test or Mann-Whitney U test.

The impact of DR management on NICU admission was evaluated using linear regressions.

A p-value < 0.05 was considered statistically significant.

Results

During the study period, 65 preterm neonates with GA between 23^{+0} and 26^{+6} weeks admitted to the NICU of Centro Hospitalar Universitário de São João were eligible from a total of 197 and included in this study. Maternal data is described in **Tab. 1** whereas newborn data is summarized in **Tab. 2**.

Comparing neonates with 24-25 weeks of GA (n = 33) to 26 weeks of GA (n = 27), the univariate analysis in **Tab. 1** showed statistically significant differences in gemelarity (19 [57.6%] vs 6 [22.2%]; p = 0.006), gestational diabetes (4 [12.1%] vs 10 [37.0%]; p = 0.033), preeclampsia (1 [3.0%] vs 6 [22.2%]; p = 0.039) and abnormal umbilical flow (0 vs 5 [18.5%]; p = 0.015). In **Tab. 2**, we also found through the univariate analysis that there were statistically significant differences between the two groups regarding body weight at birth (695.6 [± 126.8] vs 840.7 [± 179.5]; p = 0.001), eutocic delivery (24 [72.7%] vs 7 [25.9%]; p < 0.001), endotracheal intubation in DR (30 [90.9%] vs 17 [63.0%]; p = 0.026), invasive MV in DR (31 [93.9%] vs 18 [66.7%]; p = 0.009), early CPAP in DR (2 [6.1%] vs 10 [37.0%]; p = 0.004), surfactant in DR (15 [45.5%] vs 5 [18.5%]; p = 0.028) and death (24 [72.7%] vs 8 [29.6%]; p = 0.001).

Multivariate regression analysis of our sample was performed to control potential confounding variables and is shown in **Tab. 3**. The admission

pH was associated to the administration of epinephrine in DR (B = -0.786; p = 0.003; 95%CI [-1.282; -0.290]); body temperature was also related to epinephrine administrated in DR (B = -1.703; p = 0.001; 95%CI [-2.692; -0.714]); the blood glucose level to body weight on birth (B = 0.253; p = 0.006; 95%CI [0.078; 0.428]) and epinephrine in DR (B = 72.719; p = 0.02; 95%CI [12.530; 132.908]); and hemoglobin level to early CPAP in DR (B = 6.008; p = 0.013; 95%CI [1.356; 10.660]).

About the 5 preterms with 23 weeks of GA: 3 (60%) cases were in multiple gestations; 4 (80%) mothers had antenatal corticotherapy but no complete cycles; 1 mother (20%) had preeclampsia; 1 (20%) had HELLP syndrome; and 3 (60%) had clinical chorioamnionitis. 100% of the preterms were intubated, submitted to invasive MV, and had surfactant administration and oxygen supplementation.

Discussion

A preterm infant is fragile and immature and needs special care, time, and attention. Prenatal risk factors, GA, likelihood of survival, potential complications, and parental wishes should be factors taken into consideration when planning the management in DR [16, 17].

A study performed in our centre states that ELGANs delivered between 23 and 25 weeks of GA have high morbidity at discharge since there is an increased risk of respiratory distress syndrome, patent ductus arteriosus, early or late sepsis, intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity and necrotizing enterocolitis. This poor prognosis makes it difficult to decide whether or not to intervene [18]. Soares et al. concluded that from 2010 to 2012 there were more newborns in our NICU that had their therapy limited, DNR (do not resuscitate) decision, or were submitted to palliative care when compared to investigations from years before [19].

We must heed the concept of viability when defining management strategies. Newborns delivered between $23^{0/7}$ and $24^{6/7}$ weeks of GA are considered to be in the "gray zone" of viability by the Portuguese Society of Neonatology [20]. It is globally agreed that below 22 weeks of GA the

Table 1. Maternal data.

		Total [a] (n = 60)	GA = 24-25 w (n = 33)	GA = 26 w (n = 27)	p-value
Maternal age < 35 years		26 (43.3)	4 (12.1)	22 (81.5)	0.294 [b]
Previous gestations		28 (46.7)	14 (41.4)	14 (51.9)	0.228 [b]
Multiple gestation		25 (41.7)	19 (57.6)	6 (22.2)	**0.006** [b]
Feto-fetal transfusion syndrome		4 (6.7)	2 (6.1)	2 (7.4)	0.530 [c]
Assisted reproductive technology		14 (23.3)	10 (30.3)	4 (14.8)	0.223 [c]
Maternal exposure	**Tobacco**	4 (6.7)	1 (3)	3 (11.1)	0.318 [c]
	Alcohol	2 (3.3)	1 (3)	1 (3.7)	0.999 [c]
	Drugs	1 (1.7)	0	1 (3.7)	0.450 [c]
	Medication	18 (30)	9 (27.3)	9 (33.3)	0.610 [b]
Antenatal corticotherapy		57 (95)	31 (93.9)	26 (96.3)	0.999 [c]
Complete cycles		38 (63.3)	19 (57.6)	19 (7.4)	0.568 [c]
Magnesium sulfate		3 (5)	1 (3)	2 (7.4)	0.583 [c]
Gestation diseases	**Gestational diabetes**	14 (23.3)	4 (12.1)	10 (37)	**0.033** [c]
	Renal failure	1 (1.7)	0	1 (3.7)	0.450 [c]
	Hypertensive disease	0	0	0	-
	Preeclampsia	7 (11.7)	1 (3)	6 (22.2)	**0.039** [c]
	HELLP syndrome	3 (5)	0	3 (11.1)	0.085 [c]
Chorioamniotitis		33 (55)	15 (45.5)	18 (66.7)	0.100 [b]
Placental abruption		14 (23.3)	6 (18.2)	8 (29.6)	0.297 [b]
Placenta previa		0	0	0	-
Fetal growth restriction		9 (15)	3 (9.1)	6 (22.2)	0.276 [b]
Abnormal umbilical flow		5 (8.3)	0	5 (18.5)	**0.015** [c]
Membrane rupture > 18 h		6 (10)	3 (9.1)	3 (11.1)	0.989 [c]

Data are presented as n (%).
GA: gestational age; w: weeks; HELLP syndrome: hemolysis, elevated liver enzyme levels and low platelet count.
[a] 5 newborns with 23 weeks of GA were excluded from the analysis; [b] Chi-squared test; [c] Fisher's exact test.

Table 2. Newborn data.

		Total [a] (n = 60)	GA = 24-25 w (n = 33)	GA = 26 w (n = 27)	p-value
DR					
Gender	**Male**	31 (51.7)	20 (60.6)	11 (40.7)	0.126 [b]
	Female	29 (48.3)	13 (39.4)	16 (59.3)	
Birth anthropometrics	**Body weight (g), mean (± SD)**	760.9 (168)	695.6 (126.8)	840.7 (179.5)	**0.001** [d]
Type of delivery	**Eutocic**	31 (51.7)	24 (72.7)	7 (25.9)	**< 0.001** [b]
	C-section	29 (48.3)	9 (27.3)	20 (74)	
Abnormal amniotic fluid		7 (11.7)	6 (18.2)	1 (3.7)	0.116 [c]
Fetal presentation	**Cefalic**	45 (75)	25 (75.8)	20 (75)	0.658 [b]
	Pelvic	15 (25)	8 (24.2)	7 (25.9)	
Apgar 1st min < 5		36 (60)	22 (66.7)	14 (51.9)	0.051 [c]
Apgar 5th min < 7		27 (45)	14 (42.4)	13 (48.2)	0.659 [b]
Oxygen		60 (100)	33 (100)	27 (100)	-
Endotracheal intubation		47 (78.3)	30 (90.9)	17 (63)	**0.026** [b]
Compressions		7 (11.7)	4 (12.1)	3 (11.1)	0.999 [c]
Epinephrine		7 (11.7)	4 (12.1)	3 (11.1)	0.999 [c]
Invasive MV		49 (81.7)	31 (93.9)	18 (66.7)	**0.009** [c]
Early CPAP		12 (20)	2 (6.1)	10 (37)	**0.004** [c]
Surfactant		20 (33.3)	15 (45.5)	5 (18.5)	**0.028** [b]
Umbilical cord pH, median (min-max)	**Arterial**	7.3 (3.4-7.4)	7.3 (7.2-7.4)	7.3 (3.4-7.4)	0.459 [d]
	Venous	7.3 (7-7.4)	7.3 (7.2-7.4)	7.3 (7-7.4)	0.662 [d]
NICU					
Admission pH, median (min-max)		7.3 (3.4-7.5)	7.3 (6.9-7.5)	7.3 (3.4-7.5)	0.376 [d]
Admission pH < 7.25		22 (36.7)	14 (42.4)	8 (29.6)	0.446 [b]
Hemoglobin (g/dL), mean (± SD)		15.02 (2.5)	14.54 (2)	15.59 (2.9)	0.112 [d]
Hemoglobin < 12 g/dL		5 (8.3)	3 (9.1)	2 (7.4)	0.989 [c]
Platelets ($10^3/\mu L$), mean (± SD)		186.29 (53.2)	192.36 (43.2)	178,13 (64.5)	0.336 [d]
Blood glucose level (mg/dL), mean (± SD)		86.80 (60.1)	92.62 (49.9)	79.25 (71.9)	0.461 [d]
Blood glucose level < 40 mg/dL		7 (11.7)	2 (6.1)	5 (18.5)	0.213 [c]
SpO_2, median (min-max)		95 (36.4-100)	93.5 (36.4-100)	96 (64-100)	0.417 [d]
SpO_2 < 94%		25 (41.7)	15 (45.5)	10 (37)	0.458 [b]
Respiratory rate (cpm), mean (± SD)		45.9 (14.1)	45.7 (13.6)	46.2 (15)	0.886 [d]
Heart rate (bpm), mean (± SD)		154.1 (21.5)	156 (24.7)	151.8 (17)	0.461 [d]
BP (mmHg), mean (± SD)	**Systolic**	46.3 (12.7)	44.7 (11.1)	48.2 (14.3)	0.320 [d]
	Diastolic	25.8 (12.5)	24.9 (8.9)	26.9 (15.3)	0.545 [d]
	Mean	32.6 (11.5)	31.5 (8.7)	34 (14.4)	0.442 [d]
	Mean BP < GA	13 (21.7)	5 (15.2)	8 (29.6)	-
Temperature (°C), mean (± SD)		36 (1.2)	36 (1.3)	36 (0.9)	-
Temperature < 36.5°C		35 (58.3)	18 (54.6)	17 (63)	0.347 [b]
Death		32 (52.3)	24 (72.7)	8 (29.6)	**0.001** [b]

Data are presented as n (%) if not otherwise indicated.
GA: gestational age; w: weeks; DR: delivery room; MV: mechanical ventilation; CPAP: continuous positive airway pressure; NICU: Neonatal Intensive Care Unit; BP: blood pressure.
[a] 5 newborns with 23 weeks of GA were excluded from the analysis; [b] Chi-squared test; [c] Fisher's exact test; [d] Independent t-test.

Table 3. Multivariate analysis by linear regression.

NICU outcome	Independent variable [a]	B value	95%CI	p-value
Blood glucose level	**Epinephrine in DR**	72.719	12.530; 132.908	**0.020**
	Birth body weight	0.253	0.078; 0.428	**0.006**
Temperature	**Epinephrine in DR**	-1.703	-2.692; -0.714	**0.001**
Hemoglobin level	**Early CPAP in DR**	6.008	1.356; 10.660	**0.013**
pH level	**Epinephrine in DR**	-0.786	-1.282; -0.290	**0.003**

NICU: Neonatal Intensive Care Unit; 95%CI: 95% confidence interval; DR: delivery room; CPAP: continuous positive airway pressure.
[a] All associations were adjusted for gestational age, birth weight, complete cycles of corticotherapy, gestational diabetes, preeclampsia, chorioamniotitis, abnormal umbilical flow, type of delivery and DR interventions (compressions, epinephrine administration, surfactant, endotracheal intubation, early CPAP and invasive mechanical ventilation).

likelihood of death is high, and infants born with 26 weeks or more of GA have a high likelihood of survival [21]. This definition is changing over time due to progresses that have been made in treatments and biomedical technology [21]. The mortality rate of preterm infants ≤ 24 weeks of GA in Portugal was 71% in 2005 and 63.7% in 2009. However, this was not followed by a decrease in neurological sequelae [22]. In our institution, preterm neonates of 22 weeks are resuscitated only if there is evidence of viability, doubt on datation of pregnancy, or according to parents' wishes [22]. Initiating and withdrawing intensive care is a question that has been discussed over time, but more longitudinal studies, including large numbers of preterm neonates, are warranted to help neonatologists in the clinical decision-making process. Each NICU should also share its results and statistics in order to reach a consensus and establish policies [22, 23].

However, it is known that in many cases "Golden Hour" interventions have a notorious role as they can avoid neonatal mortality in preterms and minimize complications such as bronchopulmonary dysplasia, severe neurologic injury, retinopathy of prematurity, necrotizing enterocolitis, and hospital-acquired infections [8]. The main goal of DR management in the first hour of life is a better neonatal outcome, and these medical procedures based on the best available evidence are very important, especially in ELGANs [9].

Our main search question was to determine how the early management of preterms born before 27^{+0} weeks of GA interferes with clinical parameters on NICU admission. DR interventions have a huge impact on the transition of the newborn to the extrauterine life, and we must be concerned that this impact can be positive or negative [24].

The infusion of epinephrine can be required in neonatal reanimation. Cardiopulmonary arrest leads to poor tissue perfusion. This can cause elevation of blood lactate levels which reflect insufficient transport of oxygen to the tissues and a decrease of pH values, potentially complicating metabolic acidosis [25]. This is a possible explanation for the association found between the administration of catecholamines and its effect on decreasing pH values in NICU admission. There are not many studies exploring the relationship between these 2 variables in the preterm newborn, so it would be pertinent to enhance research in this field.

Nevertheless, a recent study from 2020 reports that lower pH values during neonatal transition causing progressive acidosis and hypoxemia are themselves causes of bradycardia or asystole [26]. The measure of pH values on the umbilical cord is recommended for infants in high-risk situations or Apgar scores < 7; however, there is also a risk of acidosis in normal range Apgar levels, so there is potential utility in measuring cord blood pH values universally [27]. In our centre, obtaining and recording the umbilical cord pH values on delivery was not a usual practice, especially before 2010. There was evident missing data on this variable. As a consequence, we cannot be assured that the acidosis on NICU admission was caused by the same mechanisms that caused umbilical cord acidosis, which promoted cardiac arrest, or if it was a consequence of cardiac failure and poor tissue perfusion. As mentioned before, more investigation must be done.

Even though WHO recommendations [28] to maintain body temperature are respected during stabilization and transfer to NICU, epinephrine administration is the last step on neonatal resuscitation algorithm [25]. Cold stress is common during stabilization in the DR because the infant was used to the warm intrauterine environment [29]. DR temperatures are kept at least at 25ºC, and a polyethylene bag is used to cover the premature neonates, but they are more likely to suffer from this temperature stress since they require more intervention [29]. Premature infants have immature thermoregulatory mechanisms, and their skin is thinner compared to term infants, which leads to higher heat loss through evaporation [29]. These results are not consistent with a study performed among preterms that states that the incidence of hypothermia in NICU admission was lower in preterms that required DR interventions [28]. However, the inclusion criteria of their sample and population differences may contribute to these contradictory results, so we should not discard our findings.

After birth, there is a switch in insulin/glucagon ratio and other factors that trigger gluconeogenesis. This process is highly dependent on precursors such as fatty acids, glycerol, amino acids, and lactate. An increase in body weight can be explained by more fat sources, which will allow glucose production and, therefore, a rise in blood glucose level [30]. Within our cohort, the increase of 1 g in body weight was associated with an increase of blood glucose level measured on NICU admission. However, we

must be aware that glucose metabolism is uncertain and unstable in extremely preterm infants [31]. The first 2 hours after birth are known to be a metabolic period of adaptation [30]. Our conclusion is applied to our sample, which does not discard that lower body weight can be related to higher glucose level as stated in other studies [32]. Each case is individual, and many external and internal factors are involved in the neonatal glucose pathway. The normal glucose level is not well established in neonatology, despite the extensive literature, but we must be informed about the range that is globally accepted since both extremes can have deleterious neurodevelopmental effects [30, 32, 33].

Epinephrine administration also seems to be associated with blood glucose level. The neonatal release of endogenous catecholamines is stimulated by the physiological stress of transition to life outside the uterus [33]. Since they share similar receptors, exogenous epinephrine will have the same effects: it maintains BP, blocks insulin release and action, promotes liver glycogenolysis, stimulates gluconeogenesis and, consequently, blood glucose level increases [32, 33].

The *2019 Update* of the *European Consensus Guidelines on the Management of Respiratory Distress Syndrome* states that spontaneously breathing neonates should be early stabilized in DR with CPAP instead of being intubated to reduce bronchopulmonary dysplasia [34]. A 2019 study in our center agrees that CPAP failure is associated with an increased risk of mortality and morbidities, mainly in infants with < 29 weeks of GA [unpublished data]. What we do know is that anemic preterms require more time on early CPAP to successful weaning [35]. However, how does early CPAP in DR increase hemoglobin concentration? We can think that preterms that require early CPAP are in a better clinical state than those who are intubated, so their clinical parameters are more likely to be normal ranged, and this includes hemoglobin levels. This is definitely a question that has to be investigated since the literature fails to explore this association.

The main strengths of this study were the detailed data included and the innovative research question. Literature extensively lacks in studying DR management and the effect in the clinical condition of preterms in NICU, so it would certainly be valuable to design more and larger clinical trials with this study question.

We should recognize the inherent weaknesses of a retrospective study. This is a limitation of this investigation, but it is difficult to perform prospective studies in ELGANs as the prevalence of cases in our NICU is very low. Indeed, the number of patients was not large enough to have statistically significant results in all outcomes. Another limitation is that we only included data from a single institution.

Conclusion

DR procedures can have benefic effects and improve the outcomes of extremely preterm neonates. However, they may unexpectedly interfere with clinical parameters and have undesirable repercussions. More investigation has to be done in this field in order to optimize the NICU management of this particular and challenging neonatal group.

Declaration of interest

The Authors report no conflicts of interest.

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