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CLINICAL RESEARCH ARTICLE

Vasopressin in newborns with refractory acute pulmonary hypertension

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BACKGROUND: Acute pulmonary hypertension (aPH) in newborns can be life threatening and challenging to manage. In newborns with refractory aPH, there is currently limited therapeutic agents.
METHODS: Retrospective single-center cohort study in newborns less than one month old who were treated with vasopressin for a minimum of one hour in the context of refractory aPH in the neonatal and pediatric intensive care units of a tertiary university center between 2016 and 2022. The objective was to evaluate the efficacy and safety of vasopressin in newborns as an adjuvant treatment for refractory aPH.
RESULTS: Twenty-five patients met inclusion criteria. In patients who received vasopressin, oxygenation index improved from 28.4 to 14.4 ($p = 0.004$) after twelve hours of continuous infusion. Oxygen requirements (FiO_2) decreased from 0.91 to 0.50 ($p = 0.004$) and mean arterial pressure increased from 41 to 51 mmHg ($p = 0.001$). In our cohort, 68% of patients presented an episode of hyponatremia (serum sodium <130 mmol/L).
CONCLUSIONS: The use of vasopressin may be associated with improvement in oxygenation and hemodynamic status of neonatal patients with aPH refractory to initial therapy. Further prospective studies are needed to establish the safety profile of vasopressin in newborns, particularly in preterm infants.

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IMPACT:

- Vasopressin may be an effective cardiotropic agent to improve oxygenation and hemodynamic status in newborns with acute pulmonary hypertension.
- Careful monitoring of serum sodium levels are warranted in newborns who are receiving vasopressin infusion.
- This provides additional evidence for the consideration of vasopressin in newborns with acute pulmonary hypertension refractory to inhaled nitric oxide.

INTRODUCTION

Acute pulmonary hypertension of the newborn (aPH) arises from the inability to relax pulmonary vascular resistance during the postnatal transition, leading to an alteration in pulmonary vasoreactivity.[1,2] This condition manifests as a reduction in pulmonary blood flow, which in turn affects left atrial preload. Consequently, there is a preferential filling of the left atrium through right-to-left shunting via the interatrial communication. This shunting phenomenon, often coupled with concomitant right ventricular pressure overload, is exacerbated by the presence of a patent ductus arteriosus, leading to the entry of hypoxemic blood into the systemic circulation both pre- and post-ductal levels. This clinical presentation is labeled as hypoxemic respiratory failure.[1] Importantly, beyond the transitional period, newborns, particularly preterm infants, are also susceptible to acute pulmonary hypertension, especially when confronted with complications such as sepsis.

The primary treatment approach for aPH typically involves ventilatory support in combination with inhaled nitric oxide (iNO), a pulmonary arterial vasodilator aimed at improving ventilation-perfusion matching by stimulating cyclic guanosine monophosphate (cGMP) production.[3–6] However, a significant challenge arises, as nearly 40% of newborns do not improve oxygenation or aPH echocardiography markers with first-line therapy. As a result, alternative therapeutic agents are often necessary.[4] In cases where newborns remain unresponsive to iNO or exhibit refractory aPH, the available therapeutic options are limited. This limitation underscores the importance of exploring additional treatment strategies to avoid the need for escalation to extracorporeal membrane oxygenation (ECMO) in term infants.[4–6]

Arginine vasopressin is a neuropeptide naturally secreted by the posterior pituitary gland, which regulates sodium homeostasis and serum osmolality. It is released in response to high plasma osmolality or hypovolemia, and exerts a direct systemic

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vasoconstrictor effect through its action on V1 receptors. Activation of V1 receptors by exogenous vasopressin in the pulmonary circulation has been described to be associated with a pulmonary vasodilation effect, through the production of nitric oxide within the pulmonary endothelium.[3,7] Vasopressin also plays an important homeostatic role in shock, as its vasoconstrictive effects are preserved during severe hypoxia and acidosis.[8–12] Cases reports and series have documented promising outcomes associated with vasopressin infusion as a potential therapeutic option in newborns with aPH.[13–17] Despite vasopressin's use in pediatric septic shock and its demonstrated efficacy in premature infants with systemic hypotension refractory to inotropic agents, there is a paucity of data in the current literature supporting its systematic application in the context of hypoxemic respiratory failure secondary to aPH, both in term and preterm infants.[14,16,17]

Our study aims to assess the effectiveness of vasopressin infusion as an adjunct to iNO in managing refractory neonatal aPH, as well as provide insights into its safety profile.

METHODOLOGY

Study population

This was single center retrospective cohort study. All newborns, preterms and terms, were included if vasopressin was used within the first 30 postnatal days, and when hospitalized between January 1ʳ 2016, and May 1ʳ 2022, in the academic tertiary care neonatal or pediatric intensive care units at the CHU de Québec. Patients, who were already receiving iNO for management of aPH, had to be exposed to vasopressin for a minimum of one hour in order to be included in this study. Patients were excluded if acute pulmonary hypertension resulted from lethal congenital diseases (e.g., bilateral renal agenesis with pulmonary hypoplasia), decision to redirect care prior to the use of vasopressin and if patients did not have arterial access such as arterial umbilical line or peripheral arterial line.

This study was approved by the CHU de Quebec research ethics board committee.

Definitions

aPH was defined by echocardiography: bidirectional or right to left shunt at the ductal or atrial level(s), and/or isosystemic or suprasystemic pulmonary artery pressure to systemic pressure estimated by tricuspid regurgitation (TR) jet, and/or flat or bowing interventricular septal movement.

Refractory aPH was defined as: non-improvement or worsening pulmonary hypertension on echocardiography (indicated by increasing estimated systolic pulmonary artery pressure by TR jet and/or deteriorating interventricular septal movement in systole and/or change in direction of flow to right to left shunt from baseline), or persistent pre-and post-ductal saturation differential >10%, or lack of improvement in oxygenation status (indicated by no reduction in FiO_2 despite use of iNO at 20 ppm and optimized ventilatory support).

Hyponatremia was defined as serum sodium <130 mmol/L. Thrombocytopenia was defined as platelet count <150. Ischemic events were defined as necrotizing enterocolitis (NEC) defined as stage 2 or more according to the Bell's classification, spontaneous intestinal perforation, peripheral vascular ischemia and hepatic necrosis.

Outcomes

The primary outcome for vasopressin efficacy was change in oxygenation index (OI = mean airway pressure x FiO_2 x 100/PaO_2 measured by arterial access) from baseline to 12 and 24 h after initiating vasopressin infusion.

Secondary outcomes for vasopressin efficacy were changes in PaO_2, FiO_2, blood pressure, urine output, and blood lactate from the time of initiating vasopressin to 12 and 24 h of vasopressin infusion. Moreover, echocardiographic parameters of pulmonary hypertension (direction of shunt, interventricular septum position in systole, estimated systolic pulmonary artery pressure) were examined during vasopressin infusion. For safety outcomes, we evaluated the occurrence of hyponatremia, worsening of renal (urea/creatinine) and hepatic (AST: aspartate aminotransferase/ ALT: alanine aminotransferase, INR) biomarkers, thrombocytopenia, occurrence of thrombosis and ischemic events and mortality.

Clinical parameters

A single investigator manually carried out data extraction and medical record revision. Newborns who received vasopressin were identified through the hospital pharmacy database. Baseline demographic characteristics such as gestational age, birth weight, sex and Apgar score were collected. In addition, the following clinical variables were extracted prior to, at the time of initiating vasopressin and after 12 and 24 h of vasopressin infusion: invasive blood pressure (systolic, diastolic and mean) measured at the peripheral arterial line or at the arterial umbilical line level, FiO_2, PaO_2, urine output, lactate and number of inotropes and vasopressors used (including hydrocortisone). Descriptive variables for the use of vasopressin such as starting dose, maximal dose, duration of infusion and age and weight at vasopressin initiation were collected. The following variables were collected (and compared to baseline prior to vasopressin initiation) to assess safety after 12 and 24 h of vasopressin infusion: sodium levels, platelets count, and serum creatinine. Lowest sodium level during infusion as well as ischemic and thrombotic events and mortality were collected. The following echocardiography parameters were collected: estimated systolic pulmonary artery pressure by TR jet, direction of flow through the patent foramen ovale and the patent ductus arteriosus, and interventricular septum position (round, flat or bowing) in systole.

Drug administration

Vasopressin was administered through a central line at a concentration of 0.2 mg/mL prepared in sodium chloride 0.9%. The bag was changed every 12 h for stability. In accordance with our unit guidelines, the recommended initial dosage was 0.3 µU/kg/min, with a maximum dosage of 1 µU/kg/min. Dose escalation, based on clinical and/or echocardiography assessments, was suggested by the neonatal hemodynamics team or by the attending neonatologist/intensivist at a rate of 0.3 µU/kg/min every 30–60 min.

Statistical analysis

Continuous variables are described as median with interquartile range and categorical variables as counts and percentages. Wilcoxon rank test was used to analyze continuous data and chi-square test was used for categorical data comparisons. In case of multiple comparisons, the Bonferroni adjustment was applied. Generalized Estimating Equation (GEE) linear regression models were fitted to test the repeated measures data. The structure of the GEE correlation matrix was chosen by minimum quasi-likelihood under the criterion of the independence model. Period-specific comparisons were made by the paired Wilcoxon signed rank test. Finally, McNemar's tests were used to test the data dichotomized by periods. Statistical analyzes were performed using SAS v.9.2 statistical software (SAS Institute, Cary, North Carolina) with a two-sided significance level set at $p < 0.05$.

RESULTS

Demographics

Thirty patients were identified from the hospital pharmacy database and twenty-five patients met study inclusion criteria. Five patients were excluded for missing data for both primary and secondary outcomes. There were 14 term infants and 11 preterm

Table 1. Demographics.

	N = 25
Gestational age (weeks)	37.5 (34.4–39.6)
Birth weight (g)	2790 (1855–3170)
Sex – no. (%)	
– Female	14 (56)
– Male	11 (44)
Apgar Score	
– 1 min	4 (1–6)
– 5 min	6 (5–8)
– 10 min	7 (6–9)
Reason to initiate Vasopressin– no (%)	
– Hypoxemic respiratory failure	8 (32)
– Cardiovascular compromise	2 (8)
– Hypoxemia and cardiovascular compromise	15 (60)
Age at initiation of vasopressin (days)	2 (1–4)
Weight at initiation of vasopressin (g)	2930 (2060–3300)
Duration of vasopressin use (hours)	72 (42–122)
Medication use prior to vasopressin initiation, no (%)	
– Inhaled nitric oxyde	25 (100)
– Hydrocortisone	20 (80)
– Epinephrine	16 (64)
– Milrinone	8 (32)
– Dopamine	6 (24)
– Sildenafil	3 (12)
– Dobutamine	1 (4)
Vasopressin dose (μU/kg/min)	
– At initiation	0.3 (0.3–0.3)
– Maximal dose	0.6 (0.4–0.8)
Length of hospitalization (days)	42 (8–94)
Invasive ventilation (days)	8 (4–16)
Mortality, *n* (%)	9 (36)
Age at death (days)	6 (4–10)

Data are presented as median (IQR), categorial data as counts (n) and percentages (%).

infants (of which 5 were <32 weeks gestational age at birth). There were 23 patients with aPH in their transitional phase (after birth) and two patients with late-onset aPH (after first week of life). Patient demographics and outcomes are shown in Table 1. The median gestational age was 37 weeks and median birth weight was 2790 g. All patients had a confirmed aPH diagnosis by echocardiography. Refractory aPH was diagnosed by echocardiography prior to the initiation of vasopressin in 22 patients, and three patients were diagnosed based on both persistent pre-and post-ductal saturation differences and a lack of improvement in oxygenation.

Vasopressin was started at a median age of 2 days of life, at median dose of 0.3 μU/kg/min and for a median duration of 72 h of continuous infusion (minimum use: 6 h, maximum use: 300 h). Prior to the introduction of vasopressin, all patients received iNO at median concentrations of 20 ppm (Table 1).

Primary outcomes

As shown in Table 2, there was improvement in OI under vasopressin (median 28.4 to 14.4 after 12 h of treatment, $p = 0.003$). This same effect was maintained over time as evidenced by median of OI of 12.5 ($p = 0.003$) after 24 h of treatment.

Secondary Outcomes

There was a decrease in FiO_2 requirements from a median of 0.91–0.50 ($p = 0.004$) and a concomitant increase in PaO_2 after 12 to 24 h of treatment with vasopressin. The mean arterial pressure increased from 41 to 51 mmHg ($p = 0.001$) following 24 h of continuous vasopressin infusion (Table 2). The same effect was observed with the systolic and diastolic arterial pressures over the first 24 h of vasopressin infusion (Fig. 1).

Echocardiography assessment after vasopressin initiation was available for 17 patients. The estimated systolic pulmonary artery pressure by TR jet improved from a median of 74 mmHg before vasopressin to a median of 56.5 mmHg after 24 h of vasopressin ($p = 0.13$, $n = 8$). The interventricular septum position in systole was flat or bowing in 52% of patients before vasopressin and in 40% of patients after 24 h of vasopressin ($p = 0.31$, $n = 17$). Direction of flow in the foramen ovale was right to left in 20% of patients before vasopressin and in 12% of patients after 24 h of vasopressin ($p = 0.16$, $n = 17$).

In our cohort, 17 (68%) patients treated with vasopressin experienced an episode of significant hyponatremia (Table 3) with a mean minimum serum sodium of 128.8 (±6.7). No statistically and clinically significant changes in renal and hepatic biomarkers were observed. No cases of hepatic necrosis or peripheral ischemia were reported. One case of spontaneous intestinal perforation and three cases of NEC were noted in the seven days following initiation of vasopressin infusion. No patients received ECMO. In the cohort, 9 (36%) patients died from conditions related to their initial illness (6 patients) or following a decision to redirect care (3 patients).

DISCUSSION

Our retrospective cohort study aimed to assess the efficacy and safety of vasopressin in the management of aPH in a population of twenty-five newborns. The findings from this study demonstrated potential benefits and considerations surrounding the use of vasopressin in this specific clinical context.

Efficacy of vasopressin

One of the key observations in our study was the improvement in oxygenation indices after twelve and twenty-four hours of vasopressin infusion. This finding aligns with previous reports on the effects of vasopressin in persistent pulmonary arterial hypertension in both preterm and term neonates.[11,12,18–20] The ability of vasopressin to significantly increase mean arterial pressure and reduce oxygen requirements, especially in premature infants experiencing vasodilatory shock, has been documented.[17]

Our results also demonstrated a progressive increase in PaO_2 and a corresponding decrease in the fraction of oxygen support required in patients exposed to vasopressin. This improvement in oxygenation is a critical factor in mitigating the hypoxemic respiratory failure seen in aPH. Moreover, vasopressin contributed to enhancing systolic, diastolic, and mean arterial pressures after twelve hours of treatment, suggesting its potential role in improving systemic perfusion and cardiac function.

Importantly, we observed a trend towards decreasing blood lactate levels and increasing diuresis in patients receiving vasopressin. These findings indicate that vasopressin did not exacerbate metabolic acidosis or renal dysfunction, and it may even have a positive impact in these aspects.

Rationale for vasopressin in aPH

Our study underscores the rationale for considering vasopressin as a therapeutic option in refractory aPH. Acute pulmonary

Table 2. Efficacy of vasopressin.

Efficacy	Pre-treatment	12 h per-treatment	24 h per-treatment
Oxygenation index	28.4 (26.3–35.7)	14.4 (8.8–27.9)*	12.5 (6.7–23.2)*
FiO_2	0.91 (0.69,1.0)	0.5 (0.4–0.9)*	0.5 (0.4–0.8)*
PaO_2 (mmHg)	42 (33–47)	48 (44–59)*	56 (39–79)*
Systolic blood pressure (mmHg)	52 (44–62)	60 (51–73)*	67 (60–76)*
Diastolic blood pressure (mmHg)	34 (31–39)	40 (34–48)*	41 (38–50)*
Mean blood pressure (mmHg)	41 (36–50)	51 (41–59)*	51 (47–58)*
Urine output– ml/kg/h	1.7 (0.7–2.9)	2.4 (0.9–3.2)	2.4 (1.2–3.1)
Serum lactate (mmol/L)	3.6 (2.1–6.0)	2.8 (1.8–7.3)	2.4 (1.4–5.6)

Data are presented as median (IQR).
*$P < 0.05$ (in comparison to pre-treatment status).
FiO_2 Fraction inspired oxygen, *PaO_2* partial pressure of oxygen.

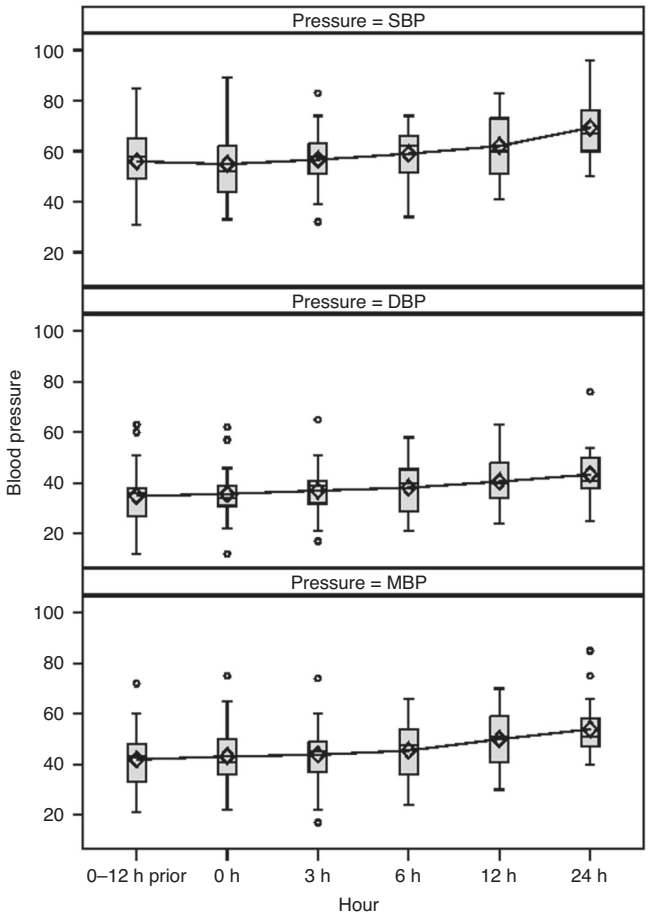

Fig. 1 Blood pressure with vasopressin infusion over 24 h. SBP Systolic blood pressure, DBP Diastolic blood pressure, MBP Mean blood pressure.

hypertension often leads to right ventricular dysfunction, reduced left ventricular preload, low cardiac output, and systemic hypoperfusion with low systemic arterial pressure.[21] Vasopressin's ability to act as a pulmonary vasodilator, as shown in animal studies, may be advantageous in reducing pulmonary vascular resistance and facilitating pulmonary blood flow. Additionally, in cases of refractory aPH with hypotension, vasopressin's systemic vasoconstrictive effects may prove beneficial by improving coronary perfusion pressure and RV preload.[22–24] Our study aligns with this hypothesis, as we observed a positive effect on oxygenation and hemodynamics.

Table 3. Safety of vasopressin.

Safety	
Minimal sodium plasma level (mmol/L), mean (±SD)	128.8 (±6.7)
Sodium plasma level (mmol/L)	
– Prior to treatment	135 (131–143)
– 12–24 h per treatment	133 (127–136)
Alanine aminotransferase (U/L)	
– Pre-treatment	24 (14–34)
– 12–24 h per treatment	31 (15–58)
Serum creatinine (umol/L)	
– Pre-treatment	71.0 (59.0–84.0)
– 12–24 h per treatment	68.5 (41.0–96.0)
Platelets count (x 10^9)	
– Pre-treatment	121 (103–178)
– 12–24 h per treatment	120 (81–182)
Ischemic events up to 7 days after vasopressin initiation, no (%)	
– Hepatic necrosis	0 (0)
– Peripheral ischemia or thrombosis	0 (0)
– Necrotizing enterocolitis	3 (12)
– Spontaneous intestinal perforation	1 (4)

Data are presented as median (IQR), categorial data as counts (n) and percentages (%).

Comparative agents in aPH

Animal study conducted on rats with pulmonary hypertension demonstrated a restoration of baseline hemodynamic parameters and cardiac function following vasopressin infusion, in contrast to the effects observed with norepinephrine and phenylephrine administration.[25] This experimental evidence suggests that vasopressin may present as a more suitable therapeutic agent than norepinephrine in cases of acute pulmonary hypertension accompanied by systemic hypotension.[25] Moreover, an ovine model of pulmonary hypertension has provided further insights, suggesting that norepinephrine might function as a pulmonary vasoconstrictor when administered concurrently with oxygen.[26] At present, there is a paucity of neonatal clinical data directly comparing both agents in the context of aPH.

Historically, dopamine has been the predominant vasopressor employed in managing such cases to enhance systemic resistance.[27] However, it is worth noting that dopamine's mechanism of action also involves an increase in pulmonary vascular resistance, potentially exacerbating hypoxia and adversely affecting right ventricular (RV) afterload.[28] Furthermore, in neonates with aPH and concomitant hypotension, there exists the risk of insufficient coronary perfusion pressure, potentially leading to myocardial ischemia and RV dysfunction.[28] In this regard, vasopressin emerges as a promising agent, as it may facilitate the restoration of adequate pulmonary blood flow to support systemic oxygen delivery while simultaneously optimizing coronary perfusion pressure.

Safety of vasopressin

As previously reported,[8] a high incidence of hyponatremia was observed within our cohort. Hyponatremia was effectively managed through a combination of fluid restriction and sodium supplementation, obviating the need for hypertonic saline treatment or discontinuation of vasopressin infusion. No patients experienced hyponatremia-related complications. Furthermore, despite the presence of low sodium levels, urine output did not decline during vasopressin infusion and exhibited a trend towards improvement ($p = 0.06$). This phenomenon can be attributed to vasopressin's antidiuretic activity mediated via renal V2 receptors. Its interaction with these receptors facilitates the integration of aquaporin 2 channels in the apical membrane of the renal collecting duct, resulting in enhanced free water reabsorption.[29] These findings underscore the importance of cautious monitoring of sodium levels, meticulous fluid management, and judicious sodium supplementation in intravenous fluids when administering vasopressin.

Within our cohort, we identified three cases of NEC. All three patients who presented with NEC were preterm infants, with two born at 30 weeks' gestational age and one at 34 weeks with intrauterine growth restriction (IUGR). None of these patients died from the condition. The population we studied displayed a particularly fragile clinical state, and many of these patients exhibited multiple comorbidities, including prematurity, which heightened their susceptibility to necrotizing enterocolitis. Furthermore, the substantial mortality rate observed in our cohort (36%), underscores the severity of illness and the critical conditions faced by the patients included in this study. It is important to note that vasopressin exposure was just one of several interventions provided to these vulnerable patients, and a direct link between vasopressin use and mortality could not be established.

Limitations

Our cohort represents one of the largest populations of newborns exposed to vasopressin in the context of acute pulmonary hypertension. We offer valuable insights into the safety profile of vasopressin, particularly its relationship with sodium level fluctuations. Nevertheless, we acknowledge the limitations inherent to our study. These limitations include the relatively small cohort size, the retrospective observational monocentric design, and the inherent complexities associated with isolating the temporal effects of a single intervention within a broader framework of management strategies, particularly in the context of severe neonatal illnesses like aPH. It is noteworthy that some patients may have experienced improvements beyond the 24-h study period, potentially influenced by the effects of vasopressin or other concurrent treatments. Furthermore, we were unable to explore the isolated impact of other concomitant treatments, such as adjustments in ventilatory support or the influence of additional medications. Although, it is worth noting that only two patients received additional cardiotropic agents (norepinephrine and milrinone) within 24 h of initiating vasopressin. Additionally, the availability of data for various echocardiographic parameters was limited in certain neonates. Lastly, the approach to managing acute pulmonary hypertension at the time of the study was clinician-driven and lacked standardization.

CONCLUSION

In conclusion, our study provides valuable insights into the efficacy and safety of vasopressin as an adjunctive therapy for aPH in neonates. The observed improvements in oxygenation, hemodynamics, and metabolic parameters suggest that vasopressin may hold promise in the management of this challenging clinical condition. However, larger, prospective studies are needed to validate these findings and establish optimal treatment protocols for aPH in neonates. Future research using vasopressin should evaluate its potential to prevent neonatal mortality in comparison to other agents commonly used in the setting of neonatal acute pulmonary hypertension and safety profile in preterm infants.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

Each author has met the *Pediatric Research* authorship requirements. S.O. contributed to conception and design, acquisition of data, analysis and interpretation of data, drafting of the article and final approval of the version to be published. C.D. contributed to conception and design, drafting of the article and final approval of the version to be published. G.M. contributed to conception and design, drafting of the article and final approval of the version to be published A.P. contributed to conception and design, drafting of the article and final approval of the version to be published. A.H. contributed to conception and design, drafting of the article and final approval of the version to be published.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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