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PERSISTENCE OF ARTERIAL PH INFLUENCE ON OXYGENATION IN THE TREATMENT OF INFANTS WITH INHALED NITRIC OXIDE: A COMPREHENSIVE ANALYSIS

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ABSTRACT

An empirical study found that infants received Inhaled nitric oxide have significant oxygenation issues due to pH. During 98 hours of life, 142 infants receiving Inhaled nitric oxide were charted for demographic details, ventilation settings, arterial blood gases (ABGs), and interventions. It was noted that there was a need for ECMO and that the patient would survive until discharge. A mean blood pressure measurement was conducted, as well as a mean airway pressure measurement. Our primary outcome of interest was the arterial/alveolar (a/A) ratio in order to assess the clinical outcomes. Fisher's exact test and simple linear regression analyses were used in the analysis, along with the multiple linear regression analysis. In order to define pH responsiveness, the correlation coefficient (CC) had to exceed 0.40 with a P value of 0.05. The mean gestational age and birth weight were 35.5 weeks and 3700 grams, respectively. PPHN was clinically diagnosed in all patients. The a/A ratio was not correlated with the MAP or MBP in 82 out of 142 infants. six responders had critical pH levels greater than 7.41. Among 26 patients who needed ECMO, eight showed some signs of responsiveness. It was necessary for six responders to receive ECMO. This small study suggested that the inability to respond to Inhaled nitric oxide could be a result of inability or failure to optimize pH levels. It is not recommended to maintain pH levels greater than 7.5 while using hyperventilation to do this.

Key words: Nitric oxide, ECMO, Hyperventilation, MAP, MBP.

INTRODUCTION

Neonates suffering hypoxemic respiratory failure require extracorporeal membrane oxygenation (ECMO) as a significant cause of morbidity and mortality. A new born's persistent pulmonary hypertension (PPHN) is due to persistent pulmonary vascular resistance (PVR). [1]. Conventional interventions are ineffective for treating severe hypoxemia caused by increased PVR, such as treating right-ventricular dilatation and tricuspid insufficiency [2]. The ECMO therapy is usually administered as a last resort to infants in the event that other treatments do not work. Several randomized controlled trials conducted over the past decade and a half have demonstrated that INO therapy improves oxygenation and reduces the need for ECMO in infants with hypoxic respiratory failure at near-term [3–8]. Based on these pivotal clinical trials, it has been calculated that up to 40% of the infants who received Inhaled nitric oxide treatment needed ECMO in order to survive. An inverse relationship exists between lung aeration and Inhaled nitric oxide response with high-frequency ventilation and exogenous surfactants. In spite of these approaches, INO is not effective in the majority of infants.

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The use of Inhaled nitric oxide as part of our treatment plan is routine during the treatment of infants who have hypoxic respiratory failure when high-frequency ventilation, oxygen, inotropic support, and surfactants haven't helped them improve. When necessary, such as in the case of respiratory dystopia in preterm babies or meconium aspiration syndrome, it is necessary to use Inhaled nitric oxide. The effectiveness of Inhaled nitric oxide seems to be greater in infants whose arterial pH is higher than 7.40-7.45, rather than for baby who has a low or acidotic pH less than 7.35. At times, the highest arterial pH may be able to restore the response of the infant to Inhaled nitric oxide which had previously failed.

Despite Heidersbach *et al.* finding that Inhaled nitric oxide -induced pulmonary vasodilation was enhanced in an animal model when systemic arterial pH > 7.40, a detailed literature review has failed to substantiate this finding clinically. Patients treated with Inhaled nitric oxide for severe hypoxemic respiratory failure were studied for arterial pH and oxygenation.

STUDY PLAN

During the five-year period of our HIPAA waiver application, the neonatal information system (NIS) database was searched for term and near-term infants treated for PPHN by inhaled nitric oxide. The medical records were numbered sequentially for organizational purposes. Based on the review of the available records, the principal investigator recorded the following information (AMB) based on the information obtained from the records: gender, ethnicity, gestational age, birth weight, maternal age, the patient's age at presentation, the primary diagnosis, and echocardiographic evidence that she has PPHN (an elevated right ventricular pressure without or with right to left shunting), as well as those who were born with Dopamine and Dobutamine, epinephrine, hydrocortisone, as well as those who had been on antibiotics and did not recover without the use of ECMO). Data collection forms were used to collect and organize the data, which was then categorized by numbers on a form.

Moreover, a number of additional data were also collected for each infant in the study, including a baseline arterial blood gas (ABG), which refers to the arterial blood gas before the iNO therapy was initiated. During the initial stage of iNO therapy, the infant's age was taken into account, along with a baseline ventilation mode and setting, as well as a post-iNO ABG (the first gas after initiation of iNO therapy)

It has been determined that after the patient was on iNO for 96 hours (or until the patient was removed from the iNO system for recovery, ECMO, or death), we collected all available ABG results. We were able to calculate the mean blood pressure during the blood gas measurement. We calculated the mean airway pressure during the blood gas measurement as well. Among other interventions, we changed ventilation, administered pH interventions (sodium bicarbonate, THAM, fluid bolus), and added surfactants. As with the outcome, the extent of PPHN was determined by echocardiography (increased right ventricular pressures due to right-to-left shunts) and the type of inborn or out born status, amount of dopamine administered, amount of dobutamine administered, or use of epinephrine administered, antibiotic administered, and the outcome (death, ECMO, or recovery without ECMO). Documentation of the information was done using a data collection form. It is routine in our NICU to use fluid boluses and sodium bicarbonate in order to correct metabolic acidosis in infants with PPHN. If symptoms of hypovolemia such as tachycardia and poor perfusion are present, fluid boluses may also be used to maintain blood pressure. Whenever metabolic acidosis is accompanied by poor ventilation (excessive $PaCO_2$), THAM is used. For the purpose of induced alkalosis, sodium bicarbonate or THAM are not recommended. The majority of patients with hypotension who are refractory to volume expansion and need the maximum amount of dopamine and dobutamine are administered hydrocortisone in our unit. Blood gas determinations are usually taken on the hour for all PPHN patients, and MAP and MBP are performed on a daily basis. Blood gas determinations were based on the MAP and MBP of the subjects closest to the time of the measurements. Once you've stabilized an infant, ABG measurements should be performed every two to four hours (or more often) depending on their clinical condition.

STATISTICAL METHODS

Following univariate analyses of pH, MBP, MAP, and the time since the onset of iNO versus the a/A ratio, the correlation coefficient (CC) was determined. It is known that the pH sensitivity of infants decreases as they begin to experience vasoconstriction, therefore, if a correlative coefficient of >0.40 and a probability of 0.05 were considered, the analysis was limited to the duration of the period of responsiveness, if any. Investigators determined this period by examining pH and PaO_2 data. Based on pH, MBP, MAP, and time, a multiple linear regression analysis was conducted to determine whether each dependent variable impacted responsiveness independently. ECMO requirements for pH responders and non-responders were compared using Fisher's exact test. The "critical pH" at which oxygenation responds was determined by examining pH versus PaO_2 graphs for each patient. An inflection point on the a/A ratio versus pH graph was used to determine the critical pH of a patient. Of 62 inflection points, 38 were for pH-responsive infants. We arbitrarily chose a pH for the remainder of the infants whose PaO_2 exceeded 100 mmHg at FiO2 of 1.0 at which pH and a/A ratio tended to be linear.

Table 1: The demographics of study participants according to their level of pH sensitivity.

	Respondents (*n* = 42); (29.57%)	Non-respondents (*n* = 60) (42.25%)
Mean birth weight Mean gestational age Males: females	3200 gm (2030-5165) 37 wk (35.12–40.76) 44: 34	3157gm (2670–4200) 37.4 wk (35.14–41.71) 42: 22
Primary diagnosis		
Meconium aspiration syndrome (MAS)	26 (18.30%)	28 (19.71%)
Congenital diaphragmatic hernia (CDH)	2 (1.4%)	6 (4.22%)
Asphyxia	2 (1.4%)	6 (4.22%)
Pneumonia	10 (7.04%)	12 (8.45%)
Blood aspiration	6 (4.22%)	0
Sepsis	12 (8.45%)	10 (7.04%)
Cardiomyopathy	14 (9.85%)	0
Respiratory distress syndrome (RDS)	8 (5.63%)	0
ECMO	8 (5.63%)	18 (12.67%)
Mean age at iNO initiation	22.8 hours	24.2 hours
Survival to discharge	82 (57.74%)	58 (40.84%)
No ECMO	56 (39.43%)	24 (16.90%)

RESULTS

It can be seen in Table 1 that the study participants have a variety of demographic characteristics. Comparing pH responders with non-responders revealed that statistical significance of comparing pH responders and non-responders showed that average birth weight, primary diagnosis, primary age at which the patients were initiated to iNO treatment, and the mean age at which they responded to iNO treatment did not differ significantly from the average birth weight, primary diagnosis, or primary age at which the patients were initiated to iNO treatment. In both groups, there were a greater proportion of male patients in comparison to female patients, and there was a greater proportion of male patients in the group that did not respond to pH.

The percentage of out born infants was 92%. There was a need to treat possible sepsis in all of the infants before providing antibiotics to prevent possible sepsis, as well as dopamine and dobutamine (at maximum doses of 20 mg/kg/min) to support the infant in order to alleviate the symptoms of sepsis. 64 out of 142 patients (63%) were treated with hydrocortisone for low blood pressure. There was an elevation in the right cardiac pressure in 94 of 142 infants indicating pulmonary hypertension. It was found that 70% of babies who responded to pH were on high-frequency ventilation (HFV) when iNO was initiated, compared with 77% of those who didn't. Among the 70 infants in each group, one infant was treated with HFOV (high-frequency oscillatory ventilation), while the other 70 were treated with HFJV (high-frequency jet ventilation). In order to ensure a good start in life, all infants should be administered 20 ppm iNO at birth. 82 out of 142 infants were classified as pH responders according to the statistical methods section. Responders generally had a critical pH of 7.4 to 7.6, with fourty of the eighty-two infants having a critical pH of 7.5 or higher. More than 7.55 was the critical pH in only six cases.

Based on the analysis of the methods section of this paper, we have observed two patterns of pH responsiveness observed for individuals. A linear relationship was observed between pH and a/A ratio; a more complex response was observed between a/A and pH. As oxygenation increased, pH's influence on oxygenation declined as the infant transitioned from predominantly air to predominantly oxygen.

There was no correlation between pH and oxygenation and mean blood pressure when multiple logistic regression was used. pH-responsive infants had weak correlations between MBP and oxygenation, while pH-unresponsive infants didn't have any correlations. While oxygenation usually correlated positively with MAP, MAP correlated negatively with the a/A ratio. In the infants, extrapulmonary shunting rather than intrapulmonary shunting caused hypoxemia, so increased MAP did not improve their condition. All other therapeutic interventions we investigated failed to show a significant correlation with a/A ratio.

In spite of the fact that the critical pH of individual patients varied greatly from those of other patients, there was a significant positive correlation with the correlation for

individual patients (range 0.427 to 0.938, P = 0.0001 to 0.04) than it was with the correlation for the entire pH responder group (CC = 0.303, P < 0.0001).

DISCUSSION

In order to facilitate iNO responses, blood pressure levels must be supported, lung ventilation must be optimal, and sedation must be adequate. For many years, alkalosis has been the mainstay of treatment for PPHN despite the lack of long-term safety evidence (without long-term follow-up) [9]. Heidersbach and colleagues observed dose-dependent vasodilation in lambs after oxygen, alkalosis, and nitric oxide inhalation. iNO-induced pulmonary vasodilation was enhanced by systemic arterial pH over 7.40 when the therapies were combined in the absence of each other [10]. The purpose of this review is to examine whether the empiric observation that iNO treatment restores pH responsiveness to babies with PPHN is valid. Using the previously described criteria (positive correlation coefficient of > 0.40 with a *P* value of < 0.05, for a/A ratio versus pH), pH responsiveness was found in 61% of the infants studied—however, some degree of responsiveness was seen in many other infants who did not meet the strict criteria for pH response. On iNO, ten infants maintained a pH > 7.40 and good oxygen saturation at all times. In spite of not having been tested for pH sensitivity, our definition of non-responders includes them. It usually takes a few hours for pH responsiveness to appear during the early stages of iNO therapy [11].

The critical pH of most infants with pH-responsiveness ranged between 7.4 and 7.5. All six pH responsive infants who eventually required ECMO had a “critical pH” greater than 7.5. In some cases, alkalosis was intentionally avoided, and ECMO was required to maintain adequate oxygenation. We conclude that modest degrees of alkalosis may not be enough to achieve sustainable benefit unless inhaled nitric oxide responsiveness is achieved. Hypocapnia compensates for hypoxic vasoconstriction, thereby increasing blood flow in infants with PPHN [12]. Considering that over ventilating infants for this purpose could lead to long-term lung damage, it is not recommended to over ventilate them for this purpose. Using the previously described criteria (positive correlation coefficient of > 0.40 with a *P* value of < 0.05, for a/A ratio versus pH), pH responsiveness was found in 61% of the infants studied—however, some degree of responsiveness was seen in many other infants who did not meet the strict criteria for pH response. In ten cases, all infants demonstrated good oxygen saturation and pH > 7.40 while on Inhaled nitric oxide [13]. Non-responders are included in our definition of non-responders even if they were not tested for pH sensitivity. After iNO therapy starts, pH responsiveness typically takes hours to appear.

There are several limitations to this study, including that it is retrospective, there is limited follow-up and the sample size is quite small, in addition to the fact that it is a retrospective study. As some infants had a wide range of pH experiences, it was impossible to determine how pH affected infant iNO response. In the laboratory, similar relationships have been observed, and the observed relationship clearly has a pathophysiological explanation [14]. However, the relationship presented here is merely an association and may not be causal. According to this theory, improved oxygenation is related to higher pH, since well-ventilated lung regions are selectively vascularized. In a number of instances, however, as the level of oxygenation immediately improved at a higher pH, the ventilator settings were reduced and, as $PaCO_2$ rose and pH declined, hypoxemia reverted back, even though Inhaled nitric oxide therapy was continued for a considerable time [15]. Therefore, the effect goes beyond Inhaled nitric oxide directly influencing ventilation effectiveness. The main factor contributing to pH changes was a reduction in pH levels as a result of lower PCO_2 levels, which was occasionally treated with sodium bicarbonate infusions. In other words, increasing ventilator support and improving lung aeration might also contribute to some of the observed "pH responsiveness."

CONCLUSION

Our findings suggest that pH optimization in the high normal range can be an effective adjunct to inhaled nitric oxide therapy despite these limitations. In order to maximize the chances of a new born's optimal response to iNO, this strategy should be included on the list of actions one might take. It is impossible to analyse whether mild to moderate alkalosis prevented ECMO because follow-up data on adverse neurodevelopmental outcomes are lacking. A prospective randomized trial with long-term follow up is necessary to accurately assess the risks and benefits of mild alkalosis.

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