Case report

Inhaled nitric oxide therapy for severe hypoxemia in hyperinflated mechanically ventilated bronchiolitis patient

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ABSTRACT

Management of hospitalized bronchiolitis patients comprises supportive care including non-invasive and invasive mechanical ventilation. Inhaled nitric oxide (iNO) therapy has been used in bronchiolitis patients to manage pulmonary hypertension, acute respiratory distress syndrome, bronchoconstriction or inflammation. We report the role of iNO in management of severe hypoxemia in a 7-month-old mechanically ventilated bronchiolitis patient on 100% oxygen and high ventilator settings who had hyperinflation on chest x-ray, and diffuse bronchospasm on clinical assessment. We believe iNO improved hypoxemia in our patient by optimizing the ventilation/perfusion mismatch, decreasing dead space ventilation and relieving elevated pulmonary vascular resistance associated with alveolar overdistention.

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1. Introduction

Acute bronchiolitis is a common clinical condition affecting infants and young children, with lack of specific treatment besides supportive care [1]. 2%–3% of bronchiolitis patients are hospitalized in the USA and 10%–15% of these patients require additional noninvasive or invasive mechanical ventilatory support [2,3]. Inhaled nitric oxide (iNO) therapy has demonstrated a beneficial role in bronchiolitis patients in the management of pulmonary hypertension/elevated pulmonary vascular resistance [4,5], pediatric acute respiratory distress syndrome (PARDS) [6–8], bronchoconstriction [7], and inflammation [9–11]. We report a role of iNO therapy in the treatment of severe hypoxemia in a hyperinflated mechanically ventilated bronchiolitis patient in the absence of pulmonary hypertension. Addition of iNO therapy to conventional mechanical ventilation ameliorated further escalation of care in our patient.

2. Case report

A written informed consent was obtained from the parents of the patient for publication of this case report. Institutional IRB waivers approval for the production and publication of case reports. A 7-month-old female infant weighing 6.1 kg, an ex-34 week preemie with bronchopulmonary dysplasia on 1/4th liter/min nasal cannula oxygen therapy at baseline, was hospitalized for the management of corona (non-SARS-CoV-2) virus bronchiolitis. She had moderate respiratory distress, diffuse wheezing on auscultation,
and hyperinflated lung fields on her chest x-ray. She was intubated on 2 L/kg of high flow nasal cannula support, continuous albuterol nebulization, and methylprednisolone. She was intubated within 12 hours of admission for persistent respiratory distress and oxygen desaturation to 84–86%. She was placed on a pressure control mode of ventilation and bronchodilator (terbutaline and ketamine) and neuromuscular (cis-atracurium) infusions were added to her management. She continued to demonstrate hypoxemia (oxygen saturations of 82–84%) and hypercarbia (venous blood gas PaCO\(_2\): 77 torr [10.3 kPa]) and her ventilator settings were adjusted to Peak Inspiratory Pressure (PIP): 36 cm H\(_2\)O, Positive End-Expiratory Pressure (PEEP): 10 cm H\(_2\)O, respiratory rate (RR): 20/min and 100% FiO\(_2\). Her chest x-ray revealed her to be having hyperinflation with patchy atelectasis in both lung fields. Her ventilator settings revealed a plateau pressure (PPLAT): 28 cm H\(_2\)O, auto-PEEP: 11 cm H\(_2\)O, and a concave expiratory curve on tidal breathing flow volume loops (Table 1). She was initiated on iNO therapy at 20 ppm empirically for the management of persistent oxygen desaturation of 85–86% and oxygenation index (OI) of 34 on significant ventilator settings and 100% oxygen therapy. Addition of iNO therapy resulted in significant improvement in her oxygenation and dead space ventilation without much change in her lung compliance or airway resistance (Table 1). A transthoracic echocardiogram within the next 4 hours revealed good biventricular function, without any evidence of pulmonary hypertension. Her echocardiogram in the previous month had revealed normal right ventricle size and function, less than half systemic pulmonary artery pressure and her chest computerized tomography study had revealed normal pulmonary parenchymal architecture. She was weaned off iNO therapy in 3 days, extubated after 6 days, and discharged home 2 weeks later.

3. Discussion

Bronchiolitis is a disease process characterized by extensive inflammation and edema of the airways, increased mucus production, and necrosis of airway epithelial cells that result in extensive bronchiolar obstruction and lung hyperinflation [12]. Pulmonary function tests of intubated and mechanically ventilated bronchiolitis patients reveal increased functional residual capacity, increased pulmonary resistance, and decreased pulmonary compliance as also seen in our patient [13,14]. A widespread ventilation perfusion (VA/Q) mismatch with lack of association between radiological examination and lung perfusion scintigraphy has been reported in bronchiolitis patients [15]. Hypoxemia is associated with an increase in dead space/tidal volume (Vd/Vt) ratio in mechanically ventilated bronchiolitis patients secondary to VA/Q mismatch and alveolar overdistension [16]. In heterogeneous obstruction of the airways, as seen in bronchiolitis patients, ventilation is preferentially distributed to units that impose less airflow resistance and have faster time constants [17]. As a result, when iNO was added to the ventilator circuit in our patient, it was preferentially delivered to the well-ventilated alveoli with faster time constants. We believe that the selective vasodilator action of iNO in these well-ventilated alveoli facilitated the redistribution of pulmonary blood flow, improved VA/Q mismatch, and associated changes in alveolar gas exchange and hypoxemia in our patient [18,19]. In addition, iNO may have also relieved some of the increase in pulmonary vascular resistance due to the physical compression of the microvasculature seen with alveolar overdistension [20,21]. It is less likely that iNO therapy in our patient had any role on pulmonary hypertension, PARDS, bronchoconstriction, or inflammation as previously reported [4–11]. Echocardiogram in our patient prior and at the time of illness did not reveal pulmonary hypertension. Previous reports of iNO therapy in PARDS and pediatric acute hypoxemic respiratory failure patients have demonstrated an improvement in hypoxemia even in the absence of pulmonary hypertension [22,23]. Our patient did not have any new infiltrate on chest imaging to qualify for PARDS [24]. INO therapy did not have bronchodilatory affect as there were no changes in auto-PEEP or airway resistance after iNO initiation.

Table 1
Mechanical ventilation and gas exchange parameters before and after initiation of inhaled nitric oxide therapy.

| Parameters          | 0 hours on iNO | 1 hour on iNO | 3 hours on iNO | 6 hours on iNO |
|---------------------|----------------|---------------|----------------|----------------|
| Tidal volume (ml/kg)| 6.2            | 6.2           | 5.9            | 6.2            |
| RR/minute           | 20             | 20            | 20             | 20             |
| PEEP (cm H\(_2\)O)| 100            | 100           | 80             | 60             |
| PIP (cm H\(_2\)O)  | 36             | 36            | 34             | 34             |
| PLAT (cm H\(_2\)O)| 28             | 28            | 27             | 27             |
| FIO\(_2\)           | 100            | 100           | 80             | 60             |
| FiO\(_2\)           | 6.2            | 6.2           | 5.9            | 6.2            |
| PaCO\(_2\) (torr)   | 37             | 37            | 38             | 38             |
| ETCO\(_2\) (torr)   | 18             | 24            | 41             | 28             |
| V\(_d\)/V\(_t\)     | 0.51           | 0.35          | 0.29           | 0.26           |
| C\(_stat\) (ml/cm H\(_2\)O/kg)| 0.34 | 0.34 | 0.35 | 0.36 |
| B\(_res\) (cm H\(_2\)O/liter/second)| 8   | 8   | 7   | 7   |

iNO: inhaled nitric oxide; ml/kg: milliliters/kilogram; RR: Respiratory Rate.
I\(_t\): Inspiratory time; FiO\(_2\): Fractional of inspired oxygen.
cm H\(_2\)O: centimeters of water; PIP: Peak Inspiratory Pressure.
PLAT: Plateau Pressure; PEEP: Positive End-Expiratory Pressure.
PaCO\(_2\): Partial pressure of oxygen; OI: Oxygenation Index.
PaCO\(_2\): Partial pressure of carbon dioxide; ETCO\(_2\): End-tidal carbon dioxide.
V\(_d\)/V\(_t\): Dead space/Tidal volume ratio; C\(_stat\): Static compliance.
B\(_res\): Airway resistance; kg: kilograms.
The rapid response to iNO therapy precluded its role as an anti-inflammatory and antiviral agent.

Limitation of our report includes lack of formal pulmonary function testing to demonstrate abnormalities in functional residual capacity and pulmonary compliance and lack of lung perfusion scan to demonstrate VA/Q mismatch. However, we evaluated bed-side pulmonary compliance, airway resistance, and end-tidal CO₂ measurements and performed serial chest x-rays to demonstrate hyperinflation with patchy atelectasis.

In summary, it may seem reasonable to consider the use of iNO as an off-label therapy in hyperinflated mechanically ventilated bronchiolitis patients who present with severe hypoxemia. It may not directly affect the bronchiolitis disease process, however, it may improve hypoxemia by optimizing the VA/Q mismatch and relieving the elevated pulmonary vascular resistance secondary to alveolar overdistention.

Author contributions

Study conception and design: Samir Latifi, Hemant Agarwal.
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Analysis and interpretation of data: William Hanna, Hemant Agarwal.
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Declarations of competing interest

None.

References

[1] S.L. Ralston, A.S. Lieberthal, H.C. Meissner, et al., American Academy of Pediatrics: clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. Pediatrics 134 (2014) e1474-e1502.
[2] S.H. Sosnick, C.L. Carroll, A.S. Cowl, Increased use of noninvasive ventilation associated with decreased use of invasive devices in children with bronchiolitis, Crit. Care Explor. 1 (2019) e0026.
[3] A. Greenough, Role of ventilation in RSV disease: CPAP, ventilation, HFO, ECMO, Pediatr. Respir. Rev. (2009) 26–28, 10 Suppl1.
[4] S.H. Abman, J.L. Griebel, D.K. Parker, et al., Acute effects of inhaled nitric oxide in children with severe hypoxic respiratory failure, J. Pediatr. 124 (1994) 881–885.
[5] D. Kimura, I.F. McNamara, J. Wang, et al., Pulmonary hypertension during respiratory syncytial virus bronchiolitis: a risk factor for severity of illness, Cardiol. Young 29 (2019) 615–619.
[6] T. Hoehn, M. Krause, M. Krueger, et al., Treatment of respiratory failure with inhaled nitric oxide and high-frequency ventilation in an infant with respiratory syncytial virus pneumonia and bronchopulmonary dysplasia, Respiration 65 (1998) 477–480.
[7] F. Leclerc, Y. Riou, A. Matinot, et al., Inhaled nitric oxide for a severe respiratory syncytial virus infection in an infant with bronchopulmonary dysplasia, Intensive Care Med. 20 (1994) 511–512.
[8] K. Okamoto, T. Tashima, I. Kukita, et al., Successful use of inhaled nitric oxide for severe hypoxemia in an infant with acute exacerbation of bronchiolitis due to sepsis, J. Anaesth. 9 (1995) 81–84.
[9] A. Goldhart, I. Golan-Tripto, G. Pillar, et al., Inhaled nitric oxide therapy in acute bronchiolitis: a multicenter randomized clinical trial, Sci. Rep. 10 (2020) 9605.
[10] A. Tal, D. Greenberg, Y. Av-Gay, et al., Nitric oxide inhalations in bronchiolitis. A pilot, randomized, double-blinded, controlled trial, Pediatr. Pulmonol. 53 (2018) 95–102.
[11] L. Chen, P. Lui, H. Gao, et al., Inhalation of nitric oxide in the treatment of severe acute respiratory syndrome: a rescue trial in Beijing, Clin. Infect. Dis. 39 (2004) 1531–1535.
[12] S. Ali, A.C. Plint, T.P. Klassen, Bronchiolitis, in: R.W. Wilmott, E.L. Kendig, F. Chernick (Eds.), Kendig and Chernick Disorders of the Respiratory Tract in Children, Eight Edition, Elsevier Saunders, Philadelphia, 2012, pp. 443–452.
[13] P.D. Phelan, H.E. Williams, M. Freeman, The disturbances of ventilation in acute bronchiolitis, Aust. Paediatr. J. 4 (1968) 96–104.
[14] R.L. Henry, A.D. Milner, G.M. Stokes, et al., Lung function after acute bronchiolitis, Arch. Dis. Child. 58 (1983) 60–63.
[15] F.R.A. Carvalho, R.D. Cunha, S. Menas Barreto, Pulmonary blood flow distribution in acute viral bronchiolitis, J. Pediatr. 78 (2002) 133–139.
[16] A.A. Almeida-Junior, M.T. Nolasco da Silva, C.C.B. Almeida, et al., Relationship between physiologic deadspace/tidal volume ratio and gas exchange in infants with acute bronchiolitis on invasive mechanical ventilation, Pediatr. Crit. Care Med. 8 (2007) 372–377.
[17] A.J. Woodcock, N.J. Vincent, P.T. Macklem, Frequency dependence of compliance as a test for obstruction in the small airways, J. Clin. Invest. 48 (1969) 1097–1106.
[18] N. Roger, J.A. Barbera, J. Roca, et al., Nitric oxide inhalation during exercise in chronic obstructive lung disease, Am. J. Respir. Crit. Care Med. 156 (1997) 9880–9886.
[19] J.W. Skimming, M.J. Gribel, D.K. Parker, et al., Acute effects of inhaled nitric oxide in children with severe hypoxic respiratory failure, J. Pediatr. 124 (1994) 881–885.
[20] J.B. Glazier, J.M.B. Hughes, J.E. Maloney, et al., Measurements of capillary dimensions and blood volume in rapidly frozen lungs, J. Appl. Physiol. 26 (1969) 65–76.
[21] J.C. Dowell, N.J. Thomas, N. Yehya, Association of response to inhaled nitric oxide and duration of mechanical ventilation in pediatric acute respiratory distress syndrome, Pediatr. Crit. Care Med. 18 (2017) 1019–1026.
[22] J.T. Berger, A.B. Maddux, R.W. Reeder, et al., Inhaled nitric oxide use in pediatric hypoxic respiratory failure, Pediatr. Crit. Care Med. 21 (2020) 708–719.
[23] Pediatric Acute Lung Injury Consensus Conference Group, Pediatric acute respiratory distress syndrome: consensus recommendations from the pediatric acute lung injury consensus conference, Pediatr. Crit. Care Med. 16 (2015) 428–439.