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CLINICAL REPORT

Successful treatment of acute respiratory distress syndrome after hysterectomy for life-threatening atonic bleeding by inhaled nitric oxide

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Abstract We report a case of a 33-year-old female who developed severe acute respiratory distress syndrome (ARDS) after emergency hysterectomy for life-threatening atonic bleeding. A marked decline in pulmonary oxygenation was observed during the surgery, which led to a diagnosis of ARDS. Following admission to the intensive care unit, hypoxia became critical, with a PaO_2/F_IO_2 value of 52 even after recruitment maneuvers. Inhaled nitric oxide (NO 10 ppm) was administered to the patient as a rescue treatment, resulting in a gradual but dramatic improvement in pulmonary oxygenation. Although several randomized trials have failed to confirm the beneficial effects of NO on morbidity in patients with ARDS, NO administration is worth consideration as treatment prior to invasive treatments, such as extracorporeal membrane oxygenation, for patients with acute lung injury/ARDS.

Keywords Nitric oxide · ADRS · Atonic postpartum hemorrhage

Introduction

Inhaled nitric oxide (iNO) therapy has been shown to improve arterial oxygenation and pulmonary hemodynamics in patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS) [1, 2]. However, subsequent randomized control trials have failed to provide evidence that iNO actually does improve clinical outcomes, such as mortality and ventilator-free days, in patients with ALI/ARDS [3, 4]. We report a case in which iNO therapy dramatically improved pulmonary oxygenation in a 33-year-old female who developed severe ARDS after hysterectomy for atonic postpartum hemorrhage.

Case report

A 33-year old female (height 153 cm; weight 56 kg) was diagnosed with gestational diabetes mellitus, pregnancy-induced hypertension and fetal macrosomia at 38 weeks' gestation. She transvaginally delivered a 4800-g baby at 39 weeks' gestation, but became critically ill due to life-threatening atonic postpartum hemorrhage 2 h after the delivery, developing cardiac arrest with ventricular fibrillation. She was immediately resuscitated with cardiac massage and defibrillation; rapid blood transfusion and bolus administration of adrenaline (total 3 mg) were also performed. However, her hemodynamics was quite unstable, and she was transferred to the intensive care unit (ICU) with mechanical ventilation 25 min after the resuscitation. At admission to the ICU, her blood pressure was 70/40 mmHg and heart rate was 115 bpm. She was not responsive to verbal stimuli. She remained in shock despite continuous blood transfusion and bolus and continuous intravenous administration of adrenaline (2 mg and 0.3 μg/kg/min, respectively). Laboratory testing revealed marked metabolic acidosis and anemia (pH 6.57, PaO_2 503 mmHg, $PaCO_2$ 26.1 mmHg, base excess −30.4 mEq/l, hemoglobin 4.6 g/dl, hematocrit 14.7%, lactic acid 23 mmol/l) under mechanical ventilation with 100% oxygen. Counted blood

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loss after the delivery was approximately 5800 g, but much more bleeding was suspected considering her unstable hemodynamics and the severe anemia. She also suffered from disseminated intravascular coagulation (DIC). As she had continuous vaginal bleeding at a rate of about 1000 g/h despite the hemostasis with uterotonics and blood transfusion [including fresh frozen plasma (FFP) and platelet concentrate (PC)], an emergency hysterectomy to stop the postpartum hemorrhage was performed under general anesthesia 4 h after admission to the ICU. Her general anesthesia was maintained with ketamine and fentanyl, accompanied with vecuronium bromide. During the operation, active bleeding from the anterior surface of the uterus was observed, and a large hematoma had formed in the retroperitoneal space around the urinary bladder and uterus. The amount of blood loss and urine output during the operation were 2330 g and 10 ml, respectively, and 10 units of RCC, 25 units of FFP, 20 units of PC, 500 ml of fresh whole blood, 270 ml of salvaged red cells and 1250 ml of 5% albumin were transfused into the patient. Pulmonary oxygenation gradually decreased during the operation, and at the end of surgery, the patient's PaO_2/F_IO_2 ratio (ratio of partial pressure of arterial O_2 to the fraction of inspired O_2) was 78 mmHg. She was diagnosed with ARDS following a chest X-ray taken in the ICU showing bilateral slight infiltrations and diaphragmatic elevation due to the residual intra-abdominal bloody ascites and intestinal distension.

Pulmonary oxygenation deteriorated to a critical level: the patient had a PaO_2/F_IO_2 ratio of 52 mmHg 1 h after the operation while on a conventional ventilator with synchronized intermittent mandatory ventilation plus pressure support [F_IO_2 1.0, rate 20 bpm, positive end-expiratory pressure (PEEP) 10 cmH_2O, peak inspiratory pressure 26 cmH_2O]. Trans-thoracic echocardiography revealed good left ventricular wall motion, bilateral collapse of the dependent lung and a small amount of pleural effusion. Therefore, we repeatedly applied lung recruitment maneuvers to inflate the collapsed lung with an airway pressure of around 35 cmH_2O for 10 s, but this was not effective. As specific ventilator modes with high mean airway pressures, such as airway pressure release ventilation (APRV) or high-frequency oscillatory ventilation (HFOV), were not available in our hospital at that time, we considered initiating extracorporeal membrane oxygenation (ECMO). However, attempts at this procedure were abandoned due to difficulty encountered in puncturing the femoral artery and vein as a result of the massive hematoma that had formed during resuscitation and the potential for prolonged hemoperitonium suggested by the intra-abdominal echo-free space and bloody ascites from abdominal drainage. Therefore, we chose iNO therapy as a rescue treatment. Following the administration of 10 ppm NO, pulmonary oxygenation showed a gradual but marked improvement, and the improvement was maintained until the iNO therapy was stopped the following morning (Fig. 1). In addition, $PaCO_2$ decreased from 39.6 to 25.8 mmHg with same ventilator setting as described above 1.5 h after the commencement of iNO. These data implied that improvement of the ventilation–perfusion mismatch of the lung in response to iNO resulted in improved oxygenation and that the improved CO_2 removal was caused either by reducing alveolar dead space or improving lung compliance. Laboratory examinations on the first postoperative day showed liver damage, renal dysfunction and a prolonged DIC state. We introduced continuous hemodiafiltration for the acute kidney injury. In addition, unstable blood pressure and anemia led us to suspect continuous bleeding into the abdominal cavity. A computed tomography scan revealed bilateral collapse of the dependent lung with a small amount of pleural effusion and active bleeding from the right deep circumflex iliac artery; these results were confirmed by angiography. Transarterial embolization was performed by a radiologist on the second post-operative day, following which the patient's hemodynamics stabilized without the need of catecholamine administration. The DIC state had improved by the third post-operative day. The patient was weaned from the ventilator on the fifth post-operative day. Although she still needed hemodialysis, she was moved from the ICU to the gynecology ward on the eighth post-operative day. The patient was discharged on the 40th post-operative day without hemodialysis.

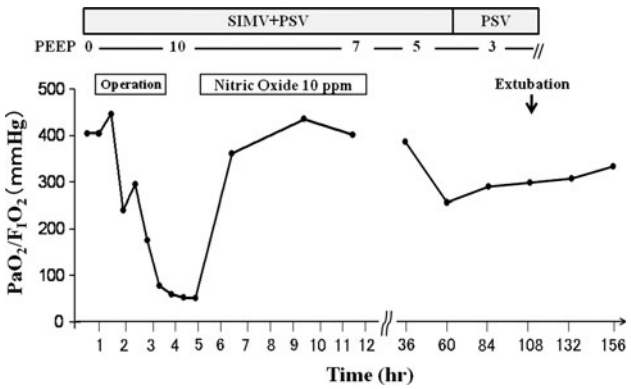

Fig. 1 Changes in the ratio of partial pressure of arterial O_2 to the fraction of inspired O_2 (PaO_2/F_IO_2) during and after the operation. The PaO_2/F_IO_2 ratio rapidly decreased during the operation and reached a critical level with the value of 52 mmHg. Immediately after the inhalation of 10 ppm nitric oxide (NO) the PaO_2/F_IO_2 dramatically increased to 362 mmHg. Although inhalational NO was discontinued in the next morning, improved pulmonary oxygenation lasted, and the patient was weaned from the ventilator on the fifth post-operative day. *PEEP* Positive end-expiratory pressure, *SIMV* synchronized intermittent mandatory ventilation, *PSV* pressure-support ventilation

Discussion

Although ALI/ARDS related to pregnancy is uncommon, overall mortality for both the mother and the fetus has been reported to be high, and significant morbidity can persist even after initial recovery [5, 6].

Our patient rapidly developed ARDS during hysterectomy for life-threatening bleeding due to uterine atony. Although the obvious pathogenesis of ARDS in this patient was unknown, hemorrhagic shock, massive transfusion, transfusion-related ALI and/or venous air embolism during emergency hysterectomy were suspected. Aspiration pneumonitis or amniotic fluid embolism was not considered as diagnosis because pulmonary oxygenation deteriorated several hours after vaginal delivery.

A number of ventilator-focused rescue therapies, such as APRV and HFOV, for refractory hypoxemia have been introduced in clinical practice [7]. However, those specific respiratory therapies were not available in our hospital at that time, with the exception of recruitment maneuvers, iNO and ECMO.

It has been suggested that iNO selectively relaxes vessels at the well-ventilated regions of the lung and that this results in improving the ventilation–perfusion mismatch and, therefore, improved oxygenation in ARDS patients [8]. In our case, iNO was considered to have redistributed pulmonary blood from the poorly ventilated regions to the well-ventilated regions. In addition, iNO might play a favorable role in the recruitment of the consolidated lung with relatively high PEEP, as improved ventilation was apparent based on the data showing a decreased $PaCO_2$ level following iNO administration. Johannigman et al. [9] demonstrated that PEEP and iNO have a synergistic effect on the PaO_2/F_IO_2. The optimal dose of iNO to achieve the maximum effect in terms of improving oxygenation has been reported to vary from 1 to 20 ppm [8, 10–12], while high doses of iNO of >10 ppm [11, 12] or >20 ppm [8] have also been shown to worsen oxygenation. One theory for this latter result is that a high dose of iNO can enter the poorly ventilated area, causing vasodilation of this area, possibly reducing the improvement in the ventilation–perfusion mismatch [8]. We started to administer iNO at 10 ppm to determine the patient's initial response to iNO and observed that iNO dramatically improved oxygenation without any adverse effects. We ceased administering iNO in the following morning to avoid possible complications, such as methemoglobinemia.

Several randomized controlled trials have failed to confirm the beneficial effects of NO on morbidity or ventilator-free days in patients with ALI/ARDS [3, 4]. Another systematic review and meta-analysis of NO even suggested possible increased mortality and renal dysfunction with iNO [13]. One of the reasons why iNO may not be beneficial is that most of the patients with ARDS in the studies died of organ failure rather than refractory hypoxemia [14]; consequently, small changes in oxygenation may not have led to improvements in outcome [13]. However, the use of NO as a rescue treatment is still considered reasonable in patients with severe hypoxemia [15]. Cole et al. [5] also proposed iNO as a special treatment in their strategies for ARDS in pregnant patients failing to respond on conventional mechanical ventilation. Some studies have demonstrated that the response to iNO is associated with an etiology of ARDS. In two studies, ARDS patients without septic shock had a higher response rate to iNO than those with septic shock [8, 16]. It has been also suggested that nonsepsis-induced ARDS, such as ARDS after trauma, tends to be more sensitive to iNO than sepsis-induced ARDS [8], although the involved mechanisms still need to be elucidated.

ECMO has been demonstrated to achieve a significant improvement in survival without severe disability at 6 months in patients with severe acute respiratory failure compared with continued conventional ventilation in a randomized controlled trial [17]. However, as in our case, application of ECMO for patients with bleeding complications should be avoided due to the necessity of anticoagulation.

In conclusion, iNO is still worth a try in patients with ALI/ARDS, especially in patients with hemorrhagic complication for whom invasive treatments, such as ECMO, are being considered.

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