Noninvasive Ventilation in a Pregnant Patient With Respiratory Failure From All-Trans-Retinoic-Acid (ATRA) Syndrome

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We saw a 34-year-old pregnant woman with acute promyelocytic leukemia, who developed acute respiratory failure from all-trans-retinoic acid (ATRA) syndrome. We applied noninvasive ventilation (NIV, continuous positive airway pressure plus pressure-support ventilation) to try to improve gas exchange, reduce the work of breathing, and prevent intubation. Initially we applied NIV continuously (24 hours a day), then gradually reduced the daily amount of time on NIV as her condition improved. She was discharged from the intensive care unit after 12 days. Three months after hospital discharge she gave vaginal birth to a healthy female baby. NIV was effective and safe for the mother and fetus, and NIV should be considered for respiratory failure in pregnant patients, especially if immunosuppressed. *Key words: pregnancy, promyelocytic leukemia, all-trans-retinoic acid syndrome, ATRA, noninvasive ventilation, acute respiratory failure, mechanical ventilation.* [Respir Care 2009;54(7):969–972. © 2009 Daedalus Enterprises]

Introduction

Neoplastic diseases occur in approximately 0.02–0.1% of all pregnancies.[1] Acute myeloid leukemia is the leukemia type most commonly diagnosed in pregnancy,[2] and its incidence is approximately 1 in 75,000 pregnancies.[3] All-trans-retinoic acid (ATRA) is frequently used to treat acute promyelocytic leukemia (a subtype of acute myeloid leukemia), because ATRA has pro-apoptosis and cell-differentiation-induction effects.[4] ATRA has marked teratogenicity (85% of the cases) when administered in the first trimester.[2]

The most serious (and potentially fatal) adverse effect of ATRA is the ATRA syndrome, which is a systemic complication manifested mainly by pulmonary infiltrates, fever, pleural and pericardial effusions, renal and heart failure, and hypotension.[5] The lungs seem to be the most affected organ; they develop edema, fibrinous exudate,[6] intra-alveolar hemorrhage,[7] and respiratory distress in approximately 90% of cases.[5] ATRA syndrome is estimated to occur in up to 27% of the patients who receive ATRA, of whom 30% develop lethal organ dysfunction.[4] Symptoms usually appear 10 days after the beginning of ATRA treatment, although they may occur as early as the second day.[8] Early recognition of ATRA syndrome, administration of intravenous corticosteroids, hemodynamic monitoring, and ventilatory assistance are critical.[4,8]

Case Report

We saw a 34-year-old pregnant woman (23 weeks plus 5 days gestational age, gravida 2, para 1), who was referred from the emergency department of our hospital for generalized body pain and mild fatigue. The initial examination revealed a dental abscess, but no fever. Laboratory blood analysis showed pancytopenia.

She was admitted to the obstetric pathology ward for treatment of the abscess and hematologic investigation. Clinical and laboratory investigation led to a diagnosis of acute myeloid leukemia, specifically acute promyelocytic leukemia, which was confirmed via bone-marrow biopsy.

The patient was transferred to the intensive care unit (ICU) for hemodynamic monitoring and clinical support

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The authors have disclosed no conflicts of interest.

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Table 1. Patient Data at ICU Admission and During All-Trans-Retinoic-Acid Syndrome

	At ICU Admission	ATRA Syndrome Day			
		1*	4†	5†	8†
Hemoglobin (g/dL)	7.5	9.5	ND	ND	10.4
Hematocrit (%)	21.2	26.7	ND	ND	ND
Leucocytes ($10^3/\mu L$)	0.86	1.00	ND	ND	0.90
Platelets ($10^3/\mu L$)	11.0	9.0	ND	ND	18.0
pH	ND	7.40	7.45	7.43	7.38
P_{aO_2} (mm Hg)	ND	59	64	69	86
P_{aCO_2} (mm Hg)	ND	39	42	40	37
HCO_3^- (mmol/L)	ND	23	29	26	22
Base excess (mmol/L)	ND	–1	4	2	–2
Oxyhemoglobin saturation (%)	ND	89	93	94	96
Supplemental oxygen delivery	None	Face mask: 15 L/min	Reservoir mask	Air-entrainment mask: F_{IO_2} 0.50	Air-entrainment mask: F_{IO_2} 0.35

* Blood drawn before initiation of noninvasive ventilation.
† Blood drawn after approximately 30 min on supplemental oxygen.
ATRA = all-trans-retinoic acid
ICU = intensive care unit
ND = no data collected
F_{IO_2} = fraction of inspired oxygen

during chemotherapy. At that time she was afebrile, eupneic, and had normal auscultation. Treatment with ATRA and daunorubicin was started, and on the second day of treatment she developed acute respiratory failure and bilateral subconjunctival hemorrhage, but she was still afebrile. She was kept on supplemental oxygen via face mask (15 L/min) and her oxyhemoglobin saturation (measured via pulse oximetry [S_{pO_2}]) was 85% (Table 1). Chest radiograph showed bilateral, diffuse pulmonary infiltrates. Auscultation revealed decreased vesicular murmur and bibasilar crackles. ATRA syndrome was diagnosed based on clinical and radiologic evaluation. The hematology team prescribed intravenous dexamethasone and temporary interruption of ATRA while continuing conventional chemotherapy.

Considering the transience of the respiratory symptoms of ATRA syndrome and the risk of infection and other complications related to intubation and invasive ventilation in an immunocompromised, pregnant patient, we chose noninvasive ventilation (NIV, continuous positive airway pressure with pressure-support ventilation, with an Inter 5 ventilator [Intermed, Brazil[) via a non-vented face mask. The patient was intermittently medicated with intravenous midazolam (for anxiety control) and tramadol and dipyrone sodium (for analgesia), according to the evaluation of the intensive-care physician on duty. The patient remained fully conscious throughout her ICU stay.

During the first 2 days of ATRA syndrome she was kept on NIV 24 hours a day, in either a semirecumbent position (head of the bed elevated 45°, to prevent aspiration) or a left-lateral recumbent position whenever possible (for hemodynamic stability). The ICU physician and physiotherapist on duty closely monitored the patient, auscultated hourly, and performed bronchial secretion-clearance as needed. The initial ventilator settings were peak inspiratory pressure 25 cm H_2O, positive end-expiratory pressure 15 cm H_2O, and fraction of inspired oxygen (F_{IO_2}) 0.60, to keep $S_{pO_2} > 90\%$ and respiratory rate < 35 breaths/min. Changes to the ventilator settings were based on clinical examination, S_{pO_2}, and blood-gas values.

On the third and fourth days of NIV the patient tolerated spontaneous breathing with supplemental oxygen via reservoir mask for one out of every 3 hours (see Table 1). NIV was continued between the spontaneous breathing trials and at night. On the fourth NIV day ATRA was resumed at half the initial dose.

On the fifth day, daytime NIV was decreased to two 2-hour periods of NIV a day. Between the NIV periods she was on supplemental oxygen (F_{IO_2} 0.50) via air-entrainment mask, and S_{pO_2} was $> 95\%$ (see Table 1).

On the sixth day her respiratory pattern and clinical examination findings showed improvement, so we changed the ventilator settings to peak inspiratory pressure 23 cm H_2O, positive end-expiratory pressure 10 cm H_2O, and F_{IO_2} 0.40, and maintained those settings until her discharge from the ICU. Further improvement was evidenced by success in spontaneous breathing (with an F_{IO_2} of 0.50 via air-entrainment mask, later decreased to 0.35) during the whole sleep period, with an S_{pO_2} of 96–97% (although we shortened the NIV sessions to 40 min), and normalization of blood gases (see Table 1). After 10 days of NIV

she was discharged on supplemental oxygen (1 L/min via nasal cannula) and her S_{pO_2} was 97–98%.

Three months after ICU discharge she gave vaginal birth to a 2,300-g female baby who had Apgar scores of 5 and 8 at the first and fifth minutes, respectively. There was no evidence of sequelae from the ATRA syndrome or NIV, and the newborn did not require intensive care. Mother and child were discharged from the hospital 3 days later.

Discussion

NIV via mouthpiece or mask[9,10] has been used to treat acute respiratory failure of several etiologies. The main goals are to improve gas exchange and reduce the work of breathing.[9-11] NIV may also prevent intubation and its potentially severe complications, such as pulmonary and upper-airway infection, which are associated with a higher mortality risk.[9,11] Furthermore, intubation of a pregnant patient may be complicated by pregnancy-related anatomical changes.[12] Failed intubation is 8-fold more frequent in the obstetric population than in the non-pregnant surgical population. Soft-tissue (including mucosa) edema can hinder visualization of airway anatomy[13] and increase the risk of hypoxemic cardiac arrest and/or pulmonary aspiration.[12]

In cancer patients the need for invasive ventilation is statistically associated with mortality,[14] which reaches 70–80% in patients with hematologic malignancies,[11] whereas better outcomes have been reported among patients who receive NIV.[14] This may be explained by the greater risk of severe infection with intubation in immunocompromised patients. The use of NIV for respiratory failure in patients with hematologic malignancies is well established as safe and effective,[10,11,14] and NIV success was reported in a male patient with ATRA syndrome.[15] As far as we know, there have been no controlled studies on NIV in pregnant women with respiratory failure from ATRA syndrome. The only previous case report of pregnant women with ATRA syndrome[16] described a 16-year-old patient (fetus 25 weeks gestational age) who developed severe respiratory failure, then intracranial hemorrhage, which required invasive ventilation.

The use of NIV during pregnancy is controversial[17] and there have been few studies. Al-Ansari et al[18] reported a series of 4 cases of pregnant women with acute chest syndrome (a severe complication of sickle-cell disease) who were successfully treated with NIV. Al-Ansari et al concluded that NIV may be effective and safe for the mother and fetus.

Maternal physiologic adaptations to pregnancy should be considered when treating a critically ill pregnant patient. Pregnant women have higher risk of aspiration of gastric contents because of decreased gastric-emptying time (owing to increased plasma progesterone, decreased motilin, and displacement of the stomach by the fetus) and increased abdominal pressure from the gravid uterus.[19] We took those factors into consideration with our patient and kept her semirecumbent. Additionally, in the supine position the enlarged uterus can cause venocaval compression, which can decrease venous return, stroke volume, and cardiac output. About 8% of pregnant women have "supine hypotensive syndrome" (bradycardia, hypotension, and syncope).[20] We tried to minimize that risk with left-lateral recumbent positioning.[21]

NIV must be applied by well-trained professionals who are familiar with NIV equipment, aware of the indications, and, most importantly, who can identify signs that NIV is not providing the necessary improvement, in which case intubation should be considered. With our patient the whole team kept her under close observation for signs of NIV failure, such as depressed consciousness, consistent lack of improvement of blood-gas values, substantial hypoxemia ($P_{aO_2} < 60$ mm Hg), hypercapnia and respiratory acidosis (pH < 7.25), hemodynamic and/or airway instability, or abundant pulmonary secretions, especially if the patient has ineffective cough. It is important to emphasize that the patient's collaboration is essential for NIV success.

In our pregnant patient with ATRA syndrome, NIV was safe and effective and provided adequate gas exchange and decreased the work of breathing until the resolution of the respiratory failure, and thus prevented intubation. In addition we stress that with a pregnant woman there are 2 patients, rather than only one, and that the condition of the fetus reflects that of the mother. We conclude that NIV was favorable for the outcome of both mother and fetus. Nevertheless, controlled studies are needed to provide stronger evidence on the use of on NIV in pregnant patients.

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