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SEMINAL OBSERVATIONS

Continuous Inhaled Nitric Oxide Therapy in a Case of Sickle Cell Disease With Multiorgan Involvement

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ABSTRACT

A 27-year-old female with sickle cell disease (HbSS) was admitted presenting with severe bone pain and fever. She refused blood transfusions throughout her hospital stay for religious reasons. During the first 9 days of admission, the patient's clinical presentation became worse despite antibiotic coverage. The patient exhibited pulmonary infiltrates and mild hypertension, increased pain, fever, tachycardia, and decreased hematocrit. After day 8 of admission, her laboratory findings and clinical presentation indicated that her disease was markedly worse. With the patient's consent, inhaled nitric oxide therapy (iNO = 40 ppm) was initiated and continued for 3.2 days. After a full day of iNO therapy, the clinical improvement was limited to temperature normalization and stabilization of her hemoglobin levels. After 2 more days of iNO therapy, her multiple clinical complications of sickle cell disease improved markedly and she was discharged 3 days after completion of the iNO treatment. The complications of NO therapy, such as methemoglobulinemia or decreased blood pressure, were not detected during the iNO therapy. Although limited to a single individual, we propose that our anecdotal experience suggests that iNO therapy may (i) need to be continuous for several days to provide improved benefits, (ii) treat several of sickle cell complications besides pain, and (iii) exhibit few complications. These proposals need to be confirmed in clinical trials.

Key Words: nitric oxide, sickle cell, thrombocytosis, vaso-occlusion

The pathogenesis of sickle cell disease (SCD) is complex and this likely leads to a disease syndrome rather than a single presentation of disease. Kato et al.[1] propose that there are 2 major pathogenic pathways for SCD: (1) hemolysis-endothelial dysfunction and (2) vascular occlusion. In the first pathogenic pathway, patients exhibit high levels hemolysis for as yet undefined reasons and consequently high cell-free hemoglobin (Hgb) and arginase levels. The free Hgb stoichiometrically scavenges nitric oxide (NO) in the vasculature[2] but may also generate superoxide that also scavenges NO.[3] Production of NO by nitric oxide synthase isoforms may be decreased by the reduced levels of arginine as a consequence of the released arginase.[4] Collectively, the previously mentioned factors lead to a state of low NO bioavailability during SCD. Nitric oxide is an important regulator of endothelial cell adhesion molecule expression, red cell deformability, platelet aggregation, thrombosis, and vascular tone.[4] Pulmonary hypertension is associated with SCD and other hemolytic anemias, suggesting that low NO bioavailability may contribute to this complication.[4] If this hemolytic pathway is correct, then prospective studies may determine whether inhaled nitric oxide (iNO) therapy is the therapy of choice for this subpopulation of patients.

In the second pathogenic pathway, patients with higher Hgb levels exhibit a greater propensity for vaso-occlusive complications, such as vascular occlusive crisis mediated by the sickling and vascular adhesion of erythrocytes.[1] The vascular occlusive crisis leads to severe pain secondary to hypoxia, acute chest syndrome, and osteonecrosis due to poor perfusion of the bone. Patients in this pathogenic pathway are predicted to respond well to hydroxyurea, which decreases erythrocyte sickling by increasing the expression of HgbF.[5]

We present here a case report of patient with sequelae from both pathways (namely acute chest syndrome, bone pain, and hemolysis), who for religious reasons would not accept many of the standard treatments for her disease. Her clinical course and recovery after continuous inhaled nitric oxide therapy for 3.2 days suggest that continuous

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treatment may be beneficial for severe SCD and provides clues about sites of action of iNO in SCD pathogenesis.

■ CASE REPORT

The patient, female, 27-year-old Jehovah's Witness of African origin with homozygous SCD, was admitted to Scripps Memorial Hospital La Jolla because of generalized bone pain and severe back and leg pains consistent with vaso-occlusion. She had been admitted to a hospital for sickle cell crisis when she was 5 years old, and more recently at our hospital when she was 26 years old. After these discharges, she had no medical follow-up and consequently was not on hydroxyurea maintenance therapy. The patient reported feeling sick for 5 to 6 days before admission with a low-grade fever and sore throat.

Treatment

Opioid analgesic and hydration therapy were started after admission (Fig. 1A). She was provided oral opioids until day 7 when a patient-controlled analgesia pump was started. The hematology consultant initiated O_2 supplementation and proposed immediate treatment with hydroxyurea to reduce the elevated WBC and to initiate the switch from HbS to HbF, which requires months to complete; the patient, however, declined to take hydroxyurea until 3 days later (Fig. 1A). Her Hgb electrophoresis showed 86% HgbS, 7% HgbF, and 3.9% HgbA2. Hydroxyurea was discontinued on day 9 because of continued anemia. Patient remained afebrile for 1 day after ibuprofen treatment (Fig. 1A) but this treatment was discontinued because of concerns about her kidney function. Besides a drop in maximum daily temperature (Tm), no other changes occurred in the clinical picture with ibuprofen. The iNO therapy was initiated late on day 9.

Patient's infectious disease workup was negative, but she was on antibiotics throughout her admission (Fig. 1A). She was empirically started on the antibiotic ceftriaxone upon admission. All blood cultures obtained upon admission exhibited no bacterial growth. Chest x-ray on the 4th day showed right lower lobe infiltrate, and she had fever (Fig. 1B), so levofloxacin was added. On day 6, patient's Tm was still elevated (Tm 102.7°F), so her ceftriaxone antibiotic was changed to piperacillin/tazobactam (Fig. 1A). Her urine *Streptococcus pneumonia* antigen, negative; urine *Legionella* antigen, negative; *Mycoplasma* rapid IgM, negative; *Chlamydia*, *Legionella*, and *Coccidioides* antibody, negative; *Parvovirus* B19 PCR, negative.

Clinical Course

The day after admission, patient developed maximum daily Tm of 102.8°C (Fig. 1B) and was tachycardic. Her creatinine level was low 0.4 mg/dL, and her total bilirubin, alkaline phosphatase (Alk Phos), and aspartate aminotransferase (AST) were high and 1.8 mg/dL, 148 U/mL, and 138 U/mL, respectively. Computed tomography of abdomen and pelvis with contrast were read as negative by the radiologist. Patient's Hgb and hematocrit (HCT) were 7.2 G/dL and 19.9%, respectively, on admission and declined to 5.2 G/dL and 16.8% 3 days after admission (Fig. 1C).

Four days after admission, patient again had severe fever (Tm 103.1°F). Chest x-ray that day showed right lower lobe infiltrate. The patient exhibited increased O_2 requirements (Fig. 1D), and bilateral vaso-occlusive crisis with chest syndrome; the 2-dimensional echocardiogram was difficult to assess because of tachycardia but showed left ventricular hypertrophy with normal systolic function and mildly elevated pulmonary artery systolic pressure, estimated at 35 mm Hg. The patient's Hgb and HCT declined further 6 days after admission to 5.0 G/dL and 14.4%, respectively with persistently elevated white blood cell count of 28,000/μL of blood and further increased right middle lobe infiltrates detected in a chest x-ray; these findings resulted in an infectious disease consultation on day 6 of admission. She did cough up thick sputum after her albuterol breathing treatment but otherwise had no cough. Her sputum culture grew only normal flora. Patient denied pleuritic chest pain, but she was using her patient-controlled analgesia for pain control (Fig. 1B). Her lactate dehydrogenase was markedly elevated at 2804 U/L. A new computed tomography of her chest showed multiple peripheral infiltrates consistent with infarcts but no pleural effusion.

On day 8 after admission, the clinical team was concerned that the patient was on the verge of developing multiorgan failure (total bilirubin level 5.8 mg/dL; alanine aminotransferase 50 U/mL; AST, 189 U/mL; Alk Phos, 402 U/mL; and creatinine level 1.0 mg/dL). The increase in creatinine level from 0.4 to 1.0 mg/dL, which suggests kidney damage in sickle cell patients, occurred before treatment with ibuprofen, so the increase cannot be attributed to ibuprofen toxicity. The patient exhibited prolonged partial thromboplastin time (37 seconds) and prothrombin time (14 seconds), suggesting either hepatic dysfunction or possibly consumptive coagulopathy. The following day, the patient seemed more forgetful of details, was tearful and frightened, and was complaining of such severe right distal thigh pain that she now exhibited difficulty moving her leg. Her Hgb was critical at 3.8 G/dL. Her second 2-dimensional echocardiogram showed biatrial and right ventricle enlargement, mild mitral and tricuspid insufficiency, tricuspid regurgitent jet velocity of 2.7 m/second, and an estimated pulmonary artery systolic pressure of 34 mm Hg. Her laboratory values were: total bilirubin level 1.5 mg/dL; alanine aminotransferase 105 U/mL; AST 259 U/mL; Alk Phos 358 U/mL; and creatinine level 0.4 mg/dL. She was again offered a

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blood transfusion, which she continued to refuse. The team discussed the option of inhaled nitric oxide therapy (iNO), which is used routinely in our facility for pulmonary hypertension. The potential benefits of inhaled nitric oxide therapy were presented to the patient with caveats including that only limited clinical studies had been performed for vaso-occlusive crisis.[6–8]

The patient agreed to therapy and continuous 40 ppm iNO therapy with 5 L/minute oxygen via the nasal prongs was started in the late afternoon of the 9th day of admission. The therapy was administered for an additional 3 days. Her methemoglobin levels were 0.7, 0.5, 0.9, and 1.2% on day 0 through 3 of iNO therapy, respectively, and her blood pressure did not decline. The

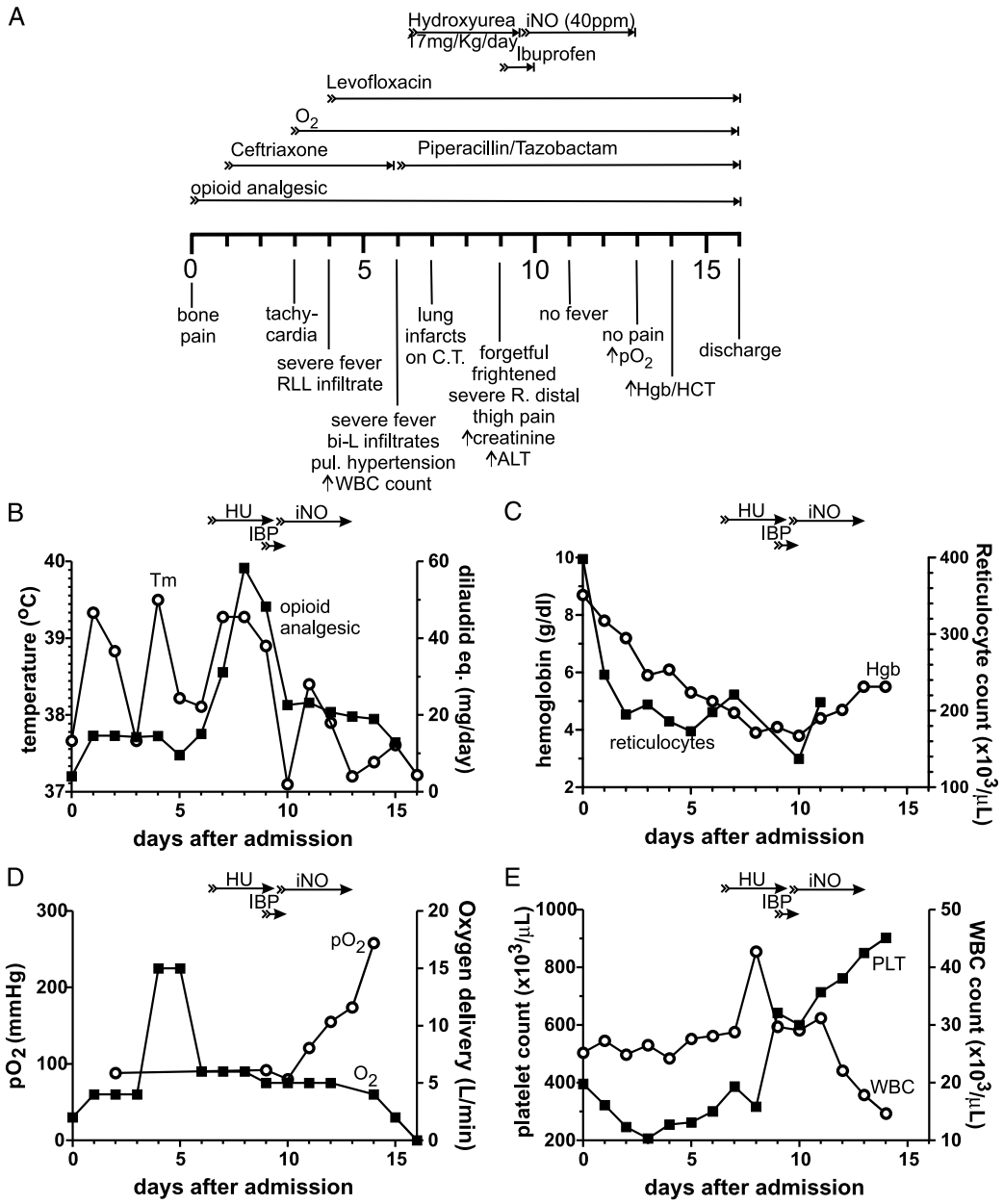

FIGURE 1. Clinical course of a patient with SCD, who was treated with iNO therapy. The key clinical observations and treatments are summarized (A) with the clinical observations below the time line and the treatments above the time line. Her daily Tm in °F and use of opioid analgesics (B), Hgb and absolute reticulocyte count (C), P_{O_2} and oxygen delivery (D) and white blood cell and platelet counts (E) are plotted when ordered as part of her care. All her opioid analgesics (hydrocodone and morphine during days 0–7 after admission) were converted to hydromorphone equivalents using the drug information handbook. MetHb levels did not exceed 1.5% while on iNO therapy. The timing of key treatments (hydroxyurea, ibuprofen, and iNO) is indicated in each panel. HU indicates hydroxyurea; Eq., equivalent; IBP, Ibuprofen.

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patient's fever resolved 24 hours after initiation of iNO therapy, her Po_2 also improved markedly from 80 mm Hg on the day of initiation of therapy to 155 mm Hg upon completion of therapy. Patient also reported no pain upon completion of iNO therapy. Her Hgb and HCT remained stable then gradually increased to 5.5 G/dL and 16.8%, respectively, the day after cessation of iNO therapy (Fig. 1C). A chest x-ray performed on the day of discharge indicated a marked improvement in pulmonary infiltrates and left lower atelectasis. She was discharged 3 days after stopping iNO therapy with oral hydrocodone/tylenol for bone pain but without antibiotics.

■ DISCUSSION

A recent clinical trial reported that SCD patients with vaso-occlusive crisis also exhibited pulmonary hypertension[6] and the patient exhibited clinical signs of both proposed pathogenic pathways.[1] She exhibited critically low Hgb levels, reticulocytosis, multiorgan involvement, and pulmonary hypertension, which suggests that the hemolysis-endothelial dysfunction pathogenic pathway was operative, but she also exhibited bone pain, which is the phenotype of the vaso-occlusive pathway.

After iNO therapy, the patient's clinical parameters all reversed, enabling her to be discharged 3 days after completion of the therapy and 6 days after being critically ill. The prospective study of Weiner et al.[6] indicates that iNO therapy (80 ppm for 4 hours; n = 10) provides immediate and some delayed improvement in pain for SCD patients with vaso-occlusive crises. Although limited to a single patient, we propose that our anecdotal experience suggests that iNO therapy is beneficial against several complications besides pain. The patient exhibited pain secondary to vaso-occlusive crisis, but also severe anemia, and lung infiltrates consistent with acute chest syndrome, which all improved after the iNO therapy. Two case reports suggest that iNO therapy alleviated the acute chest syndrome,[7,8] which supports the concept that iNO therapy may alleviate several sequelae of SCD besides pain. Thus, iNO could be beneficial for the treatment of vaso-occlusive pathogenic pathway[6] and possibly the hemolysis-endothelial dysfunction pathway. This proposition agrees with clinical and experimental models where low NO bioavailability predisposes to thrombosis[9] and decreased erythrocyte deformability[10,11]; both factors are likely to contribute to vascular occlusion.

It is possible that the discontinuation of hydroxyurea treatment with its cytostatic and myelotoxic effects may be responsible for the clinical improvements of the patient rather than iNO. We believe this is unlikely because the response to treatment was much more rapid than restoration of bone marrow function would predict. Dexamethasone is a treatment of acute chest syndrome, which has been evaluated in a randomized controlled clinical trial.[12] However, this immunosuppressant was not used because we had not ruled out the possibility of fungal infection.

This case report suggests that iNO treatments can continue longer than the 4 hours used by Weiner et al.[6] After 24 hours of iNO therapy, the patient only exhibited limited clinical benefit (Hgb levels were no longer descending and normal Tm). Thereafter, her clinical picture improved markedly: her lung sounds returned to normal in 2 days, and her pain, oxygenation, and fever were markedly improved on the third day of iNO therapy. The patient did not exhibit methemoglobinemia during the iNO therapy because her maximal methemoglobin level of 1.2% on day 3 of iNO therapy was below the 1.5% maximum normal value. Moreover, she did not exhibit declines in her blood pressure, which suggests minimal NO toxicity during continuous iNO therapy for 3 days. It should, however, be emphasized that our contentions are based mainly on temporal correlations in this single case report, so validating whether (i) continuous iNO therapy should be longer, (ii) iNO improves multiple complications of SCD besides pain, and (iii) is well tolerated in SCD awaits the results of the prospective clinical trial being performed by the NIH (ClinicalTrials.gov NCT00094887 and NCT00142051).

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