# The Effectiveness of Long-term Inhaled Iloprost in Addition to Oral Sildenafil Treatment in Severe Pulmonary Hypertension Associated with Sickle Cell Disease

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**Abstract**

Pulmonary arterial hypertension (PAH) is a common complication of sickle cell disease (SCD). A 21 year-old female patient with SCD was presented with dyspnea and palpitation during slight effort. Pulmonary arterial systolic pressure (PASP) was 115mmHg on echocardiogram. No improvement of symptoms was achieved with the classical treatment and oral sildenafil was given. In the second week of therapy, PASP decreased to 75mmHg. She was presented with chest pain, left shoulder pain and dyspnea six months later. PASP was 125mmHg. No improvement was achieved with the treatment and inhaled iloprost was added to sildenafil treatment. PASP decreased to 65mmHg.

**Keywords:** Sickle cell disease, pulmonary hypertension, sildenafil, iloprost

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## INTRODUCTION

Sickle cell disease (SCD) occurs in individuals who are homozygous for their hemoglobin (HbS), much less soluble then normal hemoglobin (HbA) when deoxygenated [1]. Approximately 250.000 children worldwide are born with homozygous sickle cell anemia every year [2]. Rigid, dense and sickled cells become entrapped in the microcirculation producing ischemia and reperfusion injury, propagating inflammatory, thrombotic and oxidant stress [1].

Acute and chronic pulmonary complications of SCD are common but often under- appreciated by health care providers. Acute complications include asthma and acute chest syndrome and chronic complications include pulmonary fibrosis, pulmonary hypertension and cor pulmonale [3].

Pulmonary arterial hypertension (PAH) is a common complication of SCD, with a reported prevalence of approximately 30%, and has a major mortality risk [1, 4]. There are currently limited specific data about any treatment modality for PAH in SCD.

Sildenafil citrate is a selective inhibitor of cyclic guanosine monophosphate specific phosphodiesterase-5 isoenzyme which promotes selective smooth muscle relaxation in lung vasculature and has been utilized successfully in the treatment of PAH [5, 6].

Iloprost infusion is an effective treatment for peripheral artery disease, several forms of vasculitis and PAH. The pharmacological action of this stable prostacyclin ($PGI_2$) analogue includes arterial and venous dilatation, stabilization of endothelial function and inhibition of thrombocyte, leukocyte and red cell activation [7]. It has been reported that inhalation of Iloprost cause pulmonary vasodilatation. It has also been shown that long-term use of inhaled Iloprost improves exercise capacity and hemodynamic variables in patients with IPAH [8].

We report a case of severe PAH associated with SCD who benefited from oral sildenafil plus inhaled iloprost treatment.

## CASE REPORT

A 21 year-old female patient with SCD was presented with dyspnea and palpitation during slight effort, deteriorating for several months. She had the diagnosis of cardiac failure and her medication was including digoxine, diuretics, ACE inhibitor and Hydroxiurea. On physical examination, the patient was subicteric with a blood pressure (BP) of 90/60mmHg, heart rate of 100/min, and respiratory rate of 26/min. She was orthopneic and breath sounds were normal. The second heart sound on pulmonary focus was hardened. She had hepatomegaly but no wrist edema. Plain chest X-Ray showed cardiomegaly and hilar enlargement

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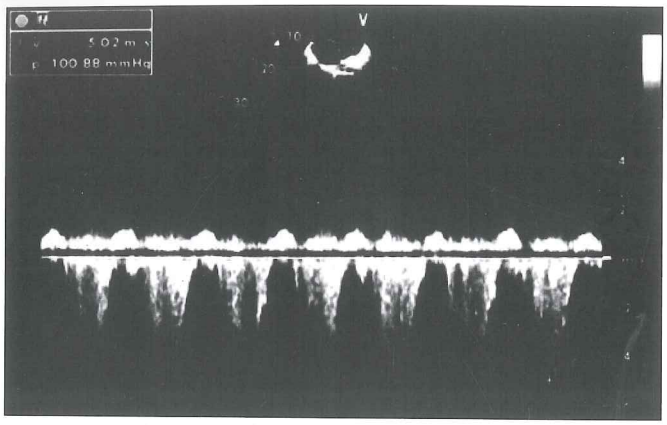


**Figure 1.** Initial echocardiogram of the patient. Pulmonary arterial systolic pressure was measured as 115mmHg.

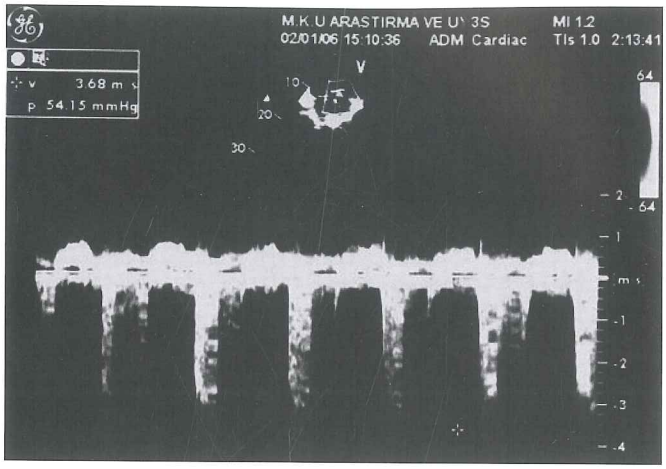


**Figure 2.** Echocardiogram after iloprost inhalation showed markedly reduced pulmonary arterial systolic pressure.

with no parenchimal abnormality. Hemoglobin, LDH and indirect bilurubin levels were 7.4, 2345 IU/L and 5.5mg/dl, respectively. Lung function test showed moderate restriction. Two dimensional Doppler echocardiography showed dilation of right ventricle and atrium with severe tricuspid regurgitation. Pulmonary arterial systolic pressure (PASP) was 115 mmHg and left ventricular function was normal (Figure 1). Abdominal ultrasound showed otosplenectomy and hepatomegaly. Computed tomography (CT) and high resolution computed tomography (HRCT) of the chest showed central and main pulmonary arterial enlargement, cardiac enlargement, mediastinal lymphadenopathy, and mosaic pattern in both lung parenchyma. Nasal oxygen support, oral furosemide, digoxine, Hydroxiurea and calcium channel blockers were given, and blood transfusion for increasing Hb level was performed. But the patient was still dyspneic, and could not perform any effort. Six minute walk distance (6MWD) could not be measured because of inability to walk. Sildenafil at the starting dose of 25mg bid was added to the therapy after informed consent was taken. When the dose was increased to 50mg bid (in the second week of the therapy) the performance status of the patient was raised from NYHA (New York Heart Association) Class IV to Class I. PASP decreased to 75mmHg and 6MWD was measured as 420m. Medication was well tolerated. In the first week, hypotension and slight nasal bleeding has occured. She was sent home with sildenafil treatment. During the second month of therapy, the patient presented with exercise dyspnea and palpitation. PASP was 100mmHg. The dose of sildenafil was increased to 50mg tid. The patient lost in follow up until acute chest syndrome occurred five months later. She was presented with chest pain, left shoulder pain and dyspnea. She had not used sildenafil regularly. PASP was measured as 125mmHg on echocardiogram. Arterial blood gas analysis showed a $pO_2$ value of 44 mmHg and an oxygen saturation value of 80%. Despite treatment with sildenafil, low molecular weight heparin, calcium channel blockers, low dose diuretics and digoxine, the patient was still dyspneic at rest and oxygen saturation was just 90% with 10 l/min oxygen via nasal mask. The clinical status of the patient was critical and we started inhaled iloprost 50µg/day with 6 inhalations per day. The conventional treatment and sildenafil regimen were not changed. Since the second day of the treatment, dyspnea and extremity pain of the patient started to improve. Immediately after the inhaled iloprost, echocardiography was performed and PASP was measured as 65mmHg (Figure 2), with an increase of arterial oxygen saturation. Ten days later, the patient was able to walk. No side effects were observed. 6MWD was measured as 360m. $SpO_2$ levels were over 90% with 2 l/min nasal oxygen. After 6 months, PASP was 65mmHg and 6MWD was 380m. The patient is still receiving combination therapy and carrying on her normal activity.

## DISCUSSION

Pulmonary complications, especially PAH, are common in the course of SCD and largely associated with death among adults with SCD [9]. The pathogenesis of PAH is probably multifactorial [1]. It has been reported that intravascular hemolysis is the most important factor [4]. It is likely that, maximization of SCD therapy would be beneficial by ameliorating the intravascular hemolysis [1]. Cardiopulmonary function might be improved with a Hb level of 8-10g/dl and a HbS level of <40%. Thus, progression of PAH can be prevented.

Pulmonary thromboembolism and progressive endothelial damage with concentric pulmonary vascular intimal

hyperplasia and in situ thrombosis may also play an important role in the pathogenesis of PAH in SCD [4].

Functional asplenia could also contribute to the development of PAH in SCD [1]. It has been suggested that the loss of splenic function increases the circulation of platelet derived mediators. It has also been speculated that senescent and abnormal erythrocytes in the circulation promote pulmonary microthrombosis and red cell adhesion to the endothelium by triggering platelet aggregation [10]. The fact that our patient had otosplenectomy supports this hypothesis.

Oxygen desaturation, especially unrecognized nocturnal hypoxemia should be investigated in these patients [1]. Severe sleep apnoea syndrome can also lead to frequent episodes of night time desaturation [1]. We carried out nocturnal pulse oxymetry record and found nocturnal hypoxemia. The patient did not have the symptoms of sleep apnoea syndrome. However we could not perform polisomnography because of inavailability. Afterwards nocturnal oxygen support was given.

According to findings of Ataga et al., in 13% of patients with SCD, PAH developed during follow up [4]. This finding suggests that in patients with SCD periodic screening echocardiogram should be performed. Kato et al. also suggested that, in a SCD patient who found to have PAH at the time of screening echocardiogram, a repeat study should be done because of the increase in PASP during acute vaso-occlusive crisis [11]. When PAH firstly detected in our case, she was not suffering from vaso-occlusive crisis and repeated echocardiograms also showed the elevation of PASP.

Cardiac catheterization is the gold standard for the diagnosis of PAH. However, this procedure is invasive and includes some risks for patients with SCD [12]. Echocardiography is a noninvasive screening tool for PAH by quantifying measurable tricuspid regurgitation [12]. In our patient, cardiac catheterization was not performed because of limited technical capacity and the risk of complication.

Machado & Gladwin recommend specific vasodilator/remodeling therapy for symptomatic patients with moderate to severe pulmonary hypertension [1]. However there is no long term data on the specific efficacy of selective pulmonary vasodilator/remodelling pharmacological agents in patients with SCD, and the choice of specific agents is largely empirical and based on the safety profile of the drugs and doctor preference [1].

NO probably plays a role in the pathogenesis of PAH associated with SCD. Therefore therapeutics that enhance NO effect, such as inhaled NO, L-arginine and sildenafil, may be beneficial in the treatment of PAH associated with SCD [1]. Sildenafil, a recently developed vasodilator, is a specific inhibitor of phosphodiesterase-5. There are a few reports about the effects of long-term therapy with sildenafil monotherapy. Machado et al. reported a 10mmHg decrease in estimated PASP and a 78m increase in the 6-MWD with sildenafil. This effect is similar to the one seen in case series of sildenafil in other forms of pulmonary hypertension [13]. In our case, a 40mmHg decrease in PASP and functional improvement from NYHA functional class IV to Class I were achieved with sildenafil.

Derchi et al. reported a significant long term decrease in PASP and improvement in exercise capacity and NYHA functional class with sildenafil in patients with hemoglobinopathies [5]. However we could not find any report in English literature about inhaled iloprost treatment in patients with SCD.

At the second hospitalization, when we decided to give additional vasodilator therapy, iloprost was the unique agent available in our country. Because of the systemic use of prostanoids produce significant systemic vasodilatation and therefore increase the potential development of high output heart failure in anemic patients, we preferred to use the agent via nebulization. No side effects occurred.

Onen et al. [14] reported a case of idiopathic pulmonary arterial hypertension who treated 100mg/d oral sildenafil. In the sixth month of therapy, they started additional inhaled iloprost treatment because of worsening of symptoms and functional clinical status of the patient. They reported a 36% decrease in PASP with inhaled iloprost.

In conclusion, SCD patients should be evaluated and screened for PAH regularly. Inhaled iloprost plus oral sildenafil could be a safe combination therapy for severe PAH associated with SCD. Large randomized trials evaluating the effects of specific therapy for PAH in these patients are also needed.

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