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Case report

Intermittent intravenous administration of Iloprost in patients with idiopathic pulmonary arterial hypertension

Majid Malekmohammad [a], Babak Sharif-Kashani [b,*], Fateme Monjazebi [c], Leila saliminejad [c]

[a] Tracheal Disease Research Center, NRITLD, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences,Tehran, Iran
[b] Tobacco Prevention and Control Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran 1955841452, Iran
[c] Chronic Respiratory Diseases Research Center, National Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

Background and objectives: Because there is no cure for idiopathic pulmonary artery hypertension (IPAH), improving survival and stabilizing disease are key aims in any treatment strategy for patients with IPAH. Intravenous (IV) administration of prostacyclin positively affects the symptoms and hemodynamic of patients with IPAH.

This study sought to assess the efficacy of cyclic Iloprost administration in Iranian patients with IPAH.

Materials and methods: This longitudinal study was conducted on 20 patients with IPAH. Upon hospitalization, the patients received intermittent IV administration of Iloprost 6 hours a day for 5 days; this cycle was repeated every 6 weeks, total duration of treatment was 12 months. New York Heart Association/World Health Organization (NYHA/WHO) functional classification (FC), 6-minute walk test (6MWT), mean pulmonary arterial pressure (PAPm), right ventricular pressure (RVP), and serum level of N-terminal pro b-type natriuretic peptide (NT-proBNP) were assessed at baseline, during and after completion of treatment course. The data were analyzed using SPSS version 13.

Results: The FC, PAPm, and RVP significantly decreased after the treatment ($P < 0.001$). No change occurred in the level of oxygen saturation during the 6MWT but the distance walked significantly increased after the intervention compared to baseline. Level of NT-proBNP significantly decreased in patients after treatment ($P = 0.009$).

Conclusion: Intermittent IV administration of Iloprost decreases the FC, PAPm, RVP, and serum level of NT-proBNP and increases the distance walked in the 6MWT by patients.

Introduction

Pulmonary hypertension (PH) refers to an increase in mean pulmonary arterial pressure (PAPm) ≥ 25 mmHg as assessed by right heart catheterization (RHC).[1] This condition can be idiopathic, congenital, or acquired, related to diseases and conditions such as connective tissue diseases, congenital heart disease, portal hypertension, AIDS, and some toxins and medications such as appetite suppressing drugs; PAH does not have a good prognosis.[2–4] Idiopathic pulmonary artery hypertension is a rare disorder with an unknown etiology, in which occlusion of small pulmonary arteries increases the PAPm and results in secondary right ventricular insufficiency.[5] The prevalence of PAH in the United States varies from 4.5 to 12.3 per 100,000 population.[1] In Europe, its prevalence has been reported to be 15–60 patients per one million individuals.[6–7] In the UK, the prevalence of PAH is 97 per one million.[1] The prevalence of PAH is 15 per one million, and the prevalence of IPAH is 5.9 per one million population in France.[8] Approximately 50% of PAH patients in all registries suffer from IPAH, heritable PAH, or drug-induced PAH.[1] Thus, it can be estimated that among the 77-million population of Iran, 150 subjects develop PAH annually.[1] Considering the survival rate of 1–2 years (without treatment), approximately 400–450 patients in Iran suffer from IPAH. The statistics of patients registered in the referral centers are close to this value taking into account some related factors. Before the development of new medications, the mean survival rate of patients with PAH was less than 3 years.[2]

Medications such as oxygen, calcium channel blockers, warfarin, digoxin, and diuretics have long been used for these patients as part of conventional therapy. These medications are selected based on the current treatment protocols for chronic cardiac and respiratory diseases and based on the pathophysiological mechanism proposed for the left heart congestive failure, hypoxia in patients with obstructive pulmonary diseases, and systemic hypertension and are referred to as symptomatic treatment.[5] Calcium channel blockers (CCB) must be prescribed only for patients with a positive response to vasodilator test; these patients

* Corresponding author. Tel.:+98 2127122499; fax: +98 2126106003.
E-mail addresses: mmalekmohammad@yahoo.com (M. Malekmohammad), babaksharifkashani@yahoo.com (B. Sharif-Kashani), fmonjazebi@gmail.com (F. Monjazebi), saliminejad.af85@yahoo.com (L. saliminejad).
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require precise follow-up and may need some specific treatments.[6,9] Medications recently recommended for these patients include endothelin receptor antagonists (ERAs), soluble guanylate cyclase stimulators such as riociguat, phosphodiesterase type 5 inhibitors (PDE-5I) such as sildenafil, and prostanoids such as epoprostenol and Iloprost.[10–11]

In patients with positive vasodilator test, who are categorized as low-risk group based on clinical examinations, CCB is the first choice of treatment. If CCB do not improve the patient's condition, specific treatment with oral ERAs such as bosentan or PDE-5Is such as sildenafil may be started. For low-risk patients with a negative vasodilator test, treatment with one of the specific medications is started.[1] For high-risk patients with a negative test, continuous treatment with IV prostacyclin can be effective; in such cases, epoprostenol, treprostinil, or Iloprost is the first choice of treatment.[12]

Prostacyclin (PGI2) is a strong vasodilator, which prevents the proliferation of endothelial smooth muscle cells; however, the synthesis of prostacyclin decreases in IPAH.[11] Evidence shows that administration of IV prostacyclin along with conventional treatments for more than 12 weeks can positively affect exercise capacity, FC, and hemodynamic of cardiovascular patients.[13] Prostacyclin is an important homeostasis regulator and is a strong short-acting prostanoid produced in the vascular endothelium. Iloprost-β-cyclodextrin clathrate, also known as Iloprost, is a synthetic, chemically strong, and stable prostacyclin.[14–15] Iloprost is an analog of epoprostenol, also known as prostacyclin (PGI2), which mimics the pharmaceutical properties of epoprostenol. It prevents platelet aggregation in vessels, causes vascular dilation, and enhances the blood flow through the vessels; thus, it also prevents polycythemia.[14,16] This drug can be administered via three routes of oral, inhalation, and injection.[11]

This drug is most commonly administered intravenously.[16] Intravenous administration of Iloprost requires hospitalization since patients should be monitored for the side effects of the drug during administration such as tachycardia, hypotension,[17] headache, and flushing.[16] Iloprost and epoprostenol are chemically similar with the exception that Iloprost is more stable, readily available, and easier for use at home.[18] Iloprost decreases the resistance of peripheral vessels and the mean arterial pressure while it increases the cardiac index and heart rate. Also, it increases the renal blood flow[19] but has a natriuretic effect and increases the excretion of sodium in urine; however, this is independent of the related hemodynamic changes.[16]The clearance of this drug is 15–20 mL/kg/min and has a half-life of 5–20 min. Most of it (70%) is excreted through the kidneys and 12–17% is excreted via other routes.[15] To obtain an effective plasma level, it must be continuously infused in an amount of 1–2 ng/kg/min.[19] By introduction of new medications such as epoprostenol and Iloprost, 1-year and 3-year survival rates of patients increased by 68–88%.[20]

Iloprost is administered in IPAH patients in two forms of continuous[21] and intermittent or cyclic infusion.[12] Continuous infusion requires adequate vascular access obtained by insertion of a permanent catheter in the subclavian vein and the drug is delivered to the patient by CADD1 infusion pumps. The drug is administered with the initial infusion rate of 0.5 ng/kg/min, which is gradually increased as long as no unbearable side effects occur. After hospital discharge, patients are visited in an outpatient setting every 6–12 weeks. In case of satisfactory clinical outcomes (based on the opinions of the attending physician and patients), the drug dosage does not change. In case of no change or aggravation of disease, the drug dosage increases unless unbearable side effects occur. Each patient visit must include history taking, physical examination, and 6MWT along with functional assessment using FC.[22] In intermittent or cyclic infusion, Iloprost is administered for five consecutive days for 6 hours a day. This cycle is repeated every 6 weeks. The initial infusion rate is 0.5 ng/kg/min, which later increases to 2 ng/kg/min.[9,12]

Following the initiation of treatment, its outcome must be evaluated in patients. Several tools are available for outcome assessment in IPAH patients such as echocardiography, assessment of hemodynamic parameters,[23] 6MWT,[24] biochemical markers such as serum uric acid,[25–26] FC,[27] and NT-proBNP.[28] Echocardiography is a non-invasive method suitable for primary and outcome assessments of treatment in these patients. This modality provides valuable information about the hemodynamic status of the right heart such as PAPm, status of the right and left ventricles, and atriums.[29–31] The 6MWT is affordable, simple, reproducible, standard, and objective[24] and has been introduced as the gold standard for the assessment of the treatment outcome in PAH patients by the European Agency for Evaluation of Medicinal Products and the Food and Drug Administration.[32–33] The 6MWT is the most important criterion for assessment of treatment outcome and severity of disease in patients in the clinical setting and in clinical trials for research purposes.[34] The level of NT-proBNP increases in IPAH patients by a reduction in the right ventricular function.[35] Studies show that in patients with PAH, the level of NT-proBNP is correlated to the functional[28] and hemodynamic[36] status of patients and can be used as a predictor of the survival of patients.[35,37]

Considering the high cost of prostacyclin medications[18] particularly in Iran, patients often cannot afford continuous treatment with this medication. Thus, patients who require IV prostacyclin according to the guidelines can only receive this drug in a cyclic fashion by hospitalization for 5 days per month and repeat this cycle every 6 weeks. No previous study has assessed the outcome and efficacy of cyclic administration of Iloprost in IPAH patients and the available ones have only focused on connective tissue diseases. Therefore, this study sought to assess the outcome and efficacy of cyclic treatment with Iloprost in Iranian patients with IPAH.

Materials and methods

This longitudinal study was conducted during 2011–2013 on patients presenting to Masih Daneshvari Hospital due to mean pulmonary artery pressure (mPAH). Only 20 patients during the above-mentioned time period required treatment with IV Iloprost. The inclusion criteria were definite diagnosis of IPAH based on right ventricular catheterization and the expert opinions of the cardiologists and pulmonologists of Masih Daneshvari Hospital, the need for treatment with IV Iloprost, and willingness for participation in the study. Data were collected using a researcher-designed questionnaire. This questionnaire included demographic information (age, sex, height, and weight of patients and duration of disease), FC, 6MWT (distance walked and drop in O2 saturation), echocardiographic findings (PAPm and RVP), hemodynamics on right ventricular catheterization (PAPm and atrial pressure), and level of NT-proBNP at baseline, in the first 6 weeks, in the second 6 weeks, and in the third 6 weeks of the study. The demographic part of the questionnaire was filled out by interviewing patients and the sections regarding clinical and paraclinical tests were filled out by the research supervisor based on the opinions of cardiologists and pulmonologists of Masih Daneshvari Hospital. The validity and reliability of these clinical and paraclinical tests have been assessed in several studies and the 6MWT is also known as the gold standard for assessment of patients with IPAH.[32,34] These tests are routinely performed for assessment of the course of treatment in IPAH patients hospitalized in Masih Daneshvari Hospital. After explaining the objectives of the study to patients, written informed consent was obtained from them. Patients were informed that they were free to leave at any time and that not participating in this study would not affect their course of treatment. Also, patients were ensured about the confidentiality of their information. Each patient

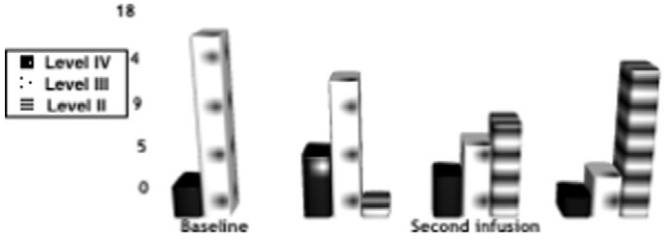

Diagram 1. Changes in the FC of patients following treatment.