https://doi.org/10.38109/2225-1685-2019-2-76-83

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ISSN 2225-1685 (Print)
ISSN 2305-0748 (Online)

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EFFECTIVENESS OF ILOPROST IN PATIENTS WITH PULMONARY HYPERTENSION FC III – IV BASED ON VORONEZH REGION REGISTRY DATA

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ABSTRACT

The purpose of the study: to study the effectiveness of the use of the drug iloprost in patients with PH III - IV FC according to the register of the Voronezh region. The material was the base register data. The effectiveness of the drug «iloprost» evaluated in patients with PH III - IV FC according to the register.

The safety of therapy «iloprost» shown on the basis of a complex of clinical and hemodynamic parameters.Clinical example presented.

Keywords: *pulmonary hypertension, iloprost, pulmonary hypertension register of the Voronezh region.*

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For citation: Королькова О.М., Черных Т.М. Эффективность илопроста больных легочной гипертензией III–IV ФК с учетом данных регистра по Воронежской области. Евразийский кардиологический журнал. 2019, Май 25; 2:76-79 [Trans. into Eng. ed.: Korolkova O. M., Chernykh T.M. Effectiveness of iloprost in patients with pulmonary hypertension FC III – IV based on Voronezh region registry data. Eurasian heart journal. 2018, May 25; 2:80-83]

INTRODUCTION

Pulmonary hypertension (PH) is a group of diseases characterized by a progressive increase in pulmonary vascular resistance that leads to right ventricular failure and premature death of patients. Recently, real opportunities have emerged for the treatment and prolongation of life for such patients [2]. It is the most efficient to track the prevalence, incidence, and the effectiveness of PAH-specific therapy based on the registry data. In 2012, the National Registry of Pulmonary Hypertension, which includes the regional segment of the Voronezh Region [1] was created in the Federal State-Funded Institution National Medical Research Center of Cardiology of the Ministry of Health of the Russian Federation. However, the treatment of pulmonary hypertension FC (functional class) III – IV is still a difficult task [3].

The aim of the study: to study iloprost effectiveness in patients with PH FC III – IV based on the PH registry regional segment data of the Voronezh region.

Material and methods. Currently, there are 30 patients in the regional segment registry of the Voronezh region (www.medibase.pro). The structure of diagnoses was distributed as follows: 11 patients – idiopathic pulmonary hypertension (IPH) – 35%; 8 patients – chronic thromboembolic pulmonary hypertension (CTEPH) – 30%; 7 patients – PH with Eisenmenger's syndrome – 22%; 1 patient – PH on the background of the systemic scleroderma – 4%; 3 patients – PH on the background of left heart region pathology – 9%. Primary diagnostics was carried out in expert centers (Moscow, St. Petersburg). Follow-up and dosage adjustment were carried out at the Budgetary Healthcare Institution of the Voronezh Region Voronezh Regional Clinical Hospital No. 1. 5 patients with PH FC III – IV (3 patients diagnosed with CTEPH; 2 patients diagnosed with IPH) who received iloprost were observed in this study. A set of parameters including echocardiography, 6-minute walking test, a set of clinical and laboratory parameters was monitored. The mean dose of iloprost was 30-45 μg/day (6–9 inhalations using the MicroAir U22 nebulizer). The data were analyzed by the regional PH registry [1]. The registry includes the following data: demographic data, life history, case history, physical examination data, instrument examination data, laboratory data and drug therapy. Right heart catheterization (RHC) was performed in all patients at the stage of diagnosis establishment.

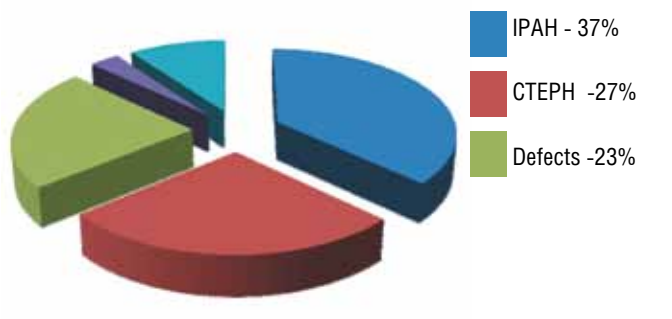

Figure 1. Registry structure N = 30

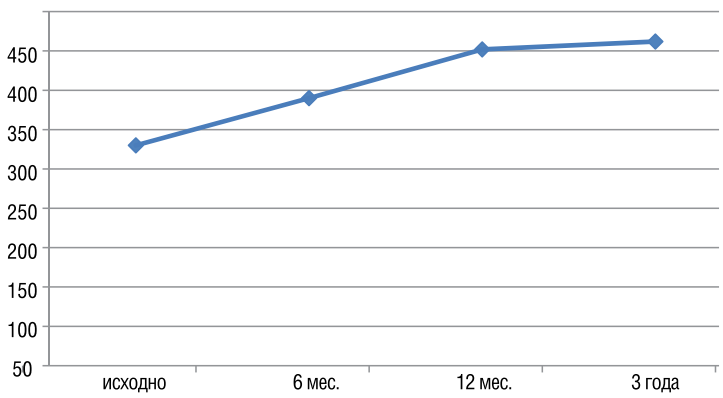

Figure 2. Flow chart of 6-MW

To assess the clinical state of the patients, a functional class (FC) according to the WHO classification, a dynamic 6-minute walk (6MW), dyspnea by the mMRC scale, pulmonary artery systolic pressure (PASP), tricuspid annular plane systolic excursion(TAPSE)), the right ventricle to the left ventricle ratio (RV/LV) were registered. The safety of iloprost use was assessed by alanine and aspartate aminotransferases (ALAT, ASAT) levels. Baseline values, their dynamics after 6 months and 12 months, 3 years of treatment with iloprost were studied.

Statistical analysis was performed using the software package Stastistica 8.0 for Windows. The values were compared using the Mann-Whitney test.

RESULTS AND DISCUSSION

Four patients received Iloprost 30 μg/day due to CTEPH FC IV, two patients – due to IPH FC III-IV. Demographic data of the patients are presented in Table 1.

Changes in the studied parameters on the background of therapy with iloprost are presented in Table 2.

The good efficacy of therapy for improved physical tolerance was noted (an increase in 6-minute walking on average by 150 m).

The 6-MW flow chart is provided below (Fig. 2).

Decreased edema, stabilized hemodynamic parameters (improvement in the right ventricle overload signs) were noted clinically. The maximum efficacy of therapy was observed after 12 months of therapy. After 3 years of therapy with iloprost, the effect remained, however, there was no apparent change. Satisfactory drug tolerability (dry, hacking cough was observed in 3 patients during first 2 weeks of the drug use) was noted. 2 patients died after a long period of stabilization (1st patient – after 6 years of iloprost use in combination with sildenafil 120 mg/day; 2nd patient – after 2 years of treatment). 3 patients have continued to take iloprost in combination with sildenafil 60 mg/day for 3 years.

Table 1. Patient Demographics

Total number of patients	N = 5
Women	4 (80%)
Men	1 (20%)
Age at the time of diagnosis establishment	51,2±9,3

CLINICAL CASE

Patient S., born in 1968. Profession – stylist. She was admitted for the first time to Budgetary Healthcare Institution of the Voronezh Region Voronezh Regional Clinical Hospital No. 1 on February 6, 2008 with the diagnosis: Thromboembolism in the pulmonary artery system? Complaints: shortness of breath during mild physical activity, feeling of lack of air; dull, girdling chest pains not related to physical exercise, lasting 15-40 minutes, aggravated when inhaling, stopping independently; attacks of accelerated heartbeat; cough with mucus sputum; edemas of the lower extremities; cramps in the lower limbs; headaches, dizziness; light-headedness; rapid fatigue, feeling of fear, anxiety, sleep disorder. 2005 – dry cough. 2006 – increased shortness of breath. On January 18, 2007, the X-ray images showed signs of middle-lobar pneumonia in the right pleural cavity; FOB: tracheal osteochondropathy, abnormal development of the right upper lobar bronchus; ECHO-CG: signs of pulmonary hypertension are found.

April 2007 – deteriorated condition, progression of dyspnea, weakness, dizziness, decreased load tolerance (Hospitalization in hospital No. 15 of Moscow with diagnosis of right-sided inferior lobar pleuropneumonia; puncture of the right pleural cavity was performed: exudative pleurisy; discharged with improvement).

Table 2. Changes in the parameters of PH patients on the background of therapy with iloprost

Parameter	Baseline	After 6 months of therapy	After 12 months of therapy	After 3 years of therapy
6-MW, m	280±98	340±72	402±48*	412±46*
Dyspnea by mMRC scale	3,2±0,4	2,9±0,6	2,2±0,5	2,4±0,3
PASP, mmHg	83,2±10,2	75,3±11,0	68,5±9,3*	69,5±9,3
TAPSE, mm	11,1±0,1	14,4±0,08	16,2±0,09	16,7±0,07
RV/LV	2,80±0,01	2,78±0,01	2,84±0,02	2,84±0,02
ALT, U/l	23,0±2,1	28,2±3,2	32,2±2,5	32,2±2,5
AST, U/l	20,0±2,1	29,2±3,2	30,2±2,4	30,2±2,4

6-MWD – 6-minute walking ; PASP – pulmonary artery systolic pressure; TAPSE – tricuspid annular plane systolic excursion; ALT – alanine aminotransferase; AST – aspartate aminotransferase.

** - significant difference from baseline*

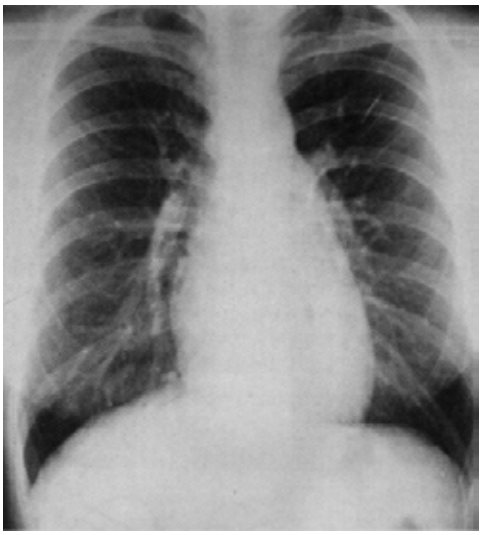

Fig. 2. Chest X-ray 2008.

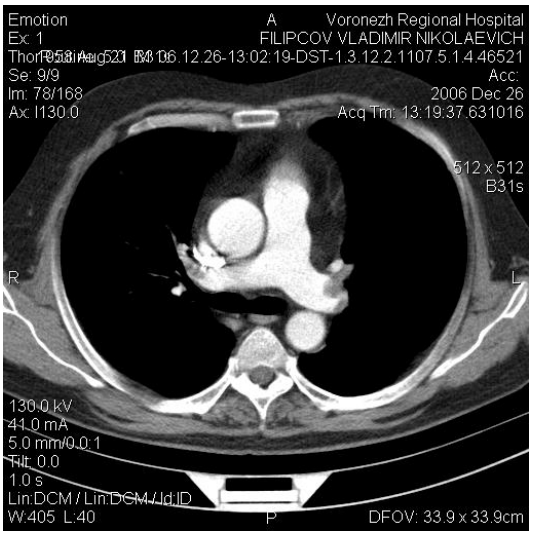

Fig. 3. Filling defects in the segmental branches of the pulmonary artery

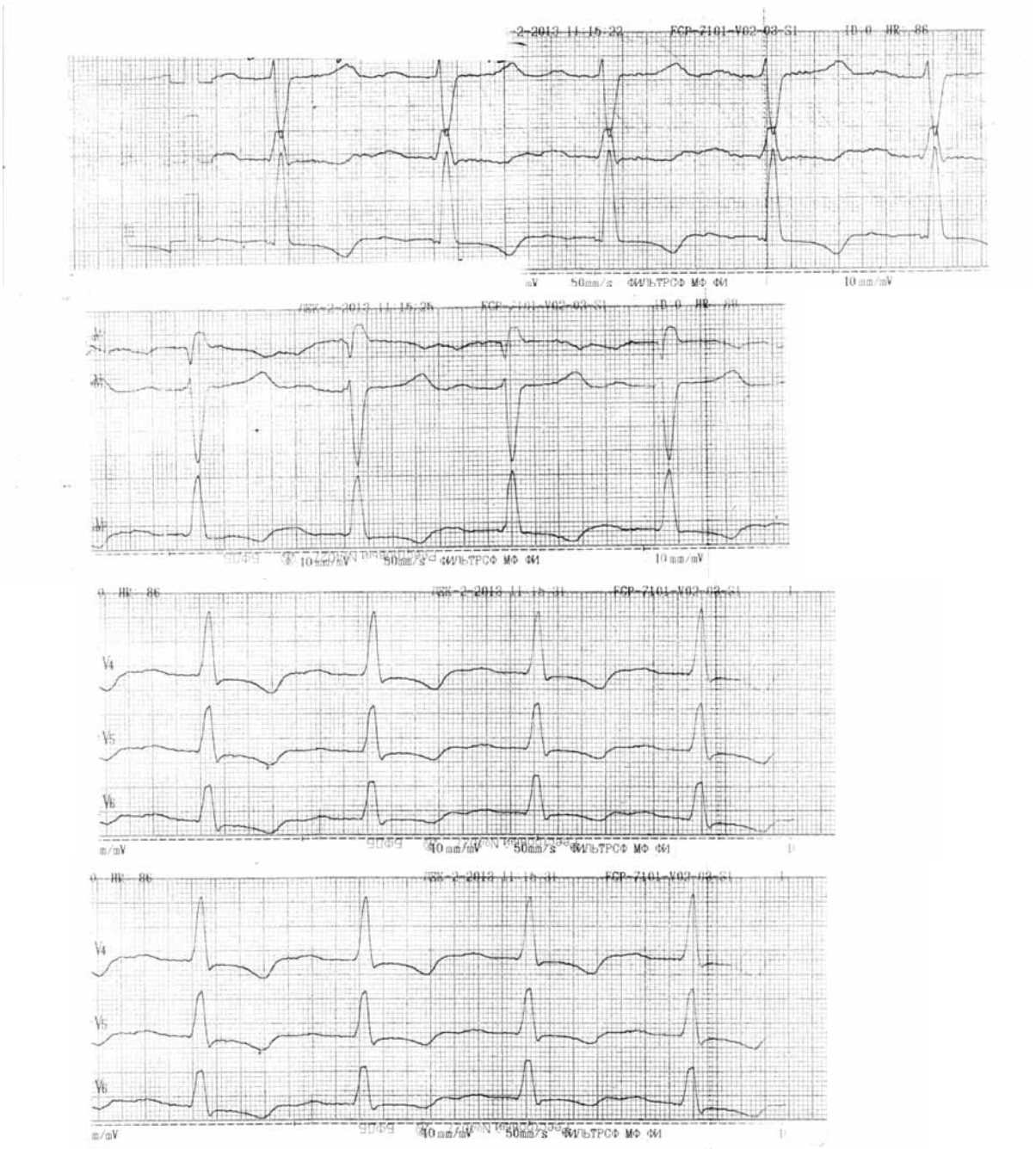

Fig. 4. Patient's ECG

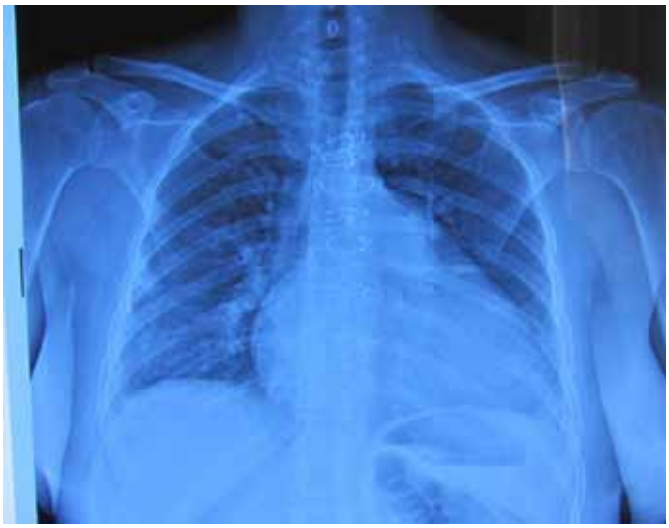

Fig. 5. Chest X-ray of March 25, 2013

July 2007 – chest CT revealed fibrous changes in S9-10 on the right side and in S10 on the left side, pleurocostal and pleurodiaphragmatic adhesions on both sides (when analyzing the X-ray archive, changes of inflammatory origin were observed in the right pleural cavity in November 2003)

October 2007 – another worsening in the condition (hospitalization in City Clinical Hospital No. 12). On November 6, 2007, the patient was discharged with improvement.

February 6, 2008 – multi-spiral computed angiography (MSCT) was performed: parietal filling defect causing 50% stenosis extending to the branches of the lower lobe segments was found in the right pulmonary artery trunk; Doppler sonography of the lower extremities: all veins are passable except for the veins of the femoral posterior surface where dilated, thrombosed veins are observed; X-ray angiopulmonography (APG): Occlusion of the large arterial branches of the middle and lower lobes of the right lung, dilation of the PA trunk, PAD = 100/30 mm Hg; Ileocavography – aneurysm-like dilation of the left iliac vein at the level of inflow into the IVC with signs of contrast delay. Cava-filter was implanted; according to echocardiography, severe dilatation of right heart chambers, tricuspid insufficiency Degree III were found.

May 5, 2008 – referred to St. Petersburg City Hospital No. 2 where the diagnosis was confirmed: Recurrent PATE. Hereditary form of thrombophilia: mutation of the fibrinogen gene, heterozygous state. Chronic thromboembolic pulmonary hypertension. Chronic cor pulmonale. Cardiopulmonary failure FC IV (NYHA). Hypertension Stage 2. Lipoma of the right gluteal region. Varicose veins of the right gluteal region and right lower extremity, small pelvis. Uterine fibromyoma. A pulmonary thrombendarterectomy was performed. The patient was discharged with improvement.

Starting February 2008, the patient received therapy with warfarin (2.5 tab./day) (INR 2.1 – 2.5), diuretics. July 2008 – sildenafil (100 mg per day); 2009 – a gradual progression in dyspnea, the dose of sildenafil (150 mg/day) was increased to allow stabilization of the patient's condition.

2013 – increased dyspnea, edema. After consultation in Myasnikov Russian Cardiology Research and Production Complex, Moscow, iloprost 30 μg/day was added to the basic therapy (6 inhalations 5 μg each per day via the Microair U-22 nebulizer)

Taking into account insufficient effect of the administered therapy, the dose of ventavis was increased to 9 inhalations per day (iloprost + sildenafil 120 mg/d) in 2014.

Until 2016, the patient felt satisfactory. However, in January 2016, she had an ischemic stroke in the right cerebral artery basin. She was hospitalized in the department of the NSO. The patient's condition further stabilized until June 2018. The patient continued to receive iloprost 30-60 μg/day + sildenafil 120 mg/day. In June 2018, the patient died with symptoms of severe pulmonary heart disease.

CONCLUSION

This clinical case shows the difficulty of PH diagnosis. Only MSCT allowed diagnosis of pulmonary artery thromboembolism (PATE). Since PATE was recurring after condition stabilization, the patient was referred to St. Petersburg City Hospital No. 2 (St. Petersburg) where a pulmonary thrombendarterectomy was performed. However, due to the combined (proximal and distal) damage of the pulmonary artery (PA) branches, residual PH remained in the patient in the postoperative period due to which drugs for pathogenetic therapy of PH of thromboembolic origin (sildenafil, iloprost) were prescribed. This allowed stabilization of the patient's condition for a sufficiently long period of time (5 years). However, over the past year, the patient's condition worsened; dose adjustment in combination with diuretics and warfarin allowed positive dynamics to be achieved.

CONCLUSIONS

Thus, the good Iloprost tolerance and efficacy in patients with pulmonary hypertension FC III-IV was confirmed.

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