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Original article

Rapid and high-dose titration of epoprostenol improves pulmonary hemodynamics and clinical outcomes in patients with idiopathic and heritable pulmonary arterial hypertension

Naoto Tokunaga (MD)[a,b,c], Aiko Ogawa (MD, PhD)[b], Hiroshi Ito (MD, PhD, FJCC)[c], Hiromi Matsubara (MD, PhD)[a,b,*]

[a] Department of Cardiology, National Hospital Organization Okayama Medical Center, Okayama, Japan
[b] Department of Clinical Science, National Hospital Organization Okayama Medical Center, Okayama, Japan
[c] Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

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ABSTRACT

Background: Intravenous epoprostenol is an effective treatment for idiopathic and heritable pulmonary arterial hypertension. We aimed to clarify factors that determine the survival of patients with severe pulmonary hypertension who received epoprostenol treatment.
Methods: This is a retrospective observational study consisting of 46 patients with idiopathic and heritable pulmonary arterial hypertension in World Health Organization (WHO) functional class III or IV and undergoing intravenous epoprostenol treatment. We compared the following factors between survivors and non-survivors: clinical characteristics, exercise capacity, hemodynamics, interval between diagnosis and treatment initiation, concomitant pulmonary arterial hypertension-targeted drugs, maximum dose of epoprostenol, and the speed of up-titration. We defined a rapid increase group as those receiving epoprostenol ≥20 ng/kg/min at 3 months and ≥45 ng/kg/min at 1 year of treatment.
Results: Thirty-two patients (70%) survived and 14 patients died during an average follow-up period of 2100 days. Mean pulmonary artery pressure, concomitant pulmonary arterial hypertension-targeted drugs, and the maximum epoprostenol dose were comparable between the two subsets of patients. WHO functional class III was more common than class IV, and the 6-min walking distance was longer in the survivor than the non-survivor group. The survivors typically showed a rapid increase in epoprostenol dose during the first year of treatment. This rapid increase group was associated with a continuous reduction in mean pulmonary artery pressure during the follow-up period, whereas the slow increase group showed no reduction in mean pulmonary artery pressure after 6 months of treatment. The 9.5-year survival rate was also significantly better in the rapid increase group compared with the slow increase group (100% vs. 64%, $p = 0.022$).
Conclusions: In idiopathic and heritable pulmonary arterial hypertension patients, a rapid increase in epoprostenol dose soon after the initiation of treatment seems to be important to achieve a continuous reduction in mean pulmonary artery pressure and to improve survival.

Introduction

Pulmonary arterial hypertension (PAH) is a life-threatening disease that deteriorates over time. Recently, prostaglandins, endothelin receptor antagonists (ERAs), and phosphodiesterase 5 (PDE-5) inhibitors have been approved for use in the treatment of PAH, and reported to improve prognosis in treated patients [1–4]. Among them, the intravenous infusion of epoprostenol sodium, a derivative of prostaglandin I_2, is considered to be the most potent therapeutic agent for PAH. Prostaglandin I_2 promotes intracellular cyclic AMP production, and inhibits thromboxane A2 production and the calcium influx into cells, causing powerful vasodilation, inhibiting platelet aggregation, and attenuating the proliferation of vascular smooth muscle cells [5,6].

Intravenous epoprostenol was shown in a multicenter, prospective, randomized trial to improve exercise tolerance, reduce

* Corresponding author at: Department of Cardiology, National Hospital Organization Okayama Medical Center, 1711-1 Tamasu, Kita-ku, Okayama 701-1192, Japan. Tel.: +81 86 294 9911; fax: +81 86 294 9255.
E-mail address: matsubara.hiromi@gmail.com (H. Matsubara).

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pulmonary vascular resistance, and improve survival in patients with PAH [7]. Similarly, a meta-analysis of controlled clinical studies found that only intravenous epoprostenol out of multiple PAH-targeted drugs improved patient prognosis [8]. Recent guidelines recommend epoprostenol treatment for patients with severe PAH that is identified as World Health Organization (WHO) functional class III and IV [9]. To date, however, there are no guidelines for the optimal protocol of intravenous epoprostenol.

The previous recommended dose of epoprostenol was 25–40 ng/kg/min [10]. However, we reported that treatment with 100 ng/kg/min of epoprostenol for an average of 3.8 years is associated with a substantial reduction in mean pulmonary arterial pressure (PAP) and pulmonary vascular resistance by 29% and 68%, respectively, in patients with idiopathic and heritable pulmonary arterial hypertension (I/HPAH) [11]. Furthermore, we reported an improved survival of I/HPAH patients with 1-, 5-, and 10-year survival rates of 98%, 96%, and 78%, respectively [4]. In this previous study cohort, 75% of patients received epoprostenol. The average epoprostenol dose at the time of hemodynamic improvement was approximately 80 ng/kg/min. Hemodynamic parameters improved significantly after treatment, with a substantial reduction observed in mean PAP and pulmonary vascular resistance by 44% and 67%, respectively, which might reflect the high prescription rates of PAH-targeted drugs.

To avoid systemic hypotension, the infusion rate of epoprostenol is gradually increased until the appropriate therapeutic dose is reached. However, it remains unknown whether the speed of up-titration can affect pulmonary hemodynamics and clinical outcomes. Thus, we conducted this retrospective clinical study to clarify whether speed of increase in epoprostenol dose affects clinical outcomes and pulmonary hemodynamics.

Methods

Study population

This is a retrospective observational study. The initial study population comprised patients with I/HPAH who were admitted to the National Hospital Organization Okayama Medical Center and Okayama University Hospital, Japan, from May 1999 to December 2011. A total of 61 patients with I/HPAH were admitted during this period (Fig. 1), and 15 were excluded who had undergone lung transplantation (Supplemental Table). Thus, the remaining 46 patients were used for analysis.

Therapeutic strategy of I/HPAH

Our goal of PAH treatment is to reduce the mean PAP as much as possible with a combination of oral PAH-targeted drugs and intravenous epoprostenol [12]. Patients were initially prescribed oral PAH-targeted drugs, but if these did not result in an adequate reduction in mean PAP, we administered a continuous infusion of epoprostenol via a central venous route. Epoprostenol was usually initiated at doses of 0.5–2 ng/kg/min, and was increased by 0.5–2 ng/kg/min every 1–2 days, as tolerated. The rate at which the dose can be increased varied between patients, and depended on the clinician's decision and on how well the drug was tolerated. After an initial level of 10 ng/kg/min was achieved, we further increased the dose as high as possible, to achieve a mean PAP of less than 40 mmHg. Some patients received doses as high as >100 ng/kg/min for sustained clinical and hemodynamic benefits. However, if severe side effects such as thrombocytopenia occurred, the speed of increase in epoprostenol dose was reduced, depending on the severity. We measured pulmonary hemodynamics with right heart catheterization within 1 week, and around 6 months, 1 year, and 2 years after the initiation of treatment where possible.

Data collection

We followed-up the patients after the initiation of intravenous epoprostenol treatment. The follow-up period for monitoring patient survival ended in December 2013. The primary endpoint for survival analysis was death related to pulmonary hypertension. One patient who died from a road traffic accident was censored at the time of death in survival analysis (included in the survivor group) and other data for this patient were included in all analyses. Patient records were used to collect clinical data, including concomitant PAH-targeted drugs, WHO functional class, 6-min walking distance, pulmonary hemodynamics, and brain natriuretic peptide (BNP) levels. We also checked the dose of epoprostenol at 7 days, 1, 3, and 6 months, and 1, 1.5, and 2 years after the initiation of the treatment.

Statistical analysis

Numerical data were expressed as mean ± standard deviation (SD). Student's *t*-test or Welch's *t*-test was used to analyze differences

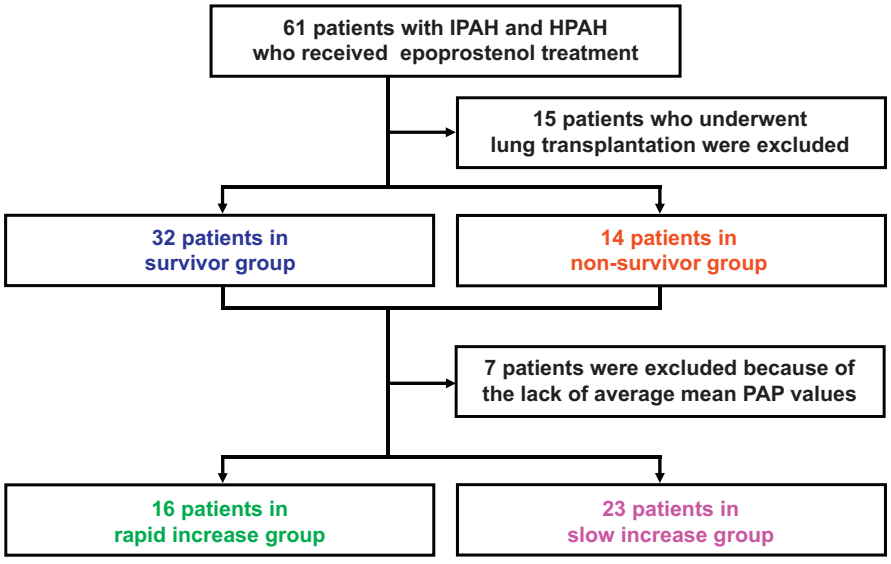

Fig. 1. Participant flow chart. IPAH, idiopathic pulmonary arterial hypertension; HPAH, heritable pulmonary arterial hypertension; PAP, pulmonary arterial pressure.

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