Ten Years' Experience in Continuous Intravenous Epoprostenol Therapy in Severe Pulmonary Arterial Hypertension

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Introduction. Primary pulmonary hypertension and its associated forms is a progressive and often fatal disease, the course of which has been favourably modified by prostacyclin therapy in the last decade.

Objective. The aim of this study is to analize retrospectively the efficacy of continuous intravenous epoprostenol (synthetic prostacyclin) therapy in pulmonary arterial hypertension, and to compare it with conventional therapy (anticoagulants, digoxin and diuretics).

Methods. Between 1990-2000, 31 patients with severe precapillary pulmonary hypertension in functional class III or IV went on continuous intravenous epoprostenol therapy, administered by a portable infusion pump through a Hickman catheter. We compared their survival with a group of 16 patients treated with conventional therapy alone.

Results. Time of follow-up was 33.25 months in the prostacyclin group and 20 months in the conventional group. The one- three- and five- year survival rates were 86%, 50% and 38% respectively for patients treated with epoprostenol compared with 40%, 40% and 8% survival rates at idetical periods for patients treated conventionally ($p = 0,02$). Functional class and the mean distance walked in the 6 minutes test were improved in patients treated with prostacyclin ($p < 0,01$). Serious complications attributable to the delivery system included 3 deaths, mainly due to infection.

Conclusion. Continuous intravenous epoprostenol therapy improves survival and exercise capacity in patients with severe pulmonary arterial hypertension despite potentially serious complications attributable to the delivery system.

Key words: *Pulmonary hypertension. Prostaglandins. Heart failure.*

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Experiencia de 10 años en el tratamiento con epoprostenol en perfusión intravenosa continua en hipertensión pulmonar arterial grave

Introducción. La hipertensión pulmonar (HTP) primaria y sus formas asociadas tienen un curso habitualmente progresivo y fatal, modificado en la última década por el tratamiento con prostaciclina.

Objetivo. Analizar retrospectivamente la eficacia del tratamiento con epoprostenol (prostaciclina sintética) en perfusión intravenosa continua en HTP primaria y sus formas asociadas, comparándola con tratamiento convencional (anticoagulación, digoxina y diuréticos).

Métodos. Entre 1990 y 2000, 31 pacientes con HTP arterial grave en clase funcional (CF) III/IV de la NYHA recibieron tratamiento con epoprostenol en perfusión intravenosa continua a través de catéter tipo Hickman y bomba de perfusión portátil. Se compara su supervivencia con un grupo de 16 pacientes tratados convencionalmente.

Resultados. El tiempo de seguimiento en el grupo de prostaciclina fue de 33,25 meses y en el de tratamiento convencional 20 meses. La supervivencia a 1,3 y 5 años fue del 86, 50 y 38%, respectivamente, en los pacientes tratados con epoprostenol, del 40% al año y 3 años y del 8% a los 5 años en los pacientes tratados convencionalmente ($p = 0,02$). Se observó una mejora en la CF y en la distancia recorrida en el test de 6 min en los pacientes tratados con epoprostenol ($p < 0,01$). El sistema de infusión fue un problema grave y causó 3 muertes fundamentalmente por infección.

Conclusión. El epoprostenol en perfusión intravenosa continua mejora la supervivencia y la capacidad funcional en los pacientes con HTP arterial, a pesar de las complicaciones graves relacionadas con el sistema de infusión.

Palabras clave: *Hipertensión pulmonar. Prostaglandinas. Insuficiencia cardíaca.*

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ABBREVIATIONS

FC: functional class.
PHT: pulmonary hypertension.
PAP: pulmonary arterial pressure.
PGI_2: prostacycline.
STOS: Spanish toxic oil syndrome.

INTRODUCTION

Primary pulmonary hypertension (PHT) is a disease characterized by a progressive increment of pulmonary arterial pressure and pulmonary vascular resistance. The disease finally evolves to right ventricular failure, functional class deterioration (FC) and death.[1] Various therapies have been proposed: vasodilator agents, anticoagulants, oxygen therapy and diuretics, but no substantial modification of the rapid progression and fatal course of this disease has been achieved (mean survival is of 2.8 years as of date of diagnosis).[2]

Epoprostenol (synthetic prostacycline [PGI_2]) is a strong vasodilator and a platelet aggregation inhibitor, that also shares antiproliferative and cytoprotective properties. Chronic treatment with epoprostenol improves noticeably the hemodynamic profile, quality of life, and exercise capacity of patients suffering from primary pulmonary hypertension.[3-5] In 3-month a placebo-controlled study, epoprostenol therapy demonstrated to improve survival.[6] The beneficial effects on survival due to long-term chronic therapy have been described in the literature, and the survival of patients undergoing treatment has been compared with the historical series of the American registry of primary pulmonary arterial hypertension.[5,7]

PHTs associated to the Spanish toxic oil syndrome (STOS) and to collagenosis share histopathological similarities with primary pulmonary hypertension. In these diseases, therapy with epoprostenol also has shown eficacy.[8]

The aim of this retrospective study is to communicate our experience of continuous intravenous perfusion of epoprostenol in patients suffering from severe pulmonary arterial hypertension. We also attempt to compare the survival rates of patients undergoing epoprostenol therapy, with our own historical series receiving conventional therapy.

METHODS

We included patients suffering from severe primary PHT or associated modalities, that were referred to our unit from September 1981 to January 2000. The evaluation protocol is summarized in Table 1. Diagnosis of PHT was established using right catheterization, when mean pulmonary arterial pressure (PAP) was higher than 25 mm Hg. Exclusion criteria were: hypoxemia secondary to pulmonary disease (established as a systemic blood saturation below 80%); any limitating pulmonary disease (defined as a total pulmonary capacity <60% of the total expected; thromboembolic disease; a left ventricular ejection fraction of <50%; pulmonary capillary pressure of >15 mm Hg or any congenital heart disease as a cause of their pulmonary arterial hypertension. As from 1995, performance of the 6 min test and the acute vasodilator test with epoprostenol was also introduced in the initial assessment. Therapy responders were defined as those showing a decrease of mean PAP over 20% of the baseline, or in excess of 10 mm Hg, without any significant decrease in cardiac output, or of systemic blood pressure. Responders received treatment with calcium antagonists.

Signs and symptoms secondary to pulmonary hypertension as well as the functional class were regularly evaluated during the follow-up period, and since 1995, the exercise capacity was also assessed regularly using the 6 min test.

Therapy with PGI_2 was initiated in our pulmonary hypertension unit as of August 1990. Those patients who received PGI_2 before year 1998 (date of approval in Spain for epoprostenol to be indicated as a treatment for PHT), received all the necessary information, and also accepted written informed consent, in acceptance of a therapy formulated as a palliative treatment. The epoprostenol therapy was commenced with a 2 ng/kg/min dose, titrated (1-2 ng/kg/min) up to optimal clinical response obtained (FC improvement and a longer number of meters in the 6 min test). In case of clinical deterioration, the dose was then increased.

Between 1990 and 1992, epoprostenol was administered using a Port-a-cath reservoir lodged inside a subcutaneous bag and connected to a catheter positioned in the subclavian vein; for perfusion of the drug a needle was inserted through the skin and the reservoir cap. Starting from 1993, chronic infusion was performed by means of an infusion system consisting of a

TABLE 1. **Evaluation protocol**

Clinical history
Physical examination
Electrocardiogram
Thoracic x-ray
Echocardiogram
Respiratory functional tests
Ventilation-perfusion scintigraphy
Thoracic computerized tomography
Functional class evaluation
6 min walking test
Baseline right catheterization
Acute vasodilator test

Hickman catheter inserted in the subclavian vein and tunnelized subcutaneously along the parasternum line, with its proximal end positioned next to skin at the fifth intercostal space. Both the needle and the catheter were connected to a portable infusion pump.

Statistical analysis

The χ^2 test was used for comparing categorized independent variables, and Fisher´s exact test was used when required. Continuous quantitative variables are described as mean ± standard deviations (SD). Mean values of distributions were compared by comparative the Student t test or the analysis of variance where appropriate. Survival rates in both therapy groups were calculated using survival tables, and compared by the log-rank test.

RESULTS

Fifty-eight patients suffering from PHT were referred from September 1981 to January 2000. Eleven were excluded due to a responsive acute vasodilator test and therefore received calcium antagonists. Sixteen patients underwent therapy before PGI_2 was available, or refused this treatment and thus constitute the historical series or control group. Finally, thirty-one received PGI_2 treatment.

Within the group of thirty-one patients that received PGI_2 since August 1990 till January 2000, sixteen of them were diagnosed as suffering primary disease, eight were related to the Spanish toxic oil syndrome, five were other collagenosis (three cases of scleroderma and two of combined illness of the connective tissues), and one was a HIV infection. The historical group was constituted by sixteen patients suffering from severe pulmonary arterial hypertension: ten were associated to the STOS, three suffered sclerodermia y and three were primary forms of PHT. Table 2 describes the demographic, clinical and baseline hemodynamics characteristics of both groups. There were no baseline significant statistical differences between both groups, only a higher incidence of PHT associated to the Spanish toxic oil syndrome (*P*=.03) in the group undergoing conventional therapy. In both groups, PHT was severe and all patients showed significant functional limitation (NYHA class III/IV), as well as a high incidence of heart failure.

The mean follow-up period of the PGI_2 group was 33.25 months (confidence interval [CI] equal to 95%, 24.07-42.44). The maximum dose reached was 12.46±6.9 ng/kg/min. During follow-up, 12 patients died (40%) and death was attributed to the following causes: 2 fatal sepsis, one iatrogenous pneumothorax, and 9 refractory right heart failure (RHF). Three patients abandoned therapy during follow-up. Five patients underwent transplantation (1 unipulmonary, 1 bipulmonary and 3 cardiac and pulmonary), after a mean interval of 26.8 months being treated with PGI_2. Eleven patients were alive and subject to therapy actively at the end of the follow-up period. The mean follow-up period for those patients undergoing conventional therapy was 20 months (95 CI, 6.14-34.47). Survival rates for the PGI_2 group after 1, 3 and 5 years accounted for 86%, 50% ,and 38%, respectively, as compared to 40% after one year and 3 years, and 8% after 5 years in the conventional therapy group. Figure 1 shows the actuarial survival curves for both groups. The comparative log-rank test also showed a significant statistical difference between both curves (*P*=.02). The mean survival period in the PGI_2 group was 36.67 months, whereas the conventional group had a mean survival rate of only 10.12 months.

TABLE 2. **Baseline hemodynamics and clinical parameters**

	PGI_2 (n=31)	Conventional (n=16)	*P*
Age	38±13	38±16	.95
Gender, M/F	9/22	5/11	1
NYHA (III/IV)	25/6	10/6	.28
PSP TTE	96.69±14.14	92.75±27.07	.57
Baseline HF	15 (48%)	11 (68%)	.22
RAP, mm Hg	12±4	13±6	.73
PAPm, mm Hg	68±14	67±11	.84
CO, L/mn	3.1±1.2	2.9±0.8	.61
STOS O2 AP, %	49±10	57±6	.06
PVR, Wood U.	20±8	21±6	.71

CO indicates cardiac output; HF, heart failure; RAP, mid-right by transthoracic echocardiography; PVR, vascular pulmonary resistance; STOS O2 PA, oxygen saturation of the pulmonary artery; M/F, male/female; Wood U., Wood units.

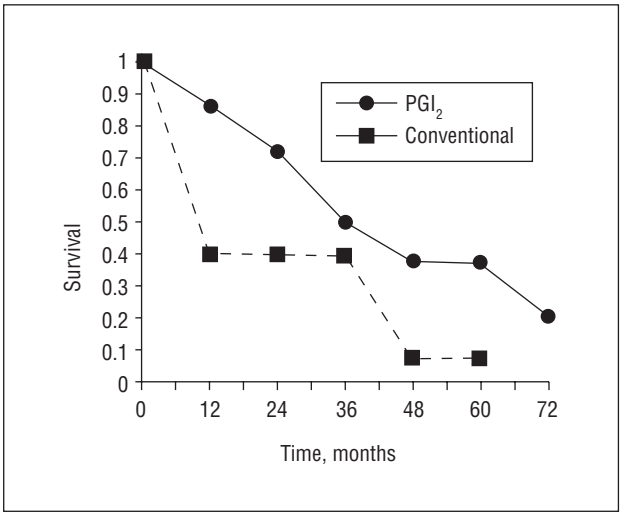

Fig. 1. Survival curves of patients under treatment with PGI_2 and under conventional therapy.

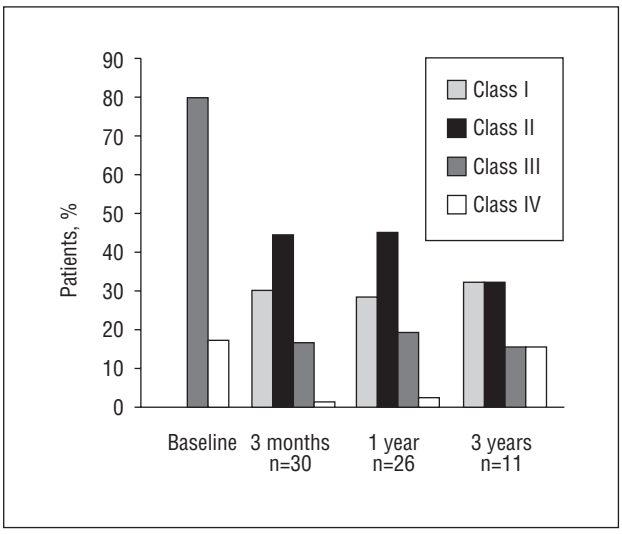

Fig. 2. Functional classes in patients under treatment with PGI_2.

The effects of chronic PGI_2 therapy on the functional capacity of patients suffering from severe PHT was assessed by analyzing the variations in the NYHA functional class during follow-up. Figure 2 describes the changes in functional class. Noticeable improvements in FC appeared rapidly, and showed statistical significance by the third month, as well as after the first and third year of follow-up.

Exercise capacity evaluation using the 6 min walking test, was planned in twenty-two of the 31 patients in the $PGI2_2$ group, but could not be performed on 4 due to functional class IV (severe exercise intolerance). The number of meters walked at enrolment (233±150) increased clearly and showed statistical significance after the third month (443±78; *P*=.000) and the first year of treatment (432±174; *P*<.0001). Differences were not significant at three years, although showed a trend toward to longer distances (388±156; *P*=.066).

Complications related to the infusion system were as follows: two catheter related fatal sepsis, one death caused by iatrogenic pneumothorax during the insertion procedure of the Hickman catheter, and four patients suffering a non-fatal sepsis. Five local infections of the entry port and nine bacteriemia related to the catheter were also registered. In total, twenty infections were registered in 11 patients, resulting in 1.8 infections per patient and an incidence rate of 0.22 total infections per patient/year (0.05 infections/patient/year for local infections and 0.06 for bacteriemia). Also, nine catheter displacements were observed. The total number of permanent catheters inserted was of 58 (10 Port-a-cath and 48 Hickman), resulting in an average of 1.8 catheters/patient.

Those patients responding to the epoprostenol acute infusion and also treated with calcium antagonists (amlodipine) showed a significant improvement of their functional class (3±0.7 to 2±0.7; *P*=.003), a longer walking distance during the 6 min. test (324±91 to 448±92; *P*=.002) and their systolic pulmonary pressure also decreased (92.6±23 to 57.1±28; *P*=.011).[9]

DISCUSSION

PGI_2 therapy was associated with a clear functional and survival improvement in our patients,, as compared to those patients undergoing conventional therapy. The efficacy of therapy with PGI_2 in patients in the presence of primary PHT is already known.[3-5] A randomized study in 81 patients suffering from primary pulmonary hypertension was performed for 12 weeks in 1996. Patients receiving PGI_2 showed an improvement in their exercise capacity, hemodynamic profile and survival rate as compared to patients undergoing only conventional therapy.[6] To assess the impact of chronic administration of PGI_2, most authors have compared their treated patients with a control group selected from the American Registry of PHT.[5,7] We have compared the difference in survival of prostacycline treated patients with our own historical series. The survival rates of patients undergoing chronic therapy with PGI_2 for severe PHT reported in the literature are similar to those of our series (86%, 72% and 50%, after 1, 2 and 3 years, respectively).

Our patients presented pulmonary arterial hypertension of different etiologies: primary, STOS, collagenosis and HIV infection. All these etiologies show a similar clinical course and their histopathological aspects are similar to those of the primary form. Within our country, the STOS epidemy allowed to characterize the progression of the pulmonary vascular disease, from its initial stage to the advanced stages of severe PHT, and cannot be distinguished from the primary form.[10] Nowadays, such forms of severe PHT are being treated with efficacy using PGI_2, and the results being obtained are nearly identical to those available in our series.[8,11-13]

Our study shows a significant improvement in the epoprostenol treated group both in the functional class and the number of meters walked in the 6 min. test. This improvement appeared early after 3 months of therapy, remained during the first and second year, and started to decline only after three years of treatment. This increase in walking distance related to PGI_2 therapy is similar to that described in other studies, such as Rubin et al,[14] Barst et al[6] and Wax et al.[15] On the other hand, there is no consensus neither on the evaluation protocol to be used for these patients nor on the optimal epoprostenol therapeutic schedule. Robbins et al[16] suggested a maximum dose interval in the range of 0.5 to 270 ng/kg/min, after collecting information from 19

centres, that included more than 500 of their patients, although with an heterogeneous dose modification schedule. The mean dose of PGI_2 in our series is lower than the dose used by other groups (12.46 ng/kg/min). This difference is probably related to the fact that the increase in dosage was determined by clinical deterioration, and not to a pre-specified protocol.

In our series, no conclusive data was obtained on variations in the echocardiograph parameters during administration of PGI_2 therapy. This is probably related to the fact that our evaluation protocol changed over time and that our study is retrospective in design. Nevertheless, assessment of the size and functionality of the right ventricle needs to be considered, because most beneficial effects of PGI_2 are due to its impact on right ventricular remodelling (related to its cytoprotective and antiproliferative properties), more than due to a direct effect on pulmonary pressures.[17]

The total rate of infections mentioned in our series is somewhat lower than previously reported,[18-20] due to a lower rate of local infections. Complications attributable to the infusion system have led to the investigation of alternative administration modalities (subcutaneous, inhaled or oral), that are showing promising results.[21-23]

We included patients receiving PGI_2 (patients suffering from severe PHT in functional class III/IV and not responding to the acute vasodilatation test), and excluded patients treated with calcium antagonists (patients with response to the acute vasodilatation test). The reason is that this group shows a more favourable prognosis, and that a decrease in pulmonary arterial pressure and mortality, as well as significant long-term clinical improvement, has already been proven in this group[24,25] (survival rate 95% after 5 years). Transplantation was reserved to those patients remaining in functional class IV, despite an optimal treatment that included PGI_2.[26]

The following are the major limitations of our study: *a)* small groups of different size (the group receiving conventional therapy being smaller), although it can be considered as a representative population given the low prevalence of this disease; *b)* a longer follow-up for the PGI_2 group, although such a difference was not of statistical significance (P=.11), and *c)* a retrospective design. The therapeutical management and the evaluation techniques were modified during the follow-up period, precluding an homogeneous analysis of the study population.

CONCLUSIONS

Despite potentially severe complications attributable to the delivery system, continuous intravenous epoprostenol therapy improves survival and exercise capacity in patients with severe pulmonary primary hypertension.

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