Long term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension

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Abstract

Objective—To investigate the relation between the severity of pulmonary hypertension and the outcome of medical treatment.

Methods—98 patients with primary pulmonary hypertension—nine (6%) with systemic disease and pulmonary hypertension and 39 (27%) with thromboembolic pulmonary hypertension—received medical treatment and were followed between 1982 and 1995. They were given long term intravenous prostaglandin treatment (either epoprostenol (n = 61) or iloprost (n = 13)) or conventional treatment with oral anticoagulants (n = 24) with or without calcium channel blockers. Event-free survival was measured to death or transplant surgery, or pulmonary thromboendarterectomy.

Results—Prognosis (hazard ratio) was affected by: New York Heart Association (NYHA) class I. A request for funding was made on the basis of the severity of their disease. The main indication was exercise intolerance, measured by a 12 minute walking distance of less than 500 m; very few of the patients were New York Heart Association (NYHA) class I.

Conclusions—Continuous intravenous prostaglandins were more effective than anticoagulants, with or without calcium channel blockers, in prolonging survival in patients with right heart failure. In these patients a capacity to vasodilate did not predict outcome of treatment. Pulmonary vasodilatation did not predict outcome of treatment.

Methods

Between October 1982 and November 1995, 146 patients with pulmonary hypertension were admitted to Papworth Hospital for investigation and treatment. Diagnosis was made by right heart catheter, recording mean right atrial pressure (mRAP), mean pulmonary artery pressure (mPAP), mean systemic arterial pressure (mSAP), and cardiac output/cardiac index. Pulmonary artery blood samples were taken for measurement of mixed venous oxygen gas tension (SvO₂%, cardiac index was taken to denote a capacity to vasodilate.

Further investigations included chest x ray, echocardiography (M mode and Doppler), full lung function tests, and a ventilation/perfusion (V/Q) lung scan, together with full immunological screening for connective tissue disease to determine the presence of secondary pulmonary hypertension. Pulmonary thromboembolic disease was diagnosed when there were two or more segmental or subsegmental perfusion defects on the V/Q scan which were normally ventilated.

A decision to treat patients with a long term intravenous infusion of prostaglandins was made on the basis of the severity of their disease. The main indication was exercise tolerance, measured by a 12 minute walking distance of less than 500 m; very few of the patients were New York Heart Association (NYHA) class I. A request for funding was then made to the patient’s local health authority. In a proportion of cases this was accepted and the infusion of epoprostenol (prostacyclin) or iloprost was started.

Despite its rarity and the effectiveness of treatment with continuous intravenous prostaglandin, many patients with primary pulmonary hypertension remain untreated. This reflects concern about the cost of the drug and uncertainty over the selection criteria for those patients who might benefit most.

To determine which patients are most likely to benefit from prostaglandin treatment we embarked on a retrospective analysis of the factors affecting survival of a large population of patients with severe pulmonary hypertension, considering in particular their treatment and the severity of their disease.
All patients were seen at three monthly intervals and the 12 minute walking distance measured. When exercise distance fell to the level seen at the time of diagnosis, patients were assigned to surgical treatment. They were offered heart-lung transplantation\(^{11}\) or thromboendarterectomy where there was central pulmonary thrombotic obstruction.\(^ {12}\) Time from this point to surgery depended on the availability of donors or access to specialist surgical facilities for thromboendarterectomy.

### Table 1: Patient characteristics and haemodynamics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prostaglandin treatment</th>
<th>Conventional treatment</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.0</td>
<td>43.0</td>
<td>0.22</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 26 Female 48</td>
<td>Male 28 Female 44</td>
<td>0.77</td>
</tr>
<tr>
<td>NYHA Grade I and II</td>
<td>3</td>
<td>32</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Grade III and IV</td>
<td>69</td>
<td>39</td>
<td>0.16</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>PPH 59</td>
<td>Secondary 23</td>
<td>0.16</td>
</tr>
<tr>
<td>Vasodilator response</td>
<td>None 24</td>
<td>Acute 37</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>&lt; 60% 42</td>
<td>&gt; 60% 30</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Median values; Mann-Whitney test used for comparison. A \(\chi^2\) test was used to compare proportions.*

CO, cardiac output; CI, cardiac index; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NYHA, New York Heart Association grade; PPH, primary pulmonary hypertension; \(S_vO_2\), mixed venous oxygen saturation.

### PROSTAGLANDIN TREATMENT

Delivery into the subclavian vein through a subcutaneous tunnel has already been described in detail.\(^7\) In the prostaglandin treated patients, the choice of epoprostenol or iloprost, an analogue of prostacyclin which became available in 1989, was made according to the patient’s preference. Iloprost is pharmaceutically equivalent to epoprostenol but is more stable and easier to use at home.\(^8\) Ease of use was the patients’ principal reason for choosing iloprost. For the purposes of this study we have combined patients using either drug into one group.

### CONVENTIONAL TREATMENT

In those patients for whom agreement to fund prostaglandin treatment was not received, anti-coagulants were continued. Patients who had shown a capacity for vasodilatation at right heart catheter study were also treated with oral calcium channel blockers in a dose to maintain a systolic systemic blood pressure of 100 mm Hg.\(^ {10}\) Calcium channel blockers included nifedipine, diltiazem, and amlodipine. This constituted conventional treatment and no patient on prostaglandins continued conventional treatment. This contrasts with the work of Barst et al.,\(^{12}\) where the patients all continued conventional treatment.

### OUTCOME MEASURES

The primary outcome measure for this study was time until death or surgery. The surgical treatment was either heart-lung transplantation or pulmonary endarterectomy. A deterioration in the patients’ clinical status determined whether a patient was treated surgically.

### RESULTS

Of the 146 patients, 98 had primary pulmonary hypertension (67%), nine (6%) had severe pulmonary hypertension associated with systemic disease (systemic lupus erythematosus in four, systemic sclerosis in four, and sarcoidosis in one), while 39 (27%) had thromboembolic pulmonary hypertension. At the end of the study, in November 1995, 20 patients (14%) had needed heart-lung transplantation, two (1%) had undergone a pulmonary thromboendarterectomy, and 72 (49%) had died, leaving 52 (36%) alive. Overall median survival to death or surgery was 695 days (95% confidence interval 546 to 844 days). For those 22 patients who underwent surgery, the median survival time was 695 days (426 to 964). For those 72 who died, the median survival time was 345 days (240 to 456).

The characteristics and haemodynamic measurements of the patients are shown in table 1, divided by treatment group into those...
receiving prostaglandin treatment or conventional treatment.

Factors such as NYHA grade and \( \text{SvO}_2 \% \) are known to be strong indicators of the severity of a patient’s condition, together with mPAP, PVR, and cardiac index. As anticipated, there was a tendency for the most severely affected patients to be given prostaglandins. Only three (9%) of the 35 patients in NYHA grade I and II were given prostaglandins, compared with 69 (64%) of the 108 patients in class III and IV. Similarly the \( \text{SvO}_2 \% \) of the prostaglandin treatment group was 6.5% lower than in the conventional treatment group. Strong evidence of a difference was also shown by the higher mPAP in the prostaglandin group (8.9 mm Hg higher than in the conventional treatment group) and the higher median PVR (4.1 units higher). All these differences were significant.

Univariate analysis was performed on each of the factors in table 1 to investigate the hazards associated with each. These results are shown in table 2.

Several variables were found to be strongly predictive of early death or surgery. The strongest predictor was \( \text{SvO}_2 \% \), with a significant hazard ratio (\( p < 0.001 \)). This ratio indicates that the lower the value of \( \text{SvO}_2 \% \), the higher the risk of death or surgery. The NYHA grade was also a strong predictor, with a significant hazard ratio (\( p = 0.009 \)), indicating that grades III or IV were associated with a greater risk than grades I or II. The other significant predictors were cardiac index, mRAP, and PVR. As previously reported, mPAP was not a significant predictor. As the data involve many hidden interrelations, the only accurate way to assess the importance of the prognostic factors—especially of treatment—is through multivariate analysis. In the univariate analysis, the effect of the patient’s condition is not taken into account, therefore strongly affecting the assessment of the treatment as the more severely affected patients were given prostaglandins. In the multivariate analysis, the patient’s condition can be accounted for, so the true value of the treatment can be assessed.

The multivariate analysis incorporated a model with a selection of the factors investi-
year, in contrast to the less severely affected patients, in whom there was no effect on survival.

Of the 50 patients who showed no vasodilation on diagnostic catheterisation, 26 received conventional treatment and 24 received prostaglandin treatment. The median survival for the conventional treatment group was 899 days (197 to 1601) and it was similar for the prostaglandin group (797 days (47 to 1547)).

There was no difference in the survival curves (p = 0.1). Of the 70 acute responders, 33 had conventional treatment and 37 prostaglandin treatment. For the conventional treatment group, median survival time was not available as only 10 (30.3%) reached the end point of death or surgery. For the prostaglandin treatment group, median survival time was 776 days (620 to 932). There was no significant difference between the two Kaplan-Meier survival curves (p = 0.07). There was no evidence that the capacity to vasodilate predicted the performance of either conventional treatment or prostaglandin treatment.

Discussion

Strong indicators of prognosis in earlier studies of the natural history of primary pulmonary hypertension, and pulmonary hypertension from congenital heart disease are NYHA grade, cardiac index, mRAP, and PVR, together with the Svo₂%. By stratifying the patients according to their Svo₂%—above or below 60%—we observed that in the most severely affected patients, prostaglandin treatment enhanced their event-free survival by almost a year. An Svo₂% value below 60% therefore predicts those patients with severe pulmonary hypertension who will benefit from long term intravenous infusion of epoprostenol or iloprost. The presence or absence of a capacity for acute pulmonary vasodilatation does not predict the performance of prostaglandin treatment.

As this study was not a randomised trial, various problems naturally occur. The statistical techniques used in the analysis are based on the assumption that the sample of patients in the study is a random one from one whole population, which is not the case. Treatments were not allocated randomly, and were intentionally given to the more severely affected patients. This could have lessened the impact on diagnostic catheterisation, anticoagulants and oral calcium channel blocker treatment offers a means of improving event-free survival.

As the medical treatment of primary pulmonary hypertension and pulmonary hypertension from the different secondary causes appears to be similar, we combined patients with thromboembolic pulmonary hypertension, pulmonary hypertension secondary to systemic disease, and primary pulmonary hypertension. For example, in patients with pulmonary hypertension from systemic diseases such as systemic sclerosis, prostaglandin treatment appears to be as effective as in primary pulmonary hypertension. Treatment with oral vasodilators and anticoagulants also appears effective in the treatment of thromboembolic pulmonary hypertension.

We cannot determine the optimum time for heart-lung or lung transplantation from this study. However, survival after transplant surgery is about 60% at 18 months in most centres, which is comparable with the results of prostaglandin treatment in our study. The relative costs and effects on the quality of life of the two treatments need to be considered in detail. From the limited data, models have been developed to describe relative cost and benefit. From these models, it appears that the relative cost per index of quality of life (quality adjusted life year) is similar for the two approaches.

A case can therefore be made for delaying transplant surgery until prostaglandin treatment fails.

We wish to thank Mr John Wallwork, director of the Papworth Hospital Cardiothoracic Transplant Unit, for continued and productive collaboration.