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Continuous infusion of epoprostenol as salvage therapy for severe pulmonary arterial hypertension

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ABSTRACT A critical appraisal and clinical application of Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *New Eng J Med.* 1996;334(5):296-301. doi: [10.1056/nejm199602013340504](https://doi.org/10.1056/nejm199602013340504).

Keywords: *pulmonary arterial hypertension, epoprostanol, survival*

Clinical Context

This patient was a 78-year-old Black woman who had been admitted four times in two months for complications of pulmonary hypertension (PAH). Her past medical history included Group I pulmonary hypertension associated with rheumatoid arthritis, right heart failure NYHA Class III, hypertension, and chronic hepatitis B. Her pulmonary hypertension medication regimen consisted of tadalafil (PDE-5 inhibitor) 40 mg daily, macitentan (endothelin antagonist) 10 mg daily, selexipag (prostacyclin agonist) 200 mg twice daily, furosemide 40 mg twice daily, and 5L oxygen via nasal cannula. She had very poor functional status with severe shortness of breath even on continuous oxygen therapy. She was unable to walk a few feet without rest; activities of daily living were severely limited.

Her most recent admission was directly from the pulmonary hypertension clinic for signs of cor pulmonale. The pulmonary team, patient, and her family discussed the advanced state of her disease, prognosis, and possibilities for management. The options were palliative care or IV epoprostenol, which has been shown to increase exercise capacity by improving dyspnea and fatigue, and reduce all-cause mortality related to decompensated right heart failure. It also decreases falls secondary to hemodynamic instability, immobility, and debility, and recurrent hospital readmission.^{1,14}

Clinical Question

Does continuous intravenous epoprostenol infusion add value to a multi-drug medication regimen in improving mortality and quality of life in severe pulmonary arterial hypertension in an elderly patient?

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Research Article

Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *New Eng J Med.* 1996;334(5):296-301. doi: [10.1056/nejm199602013340504](https://doi.org/10.1056/nejm199602013340504)

Related Literature

Literature review began with a search on UpToDate® for types of pulmonary hypertension and treatment regimens specific to those etiologies. Keywords included “pulmonary hypertension” and “treatment.” Pulmonary hypertension is defined by a mean pulmonary arterial pressure ≥ 25 mmHg at rest. It is subdivided, according to the WHO, into groups I-V based on underlying pathology, which subsequently directs treatment. Group I, or pulmonary arterial hypertension (PAH), can be idiopathic, genetic, drug-induced, or, as is the case with the patient in the above discussion, associated with connective tissue disease, e.g., rheumatoid arthritis.¹¹

An imbalance of vasodilators nitrous oxide (NO) and prostacyclin (PGI₂) with the vasoconstrictor endothelin-1 (ET-1) underlies the development of PAH.⁵ This imbalance leads to narrowing of pulmonary arterioles, increased pulmonary vascular resistance, and eventual right heart failure.

PubMed was queried for PAH therapy. Keywords were “latest treatment for pulmonary arterial hypertension.” A recent (Feb. 2017) review entitled “Steps forward in the treatment of pulmonary arterial hypertension: latest developments and clinical opportunities”³ was then utilized to find primary research articles and trials evaluating combination therapy. The focus was on combination therapy, as this was the treatment approach pursued in this patient.

Tadalafil, a PDE-5 inhibitor, was evaluated in a randomized control trial (RCT) called PHIRST-1, an initial 16-week trial with a year-long extension as PHIRST-2. Addition of tadalafil was compared to placebo in patients who were either treatment-naïve or receiving therapy with bosentan (ET antagonist). The results showed a dose-dependent increase in exercise tolerance, clinical improvement, better quality of life, and prolonged time to clinical worsening in the tadalafil group.² This trial was not chosen for appraisal because the patient’s clinical status was worsening on the medication, and a mortality benefit was not described.

The GRIPHON trial looked at long-term efficacy of selexipag, a synthetic PGI₂ agonist, in reducing primary endpoints “including death, hospitalization for PAH, need for supplemental oxygen, atrial septostomy, lung transplantation, IV prostacyclin, or clinical worsening”.¹² Patients were allowed to continue therapy with PDE-5 inhibitors, ET-1 antagonists, or both and were randomized to receive selexipag or placebo. There was no significant difference in mortality. The study found a moderate improvement in 6-minute walk distance. Most notably, only 27% of the selexipag group versus 41.6% of placebo group experienced a primary endpoint, hazard ratio 0.60 (CI 0.46-0.78, $p < 0.001$).¹²

Another large, long-term RCT examined the use of macitentan, an ET-A and ET-B antagonist. It was called SERAPHIN and compared placebo to macitentan while allowing patients to stay on their current PAH therapy. SERAPHIN examined the primary endpoint of “time from initiation of treatment to the first occurrence of a composite endpoint of death, atrial septostomy, lung transplantation, initiation of treatment with SC or IV prostanoids, or worsening of PAH”.¹⁰ Again, there was no significant mortality benefit, but patients did see improvement of dyspnea and exercise capacity scores.

The above studies all point to the fact that multi-drug therapy, attacking the pathogenic pathway at various points, leads to better quality of life, fewer hospitalizations, and increased exercise tolerance. All of the above medications are available in oral formulations with once daily dosing, making it fairly convenient for patients to administer. However, none of the above regimens were able to show a mortality benefit. The only therapy for PAH to date that has been shown to decrease mortality is continuous intravenous (IV) epoprostenol (PGI₂ agonist),⁴ as in the landmark study by Barst et al.

The Barst et al study compared the mortality benefit of continuous IV epoprostenol plus conventional therapy versus conventional therapy alone in 81 patients with severe primary pulmonary hypertension. As IV epoprostenol was an endpoint in several of the studies, use of continuous intravenous epoprostenol may be considered in patients who continue to have severe symptoms despite



conventional therapy, even if they have no short-term response to epoprostenol or if their condition has deteriorated with conventional therapy.

A repeat PubMed search was performed using the search terms: "epoprostenol OR prostacyclin AND pulmonary hypertension". This search was limited to clinical trials, humans, and English Language. The search resulted in 190 titles, one of which was an article by Barst.⁴ The "Similar Articles" function with "Best Match" yielded four papers^{2,8,9,13} none of which was more relevant than the Barst article.

Critical Appraisal

The article by Barst et al is a 12-week open-label, prospective, randomized, multicenter trial comparing continuous IV epoprostenol plus conventional therapy with conventional therapy alone in 81 patients with severe primary pulmonary hypertension (NYHA III-IV). No exclusion criteria were given. This is level 2 evidence using the SORT criteria.⁶ Optimized conventional therapy consisted of use of anticoagulants, oral vasodilators, diuretics, cardiac glycosides, and supplemental oxygen. It should be noted that our patient was on multiple newer therapies, making it hard to determine how to add epoprostenol.

The purpose of the study was to determine the effects of continuous IV epoprostenol on exercise capacity, quality of life, hemodynamics, and survival.

Right-heart catheterization was performed on all patients to determine maximum tolerated dose, and treatment dose was 4 ng/kg/min below the maximum tolerated dose. Adjustments were allowed based on clinical deterioration or adverse events.

The study outcome showed a mean increase in 6-minute walk distance (6MWD) of 32 m in the epoprostenol group versus a 15 m decrease in the conventional group ($p < 0.003$). Quality of life measures showed significant improvement in the epoprostenol group based on Chronic Heart Failure Questionnaire (4/4), Nottingham Health Profile (2/6), and the Dyspnea-Fatigue Ranking ($p < 0.01$). Functional class improved in 16 patients (40%), worsened in 5 (13%), and stayed the same in 19 (48%) of epoprostenol group. In the control group, functional class improved in only 1 (3%), worsened in 3 (10%), and stayed the same in 27 (87%; $p < 0.02$). Hemodynamic parameters, including pulmonary-artery pressure, cardiac index, and pulmonary vascular resistance were significantly improved in the epoprostenol group ($p < 0.002$). Three patients received lung transplants during the study (1 epoprostenol, 2 conventional). Eight patients died during the study, all in the conventional group. Overall survival was significantly improved in the epoprostenol group with absolute risk reduction of 20% and number needed to treat of 5 ($p < 0.001$).

The eight patients who died had significantly lower baseline 6MWD than the 73 survivors. 6MWD was found to be independently associated with mortality, making it a potential confounder. However, even after adjustment for this, survival remained improved in the epoprostenol group ($p < 0.002$). The researchers included last recorded data on individuals who died during the study to mitigate attrition bias in analysis of 6MWD, quality of life, and hemodynamics.

This study definitely had some strengths. It demonstrated good initial randomization, limiting confounding. The patients were stratified according to functional class, study center, and baseline vasodilator use. There were no differences in severity, duration of illness, use of additional medications, or NYHA functional class. One potential weakness was they didn't use 6MWD as a criterion for randomization. Being an independent predictor of mortality, this should have been included in the stratification during randomization.

There were significant biases in this study. First was selection bias due to the lack of standardization between centers with regard to dose adjustments of epoprostenol and the overall medication regimen. The treating physicians were given freedom to adjust medications to optimize symptom control, possibly treating the study arm more aggressively. During the literature review, other medications considered standard therapy demonstrated improvements in symptoms, 6MWD, and quality of life. Optimization of other medications could have modified effect size in these areas.

Second is reporting bias. By nature of the amount of effort required to administer the epoprostenol (daily mixing, refrigeration, continuous IV access), double blinding would be difficult. This would especially affect the end point assessment of subjective quality of life questionnaires, making patients who received continuous epoprostenol drip more likely to report subjective improvement.



Effort was made to mitigate this by having quality of life questionnaires and the 6MWD tests scored and administered by individuals not involved in patient care and blinded to the study arm.

In addition, the study size was small (81), and mean age was 40 years. Small study size limits the power of the study, though the results had p-values that were significant in most of their findings. The mean age limits extrapolation to older individuals who suffer from PAH associated with other conditions who may be 60-70 years old. These individuals would presumably have more independent predictors of mortality at baseline.

Clinical Application

The study by Barst et al found significant clinical improvement in hemodynamics, 6MWD, quality of life, and survival in patients with Pulmonary Arterial Hypertension treated with epoprostenol and conventional therapy versus conventional therapy alone. The patient described above was significantly out of the age range included in this study, but she met all other criteria (NYHA class III, PAH). The results may still be applied in her case if it was presented as salvage therapy in the face of an advanced, irreversible disease process.

The patient had been hospitalized due to issues with her medication regimen and may have benefited from a continuous infusion as opposed to having to coordinate three-time daily dosing of several different medications. It is very important for physicians to discuss the pros and cons of epoprostenol infusion with their patients. While patients generally reported better quality of life with the infusion due to fewer symptoms, they must tolerate being hooked up to an intravenous delivery system all the time and be able to take responsibility for mixing the medication daily. This patient was living in a nursing home and not very active at baseline. She had nurses to manage the mixing and administration of the medication, and having the pump attached probably would not have affected her quality of life. A strong social support system appears to be needed to successfully administer this therapy, and this patient had family members who were very involved in her care.

Learning points:

1. Epoprostanol infusion could be an effective salvage therapy for patients with severe refractory PAH.
2. This study is from 1996 when other forms of treatment for PAH were still fairly limited; newer studies are needed before epoprostanol can be routinely recommended.
3. PAH can affect older individuals; a study in which all the participants aren't between the ages of 35 and 45 would be helpful for clinical decision-making.

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