International Journal of Cardiovascular Research

Commentary A SCITECHNOL JOURNAL

The Importance of Prostanoids in Chronic Thromboembolic Pulmonary Hypertension Treatment

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Received date: November 16, 2021; **Accepted date:** November 30, 2021; **Published date:** December 7, 2021

Abstract

Single or recurrent pulmonary thromboemboli developing from venous thrombosis sites are thought to cause chronic thromboembolic pulmonary hypertension (CTEPH)[1]. The disease's pathophysiology has yet to be fully understood. Acute pulmonary embolism following deep venous thrombosis could be the catalyst for local variables to mediate the abnormal organisation of pulmonary thromboemboli that is diagnostic of CTEPH.

About two-thirds of CTEPH patients have a documented history of acute pulmonary embolism and/or deep venous thrombosis, including those who have a convincing history of acute pulmonary embolism despite not being diagnosed with thromboembolic disease at the time[2]. Despite a single report documenting a cumulative incidence of 3.8 percent of CTEPH within two years of a first-time acute pulmonary embolism, the vast majority of those who suffer an acute pulmonary embolism do not go on to develop CTEPH, according to the unpublished observations of many other groups[3,4].

CTEPH was initially distinguished from PAH by its major vessel involvement in the vascular remodelling process, making it accessible to surgical intervention with removal of the obstructing lesions. In contrast to PAH, which manifests in pulmonary vessels of 300m diameter, CTEPH was initially distinguished from PAH by its major vessel involvement in the vascular remodelling process,3 rendering it accessible to surgical intervention with removal of the obstructing lesions[5].

As a result, pulmonary endarterectomy (PEA) has been recommended as the therapy of choice for CTEPH, and it can be safely performed in about half of patients, depending on the surgical center's aggressiveness. Patients with CTEPH who go untreated develop right heart failure and die, though at a slower rate than those with PAH. Small vessel arteriopathy is prevalent in people with CTEPH to varying degrees. Despite the removal of considerable volumes of organised thrombus, pulmonary hypertension persists in about 10% of operated patients. Because of its link to increased morbidity and mortality, persistent pulmonary hypertension after PEA is still a major issue.

Persistent pulmonary hypertension has been linked to about a third of perioperative deaths and nearly half of long-term deaths. The discovery of small vessel arteriopathy in major-vessel CTEPH has paved the way for observational research looking into the impact of vasodilators in the treatment of CTEPH that is inoperable.

The primary component of arachidonic acid in vascular tissues is prostacyclin (PGI2), which was discovered in 1976. The most active makers of PGI2, which relaxes vascular smooth cells by binding to membrane-associated G-protein-coupled receptors, are endothelial cells. PGI2 is the most effective endogenous platelet aggregation inhibitor with antiproliferative activity. The expression of PGI2 synthase is reduced in the pulmonary arteries of PAH patients.

The development of stable analogues with distinct pharmacokinetic features but similar pharmacological effects in multiple modes of application, such as intravenous (IV), inhaled, subcutaneous (SC), and oral, has enabled the therapeutic use of PGI2. The first randomised controlled trial of intravenous epoprostenol showed that it increased exercise capacity, haemodynamics, and survival when compared to controls in 1996. However, epoprostenol's instability at room temperature and light, as well as its short plasma half-life, are significant disadvantages (2-6 minutes). Infection (0.22-0.68 per patient each year14), thrombosis, and new major vascular thromboembolism hinder ongoing administration using a permanent central venous connection. Jaw discomfort, leg and foot pain, headache, diarrhoea, ascites, and flushing are all frequent side effects of prostacyclin.

Prostanoids have been used to treat inoperable CTEPH (either with distal disease distribution or with persistent pulmonary hypertension after PEA) in a few uncontrolled studies and a solitary controlled study that was not large enough to conduct a statistical analysis of this subgroup.

Epoprostenol

Nagaya described their experience with IV epoprostenol before PEA in 12 patients with severe CTEPH, as defined by a PVR > 1,200 dynes.s.cm-5. Treatment with epoprostenol resulted in a highly significant drop in PVR, an increase in cardiac output (CO), and a decrease in brain natriuretic peptide (BNP) plasma levels, all indicating enhanced right ventricular performance. In 23 inoperable CTEPH patients, the oral prostacyclin analogue beraprost was studied. During a 21-month follow-up, Beraprost improved New York Heart Association (NYHA) Functional Class and significantly reduced mean pulmonary arterial pressure (mPAP) and total pulmonary resistance (TPR). When compared to standard care, Beraprost enhanced survival.

Bresser et al. reported that three out of nine study patients, treated for 3-9 months, showed clinical deterioration with epoprostenol treatment, with a significant increase in pulmonary vascular resistance (PVR) in two patients, at the world's biggest PEA facility in San Diego. Following PEA, cardiac index, mPAP, and TPR all showed a considerable improvement. The findings imply that individuals with CTEPH who receive continuous intravenous epoprostenol treatment prior to PEA may improve clinically and haemodynamically.

In a small, uncontrolled research, no improvement in response to inhaled iloprost was seen in a group of 12 patients, including five with CTEPH. In the multicentre AIR study, 33 patients with CTEPH did

not appear to improve clinically from inhaled iloprost compared to 22 placebo-treated patients, confirming similar findings.

Kramm et al. looked at the effects of inhaled iloprost in patients who had been diagnosed with PEA. Prior to surgery, iloprost treatment had no discernible effect on pulmonary vascular dilation. Inhalation of aerosolised iloprost lowered right ventricular afterload 12 hours after surgery, in addition to the effect of surgical disobliteration, resulting in a considerable reduction of mPAP and PVR. These effects were thought to help decrease pulmonary reperfusion injury and improve early PEA outcomes.

In a recent retrospective multicenter investigation, subcutaneous treprostinil medication was found to be helpful in a large heterogeneous patient group, including 23 individuals with CTEPH. A substantially greater number of patients (n=860) were included in a recent multicenter retrospective analysis, which was in good accord with these findings.

Treprostinil is chemically stable and has a four-hour plasma elimination half-life, allowing for continuous subcutaneous delivery without the dangers associated with a central venous catheter. Despite the need for more than double the dose when switching from IV epoprostenol to IV treprostinil, SC treprostinil therapy increased exercise tolerance, NYHA Functional Class, and survival over a 26.217.2-month observation period at a mean dose of 40ng/kg/min (range 16-84ng/kg/min21). At one and three years, survival rates were 88.6% and 70.6 percent, respectively. At the same time points, event-free survival was 83.2 percent and 69 percent, respectively, defined as survival without hospitalisation for clinical deterioration, transition to IV epoprostenol, requirement for combination therapy, or atrial septostomy.

We followed 25 consecutive class III and IV patients for 12 to 33 months of continuous subcutaneous therapy following at least one hospitalisation for right ventricular decompensation in a more extensive unpublished prospective single centre trial concentrating on CTEPH. Comparative survival analyses were performed on a historical cohort of 31 untreated individuals with inoperable CTEPH who were matched for disease severity. The six-minute walk (6-MWD) (p=0.01), functional class (p=0.001), BNP plasma levels (p=0.02), CO (p=0.007), and PVR (p=0.01) were all significantly improved in Treprostinil-treated individuals. Treprostinil plasma concentrations coincided with the drug's subcutaneous dose (p0.001), demonstrating consistent absorption in 86 percent of instances despite local site response.

At dosages ranging from 12.5 to 42ng/kg/min, treated patients in this trial had considerably better long-term survival than controls.

In North America and Europe, several prostanoid therapies for pulmonary hypertension have now been licenced (epoprostenol, iloprost, treprostinil). Despite these recent developments, vasodilator therapy for CTEPH has not been adequately investigated due to the belief that vasodilator therapy is not appropriate for a mainly major artery obstructive pulmonary arteriopathy. With a better understanding of the pathophysiology of CTEPH, it's becoming clear that certain subsets of patients with CTEPH may benefit from vasodilator therapy instead of, before, or after PEA.

Given the higher prevalence of CTEPH1 than other forms of pulmonary hypertension, randomised controlled trials comparing the benefits of various vasodilators versus PEA on survival and quality of life in CTEPH patients are needed. The BENEFIT trial, which uses the endothelin receptor antagonist bosentan, is now underway.

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