

Intravenous epoprostenol therapy in the treatment of pulmonary arterial hypertension in Singapore

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Dear Editor,

Pulmonary arterial hypertension (PAH) is a progressive disease characterised by significant morbidity and mortality. Intravenous (IV) epoprostenol (Veletri, Johnson & Johnson, US), a prostacyclin analogue, has been shown to improve exercise tolerance, PAH symptoms, haemodynamics and survival.^{1,2} However, there is a lack of data on feasibility and tolerability of this therapy in Singapore. A previous study examined the use of selexipag, an oral prostacyclin analogue, in a Singapore population.³ We aimed to describe the first Singapore experience of initiating and maintaining IV epoprostenol therapy for treating PAH patients in Singapore, and highlight the various issues and challenges encountered.

Patients from National Heart Centre Singapore who were diagnosed with PAH and remained in intermediate to high risk class with progressive symptoms, despite being on maximum tolerable doses of oral/inhaled phosphodiesterase-5 inhibitors, endothelin-1 receptor antagonists and/or prostacyclin analogues were assessed and counselled for initiation of IV epoprostenol.

A set of protocols were developed, encompassing a comprehensive assessment and support from a multidisciplinary team of physicians, specialist nurses and pharmacists (see Supplementary Materials for detailed protocol). Suitable patients underwent counselling, were given hard and soft copy information, and connected with fellow IV epoprostenol users. Another group of suitable patients were identified and underwent training sessions held by specialist nurses with simulation on the preparation of IV epoprostenol, ambulatory pump and Hickman line care. Weekly review of training and competency was done.

An admission was arranged for a Hickman line insertion followed by initiation and gradual up-titration of IV epoprostenol in a high dependency setting with close monitoring of clinical parameters

and biochemical markers for the first day, followed by further titration in the general ward in the subsequent days. Regular inpatient review was done by a multidisciplinary team, and the patient was discharged when an acceptable IV epoprostenol infusion rate was achieved. Follow-up (both telephone and in-person) was done at regular intervals. Emergency contacts were given to patient/caregiver, and emergency protocols were drafted in cases of pump or line dysfunction and other scenarios.

From 2016 to 2021, 12 patients were initiated on IV epoprostenol; 11 were female and mean age was 44 years (interquartile range [IQR] 34.5–49.3). There were 4, 5 and 3 patients who were in New York Heart Association class II, III and IV, respectively. Baseline characteristics on right heart catheterisation showed a mean pulmonary artery pressure of 53 mmHg (IQR 47–54) and pulmonary vascular resistance of 12.6 Wood units (IQR 10.0–14.2). The average time from date of diagnosis of PAH to date of initiation of IV epoprostenol was 7.3 years (IQR 5.2–11.7) and the average maximum IV epoprostenol dose reached was 12.7 ng/kg/min (IQR 9.0–14.7), outlined in Table 1.

IV epoprostenol was generally well tolerated. Diarrhoea was the most common side effect affecting 5 patients, followed by headaches and musculoskeletal complains each of which affected 3 patients. Infective complications occurred a total of 5 times in 2 different patients, necessitating a total of 3 Hickman line changes. Non-infective complications occurred 4 times (2 line dislodgement, 1 cracked line and 1 contact dermatitis from dressing) each of them resulting in a Hickman line change.

As of July 2021, 6 patients had died. In these patients, IV epoprostenol was initiated 7.2 (IQR 4.3–13.2) years after diagnosis of PAH and continued for 11.3 months (IQR 7.7–13.1) until their demise. Of the remaining 6, IV epoprostenol

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Table 1. Clinical characteristics, side effects and line complications of study population.

Baseline characteristics	
Mean age, (IQR), years	44 (34.5–49.3)
Sex, no. (%)	
Male	1 (8.3)
Female	11 (91.7)
Race, no. (%)	
Chinese	8 (66.6)
Malay	3 (25.0)
Other	1 (8.3)
New York Heart Association class, no. (%)	
I	0 (0)
II	4 (33.3)
III	5 (41.7)
IV	3 (25.0)
Comorbidities, no. (%)	
Hypertension, hyperlipidaemia, ischemic heart disease, chronic obstructive pulmonary disease, obstructive sleep apnoea, stroke, chronic kidney disease	0 (0)
Diabetes mellitus	2 (16.7)
Atrial fibrillation	3 (25.0)
Asthma	2 (16.7)
Connective tissue disease	5 (41.7)
Medications, no. (%)	
Phosphodiesterase-5 inhibitor	10 (83.3)
Endothelin-1 receptor antagonist	11 (91.7)
Soluble guanylate cyclase stimulator	2 (16.7)
Oral/inhalational prostacyclin receptor agonist	10 (83.3)
Patients on single therapy, no. (%)	1 (8.3)
Patients on dual therapy, no. (%)	1 (8.3)
Patients on triple therapy, no. (%)	10 (83.3)
Diuretics	9 (75.0)
Warfarin	0 (0)
NT-proBNP at start, median (IQR), pg/mL	1874.5 (913.5–2960.8)
Transthoracic echocardiogram parameters, median (IQR)	
RV inlet size, cm	4.8 (4.5–5.3)
TAPSE, mm	17 (13–24)
RA area, cm ²	27.9 (20.0–38.3)
RA pressure, mmHg	15 (8–15)
PA systolic pressure, mmHg	75 (65.5–86.5)
LV ejection fraction, %	62.5 (57.5–67.8)
Pericardial effusion, no. (%)	7 (58.3)
RV-PA coupling (TAPSE/PASP), mm/mmHg	0.193 (0.158–0.244)

Table 1. Clinical characteristics, side effects and line complications of study population. (Cont'd)

Baseline characteristics	
Right heart catheterisation parameters, median (IQR)	
Mean RA pressure, mmHg	10 (5.8–18.8)
RV systolic pressure, mmHg	82.5 (68.3–86.0)
RV diastolic pressure, mmHg	14.5 (9.8–17.8)
Mean PA pressure, mmHg	52.5 (47.0–54.0)
PA wedge pressure, mmHg	12 (10–16)
Pulmonary vascular resistance, Wood unit	12.6 (10.0–14.2)
LV systolic pressure, mmHg	105 (104.0–111.8)
LV end diastolic pressure, mmHg	11 (7–13)
Cardiac output via Fick's method, L/min	2.8 (2.6–4.1)
Pulmonary hypertension classification, no. (%)	
Group 1	12 (100.0)
Idiopathic	6 (50.0)
Congenital	1 (8.3)
Connective tissue disease	5 (41.7)
Group 2	0 (0)
Group 3	3 (25.0)
Group 4	0 (0)
Group 5	1 (8.3)
Time of diagnosis to time of initiation of epoprostenol (IQR), years	
Alive (n=6)	7.3 (5.2–11.7)
Demised (n=6)	7.2 (4.3–13.2)
Maximum IV epoprostenol dose achieved (IQR), ng/kg/min	12.7 (9.0–14.7)
Side effects and complications	
Side effects, no. (%)	
Diarrhoea	5 (41.7)
Headache	3 (25.0)
Musculoskeletal complains	3 (25.0)
Flushing	2 (16.7)
Palpitations	1 (8.3)
Pre-syncope	1 (8.3)
Line-related complications, no. (incidence per 1000 catheter days)	
Infective	5 (0.76)
Line changed	3 (0.46)
Line not changed	2 (0.30)
Mechanical	3 (0.46)
Other (contact dermatitis)	1 (0.15)

IQR: interquartile range; LV: left ventricle; NT-proBNP: N-terminal pro-brain natriuretic peptide; PA: pulmonary artery; RA: right atrium; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion

was initiated 7.3 months (IQR 6.3–9.9) after the diagnosis of PAH, continued for 17 months (IQR 13.9–27.3), and continued further as of July 2021. Right ventricle (RV) size on echocardiography in patients who survived remained stable (0.0 mm [IQR–0.2–0.5] RV inlet increase/year) compared to those who demised (0.9 mm [IQR 0.2–1.4] RV inlet increase/year).

While potentially lifesaving, the use of IV epoprostenol presents several medical and social challenges. The reported side effects of IV epoprostenol in this cohort were similar to those listed in the Veletri product insert,⁴ though their occurrence varied. The most common side effect in our cohort was diarrhoea and gastrointestinal issues (41.7% vs 32%), followed by headaches (25% vs 49%) and musculoskeletal complaints (25% vs 5%). Another observational study reported a similar side effect profile.⁵ These side effects were managed symptomatically, allowing patients to continue the drug if the side effects are tolerable. In our study, no patients discontinued therapy due to side effects.

Infective complications occurred at a rate of 0.76 per 1000 catheter days in our study, compared to other studies which reported a range of 0.32 to 0.43 infections per 1000 catheter days. Mechanical complications occurred at a rate of 0.46 per 1000 catheter days, compared to about 0.23 per 1000 catheter days.^{6,7} This higher incidence may be related to a skewed result from a small sample size as over half of these complications occurred in 1 of 12 patients. Regardless, line-related complications remain a significant issue in patients on IV epoprostenol.^{8,9}

Furthermore, there are other issues arising from living with an indwelling line. Patients must not only learn to care for it consistently, but also face social and psychological effects from managing an external line.¹⁰ This can significantly influence patients' daily lives as they adapt to these new responsibilities. To mitigate this, patients require strong social support to continue treatment and maintain line integrity. Psychologically, they need to be mentally prepared to live with a central line and to continue lifelong treatment, sometimes with its associated side effects. A multidisciplinary team to support these patients throughout their treatment journey is crucial.

In this study, the longer median duration to initiating IV epoprostenol therapy was partly due to the effort and resources needed to initiate and develop the service to support this therapy. With increasing experience in managing these patients and an established service, the goal is to identify

and start suitable high-risk patients on this therapy earlier.

Despite its challenges, establishing concrete protocols with multidisciplinary team support allows for the introduction of IV epoprostenol as an additional potential line of effective therapy for PAH patients in Singapore. This is particularly important as the option of transplantation currently is limited in part due to scarcity in Singapore. The main limitation of this study is the small sample size from a single tertiary centre in a developed country, which may limit the generalisability of the results. Nevertheless, this provides important data and protocols for the region to build on, and may also serve as a basic foundation for centres planning to start their programmes. These will need to be adapted to cater to local needs and setting.

Declaration

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Supplementary Materials: Detailed protocol.

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