Chapter 4

Pulmonary arterial hypertension in thalassemia

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1. Pulmonary hypertension

Definition and Clinical classification

Important definitions[1]

- Pulmonary hypertension (PH) is a pathophysiological and hemodynamic state defined as an increased pulmonary arterial pressure (mean PAP) at rest ≥ 25 mmHg with right heart catheterization assessment. PH is reported in multiple clinical groups with specific characteristics.[2-4] The clinical classification of PH (Dana Point, 2008)[2] as follows:

  i) Pulmonary arterial hypertension (PAH): idiopathic, associated with PAH (connective tissue diseases, HIV infection, congenital heart disease, *chronic hemolytic anemia*) drug and heritable

  ii) PH: left heart disease

  iii) PH: lung disease or hypoxia: Chronic obstructive pulmonary disease (COPD)

  iv) Chronic thromboembolic PH

  v) PH with unclear and or multiple factors or mechanisms: hematological disease (myeloproliferative disorders splenectomy), systemic and metabolic disorders

- PAH is a clinical condition that presence of precapillary PH in the absence of other causes of precapillary PH such as lung diseases or other diseases.

Epidemiology

The prevalence of pulmonary hypertension (defined as pulmonary artery systolic pressure > 40 mmHg by echocardiography) was 10.5% (483/4579 patients). Seventy nine percent of PH had left heart disease class ii, ten percent had lung diseases and hypoxia class iii, four percent had PAH class i, less than one percent had class iv, and seven percent of PH was unable to define a diagnosis.

Diagnosis and treatment

The process of evaluation of suspected PH patient needs the investigations to confirm the diagnosis such as the explain clinical classification of PH, echocardiography and the cause within the PAH and assess the functional class and hemodynamic status.

Clinical presentation of PAH

The symptoms of PAH are weakness, breathlessness, syncope, abdominal distension and angina. The clinical signs are lift of left parasternal, loud second heart sound (pulmonary component), tricuspid regurgitation (pansystolic murmur), pulmonary insufficiency (diastolic murmur) and third sound right ventricular. Engorged jugular vein, liver enlargement, ascites and edema are found in the patients advanced state. The physical signs may provide keys as to the PH cause. For example, the scleroderma patients have sclerodactyly and telangiectasia. The liver stigmata should be considered. Digital clubbing is found in idiopathic PAH patient with pulmonary veno-occlusive disease or congenital heart disease.[5-6]

Electrocardiogram

The electrocardiogram of PH patient shows hypertrophy of right ventricle and strain (87%) and right atrial dilatation. Right axis deviation were found 79% in IPAH patients. The electrocardiogram, a screening tool for detect PH has 55% sensitivity and 70% specificity. Supraventricular arrhythmias may be present in advanced PH cases. Ventricular arrhythmias are rare. Atrial flutter and atrial fibrillation may be observed.[5,7]

Chest radiograph

An abnormal chest radiographic findings were found 90% in the patients with IPAH,[5] including dilatated central pulmonary artery, right atrium enlargement and right ventricle enlargement were seen in advanced PH cases. The chest radiographic abnormalities do not correlate with the PH degree in any patient.

Arterial blood gases and pulmonary function tests

Pulmonary function tests and arterial blood gases are used to identify the contribution of underlying parenchymal lung or airway disease. Lung volumes reduction, decreased CO lung diffusion capacity and peripheral airway obstruction were detected in the PAH patients.[1]

Echocardiography

Transthoracic echocardiography should be done in the suspected PH case, which correlate with pulmonary arterial pressure (PAP) and right heart hemodynamics.

The PAP estimation is the tricuspid regurgitation (TR) jet peak velocity. The Bernoulli equation (simplify) illustrated the velocity of TR and the peak pressure gradient of TR relationship = 4 x (TR velocity).[8] ***PASP****= pressure gradient TR + right atrial pressure (estimate)*. Estimated right atrial pressure is based on the respiratory variation and diameter of the inferior vena cava although often a fixed value of five or ten mmHg. In spite of the correlation of the TR velocity and pressure gradient TR, in the severe TR patients use of the Bernoulli equation (simplify) may lead to understatement of systolic pressure of PA. Also exaggeration by greater than 10 mmHg for systolic pressure of PA are usual.[9]

Ventilation/perfusion lung scan

The ventilation/perfusion lung scan should be done in the PH patients to investigate chronic thromboembolic PH.

Computed tomography (high resolution), computed tomography with contrast, and pulmonary angiography

High resolution computed tomography (CT) shows detail of the lung parenchyma to investigate emphysema and interstitial lung disease. It is required to confirm the pulmonary veno-occlusive disease. The pulmonary artery CT angiography is helpful in determine the evidence of surgically accessible chronic thromboembolic PH.[10] Pulmonary angiography is required for work up of chronic thromboembolic PH.[11]

Cardiac magnetic resonance imaging (MRI)

Cardiac MRI shows a point to evaluation of morphology, size of right ventricle and function and noninvasive blood flow assessment such as cardiac output, stroke volume, pulmonary artery distensibility and right ventricular mass.[12]

Blood tests and immunology

Routine hematology, thyroid function tests and biochemistry are needed in the patients. Serological testing is helpful to detect HIV, connective tissue disease and hepatitis.

Abdominal ultrasound scan

The use of abdominal ultrasound can be reliably to exclude portal hypertension and liver cirrhosis.

Right heart catheterization (RHC)

RHC is required to prove the PAH diagnosis, to evaluate the impairment of hemodynamic and to test the pulmonary circulation vasoreactivity.[13]

Functional classification of pulmonary hypertension[14]

Patients with PH: Class

I without limitation of physical activity

II slight limitation of physical activity

III comfortable at rest, marked limitation of physical activity

IV dyspnea at rest, inability to carry out any physical activity, right heart failure

Exercise capacity

The exercise capacity assessment, the *six minute walking test* (6MWT) is used in PAH patients.

The 6MWT is a simple technique, reproducible, inexpensive and well standardized in the patient. The walking distance, Borg scale (dyspnea on exertion) and finger oxygen saturation are reported. The walking distances less than 332 metres or less than 250 metres and oxygen desaturation more than 10% indicate poor prognosis in PAH.[15,16]

Biochemical markers

Biochemical markers are non-invasive tool for monitoring and assessment of right ventricular dysfunction in PH patients. High serum uric acid levels relate to poor survival in IPAH patients.[17] Brain natriuretic peptide and atrial natriuretic peptide (BNP) are used to monitor right ventricular cardiac failure due to chronic pulmonary hypertension.[18] The prognosis and severity in PAH patients are assessed by the parameters in table 4.1.

Table 4.1 Parameters with established importance for assessing disease severity, stability and prognosis in pulmonary arterial hypertension[1,19]

Better prognosis	Prognosis determinants	Worse prognosis
no	clinical RV failure	yes
slow	symptoms progression	rapid
no	syncope	yes
I, II	WHO functional class	IV
> 500 m (depend on age)	6 minute walk test	<300 m
peak O_2 consumption >15 ml/min/kg	cardio-pulmonary exercise	peak O2 consumption <12 ml/min/kg
normal/ near normal	BNP/ NT-proBNP	very elevated and rising
no pericardial effusion tricuspid annular plane systolic excursion >2 cm	echocardiography	pericardial effusion tricuspid annular plane systolic excursion <1.5 cm
right atrial pressure <8 mmHg and cardiac index ≥ 2.5 L/min/m^2	haemodynamics	right atrial pressure >15 mmHg or cardiac index ≤ 2 L/min/m^2

BNP = brain natriuretic peptide; NT= N-terminal segment

Therapy

The PAH therapy is a complicated strategy that comprises the severity evaluation, general measures and supportive, vasoreactivity assessment, efficacy estimation and combination of various, drugs and interventions.

1. General measures

- Rehabilitation and physical activity

  The studies have reported an exercise capacity improvement in PAH patients who took part in a training programme.[20]
- Birth control, pregnancy and hormonal treatment (post-menopausal)
- Infection prevention

  The PAH patients are susceptible to be infected such as pneumonia.[5]
- Psychosocial support
- Travel
- Elective surgery

  Elective surgery increased risk in patients with PAH.

2. Supportive therapy

- Oral anticoagulants

Oral anticoagulant therapy should be reconsidered in the patients with idiopathic PAH, PAH due to anorexigens, and heritable PAH. This drug may be considered in patients with associated PAH.[1] The coagulation abnormalities in PAH have been reported.[21-23] The advantages of anticoagulation should be balanced against the disbenefits in patients with other groups of PAH.

- Diuretics

Diuretic treatment is indicated in the patients with PAH with right heart failure. There are no randomized control trials of diuretics therapy in PAH. Clinical observation shows clear symptomatic advantage in the patients with fluid retention treated with diuretic.[1]

- Oxygen

There are no randomized trials to recommend that long-term O_2 therapy is useful in the PAH patients. The oxygen administration decrease the peripheral vascular resistance in the PAH patients. Almost PAH patients except those with pulmonary to systemic shunts and congenital heart disease have arterial hypoxemia. Guidance may be based on proof

of COPD patients; when arterial blood oxygen pressure < 60 mmHg, the patients are informed to take oxygen for at least 15 hours per day.[24]

- Digoxin

Digoxin is considered in the patients with atrial tachyarrhythmias to slow heart rate.[1]

3. Specific drug therapy

- Calcium channel blockers

The calcium channel blockers (CCB) have been used in studies are amlodipine nifedipine and diltiazem. The choice of CCB is depend on baseline heart rate of the patients. These drugs that have shown efficacy in idiopathic PAH. [25,26]

- Prostanoids

Prostacyclin is the potent endogenous inhibitor of aggregation of platelet. The prostacyclin dysregulation metabolism has been reported in PAH patients as evaluated by decrease of prostacyclin urinary metabolites and of prostacyclin synthase expression in the lung arteries.[27,28]

- Epoprostenol

Epoprostenol is stable freeze dried preparation synthetic prostacyclin. The efficacy of this drug has been tested in randomized control study in the scleroderma patients with idiopathic PAH,.[29-31]

- Beraprost

Beraprost is the first orally active prostacyclin analogue. The randomized control trials have shown an exercise capacity improvement that remains three to six months.[32,33]

- Endothelin receptor antagonists

Both pulmonary tissue and plasma of the PAH patients have the endothelin system activations. Endothelin-1 exerts mitogenic effects and vasoconstrictor by binding to the receptor of smooth muscle cells of pulmonary vascular, receptors of endothelin-A and B.[34]

- Bosentan

Bosentan is an endothelin-A and endothelin-B receptor antagonist. Bosentan is reported in PAH (idiopathic, associated with connective tissue disease and Eisenmenger's syndrome) in randomized control trials that showed improvement in functional

classification, capacity of exercise, hemodynamics, time to clinical worsening and echocardiographic.[35-39]

- Phosphodiesterase type-5 inhibitors
- Sildenafil

Sildenafil is a potent selective of phosphodiesterase type-5 inhibitor. The uncontrolled clinical trials have reported beneficial effects of this drug in idiopathic PAH, PAH with congenital heart disease, connective tissue disease and chronic thromboembolism PH.[40-42] A randomized control trial of the patients treated with sildenafil has reported favourable outcomes on hemodynamics, exercise capacity and symptoms.[43]

- Tadalafil

Tadalafil is a selective inhibitor of phosphodiesterase type-5. A randomized control trial on patients with PAH treated with tadalafil has shown positive results on symptoms, time to clinical worsening, exercise capacity and hemodynamics.[44]

4. Arrhythmias treatment

5. Balloon atrial septostomy

6. Transplantation

7. Ethical issues and end of life care

Table 4.2 Assessments and timing for the follow-up of patients with pulmonary arterial hypertension[1]

	Baseline	Every 3-6 months	3-4 Months after therapy	Clinical worsening
Clinical, WHO-FC, ECG	√	√	√	√
6MWT	√	√	√	√
Cardio-pulmonary exercise	√		√	√
BNP/NT-proBNP	√	√	√	√
Echocardiography	√		√	√
Right heart catheterization	√		√	√

Criteria of inadequate response to treatments of PAH

Inadequate clinical response for patients who were initially in WHO-Functonal class II or III:

1. Resulting clinical status defined as not satisfactory and stable
2. Resulting clinical status defined as deteriorating and unstable

Inadequate clinical response for patients who were initially in WHO-Functional class IV:

1. No rapid improvement to WHO-FC III or better
2. Resulting clinical status defined as not satisfactory and stable

2. Pulmonary arterial hypertension in thalassemia

Pathogenesis

The pathogenesis of pulmonary arterial hypertension (PAH), an important complication in thalassemia, is unclear. The β-thalassemia patients who develop PAH frequently have heart and pulmonary abnormalities, which can consequence in mortality and morbidity.[45-47]

A postsplenectomy hemoglobin E/β-thalassemia (E/β-Thal) patient, lung artery pressure was 75 mm Hg and the lung artery size was 50-400 μm showed thrombotic pulmonary arteriopathy.[48] There was no lung infarction, vasculitis, deposition of iron. These findings correlative those previously reported by pathologist in 1980.[49] The elevated plasma thrombin antithrombin III (TAT) levels were supportive of hypercoagulability leading to the abnormal vascularity.[50]

Pathogenesis of thrombotic pulmonary arteriopathy is not well understood.[48] Pathophysiologic change in postsplenectomy β-Thal and leads to PAH was proposed in the previous study (Figure 4.1).[50]

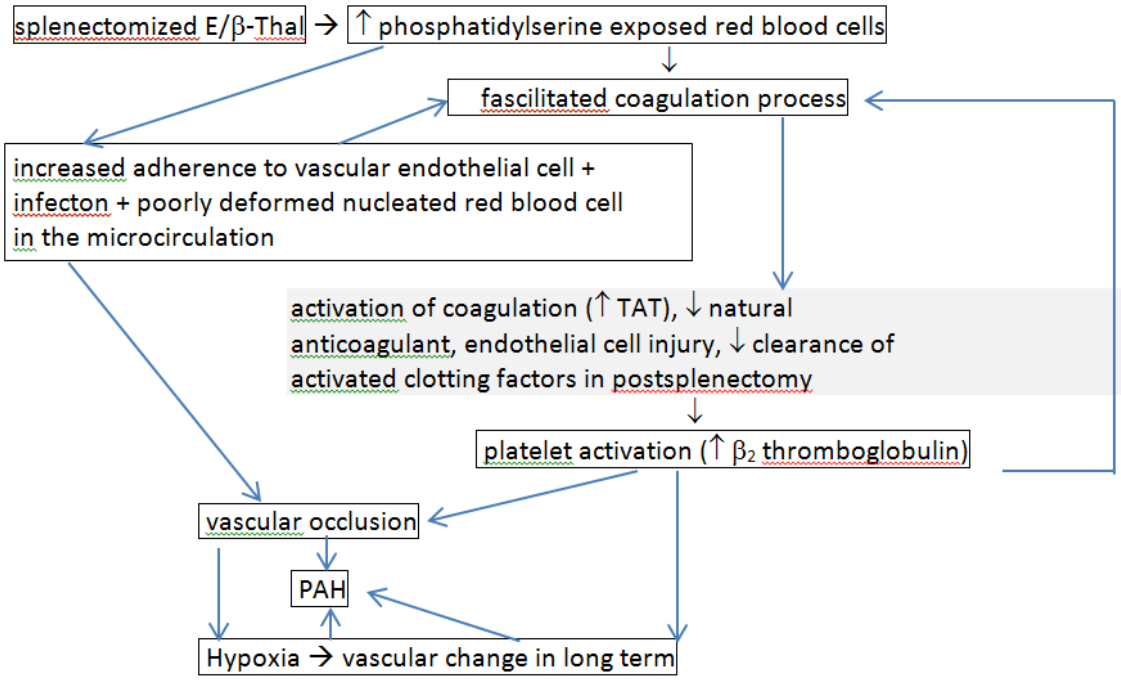

Figure 4.1 Proposed pathogenesis of pulmonary arterial hypertension

PAH in thalassemia association with platelet activation and hypercoagulable state

The frequency of pulmonary arterial hypertension (PAH) in thalassemia ranges from 10 - 74% in previous reports, and high incidence in thalassemia intermedia (TI) patients.[45,51-54] A study of TI patients reported frequency of 59% in TI who were late starters or nontransfused in receiving regular blood transfusions.[45]

The mechanisms of PAH in thalassemia are likely multifactorial. A combination of left ventricular dysfunction and anemia and chronic hypoxia causing pulmonary vascular remodeling and increased ventricular pressure have been proposed.[45,51-53]

Several studies found the PAH is significant associated with postsplenectomy status that linking heart complication and PAH to splenectomy in hemolytic disease such as thalassemia.[50,55,56]

The possible pathophysiology leading to PAH in thalassemia may involve platelet activation and the coagulation cascade.[50,55,57-59]

In PAH, vascular endothelial cell dysfunction is the cause.[48] Systemic hypercoagutability[58,60] is related to the presence of phosphatidylserine on the β-Thal red blood cell membranes

surface.[61] Splenectomy allows an increased number of phosphatidylserine exposed RBCs to circulate and stimulate hypercoagulability.[62] Thrombin formation is facilitated by decreased plasma levels of protein C, protein S, antithiombin III, and heparin cofactor II.[57,60,63,64] Thrombin from the coagulation process stimulate platelets and the platelet activation can promote the process further. Platelet activation was confirmed by an increased plasma β_2-thromboglobulin (βTG) levels and resulting release of growth factors by platelets activation may lead to changed vascularity.[48] Thrombocytosis is a known postsplenectomy consequence[65], likely increases thrombosis and vascular changes. Phosphatidylserine exposed red blood cells adhere to vascular endothelial cell. Local clot formation would be promoted by these vascular endothelial cells, particularly in the systemic hypercoagulability.

The researchers found a significant of P-selectin association, a marker of platelet activation in vivo and main element in formation of thrombus, with PAH. P-selectin is a principle marker for diagnosis of thalassemia with PAH.[55,66] Platelets activation can affect vascular endothelial disturbance, as reported by studies demonstration increase of vasoactive substances and vascular adhesion molecules levels in PAH.[67]

Supporting research study I

The study entitled “Clinical indicators for PAH in thalassemia” (Appendix B). The following is a short communication of the study.

Objectives of the study: To explore predictive characteristics for PAH in thalassemia.

Materials and methods: 224 adult thalassemia patients, who were treated at the hematology outpatient clinic, Chiang Rai Hospital, between January 2005 and June 2010, were included in this study. Pulmonary artery systolic pressure (PASP), estimated by echocardiography (ECHO), was performed on all patients.

Outcome definitions and measures: PASP > 35 mmHg

Study design: Cross-sectional study

Results and discussion: The prevalence of PAH was 29%.

Table 4.3 Multivariable association between clinical indicators and PAH. (Appendix B)

Indicators	Adjusted Odds Ratio	95% CI	p-value
Type of thalassemia			
Hb H disease or Homozygous β-thal	1	-	-
E/β-thal	1.98	1.29 - 3.01	0.002
Splenectomy	2.36	1.17 - 4.73	0.016
Number of red cell transfusion > 6 units/year	1.69	0.80 - 3.56	0.166
Hemoglobin ≤ 6 g/dl	1.15	0.56 - 2.36	0.695
Serum ferritin >1,000 μg/L	2.45	0.92 - 6.54	0.073

The authors propose that the predictive factors for PAH in thalassemia include, E/β-thal, postsplenectomy status, number of red cell transfusion > 6 units/year, hemoglobin ≤ 6 g/dl and serum ferritin level > 1,000 μg/L which were 72.15% accurate (ROC). The authors also found 2.45 times the chance to detect PAH in the patients with serum ferritin higher than 1,000 μg/L. (not statistically significant).

In conclusion, the predictive characteristics for thalassemia with PAH are E/β-Thal and postsplenectomy status.

Supporting research study II

The study entitled "Effect of acetylsalicylic acid on thalassemia with PAH" (Appendix C). The following is a short communication of the study.

Objectives of the study: To compare PASP between thalassemic patients with PAH for whom acetylsalicylic acid was and was not prescribed after 1 year.

Materials and methods:

Inclusion criteria: All new adult thalassemia with PAH (definition was PASP > 35 mmHg)

Exclusion criteria: Secondary causes of PAH, other antiplatelet and anticoagulants.

The patients were classified into two groups. Group I, ASA 81 mg was prescribed daily for 1 year. Group II, no ASA was prescribed, due to contraindications for ASA (bleeding, gastrointestinal side effects, thrombocytopenia).

Outcome definitions and measures: PASP at 1 year

Study design: Retrospective cohort study

Results and discussion:

Table 4.4 Effect of aspirin on clinical outcomes and echocardiographic findings. (Appendix C)

Outcome	Adjusted difference* (95% CI)	p-value
Functional class status: NYHA class (n [%])	0.30 (–3.18 to 3.78)	0.865
Clinical right heart failure (n [%])	–0.001 (–3.86 to 3.86)	0.999
O_2 saturation (%)	0.31 (–1.71 to 2.33)	0.757
Echocardiographic findings		
PASP (mmHg)	–0.95 (–16.99 to 15.10)	0.906

*Adjusted for propensity score

After adjusting for propensity score (based on type of thalassemia, splenectomy, O_2 saturation, NYHA classification, red cell transfusion, clinical right heart failure, hemoglobin level, platelet count, nucleated red cell, serum ferritin level, baseline PASP, left ventricular ejection fraction, main pulmonary artery diameter, right ventricular diameter, right ventricular systolic function and diastolic function) there were no statistically significant differences in the functional class status, clinical right heart failure and oxygen saturation between the two groups. ASA, as compared with no-ASA, did not significantly reduce the PASP (adjusted difference, –0.95; 95% % confidence interval [CI], (–16.99 to 15.10; *P*=0.906).

Subgroup analysis, E/β-thal; ASA, as compared with no-ASA, did not significantly reduce the PASP (adjusted difference, –3.62; 95% CI, (–11.84 to 4.60; P=0.225). The ASA group, E/β-thal compared with homozygous β-thal, did not significantly reduce the PASP (adjusted difference, 1.51; 95% CI, (–12.40 to 15.43; P=0.824). The transfusion and non- transfusion-dependent patients, ASA did not significantly changed the PASP.

In conclusion, The present findings suggested that there was no evidence that low-dose ASA would have any beneficial effects after one-year treatment of PAH in thalassemia.

Supporting research study III

The study entitled “Benefits of chronic blood transfusion in hemoglobin E/β thalassemia with PAH” (Appendix D). The following is a short communication of the study.

Objectives of the study: To compare PASP and six minute walk distance at one-year follow-up, in hemoglobin E/β-Thal with PAH patients, who received chronic blood transfusions or occasional transfusions.

Materials and methods: All adult cases of E/β-Thal with PAH (defined as PASP greater than 35 mm Hg) were evaluated and followed from the 1st month to the next 12th months. The patients were classified into 2 groups by patient preference. In one group patients received chronic blood transfusions to keep pre-transfusion hemoglobin ≥7.0 g/dl in one year. In another group, patients received occasional transfusions. All patients were treated with iron chelation when serum ferritin level ≥1000 μg/dl. PASP and the 6 minute walk distance were evaluated at baseline, six months and twelve months. Propensity score adjustment was used to control for confounding by indication and contra-indication. Multivariable regression analysis was used to evaluate the effects of chronic blood transfusion.

Study design: Non-randomized clinical trial

Results and discussion:

Table 4.5 Effect of chronic blood transfusion on clinical outcomes, pulmonary artery systolic pressure and 6 minute walk distance. (Appendix D)

Outcomes	**Adjusted β difference* (95% CI)**	**p-value**
6 months		
Clinical		
NYHA class III (n)	-0.37 (-0.37 to -0.37)	<0.001
Clinical right heart failure (n)	-0.37 (-0.37 to -0.37)	<0.001
O_2 saturation (%)	-1.53 (-15.39 to 12.33)	0.829
Echocardiographic findings: PASP (mmHg)	-6.67 (-16.68 to 3.35)	0.192
6 minute walk distance (m)	10.88 (-17.45 to 39.22)	0.451
12 months		
Clinical		
NYHA class III (n)	-0.14 (-0.15 to -0.14)	<0.001
Clinical right heart failure (n)	-0.14 (-0.15 to -0.14)	<0.001
O_2 saturation (%)	3.76 (-10.02 to 17.54)	0.593
Echocardiographic findings: PASP (mmHg)	-16.83 (-26.35 to -7.32)	0.001
6 minute walk distance (m)	46.55 (18.08 to 75.02)	0.001

*Adjusted for propensity score

Table 4.6 Adjusted β difference (95% CI) of chronic blood transfusion.

Months	PASP (mmHg)	6 Minute walk distance (m)
6	–6.67 (–16.68 to 3.35)	10.88 (–17.45 to 39.22)
12	–16.83 (–26.35 to –7.32)*	46.55 (18.08 to 75.02)*

* $p < 0.05$ compare to baseline

The chronic blood transfusion, as compared with the occasional transfusion group, after adjusting for propensity score (age, splenectomy, ASA, NYHA classification, clinical right heart failure, O_2 saturation, baseline PASP, left ventricular ejection fraction, diastolic function, hemoglobin level, platelet count, nucleated red cell, baseline serum ferritin level and baseline six minute walk distance) and right ventricular systolic function. The chronic blood transfusion group had a mean PASP reduction greater than the occasional transfusion group at 12 months (adjusted mean difference, -16.83; 95% CI, -26.35 to -7.32; p=0.001) after treatment. The mean 6 minute walk distance at 12 months in the chronic blood transfusion group was greater than the occasional transfusion group (adjusted mean difference, 46.55; 95% CI, 18.08 to 75.02; p=0.001). Chronic blood transfusion improved the clinical outcomes of the functional class status and clinical right heart failure at six and twelve months after treatment.

In conclusion, chronic blood transfusion might have beneficial effects after twelve months treatment of in thalassemia with PAH.

Conclusion

PAH can be related with all types of chronic hemolytic anaemias. The mechanism of the complication seems to involve vasoconstriction, hypertrophy of vascular wall, hypercoagulability, increased endothelin and thromboxane, local thrombosis and decreased nitric oxide and prostacycline. Platelets may have a significant role, as pro-coagulant, by augmentation of platelet release of serotonin (leading to smooth muscle proliferation and vasoconstriction), platelet derived growth factor and vascular endothelial growth factor. PAH in thalassemia associated with hypercoagulability and platelet activation.

Therapeutic plan of PAH in thalassemia are under discussion. Some authors recommend that the PAH could be confined, by starting blood transfusion and iron chelation therapy early in life for thalassemia intermedia or non-transfusion-dependent patients. Amelioration of hypercoagulability and PAH by chronic red cell transfusion was seen in a splenectomized E/β-Thal patient.

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