Chapter

Pulmonary Hypertension in Thalassemia Patients

Ahmed Shemran Mutlaq Alwataify, Sabih Salih Alfatlawy and Yahia Abid Alshahid Altufaily

Abstract

Pulmonary hypertension (PH) is defined in children as a mean pulmonary arterial pressure (PAP) greater than 25 mmHg at rest or 30 mmHg during physical activity, with increased pulmonary artery capillary wedge pressure and an increased pulmonary vascular resistance greater than 3 Wood units × M^2. it is the main cause of morbidity and mortality in the group of thalassemia, if no treatment leads to right ventricular heart failure and death. The development of pulmonary arterial hypertension (PAH) is assumed to be the result of many multifactorial pathogenic mechanisms including chronic hemolysis, iron overload, hypercoagulability, and erythrocyte dysfunction as a result of splenectomy, inflammation and nitric oxide (NO) depletion. PAH symptoms are non-specific, their signs consist of right ventricular lift, an accentuated pulmonary component of the second heart sound, a (gallop rhythm) right ventricular third heart sound, and parasternal heave meaning a hypertrophied right ventricle. The diagnosis of PAH requires a clinical suspicion based on symptoms and physical examination. Echocardiography is frequently used to screen for PAH, monitor progression over time and allow identification of patients for whom diagnostic right heart catheterization (RHC) is warranted and its treatment includes hemoglobinopathy specific treatment and PAH specific therapy.

Keywords: thalassemia, pulmonary hypertension, splenectomy, iron overload, blood transfusion, hydroxyurea, hypercoagultion, specific therapy

1. Introduction

Thalassemia are groups of autosomal recessive inherited disorders resulting from reduced or defects in one or more of the hemoglobin (Hb) chains synthesis [1]. The thalassemia syndrome is classified to which of the globin chains α or β is affected [2]. The α- and β-thalassemia are the main types of thalassemia and sickle cell thalassemia [3].

Thalassemia are found with the increased prevalence in the Mediterranean and Middle East, is caused by mutations on the chromosomes 11 and 16 for the cases of β- and α-thalassemia respectively with more than 150 different mutations [4]. β-Thalassemia presents in three clinical phenotypes, called thalassemia major, minor, and intermedia. β-Thalassemia major is resulting from homozygous or compound heterozygous to β-thalassemia and usually has early presentation and it depends on blood transfusion [1], reduced survival, has multi organs complications, frequent hospitalization and need lifelong management [5]. It is the most

severe form in patients with defective in two β-globulin genes and severe reduction in production of β-globulin [3]. β-Thalassemia minor, on the other hand, is an asymptomatic condition due to heterozygous to a β-thalassemia defect [1]. β-Thalassemia intermedia includes patients with a wide series of phenotypes [6] which is more severe than thalassemia minor and milder than β-thalassemia major [7]. β-Thalassemia intermedia patients with two defective genes is characterized by mild to moderate reduction in β-globulin production [4]. Thalassemia intermedia associated with lack of regular blood transfusion and iron chelation therapy leading to serious specific complications like gall and renal stone, leg ulcer and increased thrombophilia and right heart failure [8].

Its pathology is characterized by reduced synthesis of hemoglobin (Hb) and the survival of red blood cell (RBC), caused by from excessing the unaffected globin chain [9]. This abnormal alpha- to beta-chain ratio lead to precipitation of the unpaired chains which result in destruction of red blood cell precursors in the bone marrow called ineffective erythropoiesis and in circulation named hemolysis [10, 11]. Ineffective erythropoiesis causes expanded of marrow cavities leading to distortion of the cranium, facial and long bones and also produced lymphadenopathy, hepatosplenomegaly because of activity in extramedullary hematopoietic sites [12]. Children with β-thalassemia appear well at birth, then developed anemia that worse with time, if left no treatment resulting in early death [13] due to high output heart failure [14].

Therapy involves early and regular transfusion to maintain hemoglobin levels of at least 9–10 g/dl to make for improving growth and development and reduced hepatosplenomegaly in addition to bone deformities [15], regular blood transfusion therapy lead to prolonged survival [16], decreased the severity of the disease [17] and hemolysis because of chronic transfusion might ameliorate the ineffective erythropoiesis, and in that way reverse the pulmonary vasoconstriction and pulmonary hypertension (PH) [18].

So, regular blood transfusion, iron chelation drugs and hydroxyurea therapy are frequently working resulted in expressively improved survival, and may extend their life to the adulthood [19].

2. Mechanism of iron toxicity

It results from prolonged iron absorption especially thalassemia intermedia or repeated blood transfusion in thalassemia major. Iron is highly reactive and easily interchanges between two states iron III and iron II in a method which results in the loss as well as gain of electrons leading to generation of unsafe free radicals which damaged lipid membranes, organelles and deoxyribonucleic acid (DNA) leading to cell death and fibrosis is developed [20]. In healthy, iron is binding to transferrin so kept safe, but in iron overload, the transferrin capacity to bind iron is exceeded within cells and plasma resulting in free iron leading to damage of many tissues which fatal unless iron chelation treatment [9]. Even though, blood transfusion improved the severity of the disease, it resulted in a positive iron balance and secondary iron overload, leading to damage and dysfunction of vital organs in the second decade of life [17] (each bottle of blood transfusion contains 200 mg of iron [14]).

3. Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is defined generally as high blood pressure in the heart to lung system that delivered fresh oxygenated blood to the heart

while returning used (oxygen depleted) blood back to the lung [21]. It is defined in children as a mean pulmonary arterial pressure (PAP) greater than 25 mmHg at rest or 30 mmHg during physical activity with increased pulmonary artery capillary wedge pressure likely (due to left ventricle diastolic dysfunction as resulting from chronic iron overload) and an increased pulmonary vascular resistance (from thrombotic pulmonary arteriopathy) greater than 3 Wood units × M^2 [22].

PAH is a progressive disease [23] associated with hemoglobinopathies. It is a not uncommon in thalassemia patients, caused by pulmonary hemosiderosis [8]. It is the important cause of morbidity and mortality in this group of the patients [24].

PAH has been reported as one of the common cardiac complications in β-thalassemia patients [25]. It is characterized by vasoconstriction, and progressive increases in the mean pulmonary artery pressure and pulmonary vascular resistance, if no treatment leads to right ventricular heart failure and death [26].

A universal classification system has been used to describe the various types of pulmonary hypertension [27]:

1. Pulmonary arterial hypertension called (idiopathic): is inherited; is resulted from drugs or toxins; connective tissue disease, human immunodeficiency virus (HIV) infection, liver disease, congenital heart disease or is caused by conditions that affect the pulmonary small blood vessels [21].

2. Pulmonary hypertension due to left heart disease.

3. Pulmonary hypertension due to lung diseases and/or hypoxia.

4. Chronic thromboembolic pulmonary hypertension.

5. Pulmonary hypertension with indistinct multifactorial mechanisms including chronic hemolytic anemia shares many of the included features of group 1 and 5 due to its multifactorial mechanisms [19, 28].

4. Pathophysiology

The PAH in thalassemia syndromes is assumed to result from many multifactorial mechanisms, it includes chronic hemolysis, iron overload, hypercoagulability [29] and erythrocyte dysfunction resulting from splenectomy [19], inflammation and nitric oxide (NO) depletion free Hb inactivate nitric oxide (NO) and vasodilatory properties in pulmonary circulation and the hemolysis resulting in release of arginase enzyme which predominantly drive L-arginine to ornithine rather than NO production, therefore higher arginase activity and lower arginine bioavailability founded in thalassemia as L-arginine provides the substrate of both NO synthesis and arginase [19] as well as enhance activation of platelets and increased endothelin 1 release causing vasculopathy which are main pathogenetic mechanisms [30].

Pulmonary arterial hypertension is characterized histopathologically by vasoconstriction, vascular proliferation, intravascular thrombosis, and remodeling of the vessels walls [26].

Nitric oxide caused vasodilation and increased blood flow through inhibiting expression of endothelial adhesion molecule, proliferation of vascular smooth muscle, platelet aggregation and blood coagulation [31]. As intravascular hemolysis, arginase concurrently released from red cells into blood plasma, converts plasma L-arginine to ornithine result in high level of ornithine which produced smooth muscle proliferation and collagen synthesis resulting in vascular remodeling and

thickening in intimal leading to vascular constriction, endothelium abnormality, and intravascular thrombosis [32].

Splenectomy has been an important risk factor in the development of PAH [11] as spleen is considered as filter for erythrocytes that are damaged and other circulating blood cells. so splenectomy is caused in activation of platelets, abnormal in erythrocyte aggregation, thrombin generation acceleration and released procoagulant factors, possibly it has a larger number of abnormal erythrocytes or breakdown products of erythrocyte in the circulation and associated with excess in release of early nucleated erythrocytes leading more expression of adhesion molecules which promote local clot formation particularly in the presence of systemic hypercoagulability [33]. In addition, there was shorter life span of platelets in both splenectomized and nonsplenectomized patients with thalassemia than in non thalassemia splenectomized patients [33]. These factors may affect the ability of intravascular thrombosis producing changes in the pulmonary vasculature leading to PAH [19].

A hypercoagulable state has another finding among hemoglobinopathies. The incidence of clinically evident thromboembolism in β-thalassemia is 1–4%, with a majority of events occurring prior 30 years of age [19]. It results from a range of abnormalities, including erythrocyte aggregation, the performed splenectomy, platelets activation, abnormal circulating factors, some coexistent genetic coagulation defects, endothelial dysfunction and vasculopathy (**Figure 1**) [34]. The multifactorial mechanisms described earlier can work both independently and in combination with other mechanisms or organ dysfunction to lead clinically apparent PAH [19].

PAH is more common in thalassemia intermedia than in thalassemia major, and it may cause heart complications in patients with aging of more than 30 years [35]. Its iron load occurs as increased uptake of gastrointestinal absorption of iron due to hepcidin suppression [14] making more susceptible to pulmonary arterial hypertension [35].

In β-thalassemia major, pulmonary hypertension correlates with the severity of hemolysis [19], although transfusion therapy improved the disease severity, it resulted in a positive iron balance and secondary haemosiderosis, often leading to vital organ damage and dysfunction in the second decade of life [36], while splenectomy has important role in both types [19], yet in thalassemia patients whose disease is well treated by chronic transfusion therapy, the development of pulmonary hypertension is linked to heart dysfunction and the subsequent toxic effects of iron overload instead of hemolysis [19].

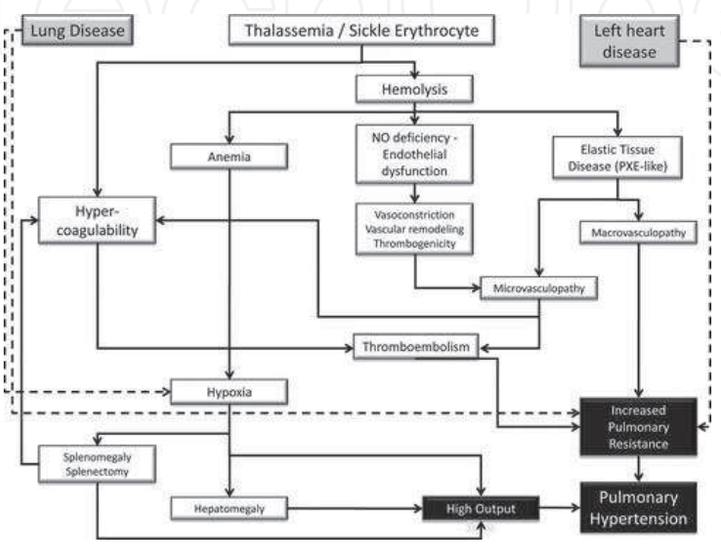

Figure 1.
The pathophysiology of pulmonary hypertension in thalassemia [34].

5. Risk factors

The risk of development of PHT can increase older age group (more often in people older than 30 years) but idiopathic PAH is more common in younger adults. Chronic iron overload and increased pulmonary vascular resistance from thrombotic pulmonary arteriopathy [29], splenectomy, hepatitis C and previous venous thromboembolism, markedly increased levels of peripheral nucleated red blood cells, platelet counts and serum ferritin levels [25] and splenectomy [37].

6. Epidemiology

The epidemiology of idiopathic PAH is about 125–150 deaths per year in the United States, and worldwide the incidence is similar to the united states at 4 cases per million. However, in the France, the incidence were 6 cases per million. Females have a higher incidence rate than males [38], thrombi in small pulmonary arteries reached in 44% of splenectomized Hb E/B thalassemia. In Greece 10% occurred in in thalassemia major and more than 50% in thalassemia intermedia, in Ardabil, Iran 41.4% in intermedia and 14.7% in thalassemia major [8], while its prevalence in Thailand was 43% [39] and Babylon, Iraq reached to 15.5% [40].

PHT increased its incidence about 2.45 times chance in patients with serum ferritin of more than 1000 ng/ml [39].

Pulmonary vascular changes with micro-thrombo-embolism founded in splenectomized thalassemia 54% in Germany [41], 33.3% in Babylon, Iraq [40] and only 16% and 13.4% in non splenectomized patients [40, 41] respectively.

PAH has a frequent finding in patients with hemoglobinopathies, on the other hand, The reported prevalence differs in the different conditions state and according to the screening method used. In thalassemia intermedia, PAH has been known as the most cardiovascular finding and the commonest cause of heart failure. In homozygous sickle cell anemia, PAH is a detected frequently and it has been thought a major factor determining the prognosis [42]. In sickle-thalassemia, a heterozygous state with 1 thalassemia and 1 sickle allele, PAH has been detected with a relatively lower frequency and absolutely lesser severity [34].

7. Signs and symptoms

PAH symptoms are non-specific: either early symptoms which include shortness of breath or exertional dyspnea, fatigue, weakness, chest pain, upper abdominal pain and decreased appetite, while later symptoms include light-headedness (syncope) and less frequently cough, fainting, edema of ankle or leg, Rarely hemoptysis, hoarseness, arrhythmias and cyanosis [43].

Physical examination: the signs consist of right ventricular lift, an accentuated pulmonary component of the second heart sound, a (gallop rhythm) right ventricular third heart sound, and parasternal heave meaning a hypertrophied right ventricle. Right sided heart failure causes signs of systemic congestion include jugular venous distension, ascites, and hepatojugular reflux, hepatomegaly and or splenomegaly, the evidence of tricuspid insufficiency and pulmonic regurgitation [44].

World Health Organization (WHO) functional classification in pulmonary hypertension (stages of PH) [45]:

I. without limitation of physical activity (ordinary physical activity does not produce undue dyspnea or fatigue, chest pain or near syncope).

II. slight limitation of physical activity (comfortable at rest; its ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope).

III. marked limitation (comfortable at rest; less than ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope).

IV. inability to carry out any physical activity without symptoms (the patients presented with signs of right sided heart failure, dyspnea and /or fatigue which manifested at rest and discomfort is increased by any physical activity).

Cardiac evaluation through chest radiograph, electrocardiogram (ECG) and echocardiography. Chest radiography (CXR) was performed in erect position, in the posterior-anterior (PA) view to look for cardiac size, pulmonary vascularity and pulmonary conus [45].

8. Complications

It includes:

1. Right-sided heart dilatation and heart failure: PAH is a deadly disease in which vasoconstriction and vascular remodeling both lead to a progressive increase in pulmonary vascular resistance. Although the increment in afterload is the first trigger for RV adaptation. Neurohormonal signaling, oxidative stress, inflammation, ischemia, and cell death may contribute to the development of RV dilatation and failure [46].

2. Blood clots: Intravascular thrombosis are found in the small distal pulmonary arteries. Dysregulation of coagulation, platelet function, and endothelial cells may contribute to a prothrombotic state [47].

3. Arrhythmia: Pulmonary hypertension can cause arrhythmias, atrial flutter and fibrillation [48].

9. Diagnosis

The evaluation of pulmonary hypertension in children required a comprehensive work up to confirm the diagnosis, assess disease severity and rule out secondary cause, so appropriate treatment course can be initiated [45].

The diagnosis requires a clinical suspicion based on symptoms and physical examination and review of a comprehensive set of investigations to confirm haemodynamic criteria are met and to describe the etiology, the functional and haemodynamic severity of the condition [49].

9.1 Transthoracic Doppler echocardiography (TTE)

It is non-invasive, an excellent screening tool with suspected PAH, it is widely available and relatively inexpensive, it is frequently used to screen for PAH and monitor progression over time and allow identification of patients for whom diagnostic RHC is warranted [50]. It documents cardiac anatomy, right ventricular size and function, left ventricular diastolic and systolic function, morphology and function of valves, and the presence of pericardial effusion or a patent foramen ovale [22].

Transthoracic Doppler echocardiography (TTE) can assess pulmonary artery systolic pressure (PASP) and give additional information about the cause and consequences of PAH [51]. It also can provide functional and structural assessment of the heart and estimate of pulmonary hemodynamics, it is widely available and tolerated by children [52]. Echocardiographic assessment is essential for the effective modality of PAH management patients as part of a good approach to therapy and prognosis (presence of pericardial effusion and increasing right ventricle to left ventricle systole ratio is associated with an increasing hazard for a clinical event [53]. It is an important tool for monitoring the response to treatment and is recommended 3–4 months after initiation of medication or a change in therapy [54].

- Pulmonary arterial systolic pressure (PASP) = RV-RA gradient + right atrium pressure.

$$\text{Mean PAP} = 0.6 * \text{SPAP} + 2 \text{ mmHg} \quad (1)$$

Generally PASP > 38 mmHg detected by echo which suggest mean PAS > 25 mmHg [54].

Right atrial pressure was estimated by the response of the inferior vena cava diameter to inspiration, the value is considered to be about 5–10 mmHg [26].

- Mean pulmonary artery pressure range:

Normal: (12–16) range, mild: (≥25–40) range, moderate: (≥40–<55) range, sever: (≥55) range.

- Systolic pulmonary artery pressure categorized as [55]:

Mild: 40–45 mmHg, moderate: 46–60 mmHg, severe: exceed 60 mmHg.

- The following associated with pulmonary hypertension in echo [56]:

1. RV, RA hypertrophy or dilatation

2. Dilated pulmonary artery

9.2 Electrocardiogram (ECG)

The ECG may proffer suggestive or supportive evidence of PAH by finding right ventricular hypertrophy and strain and right atrial dilation. Right ventricular hypertrophy is present in 87% on ECG and in 79% of patients with idiopathic PAH have right axis deviation [57]. The ECG has inadequate sensitivity (55%) and specificity (70%) to be a screening instrument for detecting significant PAH [58].

9.3 Chest radiography (CXR)

Chest radiography is usually performed as the earlier imaging study and may show features of PHT. The classic radiographic findings are evident only late in the disease process [59] including central pulmonary arterial dilatation, variable peripheral lung field that contrasts with pruning of the peripheral blood vessels associated with decreased pulmonary blood flow resulting from increment in pulmonary vascular resistance and the lung became oligemic progressively [45]. In advanced cases, right atrial and ventricular enlargement might appeared and it progressed [57].

The degree of hypertension in any given patient does not correlated with the extent of X-ray abnormalities and normal chest radiograph does not exclude PAH [49].

9.4 Right heart catheterization and vasoreactivity

Right heart catheterization (RHC) remains the gold standard for the diagnosis of pulmonary hypertension, if the patients are prospect for treatment by clinical and transthoracic echocardiographic assessment [26]. He should undergo a confirmatory catheterization of the heart [54]. It is needed to confirm the diagnosis, assessment of the severity of hemodynamic impairment (right atrial pressure, pulmonary artery pressure, pulmonary vascular resistance, to carry out vasoreactivity testing of the pulmonary circulation in selected patients to acute vasodilator testing and to rule out subtle congenital heart disease like pulmonary vein disease [53]. This was needed to performed well expert centers, the techniques have low morbidity (1.1%) and mortality (0.055%) rate [60].

This involves passing a thin flexible tube (catheter) into the right side of the heart which usually passing through vessels of the groin or arm [61].

9.5 High-resolution computed tomography, contrast-enhanced computed tomography

It is a widely available device that can give good information on abnormalities of vascular, cardiac, parenchymal and mediastinal. It can suggest the diagnosis of PAH (PA or RV enlargement), identify the cause of PAH such as lung disease, provide evidences as to the form of PAH and as well provide prognostic information [62].

9.6 Cardiac magnetic resonance imaging

Is an accurate in the assessment of right ventricular size, morphology and function because it is noninvasive so can be used to follow patients regularly, it is an important advantage upon invasive right heart catheterization because measures of RV function have been revealed to be prognostic of long term outcomes in the disease, also provide important information about a patient's disease course and response to treatment by changes in RV function [63].

9.7 Abdominal ultrasound scan

Liver cirrhosis or portal hypertension can be surely excluded through abdominal ultrasound scan and using of contrast agents can improve the diagnosis [57].

10. Treatment

There are no specific treatment guidelines [24].

There are two main parts of management:

1. Predominantly hemoglobinopathy specific treatment and

2. PAH-specific treatment.

It is important to maximize specific treatment of primary hemoglobinopathy, which includes blood transfusion, iron chelation and hydroxyurea, while PAH-specific therapy consist of anticoagulation, diuretics, digoxin, oxygen, and PAH specific vasodilator agents [24].

10.1 Transfusion therapy

Treatment of β-thalassemia depend on an accurate transfusion strategy, particularly in more severe thalassemia major, so to control chronic hemolysis. A chronic transfusion protocol, plus iron chelating therapy to prevent iron overload, is believed to prevent or even ameliorate PAH in these patients [64]. The higher level of blood transfusion may imply more severe disease in patients with PHT, additionally, more chelation therapy used in the PHT group likely reflects more aggressive treatment [33]. So, soon after the diagnosis pulmonary hypertension, regular blood transfusion and appropriate iron chelation therapy can avoid this complication [35].

β-Thalassemia major patients need transfusions throughout life to reach the target Hb level in the range (9–10 g/dl) and to support normal growth, chelation therapy is being used to prevent toxic effects of iron overload, it is generally recommended after twenty units of packed cell transfusion or when serum ferritin exceeds (1000 μg/L), this chelating agents can form complexes with iron and promote its excretion which can clear plasma non transferring bound iron, so remove excess iron from cells and make body iron at safe levels [13].

10.2 Hydroxyurea therapy

Hydroxyurea is a useful treatment, it helps to reduce hemolysis, rise Hb F production (modifies the defective hemoglobin synthesis), so prevents hemolysis and induces nitric oxide in endothelial cells, improves the clinical symptoms, so decreased requirement for blood transfusion, and prevent the acute episodes that exacerbate PAH and potentially reduce overall mortality [24] also has been shown to protect from the development of PA [65]. Additionally, hydroxyurea reduces thrombocytosis, therefore preventing hypercoagulability [34].

Hydroxyurea is an antimetabolite s-phase specific drug that reversibly inhibit ribonucleoside diphosphate reductase enzyme which catalyzes the conversion of ribonucleotides to deoxyribonucleotides which is an important step in biosynthesis of DNA, therefore prevent progression of cell. Also it induces gamma chain globin in human erythroid cell to produce HbF which distributed in RBC [66].

It is used in PAH to reduce the level of circulating immature bone marrow cell and interrupt the abnormal narrowing and occlusion of pulmonary arteries [66].

Dose 10–15 mg/kg/day with gradually increased the dose in step of 2.5–5 mg/kg/day to reach a usual dose 15–30 mg/kg/day (the maximum dose is 35 mg/kg/day) [66].

10.3 L-Carnitine

Mitochondrial dysfunction recently has gained further much attention in the pathophysiology of PAH associated with other diseases, like chronic hemolytic anemia. L-Carnitine is important for the fatty acid oxidation and the normal mitochondrial function [67]. It enhances myocardial function and could increase nitric oxide in plasma which is considered as potent vasodilator that oppose PAH [67] leading to a significant reduction in systolic PAP [22] about 10 mmHg after 3 months of therapy and it is given in a dose of 50 mg/kg/day for 3 months [19].

10.4 Supportive care

All thalassemia patients with PAH, supportive measures should be used immediately. Oxygen therapy should be given to avoid hypoxia which prevent the harmful effects of hypoxia causing vasoconstriction in the pulmonary blood vessels [24]. Physical therapy and lifestyle modifications are often doing to improve symptoms

and signs. Immunization is recommended routinely with pneumococcal and influenza vaccines annually [19].

Also, we recommended that we should not use decongestant drugs like pseudoephedrine or other stimulant type medication and avoid use oral contraceptive agent.

Vasoreactivity testing: cardiac catheterization with acute vasodilator drug is essential before select main therapy in children [53].

10.5 PH-specific therapies

These are include

10.5.1 Phospho-diesterase type 5 inhibitors

The cyclic guanosine monophosphate (cGMP) pathway is an essential target of endothelium-derived nitric oxide, an important vasodilator agent. Phospho diestrase type 5 (PDE5) rapidly hydrolyze to cGMP, inactivating its vasodilatory effect. PDE5 inhibitors have been developed that prolong the effect of cGMP through inhibiting its degradation [19].

Sildenafil citrate is a selective, potent inhibitor of the cyclic guanosine monophosphate specific phosphodiesterase-5, which stimulates selective relaxation smooth muscle relaxation in pulmonary vaessels and has been used successfully in the treatment of PAH class II–IV in adult. Prolong therapy with it has been appear to produce a significant and persistent reduction in PAH in patients with thalassemia and sickle thalassemia [68].

10.5.2 Endothelin receptor antagonists

Bosentan has a dual (endothelin) ET receptor antagonist, which reduced pulmonary artery pressure and resistance and improves exercise tolerance in pulmonary hypertension above 12 years [63] class III and IV patients and recently shown beneficial effects in class II patients [53].

Liver function test need follow up regularly as increased in 12% in adult and only 3.5% in children [53].

10.5.3 Soluble guanylate cyclase stimulator

Riociguat, acts directly on a soluble guanylate cyclase stimulating the enzyme which converts guanosine triphosphate to cyclic guanosine monophosphate, increasing sensitivity to low nitric oxide levels leading to vasorelaxation [69]. It has been beneficial in pulmonary arterial hypertension treatment [70] in adult patients with group 4 after surgical treatment or inoperable chronic thromboembolic pulmonary hypertension to optimize exercise capacity as patients with thalassemia syndrome have higher risk of thromboembolic disease leading to pulmonary pressure overload [19].

Prostacyclins: epoprostenol—prostacylin, was considered a key standard for treatment of severe cases.

Epoprostenol given as continuous infusion, it antithrombotic agent that inhibits hypoxic pulmonary vasoconstriction and antiproliferative properties [33].

It improves both the survival and the symptoms of idiopathic form of PHT compared to conventional therapy, it prolongs survival from 35–63% at 3 years [33].

11. Conclusion

Pulmonary hypertension has commonly identified as life threatening for many chronic illness like the hemolytic anemia. The pathophysiology is complex, thus, a comprehensive assessment is imperative when identify appropriate therapy by well control anemia by blood transfusion resulting less risk of pulmonary hypertension. There was no standardization therapy to these patients, therefore we must continue to rely on stories evidence and small cases scenario.

We should make effort for sustained research to improve best practice in vulnerable individuals. Consequently we recommended for annual monitoring by echocardiogram and cardiac catheterization which indicated for persistent elevation of tricuspid regurgitation jet velocity and advise the family to close follow up to maintain Hb above 9 g/dl and ferritin level of less than 1000 ng/ml.

Conflict of interest

There is no conflict of interest to be announced.

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