Pulmonary Hypertension in Hemoglobinopathies : a mini literature review

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Abstract

Blood transfusion is considered the cornerstone of treatment for patients suffering from haemoglobinopathies such as thalassemia, sickle cell disease, and anemia. It can occur in either acute care or long-term transfusion settings. Major transfusion complications have been reported in patients with hemoglobinopathies, including pulmonary hypertension, which has become a significant cause of mortality and morbidity in these patients. Although the true pathophysiology of pulmonary hypertension in patients with haemoglobinopathies is unknown, severe hemolysis is thought to be the primary cause. Dyspnea, chronic liver disease, iron overload, sleep apnea, and thromboembolism are all symptoms of pulmonary hypertension in patients with haemoglobinopathies following transfusion. There are no specific treatment guidelines for patients with hemoglobinopathy-related pulmonary hypertension. It is critical to maximize primary hemoglobinopathy treatment, correct hypoxia with chronic oxygen use, and treat associated complications like cardiopulmonary conditions. There are two aspects to management in these patients: hemoglobinopathy-specific treatment and pulmonary hypertension-specific treatment. Hemoglobinopathy is treated with blood transfusions, iron chelation, and hydroxyurea, whereas pulmonary hypertension is treated with anticoagulants, diuretics, digoxin, oxygen, and pulmonary hypertension specific vasodilator agents.

Keywords: pulmonary hypertension, heamoglobinopathy, sickle cell disease, thalassemia, treatment.

Introduction

Blood transfusion is known as the transfer of blood from a blood donor to a patient for therapeutic purposes and represents one of the most common therapeutic interventions in hospitalized patients[1,2]. Blood transfusion therapy is frequently used in the supportive care for treatment of anemia ,caused by hemorrhages or various diseases such as hemoglobinopathies[3]. Blood transfusion therapy has been used for patients with hemoglobinopathies expecting that the normal hemoglobin would compensate for the adverse events generated by the deformed hemoglobin. Acute transfusion is generally performed to prevent / reverse severe anemia or as an exchange transfusion for immediate reduction of disease related acute complications . Whereas, chronic transfusions are predominantly used for primary stroke prevention, or to prevent the recurrence of stroke among children with sickle cell disease (SCD) for example, and to reduce recurrent vaso-occlusive crisis (VOC) [4,5]. Even though this therapeutic strategy has shown great impact in expanding patients lifespan and managing such diseases [6], transfusion therapy has been identified as one of the most overused (and inappropriate) therapeutic interventions by national accreditation (Joint Commission) and medical societies, such as the American Board of Internal Medicine [3]. Blood transfusion is accompanied with several possible complication , among them are Hypertension (HTN) and Transfusion Associate Circulatory overload (TACO), iron overload, and Pulmonary hypertension (PHN)[7]. Pulmonary Hypertension is one of the most common complications of blood transfusion. It is characterized by the elevation of pulmonary pressures which may lead to increased pulmonary vascular resistance and in consequence may lead to right ventricular overload, failure and ultimately death [8].Another common complication is TACO , which plays a significant role in transfusion related mortality and is caused by heart failure which consequently leads to circulatory overload following blood transfusions [9].These post transfusion complications, and specifically pulmonary hypertension, are most documented in diseases that require excessive transfusion such as Hemoglobinopathies. Hemoglobinopathies encompass genetic diseases related to the hemoglobin molecule and its role in the circulatory system. These diseases fall into two main categories: thalassemia syndromes and structural hemoglobin variants (abnormal hemoglobin). α-thalassemia and β-thalassemia are the main types of thalassemia and the hemoglobin variant disorders are HbS (Sickle cell disease), HbE and HbC [10]. The pathophysiology however in the development of PHN in these diseases, due to the disease itself or transfusion approach differs among them . The goal of this review is to highlight the correlation between blood transfusions and pulmonary hypertension in the setting of hemoglobinopathies diseases that regularly require transfusions. We will also focus on the mode of diagnosis and treatments available if such consequences occur.

PHN in sickle cell disease

Sickle cell disease (SCD) is one of the most frequent hereditary hematologic diseases in the world, recently recognized as a global public health problem by the World Health Organization [11].It encompasses a group of disorders characterized by the presence of at least one hemoglobin S allele (which is a mutant form of the normal Hb A) and a second hemoglobin which can be either a second HBS allele thus homozygous for HbS (hbSS or sickle cell anemia (SCA) which is the most

severe and common form of SCD, or another *HBB* pathogenic variant resulting in abnormal hemoglobin polymerization or it can be a normal HbA allele (i.e. have HbAS or sickle cell trait, SCT) which is usually benign, but patients may have sickled cells when exposed to very low pressures of oxygen [12,13,14]. Mutant sickle β-globin results from substitution of valine for glutamic acid at its sixth amino acid. The resulting sickle hemoglobin (HbS) polymerizes when the concentration of its deoxygenated form exceeds a critical threshold. Thus, polymerization is governed by local oxygen tension, and promoted by both acidosis (which decreases the affinity of HbS for oxygen) and hyperosmolarity (which increases red blood cell [RBC] hemoglobin [Hb] concentration). Additionally, sickle RBCs exhibit abnormally high adhesion to the endothelium, owing to acquired membrane changes and to retained adhesion receptors on cells such as reticulocytes . This adhesion event slows microvascular transit, thereby enabling the sickling process [15]. This sickling of red blood cells (RBCs) makes the cell less deformable and more fragile and thus prone to lysis [16]. Persistent intravascular hemolysis over decades leads to chronic vasculopathy, with ∼10% of SCD patients developing pulmonary hypertension, particularly those with the homozygous genotype [17]. PHN has been documented in SCD patients either caused by the disease itself as a result of hemolysis, low nitric oxide (NO) bioavailability, and hypercoagulable state , or due to post transfusion complications such as iron overload. The hemolysis caused the disease itself is central to the development of PHN .Hemolysis has been a focus of the pathophysiology in SCD in part because it directly leads to a decline in NO bioavailability. NO is key to many processes in the lung, including vasodilation. NO binds soluble guanylate cyclase and converts guanosine-5'-triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) so that relaxation of vascular smooth muscle and vasodilation occurs. Low NO bioavailability leads to an imbalance in endothelial physiology that favors pulmonary vasoconstriction and hypercoagulability, and ultimately, PHN . Intravascular hemolysis leads to both increased consumption and decreased production of nitric oxide . Free hemoglobin released into the plasma from lysed erythrocytes directly scavenges NO. In addition to that, the released Heme has prooxidant, cytotoxic and inflammatory effects. In SCD, extracellular heme has been found to activate the innate immune response and trigger the release of neutrophil extracellular traps (NETs) that promote lung injury. Meanwhile, phosphatidylserine is expressed on the cell surface of sickled erythrocytes and this promotes adhesion to the vascular endothelium, leading to sequestration of erythrocytes in the peripheral blood vessels and thus favoring pulmonary hypertension in SCD patients [18]. Transfusions are a key component of managing SCD associated complications , and it is estimated that as much as 42% of adults with SCD receive long-term transfusion [19]. The physiological expectation for transfusion therapy in SCD is that increasing Hb levels will improve oxygen (O_2) delivery to tissues, lowering intravascular haemolytic and vaso-occlusive events. Where the heart is concerned, stroke volume and stroke work are reduced, which decreases cardiac wall stress, increases cardiopulmonary reserve, lowers pulmonary pressures and reduces risk for right heart failure. Arterial oxygen tension (PaO2) also increases along with improvement in exercise capacity. The clinical evidence for efficacy of transfusion therapy, however, is limited to observations of decreased vaso-occlusive and acute chest syndrome events and subsequently lowered risk of death with exchange transfusion

therapy. Simple transfusion therapy, when used prophylactically, appears to decrease vaso-occlusive, acute chest syndrome and stroke but may also contribute to iron overload which in turn has been proven to further favor pulmonary hypertension as well [20]. Transfusional Hematochromatosis is one of the main complications of transfusion therapy in sickle cell disease patients .iron overload typically occurs within 2 years of initiating chronic transfusion therapy or after 10 to 20 pRBC transfusions (w120 mL/kg of pRBC and therefore chronic and repeptitive blood transfusion must be coupled iron chelation to prevent such outcomes [21]. Another common complication of blood transfusion therapy, is Delayed hemolytic transfusion reactions DHTR. DHTR classically occurs after re-exposure to a red cell antigen that the patient had previously been immunized against. The mechanisms of red cell destruction in antibody-negative DHTR have not been elucidated, however hypotheses include hyperactivated macrophages and red cells with increased membrane exposure of phosphatidylserine, its most severe complication is hyperhemolysis, in which hemolysis of bystander autologous cells occurs, leading to a hemoglobin level lower than pre-transfusion levels and often life-threatening anemia [22]. Anemia, in return will favor further development of PHN as previously mentioned [23]. However, it is important to mention that all the previously mentioned complications are rarely seen in the SCT patients since the tendency for HbS to polymerize is highly dependent on the hemoglobin composition in the erythrocyte – mainly the concentration of intracellular HbS, as well as the concentration and type of non S hemoglobins. HbA and HbF present in the cell reduce the concentration of HbS, but HbF additionally has an inhibitory effect on HbS polymerization. Individuals with SCT, who have HbA in excess of HbS (30-40% of the total hemoglobin), do not typically suffer from the effects of sickling and are asymptomatic and do not require blood transfusions [24]. The diagnosis of PHN in patients with SCD can be challenging, but the development of PH appears to increase with increasing age and is a major cause of early death. As PVR or left heart pressures increase, PHN begins to develop. However, it is often not until the right heart begins to fail that patients become symptomatic [25]. Typical symptoms include dyspnea on exertion, pre-syncope and syncope, elevated jugular venous pressure, a loud P_2 heart sound and peripheral edema with weight gain [17,25]. Echocardiography can identify patients at high risk of PHN in individuals with a detectable TRV, however the gold standard for diagnosis of PHN is right heart cardiac catheterization with measure of the pulmonary artery pressure. While the prevalence of an elevated TRV in adults with SCD is 30% , the prevalence of confirmed PHN in adults with SCD based on right heart catheterization is 6-11% [18]. Management of adults with sickle-related pulmonary hypertension is based on anticoagulation for those with thromboembolism; oxygen therapy for those with low oxygen saturation; treatment of left ventricular failure in those with postcapillary pulmonary hypertension; and hydroxyurea or chronic transfusions to raise the hemoglobin concentration, reduce hemolysis, and prevent vaso-occlusive events that cause additional increases in pulmonary pressure [26].

PHN in thalassemia disease

Thalassemia is an autosomal recessive hereditary hemoglobinopathy and the most inherited disease worldwide [27,28]. According to the World Health Organization, patients with thalassemia represent approximately 5% of the world population [27]. Thalassemia refers to disorders associated with defective synthesis of α-globin or β-globin subunits of hemoglobin. Beta thalassemia results from point mutations in the beta-globin gene, in turn, this causes an overload of α chains, which precipitate in red blood cell precursors, leading to their destruction in both bone marrow and peripheral blood [29]. It is divided into three categories based on the zygosity of the beta-gene mutation. A heterozygous mutation (beta-plus thalassemia) results in beta-thalassemia minor in which beta chains are underproduced. It is mild and usually asymptomatic and does not require blood transfusion. Beta thalassemia major is caused by a homozygous mutation (beta-zero thalassemia) of the beta-globin gene, resulting in the total absence of beta chains [30]. In thalassemia major, patients undergo severe anemia (heart failure, fatigue, and cachexia) and require life long transfusions. The level of Hb might be <7 g/dl and this reduction results in bone marrow expansion to compensate the loss of RBCs which led to bone abnormalities, enlargement of spleen and restriction of growth [31]. The condition in between these two types is called beta-thalassemia intermedia with mild to moderate clinical symptoms. It is important to note that patients with two mutated beta hemoglobin genes are usually healthy at birth but disease starts to manifest after 6 months of life when fetal hemoglobin (Hb-gamma) disappears and is replaced by adult Hb [30]. Cardiovascular diseases remain the main cause of mortality in both thalassemia minor and intermediate patients, being responsible for greater than 70% of deaths. Among the cardiovascular diseases, which remain a major cause of morbidity, pulmonary hypertension and arrhythmias are exhibiting increased prevalence [32]. The prevalence of pulmonary hypertension in patients with thalassemia varied from 10% to 60%, which is higher among patients with TI than those patients with TM [33]. Similarly, a study reported that PHN on echocardiography has been described in 40–50% and 10–75% of TI and TM patients, respectively [34]. It has been noticed that prevalence of pulmonary hypertension varies greatly, especially in β-thalassaemia major, and is affected by factors such as advancing age, frequency of transfusions, and history of splenectomy [35] . The development of PHN in thalassemia syndromes is thought to be the result of numerous multifactorial pathogenic mechanisms, which include chronic hemolysis, iron overload either due to increased iron absorption toxicity in TI or frequent transfusion therapy in TM, hypercoagulability, and changes to circulating cells as a consequence of splenectomy [34]. Chronic hemolysis plays a significant role in the pathogenesis of PHN,by resulting in free hemoglobin which inactivates the intrinsic vasodilator NO. Additionally, hemolysis releases arginase, which depletes L-arginine, the substrate for NO synthesis. Decreased NO bioavailability and resistance to NO-dependent vasodilation all favor vascular resistance and consequently PHN develops [35]. A second main etiology of PHN in thalassemia patients is iron overload. Two different mechanisms play a role in iron overload in TM and TI [6]. In thalassemia intermediate, ineffective erythropoiesis contributes

to iron overload. Ineffective erythropoiesis is an increase in erythroid cells which fails to produce a corresponding increase in RBCs. Then, iron absorption is increased but the iron is deposited in the organs rather than generating more erythrocytes. Ineffective erythropoiesis leads to lower hepcidin, the only liver-producing hormone negative controlling ferroportin. Hepcidin is the master regulator of iron. It binds to ferroportin, an iron deliverer, and degrades it into lysosome. Ferroportin controls iron metabolism by expressing in enterocytes, macrophages and parenchymal hepatic cells . In TI, high erythropoietic drive causes decreased hepcidin, which increases hyperabsorption of dietary iron and depletes iron storage in macrophages, resulting in "iron loading anemia". However, frequent blood transfusion is the main source of iron overload in regularly transfused thalassemia major patients, additionally once thalassemia intermediate patients were given regular blood transfusions, they suffer from the same mechanism of iron overload as thalassemia major patients [36]. The need and quantity of transfusions clinically distinguishes the categories of thalassemia mild, intermedia, and major thalassemia [37]. Patients with thalassemia major usually have severe anemia and require blood transfusions before age 2 to survive. However, patients with TI have milder clinical features and usually do not require regular blood transfusion for survival, but may need an occasional blood transfusion in some situations e.g., pregnancy, an operation or infection. Some studies have shown that as time passes by, thalassemia intermediate might become transfusion dependent, usually after age 2. The goal is to maintain Hb at around 9 to 10 mg/dl to give the patients a sense of well being and also to keep a check on erythropoiesis and suppress extramedullary hematopoiesis.however, it has been noticed that patients with severe thalassemia who have a blood transfusion showed a significant capability of iron deposition due to lacking of iron excretory mechanisms from the body [37]. Iron overload increases oxidative stress and endothelial dysfunction,with evidence of these changes occurring very early in life. it is also associated with both right and left cardiac dysfunction through secondary hemochromatosis. Iron overload also has effects on the lungs, with excess hemosiderin deposits in the pulmonary parenchyma resulting in fibrosis, as well as arterial wall stiffening, which can lead to increases in PVR [34]. A recent study performed on the thalassemia patients in Taiwan noticed that Iron-related complications were significantly correlated with a per unit increase in red blood cell transfusion (RBCT) units among patients. Additionally, it also showed an increasing rate in percentage of patients with iron-related complications as the severity of the RBCT unit cohorts increased. This result concluded that the increase in iron-related complications in beta thalassemia patients is likely due to the additional RBCT units rather than the underlying disease [38].

The second main type of thalassemia is alpha thalassemia . Alpha thalassemia is caused by alpha-globin gene deletion which results in reduced or absent production of alpha-globin chains. Alpha globin gene has 4 alleles and disease severity ranges from mild to severe depending on the number of deletions of the alleles. Asymptomatic carriers have a single genetic mutation, while

those individuals with two genetic mutations also have a fairly benign course that rarely necessitates transfusion. Patients with three genetic mutations, termed HgH disease, are often symptomatic, but the clinical course can vary widely from those requiring transfusion only during episodes of severe infection or stressors to individuals requiring chronic transfusion therapy early in life. Finally, the presence of four genetic mutations often results in stillbirth, termed hydrops fetalis, though cases have survived to early childhood with regular transfusions started either in utero or immediately upon delivery, termed Bart's disease. PHN in -thalassemia appears to be an extremely rare complication of this disease. In one study examining pulmonary hemodynamic measurements by echocardiogram in -thalassemia patients, only 3/80 (4%) patients with either HgH or Bart's disease had echocardiographic evidence of PH as defined by a TRV greater than 2.9 m/s.48 In the largest study of HgH patients, out of 198 patients, 13 patients (7%) had TRVs greater than 2.5 m/s as measured by echocardiogram, and only three (2%) of those had TRVs greater than 3.0 m/s [34].

The clinical presentation of pulmonary hypertension is often non-specific, mainly manifesting as dyspnea (particularly on exertion), fatigue, and, in more advanced disease, signs and symptoms of heart failure. Diagnosis and assessment of pulmonary hypertension in thalassemia are similar to that suggested in SCD. It should also consist of 6-min walk test and pro-BNP levels (prognostic markers), echocardiography, and right heart catheterization. Management is directed at hemoglobinopathy-targeted treatment and general supportive therapy. As with SCD, pulmonary hypertension specific therapies have only been tried in small series or case reports. However, chronic transfusion therapy and concomitant chelation therapy has been shown to prevent pulmonary hypertension in both forms of thalassemia . The OPTIMAL CARE study, which observed treatment complications in 584 thalassemia intermedia patients, also demonstrated that transfusion and chelation therapy along with hydroxyurea was protective for pulmonary hypertension, whereas splenectomy was associated with a higher risk of pulmonary embolism and pulmonary hypertension [39].

Signs and symptoms of PHN

Pulmonary hypertension (PHN) has been defined as mPAP ≥ 25 mmHg measured by right heart catheterization (RHC) in the supine position at rest. It affects about 1% of the global population and up to 10% of people over the age of 65. While there are numerous causes of PHN, regardless of the underlying disease, it is almost always associated with worsening symptoms and increased mortality [40]. The symptoms of PH are non-specific and mainly related to progressive right ventricular (RV) dysfunction. Initial symptoms are typically induced by exertion. They include shortness of breath, fatigue, weakness, angina and syncope. Less commonly patients may also describe dry cough and exercise-induced nausea and vomiting [43]. Symptoms are initially more pronounced with exercise or exertion, but as severity progresses, symptoms at rest become more severe. It is important to note that symptoms of PHN can be difficult to distinguish from those of

comorbid conditions such as anemia, asthma, or parenchymal lung disease [34]. Abdominal distension and ankle oedema will develop with progressing RV failure. In some patients the clinical presentation may be related to mechanical complications of PHN and the abnormal distribution of blood flow in the pulmonary vascular bed. These include hemoptysis related to rupture of hypertrophied bronchial arteries, as well as symptoms attributable to pulmonary arterial dilatation such as hoarseness caused by compression of the left recurrent laryngeal nerve, wheeze caused by large airway compression and angina due to myocardial ischemia caused by compression of the left main coronary artery. Significant dilation of the pulmonary artery may result in its rupture or dissection, leading to signs and symptoms of cardiac tamponade. The physical signs of PHN include left parasternal lift, an accentuated pulmonary component of the second heart sound, an RV third heart sound, a pansystolic murmur of tricuspid regurgitation and a diastolic murmur of pulmonary regurgitation. Elevated jugular venous pressure, hepatomegaly, ascites, peripheral oedema and cool extremities characterize patients with advanced disease. Wheeze and crackles are usually absent [43].

Diagnosis of PHN in hemoglobinopathies

PHN in thalassemia and SCD is classified as a class 5 (PHN with unclear and/or multifactorial mechanisms) based on the updated clinical classification of PHN [41]. Hence the importance of assessing PHN in thalassemic patients. To diagnose PHN in thalassemia patients, it is important to assemble the widely recognized diagnostic strategy for pulmonary hypertension and the recommended evaluation of cardiac complications in thalassemia.

Echocardiography is frequently used as a screening tool to identify subjects who are at high risk of pulmonary hypertension, such as thalassemia patients. TR jet velocity (TRV) is the flow of retrograde blood across the tricuspid valve during systole and it estimates right ventricular systolic pressure and correlates with mean pulmonary arterial pressures. An important limitation should be taken into consideration regarding the use of echocardiography instead of cardiac catherization, recent studies showed that it is associated with more false-positive diagnoses of PHN [38]. In β-thalassemia patients, most specialists suggest that a TRV greater than 3.0 m/s in thalassemia patients identifies a population at increased risk of PHN who should undergo RHC, since a threshold of TRV = 3.2 m/s has shown to have a high positive predictive value (93.3%). Another limitation to echocardiography, mainly in situations of high cardiac output, such as the chronic hemolytic anemias, necessitate the direct measurement of pulmonary hemodynamics by RHC to confirm PHN. The same mPAP ≥ 25 mmHg at rest defines PHN on RHC in thalassemic patients [34,42].

High-resolution lung CT, lung ventilation and perfusion scanning, pulmonary function tests, diffusion capacity of the lungs for carbon monoxide can aid in the identification of both restrictive and obstructive defects that are common in thalassemia patients, as well as the diffusing limitations that are frequently associated with PHN [35]. T2 cardiac MRI has been shown to be comparable to echocardiography in determining the risk of PHN in a variety of disease states, and

it is also a reliable tool for determining the degree of iron burden and damage that may exist in chronically transfused individuals. Excessive blood transfusion is associated with iron overload as one of its main consequences that favor the PHN development, thus its severity of iron overload must also be determined in order to determine the effects on end-organ damage, such as cardiomyopathy, and to assess if chelation therapy is needed. Furthermore, because thalassemia is a known hypercoagulable state, a careful assessment for chronic thromboembolic disease is required. Finally, some biomarkers may be helpful in the assessment, among them, N-terminal fragment of pro-brain natriuretic peptide concentration and troponin T levels that mark the presence of a dysfunction in the right heart should be assessed [34].

Therapy of PHN

The overall treatment goal in patients with PHN is achieving a low risk status , which is usually associated with good exercise capacity, good quality of life, good RV function and a low mortality risk [43]. There are no specific guidelines for the management of pulmonary hypertension in thalassemia and SCD patients ; however the most commonly approved approaches include haemoglobinopathy directed therapies, general measures, and supportive therapy whereas specific pulmonary hypertension management is mainly based on data derived from other forms of pulmonary hypertension. Chronic transfusion therapy and concomitant iron chelation therapy prevent pulmonary hypertension in both forms of β thalassaemia as well as SCD. This can be explained by the effect of chronic transfusion in restoring tissue oxygen delivery and suppressing the synthesis of native defective erythrocytes with thrombogenic potential, leading to prevention of haemolysis, hypercoagulability, and chronic tissue hypoxia, which are all pathogenetic mechanisms of pulmonary hypertension in patients with hemoglobinopathies [35]. though, if transfusion was done exclusively alone, this would increase the risk of iron toxicity in patients and further favor pulmonary hypertension prognosis, thus it is mostly done with concomitant iron-chelation therapy .iron chelation therapy , in return, prevents iron overload and oxidative tissue damage, which are both pathogenetic mechanisms of pulmonary hypertension in patients with β thalassaemia [35,44]. Interestingly, in a study PAH was fully avoided in individuals with b-TM who were well-transfused and iron-chelated [45]. However, in another study,56% of TM and 37% of -thalassemia/HbE patients who have received regular blood transfusions and iron chelation therapy show evidence of PAH development, implying that chronic transfusion combined with iron chelation therapy may not be sufficient by themselves to prevent PHN development in these patients[46]. The only known curative approach to TM remains stem cell transplantation (SCT) early in life, which has high success rates exceeding 70% [34]. Other attempts include hydroxyurea therapy, which is recommended a first line therapy in high risk of mortality SCD patients , since it enhances HBF production, modifies the synthesis of defective hemoglobin, reduces thrombocytosis, thus preventing hemolysis and hypercoagulability and therefore demonstrated protection against the development of PHN [34,47].General measures, including immunization against influenza and pneumococcal infections, and supervised exercise rehabilitation avoiding excessive physical activity, are recommended for patients with β thalassaemia and pulmonary hypertension. Some patients might need oxygen administration,

diuretics, digoxin, or other drugs for management of cardiac arrhythmias [35]. Prothrombotic states may also be present, and careful evaluation for thromboembolic disease and appropriate therapy with anticoagulants and/or antiplatelet agents must be considered [34]. Specific medical therapy, including the use of phosphodiesterase-5 inhibitors, endothelin-1 receptor antagonists, and prostacyclin analogues, has been introduced for the management of pulmonary arterial hypertension though its role in patients with haemoglobinopathies remains unclear, and should be considered only in patients with clear haemodynamic characterisation of pre-capillary pulmonary hypertension [35]. The use of endothelin-1 receptor antagonists in a cohort of 14 patients with sickle-cell disease and pulmonary hypertension improved the 6MWT, amino-terminal brain natriuretic peptide serum levels, and echocardiographic findings at 6-month follow up [48]. Sildenafil citrate, a powerful inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase-5 and a selective smooth muscle relaxant, showed encouraging outcomes in small studies in TI (thalassemia intermedia) patients for the treatment of PHT the echocardiographic findings of a patient with thalassaemia intermedia and pulmonary hypertension were normalized after 15 months of treatment with sildenafil [49].

Conclusion

The transfer of blood from a blood donor to a patient for therapeutic purposes is known as blood transfusion. Finally, repetitive blood transfusion is a major cause of pulmonary hypertension in hemoglobinopathies, particularly SCD and Thalassemia. Although blood transfusions are intended to alleviate the symptoms of anemia, their overuse causes increased pulmonary arterial pressure. The increase in pressure with inappropriate blood transfusion frequency in sickle cell disease is primarily due to chronic hemolysis, iron overload, and delayed hemolytic transfusion reaction (DHTR).Similarly, in thalassemia, PHN is caused by chronic hemolysis, hypercoagulability, chronic tissue hypoxia, and iron overload, with the latter increasing as the number of RBCT units increases. Screening for PAH is therefore critical; it can be done using echocardiography, lung CT-scan, and T2 cardiac MRI. PAH should be controlled in hemoglobinopathies by limiting unnecessary transfusions, using a chronic transfusion regimen that reduces RBC hemolysis, and combining it with iron-chelating therapy, which protects against iron toxicity. Other therapies, such as hydroxyurea therapy, pulmonary vasodilators (L-Carnitine), an inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase-5, or a selective smooth muscle relaxant, can be added to improve efficacy functions.

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