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CASE REPORT

Recombinant Human Erythropoietin in Hemolytic Anemia in a Patient With Mechanical Heart Valve

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Introduction

The history of valve replacement surgery began more than a century ago, when Doyen, in 1913, performed the first surgical repair in a stenotic pulmonary valve. Despite all the implemented technology and efforts in recent years, there is no ideal valve replacement to date.[1] The incidence of severe complications in patients with prosthetic heart valves is approximately 3% a year.[2] The main complications include embolism, bleeding, mechanical valve thrombosis, fibrous tissue growth, paravalvular regurgitation, structural deterioration, infective endocarditis, prosthesis-patient mismatch and hemolytic anemia. Specifically, regarding hematological complications, the occurrence of hemolysis after valve replacement ranges from 5 to 15% of the patients[3] and can lead to reoperation in up to 19% of cases.[4]

The main mechanism of hemolysis after valve replacement is mechanical, non-immune and the standard therapy in these cases is of support by prescribing oral iron and folate, as well as blood transfusions. In some patients, recurrent hemolysis refractory to supportive treatment may be an indication for valve replacement.[3] However, with the aging of population, the number of patients at high risk for valve replacement surgery has increased. Thus, it is important to develop new palliative therapies for these individuals.[5]

Keywords

Heart Failure; Heart Valve Prosthesis; Aortic Valve; Mitral Valve; Anemia, Hemolytic; Erythropoietin.

Erythropoietin (EPO) is a hormone produced by the kidney that stimulates red-blood cell production in the bone marrow. It is classically indicated for the treatment of anemia secondary to chronic kidney disease. There are, in the literature, some reports of EPO being used for the treatment of hemolysis caused by heart valve prosthesis, and it is especially useful in patients in whom valve replacement surgery would be contraindicated, or for those that require multiple transfusions.[5]

In this article, we report a case of a patient receiving EPO for the treatment of hemolytic anemia secondary to the presence of mechanical prostheses in the aortic and mitral positions, with mitral paravalvular regurgitation, in whom heart surgery was contraindicated due to advanced heart failure.

Case report

Male patient, 64 years old, with aortic and mitral valve prosthesis due to previous rheumatic fever, was admitted to the Emergency Department of Hospital Universitário Antônio Pedro, Niterói (RJ) due to acute decompensated heart failure (HF). The patient had systemic arterial hypertension, type 2 diabetes, stage-2 chronic kidney disease, pulmonary arterial hypertension and atrial fibrillation as comorbidities. He had already been submitted to three heart valve replacements, always with mechanical prostheses, the first in the 1970s and the last 10 years ago. He regularly used losartan, carvedilol, digoxin, spironolactone, simvastatin, furosemide, metformin and warfarin.

On physical examination, he had pale mucosa, irregular heart rhythm, normal heart sounds, metallic

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"click" in mitral and aortic positions, mid-systolic mitral murmur of moderate intensity, pathological jugular venous distention at 90° and hepatojugular reflux. Laboratory tests are described in Table 1 and in Figure 1 and showed normocytic and hypochromic anemia, with reticulocytosis and blood smear showing schistocytes, in addition to an increase in the lactate dehydrogenase (LDH) enzyme. Blood cultures were collected, with negative results. The chest X-ray showed signs of congestion, cardiomegaly and predominant right pleural effusion. The electrocardiogram showed atrial fibrillation rhythm and ventricular extrasystoles with unspecific alterations of ventricular repolarization. The transthoracic echocardiogram showed biventricular contractile dysfunction; pulmonary hypertension (systolic pulmonary artery pressure estimated at 62 mmHg); severe tricuspid regurgitation, due to annular dilation; normal function aortic prosthesis; mitral prosthesis with a non-constrained opening, with mild regurgitation and the presence of paravalvular reflux (Figure 2); and lack of vegetation.

Table 1
Results of laboratory tests during hospitalization

Exams	Reference values	Admission	Start of erythropoietin and folate		
		Weeks			
		1	3	4	6
Blood cell count, 106 / mm³	4.60-5.4	3.0	3.0	3.0	3.4
Hematocrit,%	42-54	24.1	25.6	26.5	30.5
Hemoglobin, g / dL	14-18	7.2	8.0	8.4	9.6
MCV, μm^3	84-99	80.3	85.9	88.6	90.8
MCH, pg	26-32	24	26.8	28.1	28.6
MCHC g / dl	31.0-36.0	29.9	31.2	31.7	31.5
RDW,%	11-16	22.1	23.6	26.8	29.2
Corrected RDW %	11-16	11.8	13.4	15.8	19.8
Platelets / mm³	150.000-400.000	163.000	143.000	228.000	122.000
Serum iron, mg / dL	50-170	27	43	18	187
Ferritin, ng / dL	26.0-388	34	66	89	86
Transferrin saturation index, %	20-50	8.7	18.2	6.9	62.1
TIBIC, mg / dL	250-450	312	236	262	301
Total bilirubin mg / dL	Up to 1.0	1.59	1.39	1.21	2.03
Direct bilirubin, mg / dL	Up to 0.3	0.88	0.78	0.72	0.93
Indirect bilirubin, mg / dL	Up to 0.7	0.71	0.61	0.49	1.10
HLD U/L	85-227	1204	1222	1314	1596
Folic acid, ng / ml	3-17	15.6	20.7	>24	
Vitamin B12 pg / ml	193-982	405	742	591	
Creatinine, mg / dL	0.7-1.3	1.34	1.21	1.64	1.35
EGFR, ml / min / 1,73 m²	90-120	66.2	77.6	54.7	68.4

MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width; TIBIC: total iron binding capacity; HLD: human lactate dehydrogenase; EGFR: estimated glomerular filtration rate (estimated by MDRD: modification of diet in renal disease).

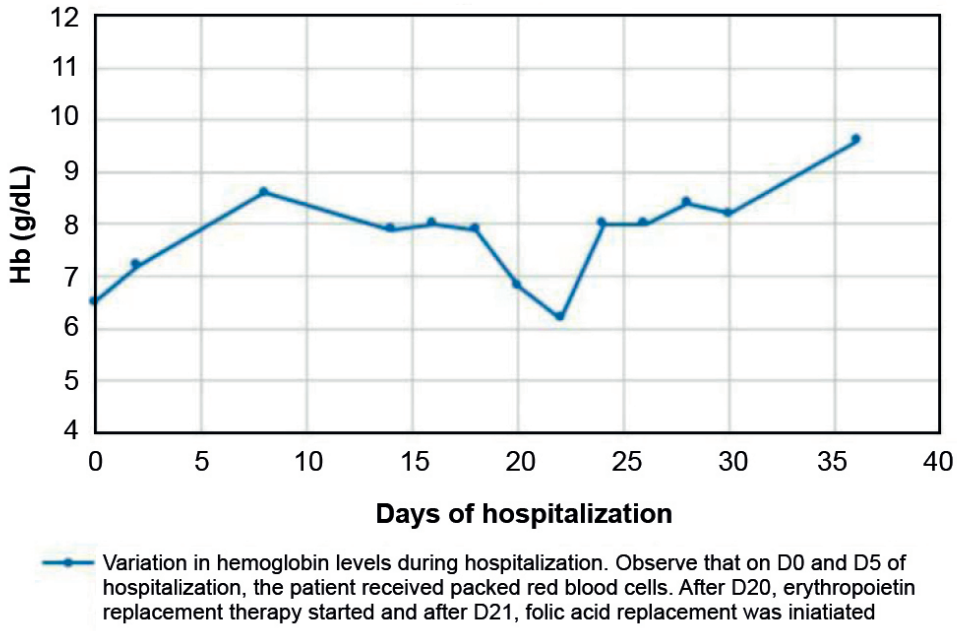

Figure 1
Hemoglobin variation during hospitalization.

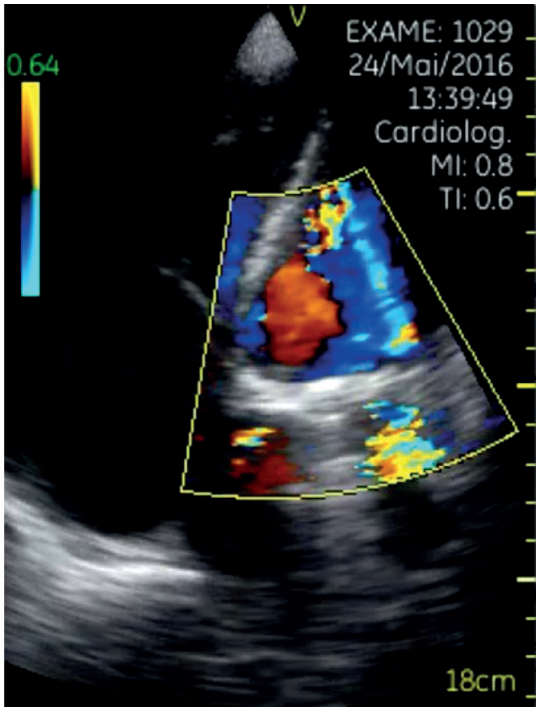

Figure 2
Transthoracic echocardiography showing paravalvular regurgitation.

Due to decompensated heart disease and serum hemoglobin < 7 g/dL, it packed red blood cells were administered and upper digestive endoscopy was performed, which showed no active bleeding signs. Intravenous diuretics were used to manage the congestion. A good clinical response was attained after 2 weeks of treatment.

Despite the HF improvement, the hemoglobin continued to show recurrent serum level reductions. Consequently, we searched for other causes of anemia. The finding of schizocytes in peripheral blood, associated with increased serum HLD, suggested the possibility of hemolysis and treatment with folic acid 5 mg once a day and EPO 4000 IU three times a week was started. The patient showed a progressive increase in hemoglobin and reticulocytes, showing good response to bone marrow stimulation (Figure 1). New transfusions were no longer needed. The patient was discharged after six weeks of hospitalization and is being followed on an outpatient basis.

Discussion

The reported case showed the use of EPO as an adjunctive treatment to iron and folic acid replacement in the management of hemolytic anemia secondary to mechanical heart valve prosthesis. The hemolysis in patients with valvular prosthesis was first described in 1954 by Rose et al., in a patient undergoing surgery for valve replacement using a Prototype type prosthesis and remains a clinical challenge to the present day.[6] The hemolysis is present in most patients undergoing valve replacement using a mechanical prosthesis, although only about 5 to 15% develop clinically relevant hemolytic anemia.[4,5] Several hemolytic anemia mechanisms after mitral valve replacement have been proposed: "whip movement" of interrupted sutures; dehiscence of the valvuloplasty annulus; "overhang" of the paravalvular suture, providing an site impact against circulating red blood cells; no endothelization of sutures or prostatic annulus; and the impact of regurgitation against the left atrial wall.[7]

The conditions that favor hemolysis in a patient with valvular prosthesis are: type of prosthesis, being worse in mechanical ones; number of valve replacements; impact of the regurgitant flow in the left atrium (in case of mitral valve prostheses); and especially the presence of paravalvular regurgitation. It is suggested that, in the current prosthesis models, the main mechanism of hemolysis is the paravalvular regurgitation and the main cause of reflux would be dehiscence of prosthetic sutures. Dehiscence is commonly observed in patients with severe prosthesis calcification or those affected by infection (endocarditis). The degree of paravalvular reflux would not be associated with the severity of hemolysis, but rather to the irregular surface of the paravalvular space and the formation of "collision angles" of the prosthesis to the regurgitant blood flow.[7] In this study, we believe that paravalvular regurgitation was determinant for the hemolysis.

In chronic, nonimmune hemolytic anemia, the depletion of iron stores is a major cause of hemoglobin level decrease. In the reported case, the kinetics of iron showed a ferritin level at the lower limit of normal. Treatment with ferrous sulfate was started, but there was no clinical response. The high HLD and schistocytes in the peripheral blood, in the context of a patient with prosthetic valve, led to the suspicion of intravascular hemolytic component. Intravascular hemolysis, the result of red blood cell fragmentation, results in release of free hemoglobin in plasma, consumption of haptoglobin and formation of schistocytes. Dissimilarly from extravascular hemolytic anemias, in the intravascular type iron deficiency occurs due to hemoglobinuria and hemosiderinuria, which deplete iron stores and transform an initially normocytic anemia into a microcytic one. The depletion of folic acid stores is also a common mechanism in hemolytic anemia, but in our case, serum levels were normal on admission. Despite the unavailability of haptoglobin measurement, the other laboratory markers of hemolysis, in the context of a patient with decompensated HF due to severe anemia, were considered sufficient for us to support the clinical decision of EPO and folic acid administration. The hypothesis of new valve replacement using a bio-prosthesis was ruled out because the patient had advanced heart failure, pulmonary hypertension and had undergone three previous valve replacements.

EPO is a therapeutic option for cases of severe hemolysis and high preoperative risk. Previous studies have described cases of patients with hemolysis after valve replacement requiring multiple blood transfusions until the time when EPO was started.[5,8,9] There have been reports of patients with hemolysis due to mechanical valve prosthesis in which EPO was prescribed, ceasing the need for blood transfusions.[5] Kornowski et al.[10] were the first to describe the successful use of EPO in a 46-year-old patient with mitral mechanical

prosthesis and hemosiderosis after multiple transfusions. Later, other authors, in sporadic case reports, also described the effectiveness of EPO in improving anemia and reducing the need for transfusions, despite the absence of advanced chronic kidney disease.[5,9] However, there are no randomized controlled trials evaluating EPO in this context.

Hemolytic anemia is a common complication in patients with mechanical heart prosthesis. With the increase in the population's survival, cases in elderly patients with multiple replacements and advanced heart failure, will become more frequent. As the valve replacement surgery has a high risk in these scenarios, we need to develop new hemolysis treatment techniques. The administration of EPO, together with iron and folic acid replacement, has shown promising results. It would be important to perform a randomized clinical trial to evaluate its effectiveness in a larger sample.

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Author contributions

Conception and design of the research: Monteiro CA, Mocarzel LOC, Lanzieri PG, Carvalho HC, Verediano KA. Acquisition of data: Monteiro CA, Carvalho HC, Verediano KA, Costa WLB. Analysis and interpretation of the data: Monteiro CA, Mocarzel LOC, Lanzieri PG, Carvalho HC, Verediano KA. Writing of the manuscript:Monteiro CA, Mocarzel LOC, Lanzieri PG, Carvalho HC, Verediano KA. Critical revision of the manuscript for intellectual content: Mocarzel LOC, Lanzieri PG. Performed the echocardiograms of the manuscript: Costa WLB.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

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