Preoperative anemia in cardiovascular surgery patients

Kardiyovasküler cerrahi hastalarında ameliyat öncesi anemi

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Anemia is the most commonly encountered hematological condition during the preoperative evaluation of the cardiovascular surgery patients. Preoperative anemia is associated with an increase in morbidity and mortality in patients who undergo cardiac surgery. In addition, it is the most important determinant of perioperative blood transfusion, with its many risks and side effects. Therefore, determining and treating the reason of preoperative anemia may resolve post-surgical untoward results. Future studies are warranted to determine whether the treatment for anemia administrated before the cardiovascular surgery will resolve postoperative untoward results.

Key words: Anemia/etiology/therapy; blood transfusion; cardiopulmonary bypass/adverse effects; comorbidity; coronary artery bypass/method; Infection/etiology; postoperative complications.

Anemi, kardiyovasküler cerrahi hastalarının ameliyat öncesi değerlendirmelerinde en sık şekilde karşılaşılan hematolojik sorundur. Ameliyat öncesi anemi kardiyak cerrahi uygulanan hastalarda mortalite ve morbidite artışı ile ilişkilidir. Ayrıca birçok risk ve yan etkisi olan ameliyat sırası kan transfüzyonunun en önemli belirleyicisidir. Bu nedenle ameliyat öncesi aneminin nedenini saptamak ve tedavi etmek ameliyat sonrasında ortaya çıkabilecek istenmeyen sonuçları ortadan kaldırabilir. Kardiyovasküler cerrahiden önce anemi tedavisi uygulanmasının, ameliyat sonrasında ortaya çıkan istenmeyen sonuçları ortadan kaldırıp kaldırmayacağının belirlenmesi için gelecekte bu konuda çalışmalar yapılması gerekmektedir.

Anahtar sözcükler: Anemi/etyoloji/tedavi; kan nakli; kardiyopulmoner bypass/yan etkiler; eşlik eden hastalık; koroner arter bypass/yöntem; enfeksiyon/etyoloji; ameliyat sonrası komplikasyonlar.

Coronary artery bypass grafting (CABG) and valvular surgery are among the most commonly performed cardiac operations. Anemia is the most commonly encountered hematological problem during the preoperative evaluation of these patients.[1]

Anemia is the presence of a decrease in the oxygen transport capacity of the blood. As this is a function of the volume of total red blood cells present in the circulation, anemia may also be defined as a decrease in the volume of red blood cells (Erythrocytes). While the measurement of chrome-labeled erythrocytes is the most accurate method to determine the volume of erythrocytes, due to its unpractical nature, hematocrit (Hct) and hemoglobin (Hb) values are used for clinical evaluation. However, it should be noted that when evaluating anemia, Hct and Hb values could be influenced by plasma volume.[2]

For patients undergoing cardiac surgery, the presence of preoperative anemia is associated with an increase of morbidity and mortality and appears as a finding of secondary disease.[3,4] Preoperative anemia is the most important determinant of perioperative blood transfusion that has many risks and side effects,[5] making it important to determine and treat the cause of preoperative anemia.[3] In the study performed by Karski et al.,[6] the reasons of anemia in patients who underwent cardiovascular surgery (CVS) include hospital-induced anemia (37.3%), iron deficiency anemia (29.3%), anemia related to chronic renal failure (10.7%), anemia of chronic disease, folate deficiency and thalassemia. Hospital-induced anemia was diagnosed when the hemoglobin drop was 9 g/L or more between admission to hospital and surgery and hemoglobin on the day of surgery was ≤120 g/L. Possible explanations are blood sampling while in the hospital and blood losses during coronary angiography.

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EVALUATION OF A PATIENT WITH ANEMIA

For patients undergoing cardiovascular surgery, the first step of the evaluation for preoperative anemia should be the medical history and physical examination. When taking the medical history, bleeding symptoms such as menstruation, melena, hematemesis, hemoptysis and hematuria should be cautiously examined. Fatigue, dyspnea, tachycardia and angina, which are compensatory responses of the body and the symptoms associated with anemia, are among the most important findings. Constitutional symptoms of diseases associated with anemia, such as malignancy, renal failure, endocrine diseases, infections and hepatic disease should be observed.

In the medical background of the patient with anemia, previous levels of Hb, treatments for anemia, the presence of blood transfusions and history of splenectomy are important. In the familial history of the patient, bleeding, the presence of hematological diseases, splenectomy and cholelithiasis with early onset should be questioned. The job of the patient, his/her alcohol consumption and all the drugs that he/she uses, including herbal ones, should be examined.

During the physical examination, most commonly seen signs are pallor of skin and mucous membranes, jaundice, findings of bleeding, petechia, purpura, hepatosplenomegaly and lymphadenopathy. Murmurs are frequently observed during the cardiac examination. To determine the source of bleeding, the gastrointestinal system (GIS) should be frequently evaluated.[3]

DIAGNOSIS OF ANEMIA

The laboratory tests performed at baseline are full blood count, peripheral smear examination and reticulocyte count. To evaluate blood loss occurring in the GIS, gaita should be examined and radiological and endoscopic evaluation should be performed. Reticulocyte counts show the erythrocyte production of bone marrow. However, reticulocyte counts should be adjusted by erythropoietin effect in bone marrow and differences seen in Hct. This is calculated by using the reticulocyte production index (RPI). The reticulocyte production index can be calculated as described below:

RPI=(Reticulocyte count x Htc of the patient) / (normal Htc x 1 / adjustment of maturation)

The cases with a RPI below two show the presence of hypeproliferative anemia or a decrease in the response given by bone marrow to anemia (Table 1). In next step, anemia is classified as microcytic, normocytic and macrocytic according to mean corpuscular volume (MCV) measured during the full blood count.

Iron deficiency anemia and thalassemia are the most common causes of microcytic anemia. As laboratory tests for microcytic anemia, serum iron, total iron-binding capacity and ferritin levels are first determined. These tests will be followed by bone marrow biopsy and hemoglobin electrophoresis. In normocytic anemia, acute blood loss should be excluded. Other causes of normocytic anemia include hepatic and renal diseases, iron deficiency anemia and early period of vitamin B12, folate deficiency, dysmorphic anemia, myelodisplastic anemia, aplastic anemia and chronic disease resulting from inflammatory diseases.

For the diagnosis of normocytic anemia, tests for hepatic and renal function and bone marrow biopsy are performed in addition to tests used for the diagnosis of microcytic anemia mentioned above. Macrocytic anemia is classified as megaloblastic and non-megaloblastic anemia. The causes of megaloblastic anemia are deficiency of vitamin B12, folic acid, drugs (anticonvulsants, chemotherapy agents) and myelodysplasia. The causes of non-megaloblastic anemia are alcohol, hepatic diseases and hypothyroidism. Laboratory tests done at baseline are tests for vitamin B12 and folic acid. Further tests include liver function tests and bone marrow biopsy.

The cases with a RPI above two may show an increased response of bone marrow to acute blood loss or hemolysis. As laboratory tests, direct and indirect bilirubin, lactate dehydrogenase level, haptoglobin level and direct and indirect Coombs test should be requested.

Peripheral blood smears may provide important clues about underlying disease. Polychromatosis and basophilic stippling are seen in hemolytic anemia; systotitis is seen in microangiopathic hemolytic anemia and spherocytes are seen in hereditary spherocytosis, autoimmun hemolytic anemia and microangiopathic hemolytic anemia.[3]

EFFECTS OF PREOPERATIVE ANEMIA IN PATIENTS UNDERGOING CARDIOVASCULAR SURGERY

The results of preoperative anemia in CVS patients have been investigated in some studies. In the study performed by Zindrou et al.,[7] which compared 62

Table 1. Hemotocrit associated with maturation

Hematocrit (%)	Adjustment of maturation (n)
36-45	1.0
26-35	1.5
16-25	2.0
≤15	2.5

patients with anemia (Hb ≤10 g/dl) and 2075 patients without anemia (Hb >10 g/dl), patients with anemia showed a three-fold increase in nosocomial deaths.

In the study performed by Cladellas et al.,[8] 42 patients with anemia (Hb ≤12 g/dl) and 159 patients without anemia (Hb >12 g/dl) were compared in terms of nosocomial mortality and morbidity. For the patients with anemia, it was determined that rates of death increased by three-fold and major complications increased by five-fold. In the study performed by Kulier et al.,[4] in 4804 patients with preoperative anemia, a strong correlation was found between cardiac and non-cardiac (cerebral, renal, gastrointestinal etc.) complications. For the hemoglobin concentrations, each decrease by 1 g/dl below 14 g/dl led to an increase in non-cardiac adverse events by 15%.[4]

In the study performed by Carson et al.,[9] it was shown that risk for mortality was increased in patients with a preoperative hemoglobin level below 11 g/dl and that 30-day mortality was 33% in patients with a hemoglobin level below 6 g/dl. In an investigation performed on 1958 patients who underwent CABG, it was observed that 30-day mortality was 33.3% in patients with a preoperative Hb level of 6 g/dl and 1.3% in patients with a preoperative Hb level of 12 g/dl. In numerous clinical studies,[10-12] it was found that during the cardiopulmonary bypass (CPB) period, serious anemia and low oxygen distribution were associated with increased risks for renal failure, stroke and death. Low Hb levels are the independent determinant of both comorbidity and short- and long-term mortality. Low preoperative Hb level is a risk factor for early and late mortality.

Compared to the general population, patients with preoperative anemia showed a worse survival than was expected.[13] For patients with preoperative anemia who underwent CABG, the reason of the low long-term survival rates was not well defined. These patients are more sensitive to anemia because increased heart rate and beat volume, which are compensatory responses occurring secondary to anemia, are restricted.[14] This restricted compensatory response leads to tissue hypoxia, cellular deficiency, organ dysfunction and failure.[15] All these causes result in an increase of mortality during the postoperative period.[13] In a study performed by Shander et al.,[16] it was shown that for preoperative CVS patients, the target Hb level for transfusion (approximately 10 g/dl) should be higher compared to patients without cardiovascular diseases.

TREATMENT FOR PREOPERATIVE ANEMIA

In iron deficiency anemia, the primary reason should be determined and treated. Therefore, the gastrointestinal system should be frequently screened. Iron replacement therapy should be initiated and, if there is no contraindication, treatment with oral iron is preferred. Each 325 mg tablet of ferrous sulphate contains 65 mg elemental iron. The daily recommended amount of elemental iron for adults is 150-200 mg. An increase in reticulocyte count is seen at day 7-10 of treatment. Hemoglobin levels increase by 1 g/dl per 2-3 weeks.

Indications for parenteral iron replacement therapy are inflammatory intestinal disease, celiac disease, intolerance of the patient for oral iron replacement therapy and chemotherapy for cancer. For parenteral iron replacement therapy, sodium ferric gluconate and iron sucrose are used.[17-19]

If the anemia results from a vitamin B12 or folic acid deficiency, it can be easily treated with replacement therapy. In the presence of folate deficiency, the treatment with 1 mg/day is administrated until the resolution of anemia. In the presence of vitamin B12 deficiency, intramuscular treatment with cobalamin is used. Therapeutic doses of cobalamin vary according to severity and symptoms of anemia. It is administrated at a dose of 1000 μg/day or 1000 μg/week. Oral cobalamin is as efficient as intramuscular cobalamin. Reticulocyte counts increase within 3-5 days and Hb levels begin to increase after 10 days.[20,21]

For anemia of chronic disease, chronic renal failure and HIV-infected patients treated with zidovudine and other hematologic diseases, preoperative use of erythropoietin may provide benefits. The use of erythropoietin increases the level of hemoglobin and thereby decreases the need for postoperative blood transfusion.[22,23] If erythropoietin is used, hemoglobin levels should be maintained below the targeted hemoglobin level of 12 g/dl and all the patients treated with erythropoietin should be given prophylaxis against thromboembolism.[24] As some studies showed that erythropoietin increases the growth of tumors, in patients with cancer, the use of erythropoietin should be avoided.[25]

BLOOD TRANSFUSION

Preoperative anemia is the most important determinant of perioperative erythrocyte transfusion that has many risks and side effects.[26,27] The aim of blood transfusion is to increase oxygen delivery. However, increasing oxygen delivery may not lead to an increase in tissue oxygenation or oxygen consumption.[28,29]

In patients who underwent cardiac surgery, it was found that blood transfusion is correlated with increased morbidity and mortality. For patients who received blood transfusions during the CBAG, it was reported that the risk for infections especially pulmonary infections was

increased and the incidence of ischemic events was higher.[30] In acute intensive care patients, limited blood transfusion (when Hb is <7 g/dl, transfusion) and liberal (Hb<10 g/dl) transfusion strategies were compared and the group that received limited blood transfusion showed lower mortality and organ failure.[31] Thereafter, investigators reviewed the results of patients with underlying cardiac disease and saw that a total of 357 patients were not different in terms of mortality but in the liberal group, organ dysfunction was more frequently observed.[32]

The American Society of Anesthesiology recommends transfusion when hemoglobin levels are lower than 6 g/dl. When hemoglobin levels are greater than 10 g/dl, transfusion is rarely required. When hemoglobin levels are between 6-10 g/dl, the decision about transfusion should be based on intravascular volume status, ischemia status of organs, predisposition to insufficient oxygenation and risks for bleeding.[3,33] If there is no ischemic heart disease and the patient is asymptomatic, a hemoglobin level of 7 g/dl may be safely used as the transfusion threshold for the majority of preoperative patients.[3] In humans, the critical Hb/Hct limit which will impair tissue oxygenition is unknown, although a previous study showed that tissue oxygenation was not impaired even at a level of 5 g/dl.[34] For patients with cardiovascular disease, the optimal transfusion threshold is not known. There is no randomized, clinical study to determine it. Transfusion should not be based on hemoglobin level alone, but also on symptoms and clinical findings of the patient.[3]

In sickle cell disease, preoperative transfusion should be administrated, because in this patient group, the perioperative complication rate is 67%. Surgical stress and trauma may increase the formation of sickle cells.[35,36]

A correlation was found between storage time of blood and mortality. A correlation was also found between the age of red blood cells given to patients during CABG and postoperative morbidity-mortality.[37] In a recently published study, data of approximately 6000 patients who underwent open cardiac surgery were reviewed and it was seen that in patients who received transfusion with blood stored for a period of more than two weeks, the incidence of complications such as nosocomial mortality, intubation lasting more than 72 hours and septicemia/sepsis were significantly higher.[38]

The refusal of Jehovah's Witnesses to accept transfusion of blood or blood products under any circumstances presents both moral and ethical challenges to surgeons and anaesthetists undertaking high-risk surgical procedures. Cardiac surgery is often associated with heavy blood loss and high transfusion requirements.[39-41] Preoperative donation and storage of autologous blood, as well as intraoperative blood storage and normovolemic or hypervolemic haemodilution, using crystalloid or artificial colloid solutions are effective in decreasing homologous blood transfusion.[42,43] The use of aprotinin has provided a potential opportunity for improving blood conservation in patients. Aprotinin has convincingly been demonstrated to reduce blood loss during and after CPB, possibly by decreasing CPB-mediated platelet activation and reduction of fibrinolytic activity.[44] The preoperative use of erythropoietin therapy among a group of Jehovah's Witnesses elevated their hemoglobin levels and faciliated autologous blood donation. Yazıcıoğlu et al.[45] reported that erythropoietin therapy helped restore Hct more quickly in patients with severe postoperative anaemia after CABG.

In conclusion, since there is a correlation between preoperative anemia and adverse events seen after cardiac surgery in patients who underwent CVS, determination and treatment of the reasons for preoperative anemia may lessen postoperative adverse events. Treatment of preoperative anemia has low risks but can lead to delays in surgical intervention.[46] Preoperative low hemoglobin levels are a determinant of both comorbidity and short- and long-term mortality. Future studies are warranted to understand whether, in patients who will undergo cardiac surgery, the strategies targeting treatment for preoperative anemia would prevent adverse cardiac events.

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