Effect of anemia on clinical outcomes in patients with coronary artery disease treated with percutaneous coronary intervention

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Abstract

Coexistence of coronary artery disease with anemia is associated with an increased risk of death, myocardial infarction and bleeding complications. Presence of anemia adversely affects the outcomes of percutaneous coronary intervention, in particular in acute coronary intervention (ACS). Incidence of anemia in patients with ACS is relatively high (approx. 19-30%), so hemoglobin levels should be evaluated upon admission, and considered in risk stratification.

Key words: anemia, coronary artery disease, percutaneous coronary intervention

Introduction

In recent years, there has been significant progress in the treatment of coronary artery disease (CAD). Pharmacological developments and myocardial revascularization techniques have led to decreased mortality and improved quality of life. Despite significant progress in its treatment, CAD is still the most common cause of death in middle-aged and elderly individuals. In addition to the well-known risk factors such as age, male gender, smoking, dyslipidemia, and impaired glucose tolerance, increasing importance is being attributed to the role of hematological disorders in CAD, such as low levels of hemoglobin (Hb). According to World Health Organization (WHO), anemia is defined as Hb levels below 13 mg/dl in men and 12 mg/dl in women [1]. The combination of CAD and anemia is a common clinical problem that leads to increased mortality and higher incidence of major adverse cardiac and cerebrovascular events (MACCE). Anemia is one of the most common hematological abnormalities in patients with CAD, occurring in 19-30% of patients with acute coronary syndromes (ACS) [2]. Elderly patients with STEMI have particularly high incidence of anemia which is reported in 10.5% [3] of older patients with myocardial infarction (MI) and 10.5% to 12.8% [4] to 12.8% [5] of patients with ST-segment elevation myocardial infarction (STEMI).

Etiology and pathophysiology of anemia in patients with coronary artery disease

The most common causes of anemia in elderly individuals include the presence of chronic diseases (35%), iron deficiency (15%), blood loss (7%), renal failure, liver disease and endocrine disease (6.5%), myelodysplasia, leukemia (5.5%), vitamin B_{12} and folic acid deficiency (5.5%) [5]. Anemia in the course of chronic disease is associated with stimulation of the immune system, infection, and inflammation. The decrease in Hb leads to reduced oxygen delivery to the myocardium, especially in the presence of significant coronary stenoses [6]. Reduced oxygen delivery leads to compensatory sympathetic stimulation, which increases cardiac output by increasing stroke volume and heart rate. The increased cardiac output contributes to the development of myocardial remodeling and left ventricular hypertrophy.

Characteristics of patients with anemia and acute coronary syndrome

Common characteristics among the population of CAD patients with associated anemia include: female gender [2, 7], advanced age [2, 7-9], hypertension [8], diabetes [7, 8, 10], heart failure (HF) [2, 7, 11-13], tachycardia [2, 7], renal failure [2, 7, 14], lower body mass index (BMI) [7, 11]

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and higher Killip-Kimball class in patient with AMI [11]. These patients are less likely to smoke cigarettes [2, 7] compared with patients with normal Hb levels. Furthermore, these patients frequently have multi-vessel coronary artery disease [8, 13], sudden cardiac arrest [13], indications for intra-aortic balloon pump (IABP) [14], and a history of CV events and revascularization (PCI, CABG) [8]. Less commonly, these patients have MI with ST segment elevation [15], and are less likely to undergo revascularization for MI during hospitalization [2].

Outcomes among patients with coexisting anemia and coronary heart disease

Coexisting anemia is associated with worse outcomes across the spectrum of ACS, HF, and stable CAD treated with primary percutaneous coronary intervention (PCI) or bypass surgery (CABG) [1, 16-19]. Hemoglobin level on admission in patients with acute coronary syndrome (ACS) is an independent risk factor for adverse CV events such as death, MI, and bleeding complications [4, 7, 8, 17]. Several studies indicate the adverse effects of anemia, but there was no clear evaluation of a Hb threshold value that leads to adverse CV events. Sabatine *et al.* [2] completed a meta-analysis of 16 clinical trials, which included a total of 39,922 patients. The goal was to assess the impact of anemia on the occurrence of MACE in 30-day observation in order to identify a threshold value of Hb that increases the risk of adverse outcomes in ACS. This study showed that the relation between the risk of CV events and Hb levels has a reverse J-shaped distribution. It is noteworthy that the value of Hb below which there was an observed increase in MACE differed for STEMI and non-ST-segment elevation ACS (NSTE-ACS) in 30-day observation. In patients with STEMI, when Hb values of 14 g/dl to 15 g/dl were used as the reference, Hb levels below 14 g/dl were associated with an increase in mortality from CV causes for each 1 g/dl decrement in Hb. In patients with NSTE-ACS, when Hb values of 15 g/dl to 16 g/dl were used as the reference, Hb levels below 11 g/dl were associated with an increase in mortality from CV causes, MI, or recurrent ischemia for each 1 g/dl decrement in Hb.

The difference in the Hb thresholds may be due to the pathophysiology of STEMI and NSTE-ACS. In STEMI, abrupt occlusion of coronary vessel reduces the chance of developing collateral circulation. In NSTE-ACS, ischemia may be caused by progressive restriction of blood flow, usually not leading to complete occlusion [2]. Wu *et al.* [20] also observed an increase in 30-day mortality among patients with coexisting anemia and ACS in a retrospective registry including 78,973 patients aged ≥ 65 years, hospitalized for MI. Shock, HF, and death during hospitalization were reported more frequently in patients with low hematocrit (HCT). Furthermore, a blood transfusion at HCT ≤ 30% was associated with decreased 30-day mortality. Another analysis compared the adverse effects of anemia in patients after PCI. The CADILLAC trial [4] enrolled 2,027 patients with AMI who had undergone PCI. Anemia at admission was associated with higher mortality at hospitalization (4.6% vs. 1.1%, $p = 0.0003$), 30-day follow-up (5.8% vs. 1.5%, $p < 0.0001$) and 1-year follow-up (9.4% vs. 3.5%, $p < 0.0001$). Cavusoglu *et al.* [21] assessed the use of anemia as an independent predictor of outcomes in 192 male patients presenting with ACS. At 24 months, the event-free survival was 64% in the group with a hemoglobin level < 13 g/dl compared with 81% in the group with a hemoglobin level > 13 g/dl. Furthermore, Lee *et al.* [8] analyzed data at two points in time, after 30 days and at 1 year post PCI. In comparison to patients with normal Hb levels, patients with anemia reported higher incidences of MACE, higher levels of troponin I, higher levels of CK-MB, and longer hospitalization after PCI. Patients were divided into three groups based on the baseline Hb level: > 12 g/dl, 10-12 g/dl, < 10 g/dl.

The best 1-year survival was observed in patients with Hb > 12 g/dl, and the worst with Hb < 10 g/dl. Notably, another study reported less than a 3-year survival rate in men with Hb ≤ 12.9 g/dl prior to PCI. Ronald *et al.* [13] analyzed the impact of anemia on the results of PCI during hospitalization in 48,851 patients. They concluded that patients with anemia were at higher risk of death, MI, and in-hospital MACCE. Outcomes of the study include gender differences, since death after PCI was more frequent in men and MI after PCI was more common in women. Anemia was an independent factor influencing mortality in men. Mortality and hospitalization rates for patients admitted with MI complicated by HF and low Hb are notably higher over a 3 year follow up period according to the OPTIMAAL trial [9].

It was noted that it is important to evaluate not only anemia upon admission, but also anemia after discharge from hospital, which is also an independent factor affecting mortality. Prognostic value of anemia in patients with STEMI and left ventricular dysfunction was documented in the TRACE study [23], which involved 1,731 patients with LVEF < 35%. Severe anemia concomitant with a decrease in LVEF was associated with higher mortality, particularly in patients with HF.

Bleeding

Bleeding is the most common non-cardiac complication in patients with ACS [8]. Anemia at admission is an independent predictor of bleeding, related and non-related to PCI in patients with ACS including STEMI and NSTE-ACS [4, 24]. The OASIS 5 and 6 trials [7], which enrolled 32,170 patients with ACS, showed an inverse relation between Hb levels at admission and major bleeding risk among STEMI and NSTE-ACS patients. There was a gradual increase in the risk of bleeding and red blood cell transfusion, which was associated with an increased risk of CV events, as Hb level decreased. The ACUITY trial compared

treatment with bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitor in 13,919 patients with ACS [24]. The analysis showed 30-day mortality in patients with bleeding of 7.3% vs. 1.2% in patients without bleeding in bivalirudin to heparin, respectively. Major bleeding was associated with higher 30-day mortality, ischemia, and stent thrombosis compared to patients without major bleeding, and was an independent predictor of 30-day mortality. In the study by Nikolsky *et al.* [4], patients with anemia frequently developed in-hospital hemorrhagic complications (6.2% vs. 2.4%, $p < 0.002$), and had higher rates of blood product transfusions (13.1% vs. 3.1%, $p < 0.0001$). Choosing the best vascular approach during PCI can significantly reduce the risk of bleeding. A radial approach reduced the incidence of blood transfusion by half and lowered the 30-day and 1-year mortality [25]. The European Society of Cardiology (ESC) Guidelines on diagnosis and treatment of NSTE-ACS recommended a blood transfusion in case of compromised hemodynamic status or haematocrit to HCT < 25% or Hb level < 7 g/dl [26].

Antiplatelet therapy and intervention

Interventional treatment in ACS is rarely practiced in patients with low Hb levels [7]. When selecting strategies, physicians should pay particular attention to the need for dual anti-platelet therapy (DAPT) after PCI. However, despite the favorable results observed with the use of DAPT after PCI, for the prevention of stent thrombosis, DAPT is unfortunately also associated with an increased risk of major and minor bleeding compared to single agent therapy [27]. Another important issue is selection of the appropriate stent during PCI in patients with anemia. The recent registry of Shishehbor *et al.* demonstrated that the use of drug-eluting stents is beneficial in term of MACE reduction in patients with mild-to-moderate anemia and reduced the mortality in comparison to bare metal stents regardless of the Hb levels [28].

Conclusions

The coexistence of CAD with anemia is associated with an increased risk of death, MI and bleeding complications. Presence of anemia adversely affects the outcomes of PCI, in particular in ACS. Incidence of anemia in patients with ACS is relatively high (approx. 15-20%), so Hb levels should be evaluated upon admission, and considered in risk stratification.

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