Anemia in Acute Coronary Syndrome: An Overview

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Abstract

Anemia is very common in patients with cardiovascular diseases. It has been shown that anemia is an independent risk factor for cardiovascular events in general population and in patients of heart failure and acute coronary syndrome (ACS). Various randomized trials have shown prevalence of anemia to be 10 to 43% in patients with ACS. The cardiac remodeling in ACS patients results in left ventricular dilation, which further increases myocardial wall stress. In the presence of anemia, this exacerbates ischemia and enhances myocardial necrosis and fibrosis and ultimately the prognosis. At present, modality of treatment of anemia in ACS patients is less established except blood transfusion. Anemia at admission may have both short- and long-term worse prognosis. Restrictive strategy of blood transfusion, as shown by REALITY trial, may have at least short-term beneficial effect. Due attention should also be given to hospital-acquired anemia (HAA) and anemia developing later, that is, after discharge from hospital. Intravenous iron therapy may be the future therapeutic option, as evidenced by its beneficial effect in treatment of heart failure with anemia.

Keywords
- Acute Coronary Syndrome
- anemia
- blood transfusion

Introduction

Anemia is very much prevalent in general population and also in patients with cardiovascular diseases. It is associated with both short- and long-term worse prognosis in patients of acute coronary syndrome (ACS). Anemia is also associated with increased prevalence of other comorbidities in patients of ACS at index hospitalization.[1–5] Therefore, it is thought to be a marker of the disease severity rather than the cause of severity of illness. In patients of ACS, anemia may be present at the time of presentation or may develop during hospitalization or after discharge from hospital. The causes of anemia are many, like inadequate erythropoietin due to primary bone marrow malfunction, renal failure causing reduced synthesis of erythropoietin, or due to hemodilution in the setting of heart failure in ACS.[6] Gastrointestinal bleeding due to use of antiplatelet drugs like aspirin and clopidogrel may be an important cause of anemia in ACS.

Nutritional deficiency like iron, vitamin B_{12}, and folic acid are important causes of anemia in patients of ACS, mostly in the elderly population.

Anemia should be corrected to provide adequate O_2 supply to the jeopardized myocardium at the earliest. This restores myocardial viability along with the guideline-directed medical treatment. Complications like bleeding following treatment with antiplatelets, anticoagulants, and thrombolytic agents may complicate the situation, more so in presence of anemia. The aim and objective of this article is to discuss about the epidemiology, pathophysiology, prognosis, and management strategy in patients with ACS.

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Definition of Anemia

Accurate definition of anemia involves absolute decrease of red blood cell (RBC) mass determined by radiolabeled blood volume analysis.[7] But in clinical practice, parameters like Hb % and hematocrit (Hct) are used to diagnose anemia. As per the 1968 WHO group report, anemia is diagnosed with Hb % < 13g/dl in adult men and < 12g/dl in adult nonpregnant women.[8]

Clinical Determinants of Hb Levels

Various workers have worked on normal Hb% level in their study population. Normal Hb% level may vary according to age, sex, and race. People of African ancestry have at least 0.5 g/dl lower Hb% compared to Caucasians. Elderly people (> 60 years) have lower Hb% compared to younger adults.[9] In one study, anemia was present in 43% of elderly patients admitted for acute heart failure.[10] So, anemia may be a marker and not a cause of an underlying disease state in elderly population. Anemia in elderly patients should be evaluated properly and corrected whenever possible.[11] Hemodilution may be the cause of anemia in patients of ACS with heart failure. This may be found in as high as 40% to 46% of patients when determined accurately by measurement of RBC mass relative to plasma volume using 131 tagged albumin.[7,12]

Epidemiology of Anemia in ACS

Anemia in ACS may be multifactorial. It may be existing prior to hospitalization for ACS. Anemia may develop during hospitalization, that is, HAA or may appear after discharge, mostly due to adverse effect of drugs, that is, antiplatelets or anticoagulants.

On- Admission Anemia:-

Anemia on admission is found to be associated with adverse outcome on long-term follow up. The prevalence of anemia was clinically significant in the ACS patients of MINAP registry in the UK. Anemic patients were older, had multiple comorbidities, and were less likely to receive guideline-directed medical treatment. Anemia was also independently associated with mortality.

Hospital Acquired Anemia (HAA)

In the study of Salisbury et al,[13] the prevalence of HAA was 57%. Mild anemia (Hb > 11 g/dl) was present in 37% of patients. Moderate HAA (Hb 9–11g/dl) and severe HAA (Hb < 9 g/ dl) were present in 15% and 5% patients, respectively. In-hospital determinants of HAA were almost same as those present on admission like age, female sex, cardiogenic shock, acute renal failure, chronic kidney disease (CKD), and extensive use of antiplatelets and anticoagulants.

In-hospital mortality due to HAA was according to its severity. It was with odds ratio (OR) of 1.38 (95% confidence interval [CI]: 1.10–1.73) in mild-to-moderate HAA and OR of 3.39 (95% CI 2.59–4.44) in severe HAA.[13] One-year mortality and cardiovascular morbidity were also higher in one study.[14]

New Onset Anemia Postdischarge

New onset anemia is defined as decrease of Hb at least 0.5 g/dl compared to hospital discharge value[15] In patient of ACS, whose HAA improved overtime had similar long-term outcome, that is, all-cause mortality and rehospitalization in acute heart failure as compared to those having no anemia at admission (hazard ration [HR] 0.8, 95% CI: 0.5–1.3). Conversely, there was increased trend in patient with persistent (HR 1.8, 95% CI: 1.2–2.5) or new onset (HR 1.9, 95% CI: 1.1–3.3) anemia.[15]

Pathophysiology of Anemia in ACS

The concept, "anemia of inflammation" may be the appropriate term in patients of ACS. It is reflection of the systemic inflammatory response syndrome (SIRS). Cytokines like interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)α, interferon (IFN)ϒ and transforming growth factor (TGF)β play major roles in pathogenesis of anemia in ACS (►**Table 1**). Mild anemia in ACS may be due to chronic inflammation, that is, anemia of chronic disease (ACD).[16]

The study by Mamas et al[17] showed anemia to be associated with several other preexisting risk factors in patients with ACS, that is, smoking, hyperlipidemia, previous myocardial infarction, previous heart failure, previous stroke, previous vascular disease, diabetes mellitus, renal disease, and chronic obstructive pulmonary disease.

Moderate anemia is associated with severe RBC dysfunction and reduced nitric oxide (NO) in blood. Vascular and cardiac nitric oxide synthase (eNOS) are also essential for the cardiocirculatory adaptation to anemia. So vascular and cardiac eNOS should be upregulated to compensate for reduced circulating NO in anemia. RBC dysfunction with eNos dysfunction may adversely affect the outcome in ACS. But endothelial dysfunction, which is associated with various comorbidities along with anemia, might contribute to left ventricular (LV) dysfunction in ACS. Patients with ACS along with diabetes and CKD (III-V) have the worst prognosis when anemia is coexisting. It doubles the 10-year mortality in these patients.[18]

Table 1 Cytokine-mediated inflammatory response in ACS (IL-1, IL-6, TNFα, IFNϒ, TGFβ)

a. Reduced half-life of RBC
b. Bioavailability of iron is reduced, so hemopoiesis is reduced
c. Reduced erythropoietin production

Abbreviations: ACS, acute coronary syndrome; RBC, red blood cell.

Iron Deficiency Anemia in ACS

The clinical significance of iron deficiency anemia in ACS patients is unclear. There is definite link between hypoxia, myocardial ischemia, and iron metabolism. Iron has protective immunomodulatory effect on macrophages, helps in healing of infarct myocardium, and improves global LV remodeling in cases of ACS.[19]

Treatment of Anemia in ACS

The treatment options for anemia in ACS are limited. The CONCORDANCE database of Australian ACS population shows anaemic patients with ACS are less likely to undergo invasive and thrombolytic therapy in view of anticipation of bleeding complications.

The preventive strategy to avoid bleeding compromises the guideline-directed medical treatment. These patients are less likely to receive dual antiplatelet therapy and anticoagulation. STEMI (ST-segment elevation myocardial infarction) patients are less likely to get thrombolysis or primary percutaneous intervention (PPCI). In-hospital complication of reinfarction, heart failure, and renal failure are common in anemic patients.[20]

Role of PRBC in Anemia of ACS

Theoretically, RBC transfusion looks promising by increasing O2 delivery to vulnerable myocardium, thereby reducing ischaemic symptoms. The beneficial effect of packed RBC (PRBC) transfusion may be counterbalanced by reduced O_2 delivery, due to rapid depletion of red cell NO content during storage. The increase in Hct also increases blood viscosity, which causes slugging of capillaries and reduces delivery of O_2 to myocardium.[21] Other complications related to PRBC transfusion are circulatory overload, immune-mediated transfusion reaction, and transfusion-related acute lung injury.[22]

There are two strategies of PRBC transfusion in patients of ACS: restrictive and liberal transfusion (►**Table 2**).

There are limited number of studies focusing on benefits of PRBC transfusion in ACS patients.

The TRICC trial by Hobert et al showed higher mortality among patients with restrictive transfusion than liberal one (26% vs. 21%; *p*-value 0.03).[23]

The CRUSADE registry by Alexander et al involving 44,242 non-ST-segment elevation (NSTE) ACS patients showed RBC transfusion had favorable outcome in patients with hematocrit of $< 24\%$ but higher mortality in patients with Hct $> 30\%$.[24]

Table 2 Restrictive versus liberal transfusion

Type of transfusion threshold	Restrictive	Liberal
	Transfusion is not indicated until Hb level is $<$ 7 to 8 g/dl.	Transfusion is not indicated until Hb level is $<$ 9 to 10 g/dl.

The pilot trial, that is, CRIT by Cooper et al categorized patients of ACS to conservative group with Hct $< 24\%$ with a target Hct 24 to 27% and liberal group with Hct $<30\%$ with a target Hct of 30 to 33%. A higher rate of primary endpoint, that is, composite of in-hospital death, recurrent AMI, or new-onset or worsening heart failure in liberally transfused group was found compared to conservative group (38% vs. 13%; $p = 0.046$).[25] The difference was mainly due to higher incidence of new or worsening heart failure. NICE guidelines stated that the optimal transfusion threshold for patients with ongoing ACS should be 8 to 10 g/dl.[26]

American Association of Blood Bank guidelines states that restrictive RBC transfusion threshold cannot be applied to ACS patients who are not hemodynamically stable.[27]

REALITY trial was the randomized trial of transfusion and strategies in patients with MI and anemia. It showed that a restrictive PRBC transfusion strategy (transfusion for Hb < 8 g/dl, goal Hb 8–10 g/dl) is noninferior to a more liberal strategy (transfusion for Hb < 10 g/dl, goal Hb > 11 g/dl).[28] Total cost toward PRBC transfusion was also less in view of limited availability in presence of increased demand in clinical practice. Incidence of infection (0% vs. 1.5% $p = 0.03$) and acute lung injury (0.3% vs. 2.2%; $p = 0.03$) were less in restrictive strategy group.

Very often, anemia in ACS is associated with other comorbidities like heart failure and chronic renal failure. Intravenous iron therapy may be the option to treat these patients. Iron therapy may improve exercise tolerance (6-minute walk time) and symptomatic New York Heart Association (NYHA) class.[29,30] It may have immunomodulatory activity and may increase the risk of infection.[31]

In view of paucity of evidence based on randomized controlled trials, RBC transfusion should be restricted to patients with Hb level < 8.0 g/dl and better avoided when Hb level is > 10 g/dl. In patients with Hb level between 8 to 10 g/dl, RBC transfusion should be prioritized to individual patients, as the clinical situation demands.

Role of Erythropoietin in Anemia of ACS

Various experimental models have shown that the hematopoietic hormone erythropoietin (Epo) produced by kidney in response of hypoxia has cardioprotective action.[32] It stimulates hematopoiesis and promotes neovascularization and angiogenesis by mobilization of endothelial progenitor cells.[33,34] It also has anti-inflammatory, antioxidative, and antiapoptotic activities.[35,36]

However, the Regeneration of Vital myocardium in ST-Segment Elevation Myocardial infarction by Erythropoietin (REVIVAL)-3 trial showed short-term use of intravenous erythropoietin (Epoetin beta) in PCI-treated STEMI patients did not improve clinical long-term prognosis. Rather the Reduction of infarct Expansion and Ventricular remodeling with Erythropoietin After Large myocardial infarction (REVEAL) study showed that there was an increasing trend for risk of death, MI, and stroke associated with Epo therapy.[37,38]

Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) trial. Treatment with darbepoetin alfa did not improve clinical outcome in symptomatic heart failure

patients with anemia as compared to placebo. Rather, thrombotic complications including stroke were higher in the darbepoetin alfa group.

The real-world scenario from CONCORDANCE registry of Australia: The ACS patients having anemia were thrombolysed less frequently than nonanemic patients (22% vs. 33%; $p < 0001$) and primary PCI was less common (45% vs. 51%, $p = 0.033$). In subgroup of ACS patients, that is, STEMI, NON-STEMI, and unstable angina, anemic patients had less coronary angiography (63% vs. 86%; $p < 0.0001$), and PCI (30% vs. 52%; $p < 0.0001$) was less in anemic patients. Use of antiplatelet agents, more so the potent ones like prasugrel (2% vs. 5%; $p < 0.0001$) and ticagrelor (11% vs. 20%; $p < 0.0001$), was less in anemic patients. Anticoagulation with heparin, either unfractionated or low-molecular weight ones, was less commonly used in anemic patients (82% vs. 88%; $p < 0.0001$).

Anemia was associated with increased incidence of cardiogenic shock (5% vs. 2%; $p < 0.0001$), recurrent ischemia (13% vs. 8%), reinfarction (4% vs. 2%; $p < 0.0001$), and death from all causes (7% vs. 3%; $p < 0.0001$). So, anemia per se and in collaboration with other risk factors like diabetes mellitus (DM) and CKD play an important role in management of ACS. The bleeding complications following therapy with antiplatelets, anticoagulants, and thrombolytic agents complicates the overall outcome in patients of ACS having anemia. ACS patients having anemia on admission or developing it during hospitalization may not be given antiplatelets and anticoagulants. The patients undergoing PCI having bleeding subsequently are very much at risk of stent thrombosis, due to withdrawal of antiplatelets and may have fatal outcome.

Prognosis of Anemia in ACS

Moderate-to-severe anemia may have short- and long-term worse prognosis in patients of ACS. These patients may not receive guideline-directed medical treatment. But judicious use of drugs and proper selection of patients for interventional procedures may avert the bleeding complications and the ultimate prognosis. In the UK MINAP registry comprising a cohort of 422,855 patients with ACS, angiography conducted with anaemic and nonanemic group was similar. The impact of anemia on mortality was independent and almost comparable across the ACS spectrum.[17] The data from Biennial Israeli ACS registry (ACSIS) has shown that universal approach by radial PCI has reduced the in-hospital bleeding complications.[39] More selective use of heparin and glycoprotein (GP IIb/IIIa) receptor blockers have contributed to this also.

Conclusion

Anemia is very much prevalent in significant number of ACS patients and is associated with both short- and long-term prognosis including mortality. However, there is still uncertainty, as to whether anemia is a marker of underlying severity of disease or has a direct effect on prognosis in ACS. Till now, only PRBC transfusion is the treatment of choice for anemia with Hb < 8 g/dl, except for hemodynamically unstable ACS patients, who could benefit from Hb level between 8 and 10 g/dl. But it is not free from complications.

In ACS patients, assessment of severity of anemia and its management should be done with judicious use of drugs, which may likely cause bleeding and further worsen the clinical condition. PCI, preferably by radial access, may lessen further deterioration of anemia due to bleeding. Intravenous iron may be the new therapeutic option for management of anemia in patients of ACS.

Conflict of Interest
None declared.

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