Erythropoietin in cardiac ischemia

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Chapter 7

Hemoglobin levels and 30-day mortality in patients after myocardial infarction

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Abstract

Background: Anemia is an independent risk factor for cardiovascular (CV) outcomes in patients with coronary artery disease and heart failure. However, the effect of hemoglobin levels on short-term CV mortality in patients with acute myocardial infarction (MI) remains unclear.
Methods: In a retrospective study we analyzed 1841 consecutive patients admitted with the diagnosis of acute MI. The primary end-point of the study was 30-day mortality. Patients were categorized according to the hemoglobin level on admission (10 g/dl or less, or greater than 10 g/dl).
Results: The overall 30-day mortality was 10.3%. The mortality was 21.6% in patients with hemoglobin levels on admission ≤10 g/dl and 9.3% in patients with hemoglobin levels >10 g/dl ($p<0.001$). Multivariate logistic regression analysis showed, that lower hemoglobin concentration is an independent predictor of 30-day mortality, when adjusted for other risk factors (HR 1.76, CI 1.08-2.85; $p=0.02$).
Conclusions: Lower levels of hemoglobin are associated with higher short-term mortality in patients with acute MI. Specific therapeutic strategies in anemic patients with MI should be further considered.

Introduction

Anemia is common in patients admitted to the cardiac intensive care unit ([1]). Although critically-ill patients are able to tolerate low levels of hemoglobin ([2]), presence of cardiovascular (CV) disease significantly increases the risk of anemia ([3]). Two large observational studies in patients with CV disease showed that lower preoperative hemoglobin levels were associated with an impaired survival following general surgery ([4]) and coronary artery bypass surgery ([5]). In both studies patients with preoperative hemoglobin levels lower than 10 g/dl had a significantly greater risk of in-hospital mortality.
Recently, two studies addressed the effect of anemia on longer-term survival in patients with established coronary artery disease (CAD). Reinecke et al. ([6]) showed that anemia is associated with reduced survival in patients with CAD after elective percutaneous coronary intervention. Al Falluji et al. ([7]) evaluated the effect of anemia on 1-year mortality in patients after myocardial infarction (MI) and concluded that anemia has no direct significant effect on survival. However, exact hemoglobin levels, as well as renal function of the patients were not analyzed in this study. Anemia is independently associated with increased risk of death during follow-up after MI in patients with renal insufficiency ([8]). In a large retrospective study, blood transfusion in elderly patients with myocardial infarction and hematocrit value below 30% was associated with reduced 30-day mortality ([9]).
Anemia is also an independent predictor of poor outcome in patients with chronic heart failure ([10;11]).
However, there are limited data on the short-term prognostic importance of anemia in patients who present with an acute MI. The aim of our study was to establish the relation between hemoglobin levels and 30-day mortality in patients with acute MI.

Table 1. Baseline characteristics

Variable	Total population (n=1769)	Hb › 10 g/dl (n= 1635)	Hb ≤10 g/dl (n= 134)	p-value
Age	62.2±0.3	61.9±0.3	67.0±1.0	‹0.001
Sex (% male)	73.1	74.6	54.5	‹0.001
Serum-creatinine (µmol/l)	107±2	104±2	138±11	‹0.001
Hemoglobin (g/dl)	12.9±0.04	13.2±0.04	9.2±0.06	-
Peak CK total (IU/l)	1525±33	1535±33	1400±143	0.36

Methods

Patients and data collection

The study population was selected from patients admitted to the coronary care unit with the diagnosis of acute myocardial infarction, between 1. January 1991 and 31. December 2003. All patients diagnosed with acute MI according to ESC and ACC criteria ([12]), who additionally developed peak creatinine kinase (CK) plasma levels above 500 IU/l during the first 96-hours of hospitalization, were included. We obtained and entered into database, data about age, sex, peak CK levels, serum creatinine levels and hemoglobin levels measured before the start of the therapy. The primary end-point of the study was 30-day mortality.

Statistical analysis

Data are given as mean ± SEM and as frequencies for categorical variables. Patients were divided into two groups: with hemoglobin concentration of 10 g/dl or less and patients with hemoglobin concentration greater than 10 g/dl. This cut-off value for hemoglobin concentration was chosen in line with previously published studies ([4;5]). Differences in basic clinical characteristics between the groups were tested by t-test for continuous variables and by chi-square test for categorical variables.

Multivariate logistic regression analysis was performed with the use of Wald backward analysis. Continuous variables were dichotomized according to the median value. Hazard ratios (HR) with 95% confidence intervals (CI) demonstrate the risk of death. All reported probability values were 2-tailed, and a p-value <0.05 was considered statistically significant. For all statistical analysis SPSS version 11.0 was used.

Results

Patient population

Between 1. January 1991 and 31. December 2003, 1841 patients were admitted to the coronary care unit of our institution with the diagnosis of acute myocardial infarction and peak CK-total concentration above 500 IU/l. Due to missing hemoglobin values on admission in 72 patients, 1769 were included in the following analysis. These patients were divided ac-

Table 2. Multivariate predictors of 30-day mortality

	HR	CI	P
Hb (≤10 g/dl)	1.76	1.08-2.85	0.02
Age (› 63.5)	4.63	3.02-7.10	‹0.001
Sex (female)	2.00	1.41-2.84	‹0.001
Serum creatinine level (›92 µmol/l)	3.34	2.27-4.93	‹0.001

cording to the level of hemoglobin into 2 groups: with hemoglobin concentration of 10 g/dl or less (n=134) and patients with hemoglobin concentration greater than 10 g/dl (n=1635). Baseline characteristics of both groups are given in table 1. Significant differences were found between the groups regarding age, sex and serum creatinine concentration.

Predictors of mortality

The overall 30-day mortality was 10.3%. The crude mortality rate was more than two times higher among patients with hemoglobin values of 10 g/dl or less (29 patients, 21.6%) than among those with higher hemoglobin concentration (153 patients, 9.3%; p<0.001).

In a multivariate logistic regression analysis, low levels of hemoglobin remained an independent predictor of 30-day mortality, even after adjusted for gender, age and serum creatinine concentration (hazard ratio 1.76, 95% confidence interval 1.08-2.85; p=0.02; table 2).

When the patients were divided in 4 subgroups with regard to hemoglobin concentration (<8 g/dl, 8-10 g/dl, 10-12 g/dl and >12 g/dl) a continuous trend towards lower mortality was present with increasing hemoglobin values (Fig.1).

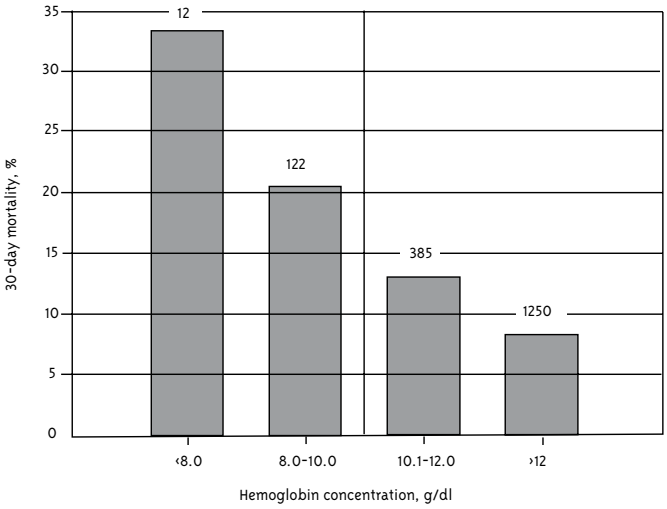
Discussion

In our study, lower hemoglobin concentrations are associated with higher mortality in patients with acute myocardial infarction. We found a statistically significant increase in 30-day mortality in patients presenting with hemoglobin concentrations lower than 10 g/dl. Since other covariates in our analysis (age, sex, renal function) were stronger predictors of survival, hemoglobin levels to a certain degree reflect also other co-morbidities or disease states. Nevertheless, even after adjustment for these variables low hemoglobin levels remained significantly related to 30-day mortality.

Our data support the study by Zindrou et al. ([5]) who showed higher in-hospital mortality in anemic patients after coronary bypass surgery. In contrast, Reinecke et al. ([6]) did not observe an effect of hemoglobin concentration on in-hospital mortality in patients after elective percutaneous coronary intervention. This could be explained by greater extent of ischemia and worse hemodynamic status in patients with acute MI/ or undergoing bypass surgery.

There are several potential mechanisms by which anemia may worsen the prognosis of patients with acute MI. Although the resting human heart can withstand acute severe isovolemic anemia as low as 5.0 g/dl ([13]), CV disease significantly impairs the heart's ability to tolerate low levels of hemoglobin ([4]).

Figure.1. Crude 30-day mortality (in %) in patients after acute MI. Both groups (Hb higher than 10 g/dl and lower than 10 g/dl) were subdivided into 2 subgroups. At the top of each column, the number of patients in the subgroup is noted.



Anemia causes hypoxia-induced vasodilatation leading to increased sympathetic activity and cardiac output. This mechanism decreases coronary reserve ([14]), which is already limited in patients with CAD because of high extraction rate of oxygen in the cardiac circulation ([1]). Manifestation of myocardial ischemia may thus occur with only mild anemia (hematocrit 20-30%) ([15]). Elevated sympathetic activity was also repeatedly associated with worse outcome after acute MI ([16]). In the long-term, these alterations lead to gradual development of cardiac enlargement and LV hypertrophy ([17]), causing higher oxygen consumption and aggravating ischemia.

Conversely, markedly elevated hemoglobin levels also have been associated with worse CV prognosis. High blood viscosity and increased thrombus formation ([18]) have been implicated as causative factors. Some studies have also suggested protective role of iron depletion and thus iron deficiency anemia in CAD development ([19]). Lower levels of redox-active iron may decrease the oxidative stress and thus attenuate endothelial dysfunction ([20]).

Studies in the general population ([21]) and recently also in patients with CAD ([6]) suggested J/U shaped relationship between levels of hemoglobin and CV morbidity and mortality. Association of high hematocrit and CV disease may however reflect presence of chronic obstructive lung disease causing both polycythemia and poorer CV survival ([22]). We have not detected any U-shape relationship between the hemoglobin level and short-term survival, although our study may have been underpowered to detect it.

Experimental data and recent studies suggest that cardiac patients are less tolerant to anemia ([23]). Consequently, hemoglobin level thresholds for the treatment of anemia in these patients should be higher, particularly in a setting of acute cardiac ischemia ([4;9;24]). In other words, hemoglobin levels that have been considered as not yet significantly lowered may in fact already be too low in patients with heart disease. In addition to blood transfusion, with its possible adverse reactions and volume overload, therapy with recombinant human erythropoietin should also be considered ([25]). Moreover, erythropoietin has been found to have also direct

cardioprotective effects, not associated with hematopoiesis ([26]). Further studies are needed to assess the benefit of anemia treatment in patients with acute coronary events.
There are some limitations to our analysis. First, although the effect of hemoglobin levels on 30-day mortality was corrected for the most important covariates, we were unable to control for CV risk factors outside the scope of the data abstraction. Second, because of retrospective data collection and limited amount of available data, no conclusions can be drawn on possible mechanisms relating anemia to short-term mortality.

Conclusion

The present study clearly shows a relation between low hemoglobin concentration and 30-day mortality in patients with acute MI. However, low hemoglobin levels are also an important marker of other concomitant diseases that affect the mortality after MI. In the future, possible treatment options for anemic patients presenting with acute MI should be considered.

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