Correlation between Anemia and Inhospital Adverse Outcome in Patients Undergoing Emergency Coronary Angioplasty

Thesis

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Presented by

Dr. Beshoy Yohanna

M.B.B.Ch

Under Supervision of

Prof. Ahmed Ibrahim Nassar

Professor of Cardiology

Faculty of Medicine - Ain Shams University

Dr. Wail Mostafa El-Nammas

Assistant Professor of Cardiology

Faculty of Medicine - Ain Shams University

Faculty of Medicine – Ain Shams University

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Introduction

Ischemia is absolute or relative shortage of oxygen, leading to tissue damage, and since oxygen is mainly bound to hemoglobin, insufficient oxygen supply due to anemia and/or coronary artery disease causes tissues to become hypoxic and in a very aerobic tissue such as the heart, necrosis usually takes about 3–4 minutes before becoming irreversible. That is why anemia is associated with an increased risk of mortality due to the imbalance between myocardial oxygen supply and demand, resulting in myocardial ischemia ***(Paul et al., 2005 and Brendan et al., 2009).***

Since the first human percutaneous transluminal coronary angioplasty procedure was performed, in 1977, the use of percutaneous coronary intervention (PCI) has increased dramatically, becoming one of the most common medical interventions performed. The technique, originally developed in Switzerland by Andreas Gruentzig, has transformed the practice of revascularization for coronary artery disease. Initially used in the treatment of patients with stable angina and discrete lesions in a single coronary artery, currently coronary angioplasty has multiple indications, including unstable angina, acute myocardial infarction (MI), and multivessel coronary artery disease. With the combination of sophisticated equipment, experienced operators, and modern drug therapy, PCI has evolved into an effective nonsurgical modality for

treating patients with coronary artery disease, to reduce symptoms, reduce the need for subsequent procedures, and relieve ischemia ***(Connolly, 2002).***

Anemia is an independent predictor of mortality after PCI and is associated with short-term adverse procedural events. Consequently, whether optimization of hemoglobin level before PCI would be beneficial in terms of reducing major adverse cardiac events is a potential venue for randomized clinical trials ***(Eugenia et al., 2007).***

Aim of the Work

We sought to explore the relationship between anemia and in-hospital adverse outcome in patients undergoing emergency coronary angioplasty.

Emergency Percutaneus Intervention In Acute Cronary Syndrome

Acute coronary syndrome (ACS) refers to a spectrum of clinical presentations ranging from those for ST-segment elevation myocardial infarction (STEMI) to presentations found in non–ST-segment elevation myocardial infarction (NSTEMI) or in unstable angina. In terms of pathology, ACS is almost always associated with rupture of an atherosclerotic plaque and partial or complete thrombosis of the infarct-related artery ***(David et al., 2012).***

In some instances, however, stable coronary artery disease (CAD) may result in ACS in the absence of plaque rupture and thrombosis, when physiologic stress (eg, trauma, blood loss, anemia, infection, tachyarrhythmia) increases demands on the heart. The diagnosis of acute myocardial infarction in this setting requires a finding of the typical rise and fall of biochemical markers of myocardial necrosis in addition to at least 1 of the following ***(Alpert et al., 2000)***:

- Ischemic symptoms
- Development of pathologic Q waves
- Ischemic ST-segment changes on electrocardiogram (ECG) or in the setting of a coronary intervention

The terms transmural and nontransmural (subendocardial) myocardial infarction are no longer used because ECG findings in patients with this condition are not closely correlated with pathologic changes in the myocardium. Therefore, a transmural infarct may occur in the absence of Q waves on ECGs, and many Q-wave myocardial infarctions may be subendocardial, as noted on pathologic examination. Because elevation of the ST segment during ACS is correlated with coronary occlusion and because it affects the choice of therapy (urgent reperfusion therapy), ACS-related myocardial infarction should be designated STEMI or NSTEMI (***O'Connor et al., 2010)***.

Attention to the underlying mechanisms of ischemia is important when managing ACS. A simple predictor of demand is rate-pressure product, which can be lowered by beta blockers (eg, metoprolol or atenolol) and pain/stress relievers (eg, morphine), while supply may be improved by oxygen, adequate hematocrit, blood thinners (eg, heparin, IIb/IIIa agents such as abciximab, eptifibatide, tirofiban, or thrombolytics), and/or vasodilators (eg, nitrates, amlodipine) (***O'Connor et al., 2010)***.

Etiology:

Acute coronary syndrome (ACS) is caused primarily by atherosclerosis. Most cases of ACS occur from disruption of a

previously non-severe lesion (an atherosclerotic lesion that was previously hemodynamically insignificant yet vulnerable to rupture). The vulnerable plaque is typified by a large lipid pool, numerous inflammatory cells, and a thin, fibrous cap ***(Anderson et al., 2007)***.

Elevated demand can produce ACS in the presence of a high-grade fixed coronary obstruction, due to increased myocardial oxygen and nutrition requirements, such as those resulting from exertion, emotional stress, or physiologic stress (eg, from dehydration, blood loss, hypotension, infection, thyrotoxicosis, or surgery) (***David et al., 2012)***.

ACS without elevation in demand requires a new impairment in supply, typically due to thrombosis and/or plaque hemorrhage. The major trigger for coronary thrombosis is considered to be plaque rupture caused by the dissolution of the fibrous cap, the dissolution itself being the result of the release of metalloproteinases (collagenases) from activated inflammatory cells. This event is followed by platelet activation and aggregation, activation of the coagulation pathway, and vasoconstriction. This process culminates in coronary intraluminal thrombosis and variable degrees of vascular occlusion. Distal embolization may occur. The severity and

duration of coronary arterial obstruction, the volume of myocardium affected, the level of demand on the heart, and the ability of the rest of the heart to compensate are major determinants of a patient's clinical presentation and outcome. (Anemia and hypoxemia can precipitate myocardial ischemia in the absence of severe reduction in coronary artery blood flow) ***(Nashef et al., 1999).***

Prognosis

Six-month mortality rates in the Global Registry of Acute Coronary Events (GRACE) were 13% for patients with NSTEMI ACS and 8% for those with unstable angina. An elevated level of troponin (a type of regulatory protein found in skeletal and cardiac muscle) permits risk stratification of patients with ACS and identifies patients at high risk for adverse cardiac events (ie, myocardial infarction, death) up to 6 months after the index event ***(Gurm et al., 2012)***.

The PROVE IT-TIMI trial found that after ACS, a J-shaped or U-shaped curve association is observed between BP and the risk of future cardiovascular events ***(Bangalore et al., 2010)***.

LeLeiko et al., (2009) determined that serum choline and free F(2)-isoprostane are also predictors of cardiac events in ACS. The authors evaluated the prognostic value of vascular inflammation and oxidative stress biomarkers in patients with ACS to determine their role in predicting 30-day clinical outcomes. Serum F(2)-isoprostane had an optimal cutoff level of 124.5 pg/mL, and serum choline had a cutoff level of 30.5 μmol/L. Choline and F(2)-isoprostane had a positive predictive value of 44% and 57% and a negative predictive value of 89% and 90%, respectively.

Testosterone deficiency is common in patients with coronary disease and has a significant negative impact on mortality. Further study is needed to assess the effect of treatment on survival ***(Ma and Tong, 2010)***.

A study by ***Sanchis et al., (2011)*** suggests renal dysfunction, dementia, peripheral artery disease, previous heart failure, and previous myocardial infarction are the comorbid conditions that predict mortality in NSTEMI ACS. In patients with comorbid conditions, the highest risk period was in the first weeks after NSTEMI ACS. In-hospital management of patients with comorbid conditions merits further investigation.

Patients with end-stage renal disease often develop ACS, and little is known about the natural history of ACS in patients receiving dialysis. ***Gurm et al. (2012)*** examined the presentation, management, and outcomes of patients with ACS

who received dialysis before presentation for an ACS. These patients were enrolled in the Global Registry of Acute Coronary Events (GRACE) at 123 hospitals in 14 countries from 1999-2007.

NSTEMI ACS was the most common in patients receiving dialysis, occurring in 50% of patients (290 of 579) versus 33% (17,955 of 54,610) of those not receiving dialysis The in-hospital mortality rates were higher among patients receiving dialysis (12% vs 4.8%; $p < 0.0001$). Higher 6-month mortality rates (13% vs 4.2%; $p < 0.0001$), recurrent myocardial infarction incidence (7.6% vs 2.9%; $p < 0.0001$), and unplanned rehospitalizations (31% vs 18%; $p < 0.0001$) were found among those who survived to discharge. Outcome in patients who received dialysis was worse than was predicted by the calculated GRACE risk score for in-hospital mortality (7.8% predicted vs 12% observed; $p < 0.05$). This suggests that the GRACE risk score underestimated the risk of major events in these patients (***Gurm et al., 2012)***.

In a study that assessed the impact of prehospital time on STEMI outcome, Chughatai et al., (2011) suggested that “total time to treatment” should be used as a core measure instead of “door-to-balloon time.” This is because on-scene time was the biggest fraction of "pre-hospital time.” The study compared groups with total time to treatment of more than 120 minutes compared with 120 minutes or less and found mortalities were

4 compared with 0 and transfers to a tertiary care facility were 3 compared with 1, respectively.

Revascularization in non-ST-segment elevation acute coronary syndromes

NSTE-ACS is the most frequent manifestation of ACS and represents the largest group of patients undergoing PCI. Despite advances in medical and interventional treatments, the mortality and morbidity remain high and equivalent to that of patients with STEMI after the initial month. However, patients with NSTE-ACS constitute a very heterogeneous group of patients with a highly variable prognosis. Therefore, early risk stratification is essential for selection of medical as well as interventional treatment strategies. The ultimate goals of coronary angiography and revascularization are mainly two-fold: symptom relief, and improvement of prognosis in the short and long term. Overall quality of life, duration of hospital stay, and potential risks associated with invasive and pharmacological treatments should also be considered when deciding on treatment strategy (***Than et al., 2011)***.

Intended early invasive or conservative strategies:

Randomized Controlled Trials (RCTs) shown that an early invasive strategy reduces ischaemic endpoints mainly by reducing severe recurrent ischaemia and the clinical need for rehospitalization and revascularization. These trials have also

shown a clear reduction in mortality and MI in the medium term, while the reduction in mortality in the long term has been moderate and MI rates during the initial hospital stay have increased (early hazard) (***Mehta et al., 2005).*** The most recent meta-analysis confirms that an early invasive strategy reduces cardiovascular death and MI at up to 5 years of follow-up (***Fox et al., 2010)***.

Risk stratification

Considering the large number of patients and the heterogeneity of NSTE-ACS, early risk stratification is important to identify patients at high immediate and long-term risk of death and cardiovascular events, in whom an early invasive strategy with its adjunctive medical therapy may reduce that risk. It is equally important, however, to identify patients at low risk in whom potentially hazardous and costly invasive and medical treatments provide little benefit or in fact may cause harm (***Fox et al., 2010)***.

Risk should be evaluated considering different clinical characteristics, ECG changes, and biochemical markers. Risk score models have therefore been developed. The ESC Guidelines for NSTE-ACS recommend the GRACE risk score as the preferred classification to apply on admission and at discharge in daily clinical practice (***Bassand et al., 2007)***. The GRACE risk score was originally constructed for prediction of hospital mortality but has been extended for prediction of long-

term outcome across the spectrum of ACS and for prediction of benefit with invasive procedures (***Yan et al., 2005)***.

A substantial benefit with an early invasive strategy has only been proved in patients at high risk. The recently published meta-analysis by ***Fox et al., (2010)*** showed a direct relationship between risk, evaluated by a set of risk indicators including age, diabetes, hypotension, ST depression, and body mass index (BMI), and benefit from an early invasive approach.

Troponin elevation and ST depression at baseline appear to be among the most powerful individual predictors of benefit from invasive treatment. The role of high sensitivity troponin measurements has yet to be defined.

Timing of angiography and intervention

The issue of the timing of invasive investigation has been a subject of discussion. A very early invasive strategy, as opposed to a delayed invasive strategy, has been tested in five prospective RCTs. A wealth of data supports a primary early invasive strategy over a conservative strategy. There is no evidence that any particular time of delay to intervention with upstream pharmacological treatment, including intensive antithrombotic agents, would be superior to providing adequate medical treatment and performing angiography as early as possible. Ischaemic events as well as bleeding complications tend to be lower and hospital stay can be shortened with an

early as opposed to a later invasive strategy. In high-risk patients with a GRACE risk score >140, urgent angiography should be performed within 24 h if possible (***Giugliano et al., 2009 and Mehta et al., 2009)***.

Patients at very high risk were excluded from all RCTs so that life-saving therapy was not withheld. Accordingly, patients with ongoing symptoms and marked ST depression in anterior leads (particularly in combination with troponin elevation) probably suffer from posterior transmural ischaemia and should undergo emergency coronary angiography. Moreover, patients with a high thrombotic risk or high risk of progression to MI should be investigated with angiography without delay (***Giugliano et al., 2009 and Mehta et al., 2009)***.

In lower risk subsets of NSTE-ACS patients, angiography and subsequent revascularization can be delayed without increased risk but should be performed during the same hospital stay, preferably within 72 h of admission (***Giugliano et al., 2009 and Mehta et al., 2009)***.

Women and elderly patients:

Although subgroups of patients such as women and the elderly may be at higher risk of bleeding, there are no data supporting the suggestion that they should be treated differently from other patients included in RCTs. A meta-analysis of eight RCTs showed that biomarker-positive women derived a benefit

from an early invasive strategy comparable to that of men. However, biomarker-negative women tended to have a higher event rate with an early invasive procedure. Thus, early invasive procedures should be avoided in low-risk, troponin-negative, female patients (***O'Donoghue et al., 2008)***.

Age is one of the most important risk indicators, yet elderly patients experience a similar or greater benefit from early invasive procedures. Among the oldest patients, one should prioritize relief of symptoms and avoidance of bleeding complications ***(Fox et al., 2010)***.

Revascularization in ST-segment elevation myocardial infarction

Primary percutaneous coronary intervention

Primary PCI is defined as percutaneous intervention in the setting of STEMI without previous or concomitant fibrinolytic treatment. RCTs and meta-analyses comparing primary PCI with in-hospital fibrinolytic therapy in patients within 6–12 h after symptom onset treated in high-volume, experienced centres have shown more effective restoration of vessel patency, less re-occlusion, improved residual LV function, and better clinical outcome with primary PCI. Cities and countries switching from fibrinolysis to primary PCI have observed a sharp decrease in mortality after STEMI (***Kalla et al., 2006).***