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Peer Review Report for "The Relationship Between Hemoglobin Level and No-Reflow Phenomenon in Patients with Myocardial Infarction Undergoing Primary PCI"

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Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (0) — 24 Jul 2020

Dear EIC,
This is a well-written article with an interesting case number and is acceptable for publishing in this journal by considering the reviewer's comments.
Thanks

Alireza Alizadeh Ghavidel: EIC | **Revision** (0) — 24 Jul 2020

Dear authors
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Regards
Alireza A. Ghavidel MD

OPEN PEER REVIEW

Revision (1)

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You can read the authors' responses to the reviewers' comments in the next page.

The relationship between hemoglobin level and no –reflow phenomenon in patients with myocardial infraction undergoing primary PCI

Abstract:

Introduction: Anemia is a predictor of no reflow with high rate morbidity and mortality particularly in patients with heart failure. The aim of this study was to investigate the relation between hemoglobin level and no -reflowing in patients with myocardial infraction undergoing primary PCI

Methods: In this retrospective cross sectional study, all patients with ST elevation myocardial infarction (STEMI) undergoing coronary angiography from 2016 till 2018 were included. According to post procedural TIMI flow, the patients were divided into two groups: patients with TIMI flow III and those with TIMI flow less than III. Patient' demographic and laboratory data such as hemoglobin, hematocrit, platelets count, white blood cells, serum creatinine level and troponin were collected. To compare the quantitative variables chi square test and to compare qualitative variables t-test were applied by SPSS software version 19.

Results: In this study 1200 patients with acute ST elevation myocardial infarction (STEMI) treated with primary PCI were included. The mean Hemoglobin level in normal TIMI group and low TIMI group were 14.15±1.49 and 13.66±1.69, respectively (P<0.001). Our results also showed a significant lower RBC count (P<0.001), lower HCT level (P<0 .001) and lower RDW (P<0.001) in those patients with lower TIMI flow . Based the multivariate regression analysis lower hemoglobin has significant association with lower TIMI flow and no-reflow (OR= 0.747, CI=0.618-0.888, P<0.001)

Our study showed that in patients with STEMI undergoing primary PCI hemoglobin level had significant association with post procedural low TIMI flow and no-reflow. Our results emphasizes the need for randomized control trials to evaluate the importance of pre simultaneous blood transfusion in patients with anemia undergoing PPCI.

Key words: hemoglobin level, myocardial infarction, coronary angiography, no-reflow phenomenon

Introduction:

Anemia affects human health adversely. There are different co-morbidities causing anemia. (1) The main role of hemoglobin is carrying oxygen to the body tissues. Hemoglobin level varies based on our body mass; hence, women have lower hemoglobin levels than men (2-5). The main factors affecting our hemoglobin level are enough erythropoiesis (Function of bone marrow), Erythropoietin (EPO) production stands for kidney function and red blood cells mass proportionate to plasma volume (dilution of the blood). (5-7)

In patients with Chronic Heart Failure anemia is very common (8, 9). Existing in up to 50% of selected patients (10,11), the Anemia is closely connected to the severity of heart failure and affects its symptoms. Anemia is also common in patients with acute coronary syndrome (12, 13). Although theoretically anemia could reduce oxygen supply to myocardium in acute coronary syndrome, still its exact clinical importance is not clear. Clinical guidelines recommend iron injection and blood infusion for its treatment (14, 15).

Anemia in acute coronary syndromes treatment can cause undesirable results. It has multiplier adverse impacts on patients, regardless of starting before, during or after hospitalization. In all cases Anemia is known as an independent predictor of in-hospital death and long term mortality (3, 16). Outcome of patients admitting with acute myocardial infarction is affected by some factors such as left ventricle performance, arrhythmia and ischemia-reperfusion injury (17, 18). Any decrease in hemoglobin level may harm enough oxygen delivery to myocardium in those coronary arteries occluded by clot and this could increase the chance of arrhythmia and cell death resulting in expanding infarcted area (19,20) No-

reflow after revascularization is a multi- factorial phenomenon with unknown etiology. Factors suggested to increase no-reflow are distal emboli, reperfusion injury that can cause Oxygen Free Radical Formation, microvascular damage, myocardial necrosis, stunning, released tissue factors from torn plaques, peripheral vasoconstriction , alpha adrenergic receptors and serotonin activity (21).

One study showed that the lower levels of hemoglobin was an independent predictor of no-reflow in patients with Acute STEMI patients treated with primary percutaneous intervention (PPCI)(21). Anemia also causes inflammatory responses that can release cytokines causing endothelial dysfunction, instability of atherosclerotic plaques and an increase in coagulation tendency (21).

Anemia increases myocardial demand for oxygen by increasing heart rate, and probably by increasing microvascular resistance and microvascular dysfunction(21).

Nowadays primary PCI has become the first line treatment in patients with STEMI and no-reflow is common in these patients (22).

Hence, no-reflow diagnosis and prevention has become an incremental concern for interventional cardiologist who want to get best results with primary PCI (23,24).

There are few studies evaluating the role of anemia in no-reflow phenomenon. We decided to evaluate the role of anemia in no-reflow and low TIMI flow in patients undergoing primary PCI to find out its importance in success rate of PPCI.

Methods

In this retrospective cross sectional study, all patients with ST elevation myocardial infarction (STEMI) undergoing coronary angiography from 2016 till 2018 were included. According to post procedural TIMI flow, the patients divided into two groups: patients with TIMI flow III and those with TIMI flow less than III. Patient' demographic data including age, sex, risk factors for atherosclerosis, history of ischemic heart disease, heart failure and laboratory data including hemoglobin, hematocrit, platelets count, white blood cells, serum creatinine level and troponin were collected. Angiography records of all patients was analyzed by two expert cardiologists. Stenosis more than 70% defined as significant stenosis and post procedural TIMI flow of all patients were calculated and no-reflow during procedure was determined according to angiography records. TIMI flow grading is defined as : grade 0 (no antegrade flow beyond stenosis), grade 1; (although contrast material passes beyond stenosis it doesn't fill entire the artery), grade 2; (although all the vessel is filled by contrast material its flow and clearance is slower than normal vessel and grade 3; (complete filling of vessel with contrast and its rapid clearance). This study was approved by ethics committee of Tabriz University of Medical Sciences with registration number of IR.TBZMED.REC.1398.490

To compare the quantitative variables chi square test and to compare qualitative variables t-test were applied by SPSS software version 19.

To analyze the independent impact of hemoglobin on no reflow phenomenon multivariate regression analysis were used.

Results

In this study 1200 patients with acute ST elevation myocardial infarction treated with primary PCI were included. The mean Hemoglobin level in normal TIMI group and low TIMI group were 14.15±1.49 and 13.66±1.69, respectively (P<0.001). Baseline characteristics of patients admitted for primary PCI according to their TIMI flow was shown in table 1.

Our results also showed a significant lower red blood cells count (P<0.001), lower hematocrit level (P<0 .001) and lower red cell distribution width (P<0.001) in those patients with lower TIMI flow. Table 2 shows laboratory findings of patients according to their TIMI flow. Table 3 shows angiographic findings of patients admitted for PPCI

Also in univariate analysis higher age, hypertension and anterior myocardial infarction had significant association with lower TIMI flow. (Table 4)

Based on the multivariate regression study left ventricular ejection fraction (OR= 0.94, CI=0.93-0.98, P<0.001),time from symptoms onset to PCI (OR= 1.14, CI= 1. 48-1.9 ,P<0 .001),thrombus burden (OR=1.57, CI=1.33-1.86, P<0 .001), reference vessel diameter: (OR: 1.59, CI=1.101-2.275, P<0.05) ,Hemoglobin (OR= 0.747, CI=0.618-0.888 0, P<0.001), hypertension (HTN) (OR= 5.114, CI=0.557-0.987, P<0.05) and reperfusion method (OR=5.114, CF=2.248-11.634, P<0.001) were found to predict lower TIMI flow in patients undergoing PPCI (Table 2).

Receiver operating characteristic (ROC) curve showed that hemoglobin level ≤ 12 had a sensitivity of 80.4% and specificity of 96.7% in predicting low TIMI flow. (Figure 1)

Discussion:

Our study showed a significant association between lower TIMI flow and anemia. In acute coronary artery syndrome anemia has been shown as a predictor of short term and long term mortality (3, 16).Also in patients with heart failure anemia is associated with higher mortality. With decreased hemoglobin level and red blood cell count blood viscosity decreases causing decreased nitric oxide synthesis resulting in adverse effect on coagulation and plaque stability. (1).

Similar to our study, Yaylak and colleagues showed that hemoglobin level with moderate efficacy was an independent predictor of no-reflow in STEMI patients treated with primary PCI. They showed that a hemoglobin level below 11.5 g/dl had a sensitivity of 83.0% in predicting no-reflow phenomenon (1).

Contrary to our results, Huang et al showed that hemoglobin level didn't have any association with TIMI flow but serum iron concentration had association with TIMI risk score. (24).

Lawler et al in a systematic review showed that in patients admitted with acute coronary syndrome, anemia had significant correlation with all-cause mortality (relative risk 2.08, 95% CI 1.70-2.55) and re-infarction (relative risk 1.25, 95% CI 1.02-1.53) (25)

Nokolsky et al by studying patients with acute myocardial infarction undergoing PCI showed that 12.8% of these patients had anemia. In this study anemia had significant association with hospital stay, mortality and stroke. In multivariate analysis anemia was an independent predictor of short term and long term mortality (26).

Dundar et al also showed that in patient admitted with acute STEMI and treated by Primary PCI, hospital mortality, heart failure and major bleeding were significantly higher than those patients with normal hemoglobin (27).

Wang et al showed that in the patients with acute STEMI undergoing primary PCI, a hemoglobin level < 120 g/L on admission had significant association with major adverse cardiac events including death, coronary artery occlusion and stent restenosis (28). Our study showed that hemoglobin ≤12 g/dl had a sensitivity of 80.4% and specificity of 96.7% in low TIMI flow prediction.

Moghaddam et al also showed that in patients with STEMI treated with primary PCI, anemia had great impact on major bleeding but not all cause mortality. They suggested that PCI was safe in anemic patients but preventing major bleeding was very important in these patients. (29). In other study with large sample size blood transfusion could decrease cardiovascular death in patients with a hemoglobin level less than 12. About 80% of patients took transfusion when they had bleeding and the influence of blood transfusion when the patient do not have bleeding is not understood well (30). (1) Rousseau et al showed that recurrent myocardial ischemia had significant association with anemia. This study shows that not only during PPCI, even after PPCI ischemia anemia continuous to affect perfusion of heart adversely(31). Because of different results of previous studies we conducted present study to evaluate the importance of anemia in no-reflow phenomenon and we found that anemia could be important factor affecting the success rate of PPCI adversely.

Limitation of study:

Our study was a cross sectional study and we had no data about the cause of anemia and the duration of anemia and its impact on no-reflow phenomenon. We didn't have long term follow up to evaluate long term effects of anemia on recurrent ischemia and chronic cardiac ischemia.

Conclusion:

Our study showed that in patients with STEMI undergoing primary PCI hemoglobin level had significant association with post procedural low TIMI flow and no-reflow. Our results emphasizes the need for randomized control trials to evaluate the importance of pre simultaneous blood transfusion in patients with anemia undergoing PPCI.

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Table 1. Baseline characteristics of patients admitted for primary PCI according to their TIMI flow

Parameter	Normal reflow (n=608)	No-reflow (n=592)	P-value
Age	59.80±10.41	63.12±10.59	<0.001
Sex (male)	(77.1)469	(76.4)452	0.75
Left ventricular ejection fraction	41.59±6.63	38.05±7.30	<0.001
Systolic blood pressue	139.02±25.00	137.47±26.72	0.300
Diastolic blood pressure	78.68±10.98	78.15±11.45	0.421
Heart rate	75.34±15.15	80.31±15.91	0.001>
Time from symptoms onset to PCI [h]	5.67±1.52	6.03±1.53	0.001>
Door to balloon time	19.94±9.27	20.29±10.19	0.540
Platelets(10^4) In eshtebahe nemitune 25 bashe	25.90±4.92	25.95±5.31	0.861
Diabetes	(16.8)102	(17.9)106	0.61
Hypertension	(37.8)230	(51.5)305	<0.001
Hyperlipidemia	(19.7)120	(23.8)141	0.09

History of smoking	(44.2)269	(41.9)248	0.41
Family history of coronary artery disease	(10.2)62	(6.1)36	0.01
Previous PCI	(6.7)41	(5.7)34	0.47
Previous CABG	(1.2)7	(1.9)11	0.31
Myocardial infarction (anterior)	(49.3)300	(66.9)396	<0.001

Table 2. Laboratory findings of patients according to their TIMI flow

Parameter	Normal reflow (n=608)	No-reflow (n=592)	P-value
White blood cells	8727.80±1556.07	8920.61±1556.41	0.032
Hemoglobin	14.15±1.49	13.66±1.69	<0.001
Mean corpuscular volume	87.06±7.17	86.50±7.54	0.187
Red blood cells	4.59±0.55	4.7±0.60	0.001
Hematocrit	44.73±5.17	43.57±4.97	<0.001

Red cell distribution width	11.78±1.90	11.31±2.10	<0.001
CKMB	68.46±16.19	68.99±16.06	0.569
Mean platelet volume	10.76±1.39	10.57±1.47	0.020

Table 3. Angiographic findings of patients admitted for PPCI

Parameter	Normal reflow (n=608)	No-reflow (n=592)	P-value
Thrombus burden	4.25±1.02	4.66±0.68	<0.001
Length of target lesion	21.68±6.09	22.13±6.18	0.203
Reference vessel diameter	3.07±0.37	3.13±0.39	0.009
Use of IIb, IIIa inhibitor	(47.9)291	(54.7)324	0.02
Thrombus aspiration	(14.1)86	(19.8)117	0.01

Outcome	(0.3)2	(3.2)19	<0.001
Number of involved vessel			<0.001
Single vessel disease (1VD)	(57.1)347	(47.1)279	
2VD	(28.8)175	(31.9)189	
3VD±Left main (LM) disease	(14.0)85	(20.3)120	
Culprit vessel			<0.001
LM	(0.2)1	(0.5)3	
Left anterior descending (Diagonal)	(47.9)291	(66.6)394	
Left circumflex artery(OM)	(19.9)121	(12.2)72	0.00
Right coronary artery	(30.9)188	(20.1)119	
Reperfusion method			
Balloon dilation	(1.8)11	(8.1)48	
Balloon predilation following Stent implantation	(61.3)373	(70.1)415	<0.001
Stent implantation	(36.5)222	(20.9)124	

Table 4:. Univariate and multivariable logistic regression analysis for prediction of no-reflow

Variable	Univariate	multivariate

	Unadjusted OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Age	1.031	1.019-1.042	<0.001	1.011	0.997-1.026	0.129
Ejection Fraction	0.930	0.914-0.946	<0.001	0.961	0.939-0.983	0.001
Heart Rate	1.021	1.013-1.028	<0.001	1.005	0.993-1.017	0.442
Time from symptoms onset to PCI [h]	1.166	1.081-1.258	<0.001	1.145	1.048-1.251	0.003
Thrombus burden	1.756	1.519-2.029	<0.001	1.571	1.330-1.856	<0.001
Reference vessel diameter	1.488	1.104-2.004	0.009	1.590	1.101-2.295	0.013
WBC	1.000	1.000-1.000	0.033	1.000	1.000-1.000	0.066
HB	0.825	0.767-0.888	<0.001	0.741	0.618-0.888	0.001
RBC	0.709	0.581-0.865	0.001	1.431	0.933-2.196	0.101
HCT	0.955	0.933-0.977	<0.001	0.969	0.925-1.015	0.189
RDW	0.891	0.841-0.943	<0.001	1.072	0.955-1.204	0.239
MPV	0.911	0.841-0.986	0.021	0.999	0.904-1.105	0.989
HTN	1.747	1.388-2.198	<0.001	0.742	0.557-0.987	0.040
Family history of coronary artery disease	1.754	1.144-2.689	0.010	1.083	0.653-1.749	0.758
MI(anterior)	2.071	1.639-2.618	<0.001	0.083	0.009-0.743	0.023
Use of IIbIIIa inhibitor	0.764	0.609-0.959	0.020	0.784	0.591-1.039	0.090

Thrombus aspiration	0.674	0.497-0.914	0.011	0.723	0.504-1.039	0.080
Outcome	10.047	2.330-43.327	0.002	3.505	0.740-16.612	0.114
No. of involved vessel(3VD±LM)			0.001			0.181
SVD	0.570	0.414-0.784	0.001	0.655	0.408-1.050	0.079
2VD	0.765	0.541-1.081	0.129	0.819	0.521-1.288	0.387
Culprit vessel(RCA)			<0.001			0.090
LM	4.739	0.487-46.096	0.180	18.006	0.426-760.846	0.130
LAD(Diagonal)	2.139	1.625-2.816	<0.001	16.868	1.912-148.801	0.011
LCX(OM)	0.940	0.649-1.363	0.744	1.096	0.703-1.708	0.687
Reperfusion method(Stent implantation)			<0.001			<0.001
Balloon diltaion	7.812	3.914-15.592	<0.001	5.114	2.248-11.634	<0.001
Balloon predilation following stent implantation	1.992	1.535-2.585	<0.001	1.562	1.157-2.109	0.004

HR: Heart Rate, WBC: White Blood Cell, HB: Hemoglobin, RBC: Red Blood Cell, HCT: HEMATOCRIT, RDW: Red Blood Cell Distribution Width, MPV: Mean Platelet Volume, HTN: Hypertension, LM: Left Main, LAD: Left Anterior Descending, LCX: Left Circumflex Artery

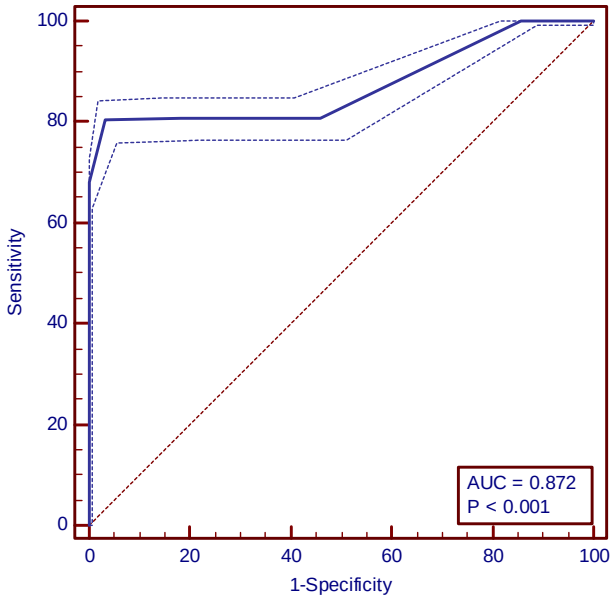


Figure 1. **Receiver operating characteristic (ROC) curve shows the best cut off point for hemoglobin level in no-reflow phenomenon.**

Hemoglobin [g/l]: ≤12	
Sensitivity	80.41
Specificity	96.71

AUC	0.872
95% Confidence interval	0.852 to 0.890

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Ata Firouzi: Associate Editor | **Revision** (1) 21 Aug 2020

Dear EIC
Based on the authors' answers to the reviewers' comments, the reviewer(s) have recommended publication.
Kind regards.

Alireza Alizadeh Ghavidel: EIC | **Revision** (1) 21 Aug 2020

Dear Authors
Thank you for revising your valuable manuscript. it is my pleasure to inform you that the article will be published in upcoming issues. Please note that you did not follow the journal standards for revising the manuscript so the reviewing process took more time.
Regards