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RESEARCH ARTICLE

Factors Affecting Ischemic Stroke Short-Term Outcome According to Hemoglobin Level

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ABSTRACT

Background and aims There seems to be a U-shaped relation between hemoglobin level and ischemic stroke severity. We aimed to explore possible causes of this relation.

Methods All patients with ischemic stroke between 2006 and 2016 admitted within 3 hours of onset were included. Hemoglobin and NIHSS score were obtained on admission. Modified Rankin Scale (mRS) score was obtained day 7. Locally weighted scatterplot smoothing (lowess smoother) curves displaying the frequencies of M1 occlusion and complications according hemoglobin level on admission and lowess smoother curves displaying mRS day 7 in patients with and without middle cerebral artery (M1) occlusion according to hemoglobin level on admission were obtained.

Results This study includes 905 ischemic stroke patients. Low hemoglobin was associated with pneumonia and urinary tract infection. Neurological worsening was not associated with hemoglobin level. Increasing mRS day 7 was strongly associated with increasing high hemoglobin in patients with M1 occlusion (correlation factor=.61, P=.02).

Conclusions Poor outcome in ischemic stroke patients with low hemoglobin is associated with complications during the hospital stay whereas poor outcome in ischemic stroke patients with increasing high hemoglobin levels is associated with occlusion of the middle cerebral artery.

Keywords: ischemic stroke, hemoglobin, prognosis, complications

Introduction

We recently reported that there is a U-shaped relation between ischemic stroke severity and hemoglobin level on admission.[1] Mechanisms causing severe stroke is likely to be different in patients with low hemoglobin and in patients with high hemoglobin. We speculated that possible causes include ischemic tissue vulnerable to infarction due to low oxygen supply in patients with low hemoglobin and high blood viscosity in patients with high hemoglobin. Complications may also differentially affect prognosis in patients with low and high hemoglobin. Other studies have reported severe ischemic stroke in patients with low hemoglobin levels[2-4] and with high hemoglobin levels.[5] A meta-analysis found a U-shaped association between hemoglobin and mortality in patients with ischemic stroke.[6]

We aimed to study the possible differential associations of factors including complications and middle cerebral artery occlusion on short-term prognosis in relation to hemoglobin level.

Methods

We included ischemic stroke patients admitted within 3 hours of stroke onset to the Center for neurovascular diseases, Department of Neurology, Haukeland University Hospital between February 2006 and June 2016 (The Bergen NORSTROKE Registry). Ischemic stroke was defined in accordance with the Baltimore-Washington Cooperative Young Stroke Study Criteria comprising neurological deficits lasting more than 24 hours because of ischemic lesions or transient ischemic attacks where CT or MRI showed acute infarctions related to the clinical findings.[7]

The National Institute of Health Stroke Scale (NIHSS) was used to assess stroke severity on admission. NIHSS score and modified Rankins Scale (mRS) score were obtained day 7 or on discharge if discharged before day 7. Neurologic worsening was defined as NIHSS score increasing ≥3 points compared to NIHSS score on admission.

Hemoglobin level was obtained on admission. The presence or not of proximal middle cerebral artery occlusion on CT angiography on admission was registered. We aimed to compare proximal middle cerebral artery (M1) occlusion against patients with occlusion of smaller vessels or no occlusion on CT angiography. In this comparison, basilar artery occlusion was excluded.

Risk factors were defined according to a predefined protocol: prior cerebral infarction, angina pectoris, myocardial infarction, peripheral atherosclerosis, hypertension, diabetes mellitus, and smoking. Current smoking was defined as smoking at least one cigarette per day. Diabetes mellitus was considered present if the patient was on glucose-lowering diet or medication. Hypertension, angina pectoris, heart disease and peripheral artery disease were considered present if diagnosed by a physician any time before stroke onset.

Complications including pneumonia and urinary tract infection during the hospital stay were also registered.

Etiology was determined by the Trial of Org 10172 in Acute Stroke Treatment classification (TOAST) and classified as large-artery atherosclerosis, cardioembolism, small vessel disease, other, and unknown.[8]

All data were collective prospectively. The study was approved by the local ethics committee.

Statistics

Locally weighted scatterplot smoothing (lowess smoother) curves displaying the frequencies of M1 occlusion, pneumonia, urinary tract infection and neurological worsening according hemoglobin level on admission were obtained. Lowess smoother curves displaying mRS day 7 in patients with and without M1 occlusion according to hemoglobin level on admission were also obtained. Pairwise correlation, Mann Whitney test and Student's t-test analyses were performed when appropriate. Logistic regression analyses with urinary tract infection, pneumonia, neurological worsening as dependent variables were performed. Regression analyses with mRS day 7 as dependent variable were performed. STATA 14.0 (Statacorp 4905 Lakeway Drive, College Station, Texas 77845 USA) was used for analyses.

Results

In total, 905 patients were included. Table 1 shows demographics of the patients. Mean age was 71 years (range 20 – 100 years). Males comprised 529 (58%) patients. CT angiography was performed in 614 (68%) patients and occlusion of the main stem of the middle cerebral artery (M1) was disclosed in 108 (18%) patients. Patients with ischemic stroke due to cardiac embolism had significant lower hemoglobin levels compared to the other etiologies (hemoglobin = 14.0 g/dl compared to 14.3 g/dl, P=.003).

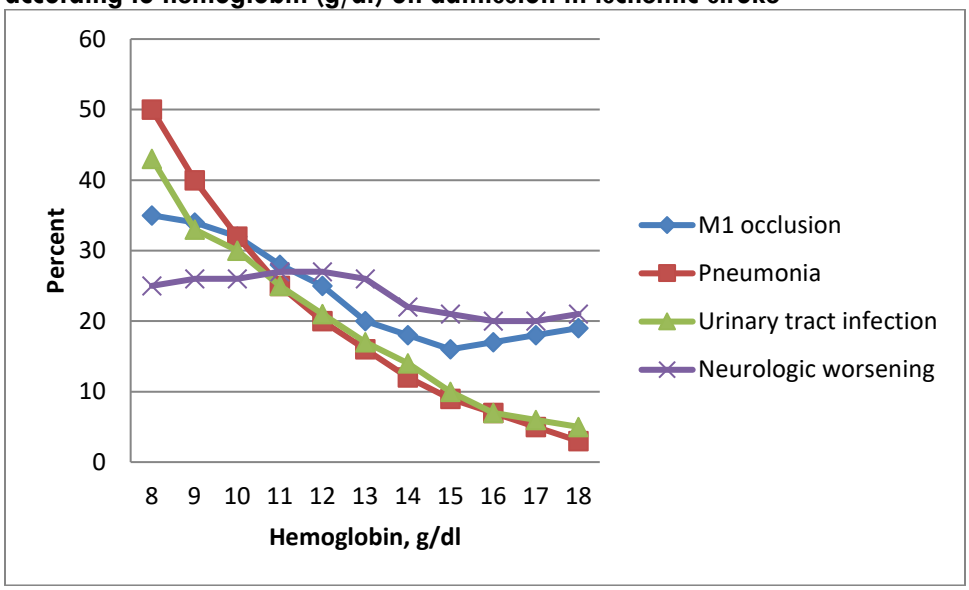
Table 1 Demographics of patients with acute cerebral infarction admitted within 3 hours

	N=905
Age, mean (standard deviation, SD)	71 (15)
Male, n (%)	529 (58)
NIHSS[1] score on admission, median (inter quartal range)	4 (2-11)
NIHSS day 7, median (inter quartal range)	2 (0-6)
mRS[2] day 7, median (inter quartal range)	2 (1-4)
Systolic blood pressure on admission, mean mmHg (SD)	159 (28)
Hemoglobin, g/dl mean (SD)	14.1 (1.6)
C-reactive protein mg/l median (inter quartal range)	3 (1-6)
Albumin, g/l median (inter quartal range)	44 (41-46)
D-dimer mg/l median (inter quartal range)	.7 (.4-1.6)
Fibrinogen g/l median (inter quartal range)	3.6 (31.-4.2)
Smoking, n (%)	174 (21)
Hypertension, n (%)	455 (50)
Diabetes mellitus, n (%)	115 (13)
Atrial fibrillation, n (%)	308 (34)
Prior cerebral infarction, n (%)	109 (12)
Prior myocardial infarction, n (%)	145 (16)
Prior peripheral atherosclerosis, n (%)	54 (6)
Thrombolysis, n (%)	537 (59)
Thrombectomy, n (%)	73 (8)
Complications	
Neurologic worsening* n, (%)	187 (21)
Pneumonia, n (%)	107 (12)
Urinary tract infection, n (%)	126 (14)
Epilepsy, n (%)	34 (4)
TOAST[3]	
Atherosclerosis, n (%)	91 (10)
Cardioembolism, n (%)	377 (42)
Small vessel disease, n (%)	55 (6)
Other cause, n (%)	26 (3)
Unknown, n (%)	353 (39)
M1 occlusion on CT angiography (n=614), n (%)	108 (18)

[1] The National Institute of Health Stroke Scale
[2] modified Rankins Scale
[3] Trial of Org 10172 in Acute Stroke Treatment classification
* NIHSS worsening ≥3 points compared to NIHSS on admission
M1: main stem of the middle cerebral artery

Figure 1 shows lowess smoother curves for pneumonia, urinary tract infection, neurologic worsening and M1 occlusion. There was a steep decline in the frequency of pneumonia from low to high hemoglobin, correlation (r)= -.16 (P<.001) and likewise for urinary tract infection, r=-.16 (P<.001). There was no association between neurologic worsening and hemoglobin (P=.18). There was a decline in frequency of M1 occlusion up to hemoglobin = 14 g/dl, r=-.14 (P=.01). There was no association between M1 occlusion and hemoglobin >14 g/dl (P=.94).

Figure 1 Lowess smoother curves showing the frequencies of complications and M1 occlusion according to hemoglobin (g/dl) on admission in ischemic stroke

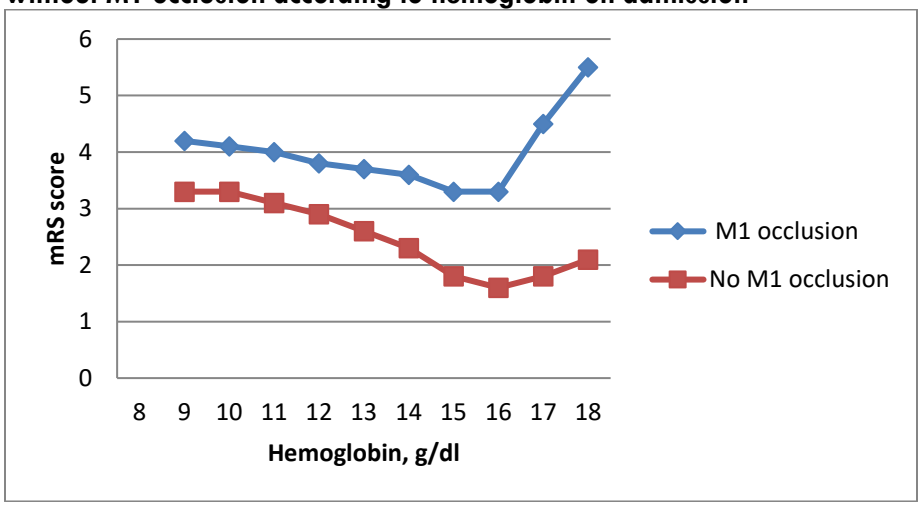


M1: main stem of the middle cerebral artery

Logistic regression analysis showed that pneumonia was independently associated with hemoglobin level on admission (odds ratio (OR)=.80, 95% confidence interval (CI) .69 - .92) after adjusting for NIHSS score on admission (OR=1.12, 95% CI 1.09 – 1.16), male versus female (OR=.41, 96% CI .25 - .67) and age (OR=1.05, 95% CI 1.02 – 1.07). Logistic regression analysis showed that urinary tract infection was independently associated with hemoglobin level on admission (OR=.88, 95% CI .77 - .997) after adjusting for age, sex and NIHSS score on admission. Adjusting for other variables from Table 1 did not change these results.

Figure 2 shows lowess smoother curves between mRS and hemoglobin levels in patients with and without M1 occlusion. Pairwise correlation analyses between mRS and hemoglobin<16g/dl showed r=-.20 (P<.001) for patients without M1 occlusion and r=-.16 (P=.05) for patients with M1 occlusion. The correlation between mRS and hemoglobin>16.3g/dl was r=.06 (P=.59) for patients without M1 occlusion and r=.61 (P=.02) for patients with M1 occlusion. Regression analyses did not change the associations between mRS day 7 and hemoglobin levels on admission after adjusting for age and sex.

Figure 2 Lowess smoother curves showing modified Rankin Scale (mRS) day 7 in patients with and without M1 occlusion according to hemoglobin on admission



M1: main stem of the middle cerebral artery

Table 2 shows a comparison between patients with proximal middle cerebral artery occlusion and patients with no intracranial occlusion on CT angiography on admission.

There were no differences in the frequencies of thrombectomy or thrombolysis in relation to hemoglobin levels on admission (P>.6). Excluding 9 patients with basilar artery occlusion did not change our findings.

Table 2 Comparison between proximal middle cerebral artery (M1) occlusion and no intracranial occlusion in patients with acute ischemic stroke

	M1 occlusion	No occlusions	p
Age, years (SD)	72 (15)	70 (15)	.21
Sex			.38
Female, n (%)	48 (44)	183 (40)	
Male, n (%)	60 (56)	276 (60)	
Hemoglobin g/dl, mean (SD)	14.0 (1.7)	14.3 (1.5)	.03
NIHSS[1] score on admission, median (inter quartal range)	17 (11.5-21)	4 (2-8)	<.001
mRS[2] day 7, median (inter quartal range)	4 (3-5)	2 (1-3)	<.001
Pneumonia, n (%)	31 (29)	39 (9)	<.001
Urinary tract infection, n (%)	27 (25)	58 (13)	.001
Neurologic worsening*, n (%)	28 (31)	89 (25)	.23

SD: standard deviation

[1] The National Institute of Health Stroke Scale

[2] modified Rankins Scale

* NIHSS worsening ≥3 points compared to NIHSS on admission

Discussion

Our study revealed some interesting differences between patients with low and high hemoglobin. Short-term prognosis was poor both in patients with low and in patients with high hemoglobin. This was especially the case in patients with high hemoglobin and M1 occlusion. Furthermore, complications such as pneumonia and urinary tract infection were frequent in patients with low hemoglobin, but infrequent in patients with high hemoglobin. One possible interpretation is that poor outcome in patients with low hemoglobin is at least partly caused by frequent complications. Patients with low hemoglobin may suffer from concomitant debilitating diseases making ischemic stroke patients susceptible to complications and poor prognosis.

The mechanisms causing poor outcome in patients with high hemoglobin are likely to differ from the mechanisms causing poor outcome in patients with low hemoglobin. We found a striking rise of the frequency of poor outcome with increasing high hemoglobin in patients with M1 occlusion. One possible interpretation is that recanalization is delayed in patients with M1 occlusion and high hemoglobin compared to

patients with M1 occlusion and lower hemoglobin. Another possible interpretation is that reperfusion is poorer even if recanalization occurs in patients with high compared to patients with lower hemoglobin. It is possible that high hemoglobin causes microemboli that lead to reduced reperfusion due to compromised microcirculation distant to the occlusion. A third possibility is that high hemoglobin is associated with increased blood viscosity that may worsen ischemia.[9] Dehydration may also be associated with high hemoglobin. We found no increase in complications in patients with high hemoglobin suggesting that complications play no major role in outcome in patients with high hemoglobin.

We found no association between neurologic worsening and hemoglobin levels. One possible cause of neurologic worsening is propagation of the thrombus. Our study does not suggest this mechanism to be associated with hemoglobin level. However, another study reported an association between low hemoglobin level and infarct growth based on imaging.[2] A limitation of our study is that we have no data of infarct growth based on imaging.

One of the strengths of the present study is the exclusion of patients admitted more than 3 hours of stroke onset thereby reducing the influence of stroke complications on the measured hemoglobin level. There are some limitations including lack of data on infarct volume, hematocrit, and possible recanalization in patients with M1 occlusion.

In conclusion, poor outcome in ischemic stroke patients with low hemoglobin is associated with complications during the hospital stay whereas poor outcome in ischemic stroke patients with increasing high hemoglobin levels is associated with occlusion of the middle cerebral artery and possible delayed reperfusion. Further studies are needed to investigate these findings.

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The authors have no conflict of interest to declare.

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