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Original Paper

Moderate to Severe Anemia Is Associated with Poor Functional Outcome in Acute Stroke Patients Treated with Mechanical Thrombectomy

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Acute stroke · Functional outcome · Mechanical thrombectomy · Anemia

Abstract
Background: Anemia will negatively affect cerebral collaterals and penumbra. Eventually, it may cause worse clinical outcomes and even increase mortality rates in stroke patients. Anemia has recently been suggested to be an independent risk factor for ischemic stroke. Therefore, we aimed to investigate the effects of the presence of anemia on clinical outcomes in ischemic stroke patients undergoing mechanical thrombectomy. ***Methods:*** This was a retrospective study involving the prospectively and consecutively collected data of 90 adult patients between January 2015 and August 2016. Hemoglobin (Hb) cutoff levels were accepted as 12 g/dL for women and 13 g/dL for men. Patients having anemia were further divided into three subgroups as severe anemia (Hb <8 g/dL for both genders), moderate anemia (Hb <10 g/dL for both genders), and mild anemia (Hb <13 g/dL for men and Hb <12 g/dL for women). ***Results:*** Forty of the subjects (44.4%) had anemia. Moderate anemia was detected in 14 out of 90 patients (15.5%) and severe anemia was found in only four of them (4.4%). Poor functional outcome (mRS 3–6) was similar in both anemic and non-anemic patients (37.5% vs. 38%, respectively, $p = 0.08$), but poor functional outcome was found to be statistically significant with severe anemic group (Hb <8 mg/dL) ($p = 0.003$). In multiple logistic regression analysis, moderate and severe anemia has been found to increase the mortality ($p = 0.032$). ***Conclusions:*** Our study demonstrated a poor functional outcome only in moderate to severe anemic patients. Clinicians should keep in mind the negative effect of moderate to severe anemia in the clinical course of acute stroke patients treated with mechanical thrombectomy.

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Introduction

Anemia is reported in up to 40% of patients with acute ischemic stroke (AIS) [1–4]. Recent clinical studies revealed that anemia seems to be significantly related with poor clinical outcome and mortality in AIS patients. Moreover, anemia has been suggested to be an independent risk factor for stroke [3, 5–8]. Although anemia is not widely accepted as a traditional risk factor like hypertension, diabetes, hyperlipidemia, and smoking for ischemic stroke, it is generally evaluated as an additional and modifiable risk factor [8]. In order to supply sufficient oxygen to cerebral tissue, hemoglobin (Hb) and hematocrit (Htc) levels should be kept within normal ranges [9]. In ischemic stroke patients with anemia, oxygen supply is extremely important for increased metabolic requirements of penumbral tissue [10, 11]. Cerebral tissue oxygen requirement is regulated by cerebral autoregulation mechanism in anemic healthy patients with Hb levels up to 8 mg/dL [7].

Nevertheless, in case of severe anemia (especially in patients with Hb levels between 5 and 7 mg/dL), blood oxygen transport capacity is reported to be markedly decreased because of the lack of sufficient cerebral arterial vasodilatation response [10, 11]. For this reason, toleration of anemia becomes much more difficult particularly in AIS patients [10, 11]. This autoregulation process is more complicated in AIS patients with anemia compared with healthy anemic patients, and the tolerable cutoff level of Hb may likely be different in this patient group [6, 8]. However, the effects of anemia on clinical and functional outcomes in ischemic stroke patients undergoing mechanical thrombectomy had not been studied previously. The mechanism of effect of anemia for acute stroke is probably similar but the important point is that there is less time for the operator for maintaining reperfusion of salvageable brain tissue at risk in anemic patients due to insufficient oxygen transport capacity. Therefore, we aimed to investigate the probable effects of anemia on the clinical outcomes of AIS patients after 3 months from the intervention.

Methods

Study Design

This was a retrospective study involving the prospectively collected data of 90 consecutive adult acute stroke patients (44 men, 46 women) who were admitted to the Interventional Neurology Unit of Ankara Numune Education and Research Hospital with intracranial large arterial occlusions and who had undergone mechanical thrombectomy between January 2015 and August 2016. This study was approved by the institutional research ethics board and the Samsun Training and Research Ethics Committee (21/02/2017-2017/3). Written consent was obtained from the patients or the relatives of the patient in the study.

Patient Characteristics

Age, gender, risk factors (hypertension, diabetes mellitus, alcohol consumption, smoking status, atrial fibrillation, coronary artery disease, congestive heart failure, previous stroke history), National Institutes of Health Stroke Scale score at admission, Hb and Htc values, and angiographic parameters (time interval between symptom onset and recanalization procedure, collateral score, the degree of revascularization after treatment) of the patients were recorded, consecutively. The degree of revascularization after treatment was defined by mTICI classification. Successful revascularization was defined as posttreatment mTICI score 2b–3. Clinical assessments were performed at the 90th day after treatment with modified Rankin scale for assessing global disability. A good functional outcome was defined as mRS score of 0–2.

Laboratory Investigations

Hb and Htc cutoff levels were accepted as 12 g/dL and 38% for women and 13 g/dL and 42% for men, respectively [11]. Patients were divided into two groups based on their Hb levels. Patients having anemia were further divided into three subgroups as severe anemia (Hb <8 mg/dL for both genders), moderate anemia (Hb <10 g/dL for both genders), and mild anemia (Hb <13 g/dL for men and Hb <12 g/dL for women). Collected data were compared between these groups.

During the clinical follow-up, erythrocyte transfusion was performed to the patients having Hb levels below 8 g/dL in acute stage, for the rest of the anemic patients, etiologic investigation and treatment were directed according to hematology clinic consultation.

Endovascular Procedure

The endovascular procedure was performed using a femoral artery approach under local anesthesia. 40 U/kg heparin was administered after guiding sheath placement. In all cases, a triaxial system was used to deliver the stent retriever (Preset™, Phenox GmbH, Bochum, Germany).

Statistical Analysis

All statistical analyses were performed by using Statistical Package for Social Sciences (SPSS) version 11.5 package programme (SPSS Inc., Chicago, IL, USA). Mean and standard deviation were used for the presentation of normally distributed continuous variables, and median values (minimum–maximum) were used for non-parametric continuous variables. Frequencies and percentages were used while presenting the categorical data. For variables which met parametric test conditions, Student *t* test and for others Mann-Whitney U test were used for two group comparisons. For the evaluation of categorical variables, chi-square (χ^2) test and if needed, Fisher exact test were used. Comparisons were made between anemic and non-anemic stroke patients in terms of demographics, comorbidities and laboratory characteristics on admission, poor clinical outcome and mortality (mRS = 3–6) at 3rd month after stroke onset. Furthermore, we used bivariate and multiple logistic regression analysis to determine effect on mortality. All probability values were calculated by assuming a two-sided p value of <0.05 with confidence intervals (CI) at the 95% level.

Results

Totally 90 adult acute stroke patients were enrolled in this study and 44 (48.8%) of them were male. The mean age of study population was 61.4 ± 1.2 years. We achieved to give intravenous tissue plasminogen activator (iv-tPA) treatment to 53 patients (58.8%). Mean Hb and Htc levels were 10.2 ± 1.6 g/dL and 31.8 ± 5.5% in anemic group, 14.0 ± 1.5 and 41.9 ± 4.8 in non-anemic group, respectively (Table 1). The characteristics of patients with anemia and non-anemia are shown in Table 1.

Forty patients (44.4%) had anemia and the rest 50 patients (55.6%) were non-anemic. Hematocrit levels were under normal values in 59 patients (65.5%). Hemoglobin levels were found to be under 10 g/dL in 14 cases (15.5%) and below 8 g/dL in four cases (4.4%). A good functional outcome (mRS 0–2) was detected in 25 out of 40 (62.5%) anemic stroke patients and 31 out of 50 (62%) non-anemic stroke patients. When the patients were evaluated according to the subgroups based on Hb levels; a good functional outcome (mRS 0–2) could be achieved in 46.2% of patients with Hb levels below 10 g/dL; whereas it was found to be in 64.8% of the patients with Hb levels above 10 g/dL. None of the patients with Hb levels below 8 g/dL had a good functional outcome. This ratio was 52% for the patients with Hb levels above 8 g/dL.

In a multiple logistic regression analysis with mortality as dependent variable, Hb level below 10 g/dL was a significant predictor for mortality together with symptomatic hemorrhage, mTICI 1–2a recanalization and ASPECT score ≤6 independently from stroke severity, age and risk factors (p = 0.032, OR 9.07 for Hb level below 10 g/dL) (Table 2).

Anemic and non-anemic groups were similar regarding demographic characteristics, risk factors, successful revascularization rates (mTICI 2b–3), recanalization times. A statistical significance was found in the correlation between anemia and poor clinical outcome (mRS 3–6) only in the subgroup of patients having Hb below 8 g/dL (p = 0.003).

Time between symptom onset and groin puncture were similar in both anemic and non-anemic patients (268.1 ± 88.1 (125–420) vs. 243.7 ± 71.4 (120–380), respectively).

Table 1. Demographic, procedural, and outcome data for all patients

Characteristic	Anemia (n = 40)	Without anemia (n = 50)	p value
Sex (male)	16	27	0.251
Age	63.3±10.6 (39–80)	60±12.3 (31–82)	0.069
Smoking	6	14	0.117
Hypertension	30	27	0.057
Atrial fibrillation	15	14	0.303
Diabetes mellitus	14	10	0.098
Heart failure	4	2	0.398
LDL	115.8±33.9	118.1±27.4	0.425
Hemoglobin, g/dL	10.2±1.6 (5–12)	14±1.5 (10–18)	0.097
Hematocrit, %	31.8±5.5 (16–41)	41.9±4.8 (27–55)	0.653
NIHSS	13.9±3.7 (6–22)	13.2±4.2 (6–23)	0.756
ASPECT 8–10	32	45	0.232
mTICI 2b–3	32	37	0.416
mRS 0–2	24	30	0.954
IV tPA	13	21	0.376
Time between symptom onset and groin puncture	268.1±88.1 (125–420)	243.7±71.4 (120–380)	0.821
Collateral scoring (moderate-good)	32	43	0.947
Symptomatic hemorrhage	3	5	0.958

mTICI, modified treatment in cerebral ischemia; mRS, modified Rankin scale; ASPECT, Alberta Stroke Program Early CT score; IV tPA, intravenous tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; LDL, low-density lipoprotein.

Table 2. Multiple logistic regression analysis of factors affecting mortality

Variable	OR	95% CI for OR	p
Symptomatic hemorrhage	74.921	4.925–1,139.79	0.002
mTICI 1–2a recanalization	21.28	3.086–142.86	0.002
Hb levels below 10 g/dL	9.077	1.215–67.823	0.032
ASPECT score <7	8.447	0.856–83.364	0.068

mTICI, modified treatment in cerebral ischemia; Hb, hemoglobin; ASPECT, Alberta Stroke Program Early CT score.

Discussion

Anemia is quite frequent among AIS patients. In different series, anemia was reported in 6–40% of this patients group [2–4, 6]. Moreover it is widely suggested to be related with poor functional outcome and even with increased mortality [5–14]. Consistent with these reports, 44% of our study population was anemic. Milionis et al. [13] recently reported an investigation about short- and long-term clinical effects of anemia in AIS patients and revealed that anemic stroke patients had an increased mortality rate. In addition, when the stroke patients are assessed on the 7th day, 3rd month, and 12th month after the onset of stroke, good functional outcome was reported to be more prevalent among non-anemic patients in the same study [13]. Kellert et al. [10] (n = 217) reported worse clinical outcome and increased mortality

rates at the third-month assessment in anemic AIS patients. Similarly, in two different studies conducted on larger patient populations, De Fabbro et al. [14] (n = 890) and Tanne et al. [1] (n = 859) demonstrated an increased first-year mortality rate in anemic ischemic and hemorrhagic stroke patients compared with non-anemic stroke patients. In addition, a pooled analysis of 13 cohort studies revealed a 39% increased mortality rate in anemic stroke patients compared with non-anemic ones based on some subgroup analyses. However, in contrast, a small number of clinical studies did not find any significant relation between anemia and mortality rate in stroke patients [15–19].

In most of the clinical studies on ischemic stroke patients, anemia is widely defined as Hb levels below 12 g/dL for women and below 13 g/dL for men and anemia is reported to be related with poor clinical outcome and mortality based on this definition. None of the studies above classified anemia regarding its severity. In our study, we preferred to make the comparisons between three anemic subgroups and eventually we found a significant difference in terms of poor clinical outcome and mortality only in the severely anemic subgroup (Hb <8 g/dL).

The parameters that determine the arterial oxygen content are Hb level and arterial oxygen saturation. Arterial oxygen content and blood flow together determine the amount of tissue oxygen supply. As it can be easily seen from this equation, a decrease in Hb level is directly related with a decrease in oxygen amount-reaching tissues. The mechanisms by which anemia causes poor clinical outcome in AIS patients are still not fully elucidated [20]. Cerebral vascular autoregulation in healthy anemic individuals is maintained through several mechanisms. Heart rate, cardiac output, and cerebral blood flow increase, respectively. Subsequently, cerebral vasodilatation occurs and following elevated nitric oxide levels, cerebral blood flow increases. Eventually, continuous oxygen supply to cerebral arteries is maintained. After an ischemic stroke, oxygen transport capacity through the pial collaterals to penumbra and surrounding oligemic area is tried to be maintained with a cerebral autoregulation system [10]. In healthy anemic individuals, although anemic hypoxia can be tolerated up to Hb levels of 5–7 g/dL, the best toleration occurs at a Hb level of approximately 8 g/dL. Maximal cerebral vasodilatation may occur up to this level [20]. Especially at Hb levels below 5–7 g/dL, progressive tissue hypoxia and brain dysfunction begin to develop.

In anemic ischemic stroke patients, particularly in the presence of impaired vital parameters or in the presence of concomitant risk factors, the toleration cutoff for Hb level may change. Therefore, these patients become more sensitive to anemic hypoxia [20–22]. Low oxygen content of collateral flow cannot maintain tissue viability and cannot provide for metabolic requirements of penumbral area. Oxygen demand of penumbral tissue and oligemic areas cannot be met and as a result, penumbral infarct develops, and poor clinical outcome and mortality rate will increase [23]. Consistently, animal studies also confirm the fact that anemic hypoxia aggravates primary neurologic injury [24, 25]. However, in clinical practice, either the optimal Hb or Htc value to provide the penumbral area for increased oxygen demand or minimum tolerable Hb level in anemic AIS patients are not clear yet.

Although successful recanalization was achieved, there were no additional risk factors other than hypertension and there was a short time between symptom onset and recanalization; the clinical outcomes of 3 out of 4 of our cases were bad (mRS 6). Although clear-cut conclusions cannot be made from our results because of the small sample size, we suggest that in anemic AIS patients, especially with proximal vessel occlusion and Hb <8–10 g/dL, cerebral autoregulation probably becomes insufficient for the increased metabolic demands of penumbral area and eventually anemia most likely aggravates the hypoxic injury. In addition, as our study demonstrated a poor functional outcome in moderate to severe anemic patients, we suggest that mechanical thrombectomy may result in poor functional outcome as well as mortality in the severely anemic AIS patients. Clinicians should keep this in mind

during performing mechanical thrombectomy. Further studies with a larger number of patients and prospective design are needed to confirm these results.

Our study has several limitations. First of all, as the sample size was rather small, it would need to be larger for convincing statistical significance. We described that all 4 patients with severe anemia had died until 10 days after stroke onset, so the causes of death were unclear. We think the causes of death were underlying disease of severe anemia that most likely aggravates the hypoxic brain injury.

Conclusion

Our study demonstrated a poor functional outcome only in moderate to severe anemic patients. Based on these findings, we suggest that mechanical thrombectomy may result with poor functional outcome as well as mortality in the severely anemic stroke patients. Clinicians should keep in mind the negative effect of moderate to severe anemia in clinical course of acute stroke patients treated with mechanical thrombectomy.

Disclosure Statement

The authors have no financial disclosures to declare and no conflicts of interest to report.

References

1 Tanne D, Molshatzki N, Merzeliak O, Tsabari R, Toashi M, Schwammenthal Y: Anemia status, hemoglobin concentration and outcome after acute stroke: a cohort study. BMC Neurol 2010;10:22.
2 Corona LP, Duarte YA, Lebrao ML: Prevalence of anemia and associated factors in older adults: evidence from the SABE Study. Rev Saude Publica 2014;48:723–731.
3 Li L, Yiin GS, Geraghty OC, Schulz UG, Kuker W, Mehta Z, Rothwell PM; Oxford Vascular Study: Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. Lancet Neurol 2015;14:903–913.
4 Liu ZY, Deng W, Zhang RY, Huang JP, Wang XF, Qian DG, Xu J, Jin L, Wang XF: Anemia, physical function, and mortality in long-lived individuals aged 95 and older: a population-based study. J Am Geriatr Soc 2015;63:2202–2204.
5 Nybo M, Kristensen SR, Mickley H, Jensen JK: The influence of anaemia on stroke prognosis and its relation to N-terminal pro-brain natriuretic peptide. Eur J Neurol 2007;14:477–482.
6 Li Z, Zhou T, Li Y, Chen P, Chen L: Anemia increases the mortality risk in patients with stroke: A metaanalysis of cohort studies. Sci Rep 2016;6:26636.
7 Huang WY, Chen IC, Meng L, Weng WC, Peng TI: The influence of anemia on clinical presentation and outcome of patients with first-ever atherosclerosis-related ischemic stroke. J Clin Neurosci 2009;16:645–649.
8 Bang OY, Ovbiagele B, Kim JS: Nontraditional risk factors for ischemic stroke: an update. Stroke 2015;46:3571–3578.
9 Tsai CF, Yip PK, Chen CC, Yeh SJ, Chung ST, Jeng JS: Cerebral infarction in acute anemia. J Neurol 2010;257:2044–2051.
10 Kellert L, Martin E, Sykora M, Bauer H, Gussmann P, Diedler J, Herweh C, Ringleb PA, Hacke W, Steiner T, Bösel J: Cerebral oxygen transport failure? Decreasing haemoglobin and haematocrit levels after ischaemic stroke predict poor outcome and mortality: STroke: RelevAnt Impact of haemoGlobin, Haematocrit and Transfusion (STRAIGHT) – an observational study. Stroke 2011;42:2832–2837.
11 Kellert L, Herweh C, Sykora M, Gussmann P, Martin E, Ringleb PA, Steiner T, Bösel J: Loss of penumbra by impaired oxygen supply? Decreasing hemoglobin levels predict infarct growth after acute ischemic stroke. Stroke: Relevant Impact of Hemoglobin, Hematocrit and Transfusion (STRAIGHT) – an observational study. Cerebrovasc Dis Extra 2012;2:99–107.
12 Chang YL, Hung SH, Ling W, Lin HC, Li HC, Chung SD: Association between ischemic stroke and iron-deficiency anemia: a population-based study. PLoS One 2013;8:82952.
13 Milionis H, Papavasileiou V, Eskandari A, D'Ambrogio-Remillard S, Ntaios G, Michel P: Anemia on admission predicts short and long-term outcomes in patients with acute ischemic stroke. Int J Stroke 2015;10:224–230.

14 Del Fabbro P, Luthi JC, Carrera E, Michel P, Burnier M, Burnand B: Anemia and chronic kidney disease are potential risk factors for mortality in stroke patients: a historic cohort study. BMC Nephrol 2010;11:27.
15 Hao Z, Wu B, Wang D, Lin S, Tao W, Liu M: A cohort study of patients with anemia on admission and fatality after acute ischemic stroke. J Clin Neurosci 2013;20:37–42.
16 Sico JJ, Concato J, Wells CK, Lo AC, Nadeau SE, Williams LS, Peixoto AJ, Gorman M, Boice JL, Bravata DM: Anemia is associated with poor outcomes in patients with less severe ischemic stroke. J Stroke Cerebrovasc Dis 2013; 22:271–278.
17 Wade JP, Taylor DW, Barnett HJ, Hachinski VC: Hemoglobin concentration and prognosis in symptomatic obstructive cerebrovascular disease. Stroke 1987;18:68–71.
18 Bhatia RS, Garg RK, Gaur SPS, Kar AM, Shukla R, Agarwal A, Verma R: Predictive value of routine hematological and biochemical parameters on 30-day fatality in acute stroke. Neurol India 2004;52:220–223.
19 Lasek-Bal A, Holecki M, Steposz A, Duława J: The impact of anemia on the course and short-term prognosis in patients with first ever ischemic stroke. Neurol Neurochir Pol 2015:49:107–112.
20 Lelubre C, Bouzat P, Crippa IA, Taccone FS: Anemia management after acute brain Injury. Crit Care 2016;20: 152.
21 Weiskopf RB, Toy P, Hopf HW, Feiner J, Finlay HE, Takahashi M, Bostrom A, Songster C, Aminoff MJ: Acute isovolemic anaemia impairs central processing as determined by P300 latency. Clin Neurophysiol 2005;116: 1028–1032.
22 Gottesman RF, Sojkova J, Beason-Held LL, An Y, Longo DL, Ferrucci L, Resnick SM: Patterns of regional cerebral blood flow associated with low hemoglobin in the Baltimore Longitudinal Study of Aging. J Gerontol Biol Sci Med Sci 2012;67:963–969.
23 Hsiao KY, Hsiao CT, Lin LJ, Shiao CJ, Chen IC: Severe anemia associated with transient ischemic attacks involving vertebrobasilar circulation. Am J Emerg Med 2008;26:382.3–4.
24 Todd MM, Wu B, Warner DS: The hemispheric cerebrovascular response to hemodilution is attenuated by a focal cryogenic brain injury. J Neurotrauma 1994;11:149–160.
25 Allport LE, Parsons MW, Butcher KS, MacGregor L, Desmond PM, Tress BM, Davis SM: Elevated hematocrit is associated with reduced reperfusion and tissue survival in acute stroke. Neurology 2005;65:1382–1387.