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Original article

Elevated hemoglobin is associated with poor prognosis in Tibetans with poor-grade aneurysmal subarachnoid hemorrhage after clipping: A Retrospective Case-Control Study

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ABSTRACT

Objectives. – High hemoglobin (HGB) concentration is frequently seen in Tibetans in clinical practice; however, the impact on postsurgical prognosis in patients with poor-grade aneurysmal subarachnoid hemorrhage (aSAH) is not precisely known. Thus, we sought to understand the association between high HGB level and postoperative outcome in Tibetans with poor-grade aSAH.
Patients and methods. – Results of clipping in consecutive Tibetan patients with poor-grade aSAH were analyzed retrospectively for the period January 2012 to January 2017. Based on the upper limit (160 g/L) of normal hemoglobin levels, patients were divided to a high (HHC) and a normal (NHC) HGB-level cohort according to the first routine blood result on admission. Propensity score matching was used for baseline matching in the 2 cohorts. Postoperative complications in the 2 groups were compared. Prognosis after ictus, including 6-month neurological functional status and mortality at 30 days and 6 months were also assessed.
Results. – Risk of ischemia, pulmonary embolism and lower-limb deep venous thrombosis (DVT) was higher in HHC than NHC (62.88% vs. 21.64%; $P<0.001$; 10.30% vs. 1.31%, $P<0.005$; 24.74% vs. 7.21%, $P<0.001$, respectively). Hospital stay also differed significantly (15.82 ± 3.86 vs. 10.37 ± 4.80 days; $P<0.001$). Out of the 194 patients, 150 survived at 6 months. At 6-month neurological functional follow-up, 8 NHC patients had favorable modified Rankin scale (mRS) scores ≤ 2 at discharge, versus only 1 HHC patient, showing better outcome in NHC than HHC (8.25% vs. 1.03%; $P=0.035$). In-hospital mortality was significantly greater in HHC than NHC (17.52% vs. 7.22%; $P=0.029$). 30-day post-ictus mortality was 30.93% in HHC versus 14.43% in NHC ($P<0.006$). There was also a significant difference in mortality at 6 months post-ictus (47.42% vs. 18.56%; $P<0.001$).
Conclusion. – High HGB level was associated with increased risk of postsurgical cerebral ischemia, pulmonary embolism and lower-limb DVT and poor prognosis in poor-grade aSAH patients. Preoperative hemodilution therapy might be beneficial in reducing operative complications, reducing hospital stay and improving short-term prognosis for neurological functional recovery in aSAH patients with high HGB concentration, but further detailed research is needed.

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a life-threatening neurosurgical event associated with high morbidity and mortality. [1–3] Despite improvements in critical care and treatment options in recent years, prognosis is still frequently poor in poor-grade aSAH. According to previous studies, surgical clipping of ruptured aneurysms is effective in 30–43% of cases of high-grade aSAH [4,5]. Predictive factors for poor prognosis include rebleeding, ischemia, hydrocephalus and other systemic complications such as pneumonia and sepsis [6]. Of these, ischemia is a major factor for adverse outcome.

Though there have been many studies of aSAH in different populations, studies focusing on Tibetan aSAH patients are scarce. The Tibet plateau is the highest plateau in the world and the indigenous Tibetan people are representative of human populations living at high altitude. The plateau's atmosphere, with low barometric pressure and oxygen-thin air, induces a compensatory increase in

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hematocrit, consistent with the large proportion of Tibetans with high hemoglobin (HGB) concentrations observed in clinical practice. Whether higher hematocrit levels could increase the incidence of stroke has always been controversial, but the latest epidemiologic study revealed that higher hematocrit levels were associated with higher incidence of stroke in the Chinese population [7]. The influence of high HGB concentration on surgical prognosis after aSAH was rarely reported. Therefore, we aimed to analyze the association between high HGB level and postoperative outcome by studying poor-grade aSAH Tibetans undergoing clipping craniotomy.

2. Patients and methods

2.1. Study design

This retrospective case-control study compared surgical outcome between Tibetan poor-grade aSAH patients with high versus normal HGB concentration using the propensity score matching method: i.e., 1–to–1 matching between patients with high and normal HGB levels on the basis of the estimated propensity score of each patient.

2.2. Patient population

The study protocol was approved by the Biological and Medical Ethics Committee (BMEC) of West China Hospital. Consecutive Tibetan patients with poor-grade SAH (Hunt and Hess Grade IV or V at admission) were included from January 2012 to January 2017. On admission, place of residence, routine blood test, biochemical examinations (e.g., hepatic and renal function, electrolytes), and routine coagulation studies were collected immediately, and non-contrast cranial CT, cerebral CT angiography (CTA), Digital Subtraction Angiography (DSA) and CT perfusion were used to check SAH, aneurysm and cerebral ischemia regions for each patient. Based on the upper limit (160 g/L) of normal hemoglobin level, patients were divided to high (HHC) and normal (NHC) HGB-level cohorts according to the first routine blood result on admission. Patients were monitored during their hospital stay and at 6-month follow-up after discharge. Exclusion criteria comprised: diagnosis not confirmed radiologically; patient younger than 18 years; patient not choosing surgical clipping; HGB-level lower than the lower limit of normal (110 g/L); patient lost to follow-up.

2.3. General Management

All patients were managed according to a standard protocol that included intensive care, aneurysm clipping and aggressive prevention and treatment of intracranial hypertension. Head and lung CT scan, cerebral CT angiography and CT perfusion were re-performed on the 3rd day after craniotomy. Bedside Doppler ultrasonography was used routinely to assess lower-limb deep venous thrombosis (DVT).

2.4. Surgery

All surgeries were conducted by the neurovascular team of experienced neurosurgeons. The surgical method was chosen by the surgeons preoperatively and implemented within 24∼48 h of admission. All patients received aneurysm-clipping craniotomy via a pterion approach. Decompressive craniotomy was conducted if necessary. All clipping operations were performed under operative microscopy and followed the principle of minimal invasiveness.

2.5. Endpoints and data collection

In-hospital postoperative complications were noted: hydrocephalus, ischemia, vasospasm, seizure, pulmonary infection, pulmonary embolism, lower-limb DVT, gastrointestinal bleeding, and hospital stay. Two experienced neuroradiologists diagnosed postoperative vasospasm and ischemia by comparing CT angiography/perfusion at admission and 24 h postoperatively. Angiographic vasospasm was defined as > 30% luminal reduction, and postoperative ischemia as > 10% increase in hypoperfusion area. Patients were followed up for at least 6 months. Endpoints comprised: mortality at 30 days, mortality at 6 months post-ictus, and neurological functional status at 6 months post-ictus. Neurological functional status was assessed on modified Rankin Scale (mRS), dichotomized as favorable (mRS 0–2) or unfavorable (mRS 3–6).

2.6. Statistical analysis

Due to the inherent selection bias of retrospective observational studies, one-to-one matching analysis was performed between the HHC and NHC groups on the basis of the estimated propensity scores of each patient; to estimate propensity scores, a function was constructed by logistic regression for the results of surgery according to the patient's clinical characteristics: age, hypertension, diabetes, coronary artery disease, hypercholesterolemia, prior aSAH, current smoking, and current alcohol abuse. Cases in the 2 groups were matched according to similarity in propensity score, without replacement, by the method of nearest-neighbor matching.

Primary analysis compared postoperative complications, mortality at 30 days and 6 months post-ictus, and 6-month neurological functional outcome between HHC and NHC.

The significance threshold was set at $P < 0.05$. The Chi^2 test was used for categorical variables. Continuous variables were expressed as mean ± standard deviation (SD) and analyzed by *t*-test.

3. Results

From January 2012 to January 2017, a total of 327 Tibetan aSAH patients met the inclusion criteria. Places of residence comprised Nyingchi, Chamdo, Lhasa and Gyantse, at altitudes ranging from 3,100 m to 4,000 m. After 79 patients were excluded according to the criteria, 248 patients were eligible: 97 high HGB-level (HHC) and 151 normal HGB-level (NHC). Due to mismatch in baseline characteristics in terms of age between the 2 cohorts, propensity score (PS) matching was implemented. (Table 1) Baseline data were thus well matched, and 194 patients (97 patients per group) were included. After PS matching, mean HGB concentration was 177.2g ± 13.0 g/L in HHC versus 132.7 ± 19.3 g/L in NHC ($P < 0.001$).

In-hospital postoperative complications and outcomes according to group are shown in Table 2. Rates of ischemia, pulmonary embolism and lower-limb DVT were higher in HHC than NHC (respectively: 62.88% vs. 21.64%, $P < 0.001$; 10.30% vs. 1.31%, $P < 0.005$; 24.74% vs. 7.21%, $P < 0.001$). There was a significant difference in hospital stay (15.82 ± 3.86 vs. 10.37 ± 4.80, $P < 0.001$). Incidence of hydrocephalus, vasospasm, seizure, pulmonary infection and gastrointestinal bleeding did not significantly differ between groups (respectively: 16.49% vs. 16.46%, $P = 0.821$; 20.61% vs. 18.55%, $P = 0.603$; 7.21% vs. 6.18%, $P = 0.711$; 31.96% vs. 35.05%, $P = 0.354$; 29.90% vs. 28.87%, $P = 0.889$).

One hundred and fifty of the 194 patients were alive at 6 months. In-hospital mortality was significantly higher in HHC than NHC (17.52% versus 7.22%; $P = 0.029$). Thirty-day post-ictus mortality in HHC was much higher in HHC than NHC (30.93% versus 14.43%; $P < 0.006$). At 6 months after ictus, mortality in HHC was

Table 1
Matching Baseline Data by Propensity Score Matching (PS Matching).

	Before PS Matching			After PS Matching		
	HHC (n = 97)	NHC (n = 151)	P	HHC (n = 97)	NHC (n = 97)	P
Age, yrs	51.61 ± 14.55	55.90 ± 12.09	0.017	51.61 ± 14.55	52.34 ± 13.68	0.719
Male	57	78	0.273	57	60	0.660
Time from ictus, h	13.57 ± 12.86	13.03 ± 13.02	0.749	13.57 ± 12.86	13.46 ± 13.21	0.953
Hypertension	49	62	0.144	49	50	0.886
Diabetes	28	45	0.875	28	28	1.000
Coronary artery disease	7	12	0.833	7	6	0.774
Hypercholesterolemia	9	14	0.999	9	11	0.637
Prior aSAH	2	5	0.708	2	2	1.000
Current smoking	61	90	0.605	61	63	0.765
Current alcohol abuse	68	110	0.639	68	70	0.751

HHC: high HGB-level cohort; NHC: normal HGB-level cohort; aSAH: aneurysmal Subarachnoid Hemorrhage.

Table 2
Postoperative complications and prognosis in HHC versus NHC.

	HHC (n = 97)	NHC (n = 97)	P
Part 1 Complications			
Hydrocephalus	16	15	0.845
Ischemia	61	21	< 0.001
Vasospasm	20	18	0.717
Seizures	7	6	0.774
Pulmonary infection	31	34	0.648
Pulmonary embolus	10	1	0.005
Lower-limb DVT	24	7	< 0.001
Gastrointestinal bleeding	29	28	0.875
Hospital stay (days)	15.82 ± 3.86	10.37 ± 4.80	< 0.001
Part 2 Follow-up			
Neurological functional status[a]			0.035
Favorable	1	8	
Unfavorable	96	89	
Mortality			
IHM	17/97	7/97	0.029
1 month	13/80	7/90	0.006
6 months	16/67	4/83	< 0.001

HHC: high HGB-level cohort; NHC: normal HGB-level cohort; IHM: in-hospital mortality; DVT: deep venous thrombosis.
[a] Neurological functional status was assessed at 6 months post-ictus.

47.42%, about 2.5-fold higher than in NHC (18.56%; P < 0.001). In both groups, neurological functional outcome at 6 months post-ictus was unsatisfactory; in all, only 9 poor-grade aSAH patients had favorable outcome. However, 8 NHC patients had mRS scores ≤ 2, which was much more than only 1 HHC patient, showing better outcome in NHC than in HHC (8.25% vs. 1.03%; P = 0.035).

4. Discussion

Aneurysmal subarachnoid hemorrhage is a life-threatening neurovascular event with high incidence of poor prognosis. [8] Research data for aSAH patients living on high-altitude plateaus are scarce. Consistent with previous reports, a high rate of elevated HGB concentration in Tibetan patients' blood was seen during our clinical activities and research.[9–11] In this retrospective observational study, we aimed to study the relationship between this high HGB level and postsurgical prognosis in Tibetan poor-grade aSAH patients, by comparing in-hospital complications and post-ictus outcomes between a high HGB-level cohort (HHC) and a normal HGB-level cohort (NHC).

In our series, not all the Tibetan patients had high HGB levels. The Tibet plateau has typical high-altitude atmosphere with oxygen-thin air [12]. In that environment, HGB and hematocrit (Hct) increase due to the stimulatory effects of hypoxia on erythropoietin production, and are modulated by physiological factors affecting arterial oxygenation, red blood-cell production and plasma volume [12]. Interestingly, previous reports noted that elevation of Hct and HGB was less pronounced in Tibetan than in Andean populations at similar high altitude [13]. And Lorna et al. explained that higher average levels of effective alveolar ventilation in Tibetan individuals might lessen the physiological need for Hct and HGB compensation [12]. In addition, prior investigations showed that the mean level of HGB in Tibetans varied according to gender, age and altitude. Garruto et al. reported that, in general, adult and male Tibetans had higher HGB levels than juveniles and females, and that mean HGB in individuals living above 3,800 m altitude was significantly higher, at 157 g/L–169 g/L, than in those living around 3,200 m (135 g/L–157 g/L) [9]. In our study, PS matching eliminated age and gender differences, but altitude ranged from 3,100 m in Nyingchi to 4,000 m in Gyantse. Therefore, to the best of our knowledge, altitude of residence may induce variation in HGB level.

According to our results, high HGB was associated with longer hospital stay and more severe complications in terms of cerebral ischemia, pulmonary embolism and lower-limb DVT in poor-grade aSAH survivors. As research focusing on aSAH in the Tibetan population is lacking, no feasible theories explaining the distinctive pathogenesis seen in our series have been proposed to date. We suggest that high HGB is a risk factor for thrombotic complications, especially in poor-grade aSAH individuals with long hospital stay. Therefore, we put forward the "hemoglobin, blood viscosity, thrombosis and infarction" hypothesis. Following poor-grade aSAH, intracerebral pressure increases strongly and hence reduces the perfusion pressure associated with low flow in the neurovascular system. Longer postsurgical care is required for poor-grade aSAH patients. Besides long bed-rest, known to be a risk factor for DVT [14], high hemoglobin levels are widely believed to be risk factors for high blood viscosity. [15–17]. Several studies demonstrated the mechanism of high blood viscosity contributing to cerebral infarction on the basis of tiny thrombosis formation in the cerebral circulation system [18–20]. Similarly, in poor-grade aSAH individuals with high hemoglobin concentration, hypercoagulable state and thrombosis may more easily arise in the neurovascular, pulmonary vascular and deep venous systems, especially during prolonged decubitus with low circulatory flow. The association of high hemoglobin levels, increased blood viscosity and thrombosis formation may be the mechanism leading to the high incidence of cerebral infarction, pulmonary embolism and lower-limb DVT in poor-grade aSAH patients. According to previous literature reports, vasospasm secondary to aSAH is the most important risk factor for cerebral infarction [21,22]. Interestingly, the incidence of postsurgical cerebral ischemia in HHC is nearly 3-fold higher than in NHC, but without significant difference in terms of postsurgical vasospasm risk, indicating high incidence of non-vasospastic ischemia in high HGB-level aSAH individuals. Moreover, several studies reported that the incidence of cerebral ischemia did not decrease with reduction in vasospasm [23,24].

Thus, high hemoglobin concentrations may be a major risk factor for non-vasospastic ischemic stroke in poor-grade aSAH patients.

Regarding hospital stay and prognosis in the two cohorts, significantly longer stay and higher rates of unfavorable neurological functional outcome were observed in the HHC group. In terms of survival, the mortality in HHC was greater than in NHC, whether in hospital, 30 days after ictus or at 6 months post-ictus. Consistent these findings, Tanne et al. reported increased mortality at 1 month and 1 year in case of elevated HGB following acute ischemic stroke [25]. Perrotta PL et al. reported that the potential benefit of transfusion by increasing oxygen-carrying capacity could be counterbalanced by risk of acute complications, including infection, hemolytic reactions, volume overload, and further activation of adverse biological or inflammatory processes [26]. Concerning anemia due to chronic kidney disease, Singh et al. found that increasing hemoglobin concentration by pharmacologic treatment with erythropoietin-stimulating proteins could increase mortality [27]. A systematic review of hemodilution trials found no improvement in overall survival or functional outcome in acute ischemic stroke [28]. There is, however, insufficient evidence that elevated HGB at admission is associated with poor outcome after aSAH.

The present study had certain limitations. Firstly, the study design was non-randomized, retrospective, observational and single-center; causality could therefore not be inferred from the observed associations. Secondly, data were based on inpatient records and short-term follow-up, while long-term prognosis remained uncertain due to lack of more follow-up information. Finally, only preoperative HGB levels at admission and not postoperative levels were analyzed, and the results could therefore not exclude effects of change in HGB levels during therapy.

Apart from Tibetan people, high HGB concentrations are widely observed in other populations living at high altitude [12,13]. Triple-H (Hypervolemic, Hypertensive, Hemodilution) therapy is widely used for aSAH, [29–32]; however, there remains controversy as to whether therapeutic hemodilution may cause delayed cerebral ischemia by a decrease in the oxygen-carrying capacity of blood [33]. The optimal hemoglobin value for high-HGB patients under hemodilution therapy remains unclear. Given the lack of clinical trials, we suggest that decreasing the HGB level back to normal might be the safest and most beneficial attitude in aSAH patients with high HGB. In future, further research should aim at determining the range of hemoglobin concentrations which improve overall survival and functional outcome for aSAH patients with elevated HGB.

5. Conclusion

To date, studies of aSAH in the Tibetan population remain lacking. The present study revealed that high HGB levels were associated with increased risk of postsurgical cerebral ischemia, pulmonary embolism, lower-limb DVT and poor prognosis in poor-grade aSAH patients. The probable mechanism concerns thrombosis due to HGB elevation associated with increased blood viscosity. For aSAH individuals with high HGB, preoperative hemodilution therapy may be a means of reducing complications, shortening hospital stay and improving short-term prognosis for neurological functional recovery. Further research is needed to determine the optimal cut-off value for HGB in Tibetan aSAH patients, so as to optimize postoperative prognosis.

Disclosure of interest

The authors declare that they have no competing interest.

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