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Effect of Intravenous Iron Supplementation on Acute Mountain Sickness: A Preliminary Randomized Controlled Study

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Manuscript Preparation E
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Background:

The aim of this study was to assess the role of intravenous iron supplementation in the prevention of AMS.

Material/Methods:

This was a randomized, double-blinded, placebo-controlled study. Forty-one (n=41) healthy Chinese low-altitude inhabitants living in Beijing, China (altitude of about 50 meters) were randomly assigned into intravenous iron supplementation (ISS group; n=21) and placebo (CON group; n=20) groups. Participants in the ISS group received iron sucrose supplement (200 mg) before flying to Lhasa, China (altitude of 4300 meters). Acute mountain sickness (AMS) severity was assessed with the Lake Louise scoring (LLS) system within 5 days after landing on the plateau (at high altitude). Routine check-ups, clinical biochemistry, and blood tests were performed before departure and 24 h after arrival.

Results:

A total of 38 participants completed the study (ISS group: n=19; CON group: n=19). The rate of subjects with AMS (LLS>3) was lower in the ISS group compared with the CON group, but no significant differences were obtained (P>0.05). There were no differences in patients' baseline characteristics. The physiological indices were similar in both groups except for serum iron concentrations (19.44±10.02 vs. 85.10±26.78 μmol/L) and transferrin saturation rates (28.20±12.14 vs. 68.34±33.12%), which were significantly higher in the ISS group (P<0.05). Finally, heart rate was identified as a contributing factor of LLS.

Conclusions:

These preliminary findings suggest that intravenous iron supplementation has no significant protective effect on AMS in healthy Chinese low-altitude inhabitants.

MeSH Keywords:

Administration, Intravenous • Altitude Sickness • Randomized Controlled Trial

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Background

People ascending to high altitudes may experience a series of clinical symptoms that include headache, vomiting, loss of appetite, and confusion. Collectively, these nonspecific symptoms are known as acute mountain sickness (AMS). AMS can cause adverse health effects and seriously impact a person's physical function; in some severe cases, it may result in high-altitude cerebral edema (HACE) or high-altitude pulmonary edema (HAPE). The condition is therefore a potential threat to people traveling to a high-altitude plateau [1,2]. The primary causes of AMS are high altitude and hypoxia; indeed, hypoxia-induced pulmonary abnormalities are directly related to the development of the disease. Cold temperatures, fatigue, respiratory tract infection, and mental stress can result in increased consumption of oxygen, which may induce and aggravate AMS [3–5].

Previous studies have indicated that some drugs may prevent AMS, but these prophylactic interventions may be accompanied with serious adverse effects [6]. Recently, clinical trials with healthy volunteers suggested that intravenous iron supplementation may protect against AMS. It was hypothesized that the protective effects might result from the impact of iron supplements on the pathological and physiological responses to hypoxia. In addition, the preventative effect may be due to iron supplements easing pulmonary hypertension that may result from severe iron deficiency [7,8]. In order to test these hypotheses, a perspective, randomized, double-blinded, placebo-controlled study was carried out to determine the role of intravenous iron supplementation in the prevention of AMS.

Material and Methods

Patients

This was a perspective, randomized, double-blinded, placebo-controlled study (Application number: ChiCTR-TRC-13003590). A total of 61 healthy Chinese adult male and female volunteers residing in Beijing (low-altitude, altitude of 20 to 60 meters) for more than 10 years were enrolled in the study. The participants had never ascended to an altitude above 3000 meters. We excluded patients with: 1) coronary heart disease; 2) severe hypertension (systolic/diastolic blood pressure higher than 140/90 mmHg); 3) uncontrolled diabetes (fasting blood glucose higher than 7.0 mmol/L); 4) anemia (hemoglobin less than 120 g/L); 5) bronchial asthma; 6) chronic obstructive pulmonary disease (COPD); 7) liver or kidney dysfunction; and 8) a history of allergies.

The study was approved by the Ethics Committee of the General Hospital of the PLA. All volunteers provided written

informed consent before enrolment and were allowed to leave the study at any time.

Participants were recruited by an independent travel agency. Each participant was attributed a computer-generated 4-digit serial number with the grouping information hidden in the third digit, which was blinded to both participants and researchers. From the 61 participants, 20 were excluded according to the criteria described above. The remaining 41 volunteers were divided into intravenous iron supplementation (ISS group; n=21) and placebo (CON group; n=20) groups.

Treatment

The study protocol is summarized in Figure 1. In August 2013, the participants underwent a regular check-up and fasting blood samples were collected for blood test and serum iron examination at the General Hospital of the PLA (Beijing, altitude of 20 to 60 meters) (Day 0). Then, ISS group participants received an intravenous iron (III) hydroxide sucrose dose of 200 mg in 100 ml saline (Venofer, Impfstoffwerk Dessau-Tornau GmbH, Germany) while CON group individuals received the placebo (100 ml normal saline). Drug administration was carried out by nurses blinded to the study, and iron supplement and placebo were injected in separate rooms. Intravenous fluids containing drug or saline were labeled with the serial number; because the drug solution was not clear, a brown light-shading infusion apparatus (Weigao Medical Group, Weihai, China) was used to mask the grouping. Nurses performed injections according to serial number of participants and I.V. fluid labels.

Twelve hours after drug administration, participants and researchers flew from Beijing to Lhasa, China (approximately 2 hours). One day (24 hours; Day 1) after arrival in Lhasa (altitude 3650 meters), the Standard Lake Louise consensus symptom questionnaire was given to each participant to assess the incidence and severity of AMS. The diagnosis of AMS was based on the Lake Louise Score (LLS), which includes a headache in addition to at least 1 of the following symptoms: gastrointestinal distress (loss of appetite, nausea, vomiting), fatigue/weakness, dizziness/light-headedness, and insomnia (more than just the usual frequent waking). Blood pressure and heart rate of participants were recorded. Blood samples were collected for blood biochemistry assays. The LLS values were examined every morning, and blood pressure and heart rate of participants were examined daily at the same time for the following 4 days (Day 2–5) of high-altitude stay.

Indicators and assessment methods

The primary study endpoint was the AMS rate, and AMS was defined as LLS > 3 [9]. The AMS rate of each group was assessed 24 hours after arrival in the high-altitude city, and once daily

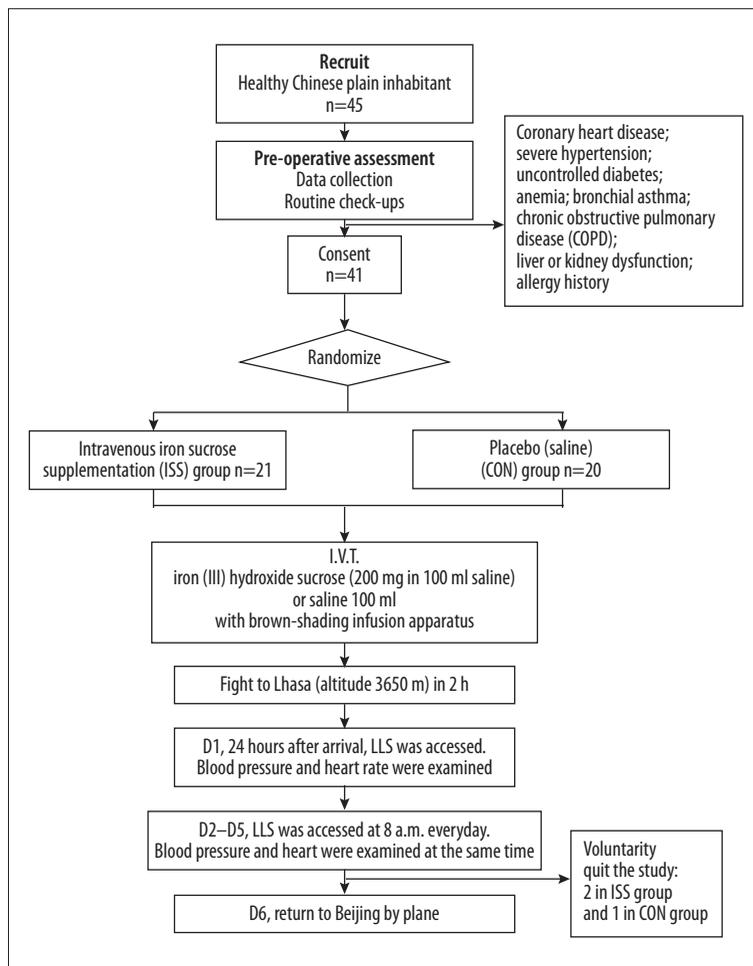


Figure 1. Study protocol.

for 5 days. The highest LLS scores for each time point were considered the final LLS data for corresponding time frame (LLS_1 =LLS of Day 1; LLS_2 =higher LLS value between Day 1 and 2; LLS_3 =highest LLS value of Days 1 through 3; etc.); the highest LLS values in 5 days were taken into account to derive total AMS rates.

Secondary endpoints included blood pressure, heart rate and laboratory indices such as oxygen saturation, hemoglobin, serum iron and transferrin saturation, which were measured at baseline and 24 hours after ascent.

The occurrence of adverse events such as metallic taste, headache, nausea, vomiting, hypotension, parasympathetic nerve stimulation, gastrointestinal dysfunction, muscle pain, fever, varicose veins, or spasm at the infusion site was daily enquired and recorded.

Statistical analysis

Data were analyzed with the SPSS software version 18.0 (SPSS, Chicago, IL, USA). Group comparison was carried out

by the independent samples t-test or Mann-Whitney U test. Proportional differences were evaluated using Fisher's exact test or the chi-square test, as appropriate. Logistic regression analysis was used to investigate the influencing factors of LLS. All tests were 2-sided, and $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of participants

A total of 41 volunteers met the study's inclusion criteria and 38 of them completed the study. Two participants in the ISS group and 1 in the CON group abandoned the study for personal reasons. The baseline characteristics of the participants who completed the study are listed in Tables 1 and 2. There were no differences in age, body weight, blood pressure, heart rate, ferritin, and transferrin saturation between the 2 groups (Table 1). In addition, no differences were observed in sex, smoking status, mild hypertension presence, and mild diabetes rate (Table 2).

Table 1. Baseline Characteristics in the CON and iron supplementation (ISS) groups.

Variables	CON group (n=19)	ISS group (n=19)	t value	P value
Age (years)	40.63±7.74	41.42±8.83	-0.293	0.771
Body mass index (kg/m ²)	24.13±3.74	25.62±3.42	-1.286	0.207
Systolic blood pressure (mmHg)	116.32±17.16	123.37±14.48	-1.369	0.179
Diastolic blood pressure (mmHg)	78.16±11.24	79.05±10.47	-0.254	0.801
Heart rate (bpm)	75.10±8.69	80.50±9.83	-1.237	0.234
Hemoglobin (g/L)	145.37±10.46	146.47±13.43	-0.283	0.779
Serum iron (μmol/L)	18.93±4.83	17.54±7.08	0.709	0.483
Transferrin Saturation (%)	27.42±10.07	30.75±8.23	-1.115	0.272
Total iron binding capacity (μmol/L)	47.07±10.52	52.97±10.95	-1.692	0.099
Transferrin (g/L)	237.00±48.57	257.11±36.48	-1.443	0.158
FVC (L)	3.96±0.82	4.15±1.15	-0.541	0.592
LLS in Beijing	0	0	NA	NA

Table 2. Constituent ratio in the CON and ISS groups.

Variables	Value	CON group (n=19)		ISS group (n=19)		X ²	P value
		n	%	n	%		
Gender	Male	9	47.4	9	47.4	0.000	1.000
	Female	10	52.6	10	52.6		
Smoking	No	15	79.0	14	73.7	Fisher	1.000
	Yes	4	21.0	5	26.3		
Mild hypertension	No	15	79.0	18	94.7	Fisher	0.340
	Yes	4	21.0	1	5.3		
Mild diabetes	No	17	89.5	18	94.7	Fisher	1.000
	Yes	2	10.5	1	5.3		

Data are presented as n (%). Mild hypertension was defined as systolic/diastolic blood pressure between 130/85 and 140/90mmHg. Smokers were defined as those who had ever smoked more than 100 cigarettes and were smoking currently.

Similar AMS rates were obtained in the 2 groups after arrival in the high-altitude city

Twenty-four (24) hours after arrival at Lhasa (altitude 3650 meters) and at 8 a.m. the following mornings (Day 2–5), LLS was assessed for each individual and the group AMS rate calculated. As shown in Table 3, the AMS rate in the ISS group was lower compared with the CON group (26.3 vs. 52.6%) at 24 hours upon arrival in Lhasa; however, the difference was not statistically significant (*P*=0.097). Similarly, no differences

were obtained between both groups in AMS rates during the 4 days of plateau stay (*P*>0.05) (Table 3).

Similar physiological indices were obtained in both groups, except for ferritin level and transferrin saturation rate

The physiological indices obtained for the 2 groups 24 hours after ascent to the high-altitude plateau are summarized in Table 4. The ferritin (serum iron) concentrations were 19.44±10.02 and 85.10±26.78 μmol/L for the CON and ISS

Table 3. Rates of AMS (LLS>3) after ascent to plateau in CON and ISS groups.

Variables	Values	CON group(n=19)		ISS group(n=19)		X ²	P value
		n	%	n	%		
Total AMS	No (LLS≤3)	9	47.4	12	63.2	0.958	0.328
	Yes (LLS>3)	10	52.6	7	36.8		
24 h LLS	≤3	9	47.4	14	73.7	2.754	0.097
	>3	10	52.6	5	26.3		
2 day LLS	≤3	9	47.4	13	68.4	Fisher	0.189
	>3	10	52.6	6	31.6		
3 day LLS	≤3	9	47.4	13	68.4	Fisher	0.189
	>3	10	52.6	6	31.6		
4 day LLS	≤3	9	47.4	12	63.2	Fisher	0.328
	>3	10	52.6	7	36.8		
5 day LLS	≤3	9	94.7%	12	63.2	Fisher	0.328
	>3	10	5.3%	7	36.8		

Wilcoxon post hoc test.

Table 4. Physiological characteristics after ascent to plateau in CON and ISS groups (mean ±SD).

Variables	CON group	ISS group	P value
24 h Systolic blood pressure (mmHg)	128.42±10.94	129.21±13.67	0.845
24 h Diastolic blood pressure (mmHg)	82.11±11.79	85.00±12.88	0.475
24 h Heart rate (bpm)	94.40±8.85	97.75±10.54	0.378
24 h oxygen saturation (%)	82.27±3.41	82.08±5.11	0.912
24 h Hemoglobin (g/L)	143.81±10.92	148.07±13.42	0.886
24 h Serum iron (µmol/L)	19.44±10.02	85.10±26.78	<0.001
24 h Transferrin saturation (%)	28.20±12.14	68.34±33.12	0.003

groups, respectively, a statistically significant difference ($P<0.001$). Compared with the CON group, the transferrin saturation rate in the ISS group was markedly increased (28.20 ± 12.14 vs. $68.34\pm 33.12\%$, $P=0.003$). Systolic and diastolic blood pressure, heart rate, arterial oxygen saturation, and hemoglobin concentration were similar between the ISS and control groups ($P>0.05$) as shown in Table 4.

Adverse reactions of the treatment

No drug adverse events or drug-induced reactions were reported over the course of this study.

Influencing factors of AMS

Logistic regression analysis was used to explore the factors influencing LLS in participants. As shown in Table 5, an odds

ratio (OR) of 1.14 was obtained for heart rate as a contributing factor of LLS and elevated heart rate was related to high LLS values ($P=0.037$). No significant correlation was found between LLS values and other variables, including diastolic blood pressure, sex, and smoking status.

Discussion

The objective of this study was to determine the role of intravenous iron supplementation in the prevention of AMS. Within the first day of landing on the high-altitude plateau in Lhasa, China, changes were obtained in LLS, blood pressure, heart rate, and oxygen saturation level. However, these variables were not significantly different in both groups. Because of strong stimulation by low temperatures, low oxygen partial pressure, and excessive ultraviolet radiation at high altitude, the body may

Table 5. Logistic regression analysis of factors that influence LLS.

Variable	Estimate	P value	OR	95%CI
Diastolic blood pressure (mmHg)	-0.024	0.645	0.98	(0.88,1.08)
Male	-0.59	0.608	0.56	(0.06,5.29)
Smoking	-12.444	0.949	<0.001	(<0.001, >999.9)
24h Heart rate (bpm)	0.134	0.037	1.14	(1.01,1.30)

undergo pituitary adrenal medullary hyperfunction, with increased levels of catecholamines and other substances in the blood circulation, enhanced peripheral resistance, increased central circulation, and hypoxia stimulation. At the same time, secretion of anti-diuretic hormones increases, which results in water and sodium retention. These physiological changes may result from reduced oxygen availability [3–5]. When adaption to rapid ascension to high altitudes is not successful, hypoxia or low-pressure-related diseases may occur. The initial reaction of the participants evaluated here was decreased oxygen saturation, increased heart rate, and elevated blood pressure. In addition to hypoxia, fatigue and insufficient energy intake, smoking cannot be ignored for its effect on AMS. Indeed, studies have shown that smoking slightly reduces the AMS risk and damages, but impairs the long-term acclimation of the lung function during extended stays at high altitude [10,11].

One day after reaching the plateau, serum iron levels and transferrin saturation rates in the ISS group were significantly higher compared with control individuals. The AMS rate (LLS>3) in the ISS group (5/19) showed a non-statistically significant decrease ($P>0.05$) in comparison with the CON group (10/19). There were no significant differences in LLS values between the 2 groups during the following 4 days. These results are not in line with previous studies [8]. Talbot et al. found that prophylactic iron load can reduce the increased AMS rate in rapid ascent to high altitude in healthy volunteers. Iron an important raw material of human blood, and patients with iron deficiency develop anemia symptoms [12]. Some intravenous iron solutions used in clinical settings include dextran iron, ferrous gluconate, and iron sucrose. Their effects on anemia treatment are similar, but the incidences of adverse reactions are different. Iron sucrose has the lowest incidence of adverse events, and has minimum allergy risk and maximum safety [13–15]. Intravenous iron sucrose is a multi-core of ferric hydroxide macromolecular complexes with low toxicity and stable structure. It is not easily cleared by the kidney, does not release the iron ion, and is currently recognized as one of the safest intravenous iron preparations [16].

In the CON group, after staying 1 day at high altitude, no change in hematocrit level was observed. This observation indicates that either hemoglobin concentration is an independent

factor or that the short-term infusion of intravenous iron was not enough to cause changes in hemoglobin concentration. Previous studies have shown that treatment with intravenous iron supplements in patients with chronic heart failure and iron deficiency could alleviate symptoms, functional capacity, and quality of life; none of these effects were related to hemoglobin concentration [17].

Through a number of signal transduction pathways depending on iron, iron-containing proteins have different functions, such as oxygen transport, cell respiration, intermediary metabolism, transcription, and regulation of DNA repair [18,19]. Hypoxia inducible factor (HIF) is an important signal transduction factor in the cell oxygen sensor pathway. The HIF pathway is regulated by concentrations of iron and oxygen. Prolyl hydroxylase and asparaginyl hydroxylase regulate the HIF alpha function subunit, and Fe^{2+} ion is the essential factor for prolyl hydroxylase. Therefore, prolyl hydroxylase cannot effectively act as a sensor and control cell homeostasis when intracellular iron concentrations are low [20,21]. In anoxic conditions, enzymes reduce the decomposition of HIF, which leads to HIF accumulation in cells and subsequent activation of target gene transcription. Iron (Fe^{2+}) is one of the most important limiting factors of these enzymes [22]. It has been proposed that iron may affect cellular oxygen-sensing pathways, but the role of iron under cellular-specific mechanism is unknown; previous studies have found a high expression of the HIF-regulated gene products VEGF and nitric oxide synthase in AMS patients, suggesting a highly significant association between iron and AMS [23,24]. Unfortunately, no study has thoroughly examined the effect of iron on AMS.

After a few days at high altitude, the AMS rates obtained for the 2 groups became closer, compared with the values obtained 24 hours after arrival in the high-altitude plateau city. A plausible explanation is that the LLS is a subjective assessment system. This may be the reason why the complex correlation coefficients and residual standard deviations are large. Another reason is that the selected indicators may not fully represent the risk factors of AMS. A recent study in a rat model of chronic mountain sickness using acetyl-L-cysteine revealed the possible relationship between disturbed metabolism and chronic mountain sickness. The body's normal metabolism will make

some adjustment to adapt to the environment and reaches a steady state in the dynamic equilibrium [25].

An important clinical problem posed by this research is whether iron deficiency may increase susceptibility to AMS or other high-altitude diseases. Although some treatments have been shown to effectively reduce the incidence and severity of AMS, gradually ascending to high altitudes seems to be the best strategy for the prevention of altitude sickness [6].

Previous studies have shown that the relationship between arterial oxygen saturation and AMS are not clear. Bartsch et al. found that after entering the plateau, hypoxic ventilatory response improved, arterial oxygen saturation increased, and the occurrence of AMS symptoms decreased [3]. In contrast, when arterial oxygen saturation decreased, incidence of AMS was higher, with a greater possibility of sodium and water retention and pulmonary edema [26]. Grant et al. reported that in terms of hypoxia reaction processing, although arterial oxygen saturation has obvious individual differences, there is no linear correlation between arterial oxygen saturation and the occurrence of AMS [27].

A number of limitations of this study should be mentioned. All participants were healthy individuals and subjects with

low serum iron or hemoglobin levels were not included (they were more likely to benefit from intravenous iron supplementation). The sample size was not large enough. A recent study [28] found that sleep disorders at high altitude seem to be associated with hypoxemia, but our study did not consider sleep disorders. Although this study excluded patients with severe cardiovascular, respiratory, and metabolic diseases, the differences of individual reaction to hypoxia were not considered. In this study, AMS was diagnosed based on a questionnaire, and an erroneous outcome cannot be excluded. Future studies will include a simple hypoxic challenge test, as previously reported [29,30].

Conclusions

Results from this preliminary study suggest that intravenous iron supplementation has no significant protective effect against AMS in healthy Chinese individuals.

Conflict of interest

The authors declare that they have no conflicts of interest.

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