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Safety and Efficacy of Therapeutic Erythrocytapheresis Treatment in Chronic Mountain Sickness Patients in Shigatse, Tibet, China

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Background: Therapeutic erythrocytapheresis (TEA) is a medical technology that separates erythrocytes from whole blood and has been used in various hematological conditions. However, reports on the use of TEA to treat chronic mountain sickness (CMS) are lacking. The aim of the present study was to evaluate the efficacy, safety, and use of TEA in treatment of CMS.

Material/Methods: A total of 32 patients living in the Shigatse area of Tibet (altitude 4000 m) who had CMS were treated with TEA. Clinical data, CMS score, Borg dyspnea score, 6-min walking test score, and NYHA classification values were collected prior to and after TEA therapy.





Results: TEA treatment significantly increased SpO₂ (93.8±2.6 vs. 80.5±5.8%, *P*<0.001) and decreased red blood cell (5.77±0.70 vs. 7.48±0.67×10¹²/L, *P*<0.001), hematocrit (53.8±5.6 vs. 69.2±4.8%, *P*<0.001) and hemoglobin (178±16 vs. 236±14 g/L, *P*<0.001). Significantly lower systolic and diastolic blood pressure were also noted (*P*<0.001). Echocardiography showed higher left ventricle diameter (4.6±0.4 vs. 4.4±0.5 cm, *P*<0.01). TEA markedly decreased CMS scores (0.45±0.85 vs. 7.58±2.31, *P*<0.001), Borg dyspnea scale scores (0.48±0.73 vs. 0.88±0.81, *P*<0.001), and NYHA classification scores (*P*<0.05). Additionally, there was marked improvement in the 6-min walking test scores (578.5±83.1 vs. 550.4±79.0 m, *P*<0.001). The procedure was well tolerated, with no complications.

Conclusions: Our novel approach of treating CMS patients with TEA safely and effectively reduced erythrocytosis, which remains a fundamental challenge in CMS patients.

MeSH Keywords: **Altitude Sickness • Cytapheresis • Polycythemia**

Abbreviations: **CMS** – chronic mountain sickness; **TEA** – therapeutic erythrocytapheresis; **Hb** – hemoglobin; **RBC** – red blood cell; **SpO₂** – peripheral oxygen saturation; **ALT** – alanine aminotransferase; **AST** – aspartate transaminase; **COPD** – chronic obstructive pulmonary disease; **PT** – prothrombin time; **APTT** – activated partial thromboplastin time; **TG** – triglycerides; **LDL-C** – low-density lipoprotein cholesterol; **GHbA1c** – glycosylated hemoglobin A1c; **CK-MB** – creatine kinase-MB; **NYHA** – New York Heart Association classification

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Background

Chronic mountain sickness (CMS), or Monge's disease, is a clinical syndrome caused by long-term living at high altitudes of more than 2500 meters. It is characterized by excessive erythrocytosis (Hb \geq 190 g/L in female patients, Hb \geq 210g/L in male patients) and severe hypoxemia [1]. The prevalence of CMS is variable among different populations living at different high altitudes and has been reported to be above 30% in plateau regions [2]. The Qinghai-Tibetan plateau is the highest and largest plateau in the world, with a population of >60 million. CMS is a common condition here, with incidence rates of 2.43–37.5% (at elevations 3000–4700 m), and increases with elevation. Compared to native Tibetans, CMS is more prevalent in Han male immigrants (17.8%) [3–6]. CMS not only seriously affects the health and quality of life of plateau residents, but also leads to chronic pulmonary hypertension via various cellular and molecular mechanisms [7–11]; it can cause increased ventricular afterload and finally lead to the development of life-threatening right-heart failure [12–15]. In addition, the excessive erythrocytosis of CMS increases the viscosity of blood, making it thick and sticky, which significantly increases the risk of thrombosis, leading to diseases such as myocardial infarction, pulmonary embolism, and cerebral infarction, resulting in multiorgan dysfunction and death.

Therefore, it is imperative to accurately evaluate and establish effective treatment methods for CMS. Several pharmacological approaches have been employed [1,16–18] but there is no specific medicine suitable for treatment. Phlebotomy is another frequent practice for treating CMS, in which certain volume of whole blood is removed. However, this technique not only decreases red blood mass and hemoglobin, but also causes loss of platelets, albumin, coagulation factor, and leucocytes and results in iron deficiency and volemic imbalance. Therefore, phlebotomy remains impractical for long-term management of CMS [1].

Therapeutic erythrocytapheresis (TEA) has been used as an alternative therapy to treat polycythemia rubra vera and hemochromatosis. It is a sophisticated form of phlebotomy in which cell separators remove red blood cells only, sparing platelets, albumin, and coagulation factors [19–21]. Thus, in the present study, we for the first time used TEA to treat CMS patients. The purpose of this study was to collect clinical data of patients with CMS in the Shigatse area of Tibet at an average altitude of 4000 m and to evaluate the safety and efficacy of TEA in CMS patients.

Material and Methods

Study design

This was a single-center, self-control study. All participants diagnosed with CMS and who received TEA were continuously

enrolled from March to December 2018 while attending the Cardiology Department of Shigatse People's Hospital, Tibet, China.

The study was approved by the Human Research Ethics Committee of Shigatse People's Hospital. All participants provided written informed consent.

Study population

CMS is diagnosed when Hb is \geq 190 g/L in females and \geq 210 g/L in males due to chronic erythrocytosis and with severe hypoxemia. Demographic data, medical history, and smoking status were collected through questionnaire. SpO₂, red blood cells, hemoglobin and hematocrit, blood pressure, liver and renal function, cardiac biomarkers, and electrolytes were regularly tested within 2 days before and after TEA. Echocardiography, 6-min walking test, the New York Heart Association (NYHA) classification, Borg dyspnea scale, and Qinghai CMS score were strictly evaluated and confirmed by 2 independent physicians before and after TEA.

Exclusion criteria were: 1) age \leq 18 or \geq 70 years; 2) NYHA functional class IV heart failure or severe liver or renal dysfunction; 3) cannot tolerate TEA or unable to complete the 6-min walking test; 4) coagulation disorders or high risk of bleeding; and 5) pregnant or lactating women.

Treatment procedure

The TEA technique was performed using a COBE® spectra™(TERUMO BCT) instrument and disposable closed tubes. Room temperature was kept at 25–26°C and all patients were placed in supine position. Two accesses were established on superficial veins connected to tubes, one on the left hand and the other on the right. One tube was used for outflow and the other for inflow. The COBE system software calculated exchange volume according to sex, height, weight, and hematocrit of patients. After removal of RBC, the plasma was returned with 0.9% saline as fluid compensation. Intraoperative heparin was used for anticoagulation. During the TEA procedure, the blood flow was 50–60 ml/min, circulating volume was 2500–3000 ml, and the collection time was limited to 1–2 h. Blood pressure, SpO₂, and heart rate were monitored throughout.

Statistical analysis

All analyses were performed with SPSS, version 13.0 (Chicago, IL, USA). Continuous variables are expressed as mean \pm SD and discrete variables as percentages. The differences in continuous variables between groups were examined by paired-samples *t* test. The differences in discrete variables between groups

were calculated by the Pearson χ^2 test. A *P* value of <0.05 was considered significant.

Results

We enrolled a total of 32 participants diagnosed with CMS, consisting of 5 Han immigrants (15.6%) and 27 native Tibetans (84.4%), living in the Shigatse area of Tibet at an average altitude of 4000 m. Most (96.7%) of the participants were male. The average age of the participating patients was 44 years. Most of the participants had a history of smoking (78.1%), averaging 20 cigarettes per day. The most common disease history of participants was hyperuricemia (78.1%), hypertension (46.9%), and dyslipidemia (28.1%). Two patients had history of stroke and 3 patients had history of COPD (Table 1).

An average of 1457 ± 207 ml blood was taken out during the TEA procedure during a period of about 2 h (Table 2).

Table 3 shows the vital signs and laboratory results before and after TEA treatment. There was significant reduction in concentration of red blood cells, hemoglobin, and hematocrit after TEA treatment ($P < 0.001$). The SpO_2 significantly improved ($P < 0.001$) and systolic blood pressure and diastolic blood pressure reduced to normal range ($P < 0.001$) compared with the values before TEA treatment. The platelet concentration increased and there was little change in albumin, AST, ALT, and electrolytes levels, which indicate that TEA also preserves these components in blood. The decrease in PT and APTT indicate that it prevents the loss of coagulation factors. Significant decreases in serum bilirubin, uric acid, TG, LDL-C, GHbA1c (all $p < 0.01$), creatinine, and CKMB ($P < 0.05$) were also noted.

Table 4 illustrates the echocardiographic measurement of the patients with CMS before and after TEA treatment. Except for the change in left ventricle diameter (4.4 ± 0.5 vs. 4.6 ± 0.4 , $P < 0.01$) no other changes were noted after TEA.

Table 5 shows the efficacy of TEA therapy in CMS patients. The Borg dyspnea scale and Qinghai CMS score decreased significantly (both $P < 0.001$), and the 6-min walking test scores improved significantly ($P < 0.001$), which clearly indicates an improvement in hypoxemia in patients with CMS after treatment with TEA. An improvement in the NYHA classification indicates TEA treatment reduced the risk of heart failure ($P < 0.05$).

Discussion

TEA has been used in treatment of patients with diseases such as polycythemia vera, hemochromatosis, and secondary erythrocytosis [20,22]. Previous studies have found that TEA

Table 1. Baseline characteristics of the participants.

	n	%
Age (yrs)	44±7	
Gender		
Male	31	96.7
Female	1	3.3
BMI (kg/m ²)	25.32±3.60	
History of hypertension	15	46.9
History of DM	1	3.1
History of dyslipidemia	9	28.1
History of smoking	25	78.1
Smoking (cigarettes/day)	20±15	
History of TIA	1	3.1
History of stroke	2	6.3
History of CHD	0	
History of angina	0	
History of COPD	3	9.4
History of hyperuricemia	25	78.1
History of CKD	0	

BMI – body mass index; DM – diabetes mellitus; TIA – transient ischemic attack; COPD – chronic obstructive pulmonary disease; CKD – chronic kidney disease.

Table 2. Parameters of the TEA procedure.

	n
Average blood taken out by TEA (ml)	1457±207
Average duration for TEA (mins)	110±20

is superior to traditional phlebotomy in reducing RBC count, hemoglobin, and hematocrit as it preserves not only the valuable blood components like plasma protein, platelets, clotting factors, and leucocytes, but also maintains the isovolumic balance. TEA has been documented to be rapid, effective, safe, and well tolerated by patients, and achieves long-term control of erythrocytosis and polycythemia [23–25].

CMS is characterized by excessive erythrocytosis in people living at high altitude [1]. The Tibetan population with long-term residence at an altitude of 3000 m to 4500 m can better adapt to hypoxia environment due to their genetic adaptability. Despite this, they still develop CMS in the plateau area. Additionally, both high-altitude natives and Han migrants show susceptibility to CMS in the plateau, but the prevalence of CMS among migrants was significantly higher compared to high-altitude natives [4,5,26]. At high altitude (the average altitude is 4000 m in Shigatse, Tibet, China), the partial pressure of oxygen is

Table 3. Vital signs and laboratory results of CMS patients before and after TEA treatment.

	Before TEA	After TEA	P value
Vital signs			
SpO ₂ (%)	80.5±5.8	93.8±2.6	<0.001
SBP (mmHg)	140±19	120±12	<0.001
DBP (mmHg)	95±14	78±14	<0.001
HR (bpm)	81±11	80±8	0.5
Lab test			
RBC (×10 ¹² /L)	7.48±0.67	5.77±0.70	<0.001
Hb (g/L)	236±14	178±16	<0.001
Hct (%)	69.2±4.8	53.8±5.6	<0.001
Platelet (×10 ⁹ /L)	135±35	159±53	<0.01
ALT (U/L)	49±31	41±20	>0.05
AST (U/L)	30±11	27±6	>0.05
Total protein (g/L)	72±10	65±6	<0.001
Albumen (g/L)	44±6	41±3	0.001
Total bilirubin (umol/L)	36±26	21±10	<0.001
Direct bilirubin (umol/L)	7±2	5±2	<0.01
Bun (mmol/L)	4.1±0.9	3.8±1.1	>0.05
SCr (umol/L)	68.9±13.9	65.1±14.5	<0.05
Uric acid (umol/L)	513.5±124.8	387.5±75.5	<0.001
Blood glucose (mmol/L)	4.7±1.6	4.6±0.8	>0.05
GHbA1C (%)	6.9±1.3	6.5±1.6	<0.01
Cardio biomarkers			
TnT (ng/mL)	0.25±0.05	0.25±0.05	>0.05
CK-MB (ng/mL)	1.58±0.54	1.35±0.53	<0.05
Electrolytes			
Na ⁺ (mmol/L)	141.61±3.23	141.32±2.39	>0.05
K ⁺ (mmol/L)	3.75±0.56	3.89±0.47	>0.05
Cl ⁻ (mmol/L)	104.24±2.98	105.03±2.20	>0.05
Ca ⁺⁺ (mmol/L)	2.33±0.015	2.28±0.13	>0.05
HPO ₄ ⁻ (mmol/L)	1.00±0.18	0.97±0.17	>0.05
Lipids			
TC (mmol/L)	4.37±0.85	3.76±0.64	0.001
TG (mmol/L)	1.34±0.56	1.15±0.66	<0.01
LDL-C (mmol/L)	2.37±0.71	1.91±0.50	0.001
HDL-C (mmol/L)	1.43±0.31	1.35±0.30	>0.05

Table 3 continued. Vital signs and laboratory results of CMS patients before and after TEA treatment.

	Before TEA	After TEA	P value
Coagulation routine			
PT (S)	13.3±3.8	11.4±1.0	<0.01
APTT (S)	41.9±18.8	30.7±5.0	<0.01
D-dimer (mg/L)	0.35±0.25	0.35±0.27	>0.05

SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; RBC – red blood cell; HB – hemoglobin; Hct – hematocrit; ALT – alanine aminotransferase; AST – aspartate transaminase; BUN – blood urea nitrogen; SCr – serum creatinine; GHbA1c – glycated hemoglobin A1c; TnT – troponin T; CK-MB – creatine kinase-MB; Na⁺ – sodium; K⁺ – potassium; Cl⁻ – chloride; Ca⁺⁺ – calcium; HPO₄⁻ – phosphorus; TC – total cholesterol; TG – triglycerides; LDL-C – low density lipoprotein cholesterol; HDL-C – high density lipoprotein cholesterol; PT – prothrombin time; APTT – activated partial thromboplastin time.

Table 4. Echocardiographic measurement in CMS patient before and after TEA.

	Before TEA	After TEA	P value
Diameter of (cm)			
Left atrium	3.2±0.5	3.3±0.5	>0.05
Left ventricle	4.4±0.5	4.6±0.4	<0.01
Right atrium	3.7±0.8	3.6±0.5	>0.05
Right ventricle	3.7±0.7	3.6±0.6	>0.05
Aorta (cm)	3.0±0.4	3.0±0.4	>0.05
Pulmonary artery (cm)	2.3±0.4	2.4±0.4	>0.05
Pulmonary pressure (mmHg)	38.7±11.2	40.3±14.1	>0.05
LVEF (%)	63±7	65±4	>0.05
LVFS (%)	34±5	35±7	>0.05

LVEF – left ventricular ejection fraction; LVFS – Left ventricular fractional shortening.

Table 5. Evaluation of severity of CMS before and after TEA treatment.

	Before TEA	After TEA	P value
6 min walking test (m)	550.4±79.0	578.5±83.1	<0.001
NYHA(n)			<0.05
I	18	27	
II	13	5	
III	1	0	
IV	0	0	
Borg dyspnea scale	0.88±0.81	0.48±0.73	<0.001
Qinghai CMS score	7.58±2.31	0.45±0.85	<0.001

low. This hypobaric hypoxia leads to hypoxemia. Hypoxemia and prolonged hypoxia cause excessive production of red blood cells [27]. Several studies have already shown that excessive erythrocytosis increases blood viscosity, which leads to pulmonary hypertension and cardiac dysfunctions.

To the best of our knowledge, this is the first time TEA was used to treat CMS, not just in Shigatse, but worldwide. We evaluated the beneficial effect of TEA on patients with CMS. After TEA treatment, red blood cell, hematocrit, and hemoglobin concentrations of the participants decreased significantly compared with the values before treatment. This reduced

hematocrit and blood viscosity improved pulmonary vascular resistance, which furthermore reduces the risk of pulmonary hypertension and related cardiac diseases. Moreover, improvement in SpO₂ after TEA treatment indicates reduction in hypoxemia. Improved oxygenation decreases pulmonary artery pressure, preventing progression to severe pulmonary hypertension, decreases right-ventricle overload, and thus prevents cor pulmonale or its progression.

Moreover, reduction of blood urea, creatinine, CKMB, GHbA1c, and bilirubin shows its additive effect in decreasing the risk of cardiovascular and renal complications and reducing long-term morbidity and mortality of CMS patients. After TEA treatment, the platelets concentration increased and liver enzymes, albumin, and electrolytes values were largely unchanged, indicating that TEA preserved important blood components in CMS patients. Reduction in PT and APTT values indicates that the coagulation factors involved in both extrinsic and intrinsic pathways of coagulation were preserved.

The Qinghai CMS score was designed to assess CMS severity on the basis of symptoms of CMS along with changes in hemoglobin [1]. In our study, after TEA treatment, CMS scores decreased, indicating the severity of CMS symptoms were also decreased. Along with this, the Borg dyspnea scale scores, which indicate difficulty of breathing, also decreased, showing that TEA reduced the risk of pulmonary hypertension. Additionally, the improvement observed in 6-min walk test scores and NYHA classification scores provides strong evidence that TEA responded positively to treatment with CMS.

Previous studies have tried to evaluate various pharmacological drugs to treat high-altitude erythrocytosis, but none are widely used since they have major adverse effects, need to be used for longer periods of time, and have little beneficial effect.

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Acetazolamide requires prolonged treatment (24 weeks) and has adverse effects, including paresthesia and diuresis [17]. Similarly, medroxyprogesterone acetate can affect the libido and enalapril has potential risk of systemic hypotension, and these drugs have to be used for longer periods of time [28,29]. In contrast, TEA therapy requires less time, with rapid effectiveness to control symptoms of CMS. Although the present study is just a preliminary study, no adverse effects were observed and the treatment was well tolerated by all patients. Thus, TEA potentially is a valuable and safe initial treatment for CMS to save lives, restore normal life expectancy and improve quality of life of high-altitude residents.

Study limitations

The major drawback of this study is its small sample size. Wider acceptance and use as a safe and effective treatment need further larger-scale study. Additionally, patients from remote mountain areas were at times unable to be followed up regularly; therefore, we could not monitor them for long periods or record any long-term adverse effects. Additional research with a larger population is essential.

Conclusions

In conclusion, this study shows that TEA is an efficient and safe treatment of CMS, which not only decrease excessive erythrocytosis but also preserves the important blood components in CMS patients. Therefore, in the future, it is likely that TEA could be used as primary treatment for CMS.

Conflicts of interest

None.

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