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Original Article

Three-Minute Step Test for Predicting Acute Mountain Sickness: A Post Hoc Analysis of *Rhodiola Crenulata* Extract for Prevention of Acute Mountain Sickness, a Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

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Background: Acute mountain sickness (AMS) often occurs in individuals who rapidly travel above 2,500 m. As the convenience of traveling and the development of mountain sports increase, AMS will become an increasingly important public health problem. However, no method to effectively predict AMS before it occurs is currently available.
Methods: This post hoc study investigated whether the 3-Minute Step Test (3MST), which evaluates physical fitness, is predictive of AMS development. The data collected in "*Rhodiola crenulata* extract for prevention of AMS: a randomized, double-blind, placebo-controlled, crossover trial" was used in the analysis. This study collected 204 observations of 102 participants who made two ascents of Hehuan Mountain (3,100 m) by bus within a 3-month period. Participants completed the 3MST at 250 m (before ascent) and 3,100 m (on Hehuan Mountain). The presence of AMS was accessed using the Lake Louise scoring system.
Results: AMS was identified in 124 observations (60.78%). In the univariate analysis, the pre-departure 3MST score (at 250 m) was not significantly associated with AMS ($p = 0.498$), but the 3MST score measured at 3,100 m, ascent number, pulse rate at 3,100 m, and saturation of peripheral oxygen (SpO_2) measured at 3,100 m were significantly correlated with the occurrence of AMS (p = 0.002, 0.039, 0.005, < 0.001, respectively). In a further multivariate analysis, only SpO_2 measured at 3,100 m had a significant association with AMS (p = 0.016 and 0.006, respectively). The trend analysis showed that for every 1-point increase in the 3MST score at 3,100 m, the AMS decreased by 4% (adjusted odds ratio [AOR] = 0.96, 95% confidence interval [CI] = 0.92–1.01).
Conclusion: The 3MST score cannot be a predictor of AMS, but it may have a potential role in predicting ascent safety in high-altitude areas.

Key words: *acute mountain sickness, three-Minute Step Test, fitness*

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Introduction

Acute mountain sickness (AMS) is a syndrome defined by the Lake Louise Consensus Group as the presence of headache in an unacclimatized person who has recently arrived at an altitude above 2,500 m plus the presence of one or more of the following: gastrointestinal symptoms (anorexia, nausea, or vomiting), insomnia, dizziness, and lassitude or fatigue.[1] While AMS is usually self-limiting, if severe, it may proceed to the more severe disease of high altitude cerebral edema.[2] Taiwan is a mountainous region that attracts many individuals who enjoy mountain activities. Recently, many convenient transportation modes, including buses and trains, have been used to facilitate rapid ascents to altitudes over 2,500 m. Therefore, many people with no mountaineering experience often travel to high altitudes and may have a high risk of AMS. The incidence of AMS reported in adults worldwide varies from 9 to 84% depending on several different factors.[3-11] The literature indicates that the rate of ascent, the altitude reached, and the sleeping altitude are the major factors associated with AMS development.[12] However, to date, there are few and controversial data that may aid in the prediction of AMS, including hypoxic ventilatory response, pulse rate, oxygen saturation, physical fitness, hyperventilatory capacity, short breathing holding time, and hypersensitive gag reflex.[13-19] Of these factors, physical fitness, according to the definition, refers to the capability of the heart, lungs and organs to consume, transport, and utilize oxygen.[20] There is a hypothesis that if poor cardiovascular fitness reduces the efficiency of the heart in pumping blood and oxygen to the body, the body becomes less efficient at using that oxygen under high attitude. Does that mean that the individual is more likely to develop AMS? Although previous studies indicated that physical fitness was not protective against AMS,[17] recent studies have revealed that the 6-Minute Walk Test at 4,365 m, a test of functional exercise capacity, is a useful screening test for predicting who would successfully reach the summit (6,962 m).[21] Based on these results, we aimed to assess the predictive value of physical fitness in determining the occurrence of AMS.

The physical fitness test used in this study was the 3-Minute Step Test (3MST), which measures the aerobic (cardiovascular) fitness level based on how quickly the heart rate returns to normal after exercise. It is simple, objective, inexpensive, reproducible and widely used in Taiwan, and it requires no advanced equipment. Furthermore, the 3MST has also been proven useful for assessing exercise tolerance in cystic fibrosis, asthma, and interstitial lung disease patients.[22-24]

The aim of this study was to develop the 3MST as a physical fitness test that can safely be performed at two different altitudes, namely, baseline (250 m) and training camp (3,100 m). The goal was to evaluate the potential role of 3MST in predicting the occurrence of AMS before departure or in making an objective decision regarding whether an individual may continue an ascent.

Materials and Methods

Subjects

The original study was designed to assess the efficacy of *Rhodiola crenulata (R. crenulata)* in decreasing the incidence of AMS, and the results revealed no significant difference between the *R. crenulata* extract group and the placebo group.[25]

Participants were randomized into two groups, receiving either the *R. crenulata* (800 mg) or the placebo, and the treatment was altered after a 3-month period. Thus, all the participants ascended twice in a 3-month interval, called ascent I and ascent II. We recruited adults aged 23 to 55 years who resided principally at an elevation of 250 m or lower and excluded those who (1) would not complete the study protocol; (2) had prophylactic medication or herbs one month before each ascent; (3) had a change in the altitude of his/her residence of more than 200 m between ascents; (4) had additional physical training or were scheduled to gain or lose weight; (5) had altitude exposure above 2,500 m within three months prior to each ascent; (6) had any history of chronic obstructive pulmonary disease, heart failure, cerebral neoplasm, mania, or renal or hepatic insufficiency; or (7) were pregnant or intended to become pregnant during the 3-month study period.

Ascent Protocol and Assessment of the 3MST and AMS Association

All 102 participants were transported by bus from an altitude of 250 m with rapid ascent to a Hehuan Mountain training camp (3,100 m) within 4 hours. All participants then remained at 3,100 m for 2 days. There were 10 checkpoints (CPs) along the ascent to check symptoms related to AMS using the following assessments: 3MST (only at CP1: 250 m and CP4: 3,100 m), pulse rate, arterial oxygen saturation (Nellcor™ NPB-40 Pulse Oximeter, Pacific Medical, Pleasanton, CA, USA), and the Lake Louise questionnaire (Fig. 1).

During the mountaineering trips, the following variables were controlled: rate of ascent, path, food type, and sleep altitude/environment. The training camp could not accommodate all subjects at the same time. Thus, the participants were divided into 2 groups in each ascent, and they ascended separately less than 10 days apart. The usual snow season of the Hehuan Mountain is between early January and early March. We chose early and mid-December 2010, late March, and early April 2011 as our 4 mountaineering dates. The atmospheric pressure and temperature were recorded at each checkpoint during every trip.

For the 3MST, all subjects stepped up and down a 35–cm custom-made single step set at a rate of 24 steps per min for 3 min in time with an electronic metronome. The tester counted heart rates at 1–1.5, 2–2.5 and 3–3.5 minutes after the completion of the test, which were recorded as heart rate 1 (HR1), HR2 and HR3, respectively. The equation (180 × 100/[HR1 + HR2 + HR3] × 2) was then used to calculate the fitness score, whereby a high score indicated good cardiopulmonary fitness.

The presence of AMS was accessed using the Lake Louise scoring system (LLS), a simple and widely accepted tool for AMS assessment developed by the Lake Louise Consensus Group.[1] The LLS rates five symptoms (headache, gastrointestinal symptoms such as nausea and vomiting, fatigue and/or weakness, dizziness and/or light-headedness, and difficulty sleeping) based on a self-reported questionnaire and three physical examination findings (altered mental status, ataxia, and peripheral edema) based on a clinical assessment. Each item is graded on a scale from 0 to 3. Thus, the LLS scores can range from 0 (no symptoms or signs) to 15 (worst rating for each symptom). In accordance with the definition used by the Lake Louise Consensus Group, AMS was defined as the presence of headache and at least 1 of the following symptoms: gastrointestinal upset (anorexia, nausea, or vomiting), fatigue or weakness, dizziness or lightheadedness, and difficult sleeping. AMS was also defined as a score of 3 points or greater on the AMS self-report questionnaire.

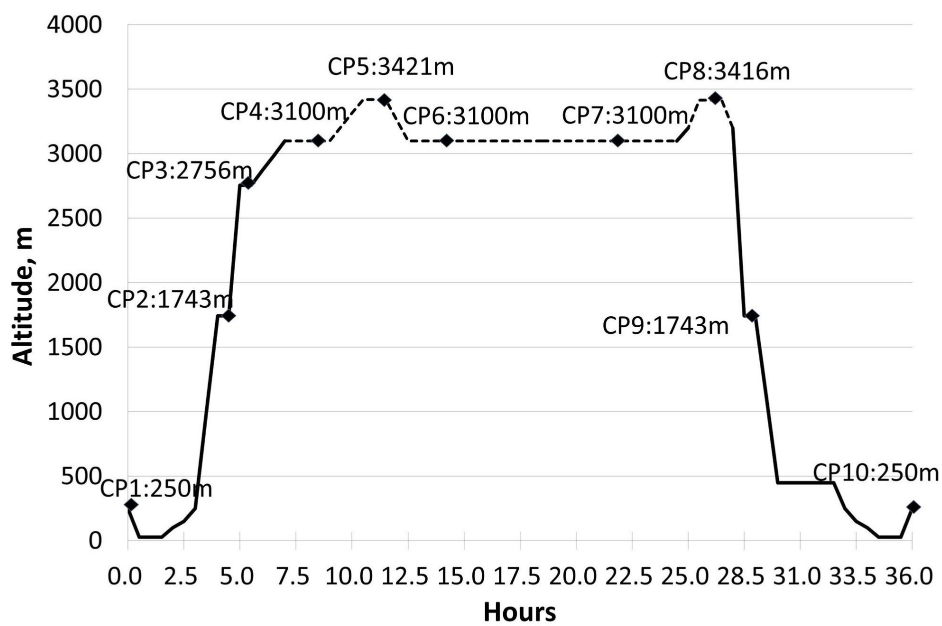

Fig. 1. Mountaineering schedule. Total 10 check points (CPs): CP1: Linkou (baseline, 250 m); CP2: Cingjing Farm (1,743 m); CP3:Yuanfeng parking lot (2,756 m); CP4: training camp (3,100 m) at noon; CP5: East Peak (3,421 m) of Hehuan Mountain; CP6: training camp in the evening; CP7: training camp in the next morning; CP8: Main Peak (3,416 m) of Hehuan Mountain; CP9: Cingjing Farm and CP10: Linkou.

Statistical Analysis

Baseline characteristics of the two groups (AMS and non-AMS) were compared by independent two-sample t-test for continuous variables and the chi-square test/Fisher's exact test for categorical variables.

The univariate and multivariate analyses to test the association between AMS and all potential risk factors were examined by a generalized linear model with a generalized estimating equation (GEE), assuming a logic link function and unstructured correlation structure. In the multivariate analyses, possible risk factors with a *p* value less than 0.2 in the univariate analysis were included.

All statistical assessments were two-sided and evaluated at the 0.05 level of significance. Statistical analyses were performed using SAS 9.2 statistical software (SAS Institute Inc., Cary, NC, USA).

Results

Subjects Characteristics

All 125 participants were recruited to the study in November 2010, and 23 participants withdrew due to (1) interim business trips (n = 4); (2) infections before ascent (n= 4, 3 with upper respiratory tract infection, 1 with leg cellulitis); (3) illness of a significant other (n = 3); (4) missed departure due to oversleeping (n = 1); and (5) postponement of the second trip (n = 11, 6 because of work shift problems and 5 due to scheduled travel abroad). The full study protocol was completed by 102 participants. All participants were exposed to the same temperatures, as no statistically significant differences were found between the four ascents. Of the 102 participants (n = 102), 50 were males with an average age of 36.31 years (standard deviation [SD] = 9.23, range 23 to 56) and body mass index (BMI) of 24.18 kg/m^2 (SD = 2.38), and 52 were females with an average age of 35.92 years (SD = 10.71, range 23 to 54) and BMI of 21.90 kg/m^2 (SD = 3.25). Table 1 show the baseline demographics and medical characteristics of the participants. Of the participants recruited, 67 (65.7%) had AMS in ascent I and 57 (55.9%) had AMS in ascent II. Comparisons between subjects with and without AMS showed no significant difference in age, gender, primary residence, body weight, body height, BMI, heart rate, baseline saturation of peripheral oxygen (SpO_2), history of mountaineering, history of AMS, or smoking and alcohol habits. Only heart rate was significantly different between the individuals with and without AMS ($p = 0.02$) in ascent II.

Association Between AMS and Possible Contributing Factors

All data from Ascent I and II (204 observations) were combined for further analysis of the possible contributing factors to AMS. Of the total observations, 124 (60.8%) had AMS. The results of the univariate analysis are presented in Table 2. The 3MST scores measured at 3,100 m ($p = 0.002$), the different ascent ($p = 0.039$) and pulse rates measured at 3,100 m ($p = 0.005$), and the SpO_2 measured at 3,100 m ($p < 0.001$) significantly correlated with the occurrence of AMS in the univariate analysis. The pulse rate measured at 3,100 m was eliminated from further analysis because it was moderately correlated with the three-minute step score and SpO_2 (Pearson correlation coefficient = -0.54 and -0.43, respectively). Then, the variables with a *p* value less than 0.2 in the univariate analysis, including 3MST scores measured at 3,100 m, ascent number, gender, SpO_2 measured at 3,100 m, and AMS history, were enrolled in a multivariate analysis. After the adjustment of all possible factors, only SpO_2 measured at 3,100 m was significantly associated with AMS ($p = 0.006$) in the multivariate analysis (Table 2). A 1% increase in SpO_2 measured at 3,100 m decreased the AMS risk by 13% (adjusted odds ratio [AOR] = 0.87, 95% confidence interval [CI] = 0.79–0.96). Although the score of the 3MST at 3,100 m ($p = 0.087$) was not significant in the multivariate analysis, a 1-point increase in the 3MST score decreased the AMS risk by 4% (AOR = 0.96, 95% CI = 0.92–1.01).

Discussion

Unlike past studies of AMS, we used a questionnaire as the main research method instead of just letting the participant ascend by him-/herself at different speeds. To reduce the possibility of individual errors, this study used a bus to take all the subjects up the mountain. It was also possible to perform the 3MST and conduct pulse oximetry, heart rate, and Lake Louise Consensus Questionnaire assessments at the same time. This study also showed that the 3MST can be performed in a harsh mountain environment.

Table 1. Demographics and baseline characteristics of subjects with and without AMS

	Ascent I			Ascent II		
	Non-AMS 35 (34.3%)	AMS 67 (65.7%)	*p* value	Non-AMS 45 (44.1%)	AMS 57 (55.9%)	*p* value
Age, years old	36.3 ± 9.2	35.9 ± 10.7	0.86	35.1 ± 10.1	36.9 ± 10.3	0.39
Gender			0.32			0.33
Male	20 (40.0%)	30 (60.0%)		25 (50.0%)	25 (50.0%)	
Female	15 (28.8%)	37 (71.2%)		20 (38.5%)	32 (61.5%)	
Drug			0.70			0.89
Rhodiola crenulata	16 (33.3%)	32 (66.7%)		24 (44.4%)	30 (55.6%)	
Placebo	19 (35.2%)	35 (64.8%)		21 (43.7%)	27 (56.3%)	
Primary residence, m	144.6 ± 106.4	156.4 ± 105.4	0.59	166.2 ± 104.9	140.8 ± 105.3	0.23
Heart rate, beats/min	70.8 ± 9.9	73.2 ± 8.8	0.22	70.2 ± 7.3	74.1 ± 10.3	0.02
Body weight, kg	64.2 ± 11.4	62.9 ± 11.7	0.61	62.5 ± 11.5	64.1 ± 11.9	0.49
Body height, cm	165.7 ± 9.2	165.3 ± 8.0	0.79	165.7 ± 8.7	165.2 ± 8.2	0.77
BMI, kg/m^2	23.2 ± 2.4	22.9 ± 3.2	0.61	22.6 ± 3.0	23.3 ± 3.0	0.25
SpO_2 at 250 m, %	98.8 ± 0.9	98.8 ± 1.1	0.90	98.8 ± 1.0	98.8 ± 1.0	0.97
History of mountaineering above 3,000 m			0.51			0.11
Never	18 (30.5%)	41 (69.5%)		24 (40.7%)	35 (59.3%)	
< 10	15 (41.7%)	21 (58.3%)		20 (55.6%)	16 (44.4%)	
> 10	2 (28.6%)	5 (71.4%)		1 (14.3%)	6 (85.7%)	
History of AMS			0.53			0.22
Yes	3 (25.0%)	9 (75.0%)		3 (25.0%)	9 (75.0%)	
No	32 (35.6%)	58 (64.4%)		42 (46.7%)	48 (53.3%)	
Smoking habit			0.45			0.46
Yes	4 (50.0%)	4 (50.0%)		5 (62.5%)	3 (37.5%)	
No	31 (33.0%)	63 (67.0%)		40 (42.6%)	54 (57.4%)	
Alcohol habit			0.24			0.45
Yes	4 (57.1%)	3 (42.9%)		2 (28.6%)	5 (71.4%)	
No	31 (32.6%)	64 (67.4%)		43 (45.3%)	52 (54.7%)	

AMS: acute mountain sickness; BMI: body mass index; SpO_2: saturation of peripheral oxygen.
Continuous variables were presented as means ± standard deviation, and compared between AMS and non-AMS using independent two sample t-test.
Categorical variables were presented as count (%) and compared between AMS and non-AMS using chi-square test/Fisher's exact test as appropriate.

3MST Before Departure (at 250 m)

The pre-departure 3MST score was not significantly associated with AMS ($p = 0.498$) in the univariate analysis. Obviously, it cannot be used as a predictor of AMS, which contrasts with the common belief that athletically fit individuals are "strong" enough to avoid AMS. As stated in the introduction, the hypothesized relationship between fitness and AMS is that poor cardiovascular fitness lowers the efficiency of the heart in pumping blood and oxygen to the body. Because the body becomes less efficient in using oxygen at high altitudes, the likelihood of AMS increases. Past studies have argued that climbers with better physical fitness climb faster, which increases their risk of AMS, so it is easy to obtain incorrect results

Table 2. Univariate analysis and multivariate analysis for possible factors associated with AMS

Variables	Non-AMS n = 80 (39.2%)	AMS n = 124 (60.8%)	Univariate analysis OR (95% CI)	Univariate analysis *p* value	Multivariate analysis Adjusted OR (95% CI)	Multivariate analysis Adjusted *p* value
3MST						
250 m	61.6 ± 9.5	60.5 ± 10.9	0.99 (0.96–1.02)	0.498		
3,100 m	54.07 ± 7.2	50.0 ± 9.6	0.94 (0.91–0.98)	0.002[a]	0.96 (0.92–1.01)	0.087
Ascent						
I	35 (34.3%)	67 (65.7%)				
II	45 (44.1%)	57 (55.9%)	0.66 (0.44–0.99)	0.039[a]	1.01 (0.56–1.82)	0.966
Drug						
Rhodiola crenulata	40 (39.2%)	62 (60.8%)	1.00 (0.67–1.48)	1.000		
Placebo	40 (39.2%)	62 (60.8%)				
Age, years old	35.5 ± 9.7	36.5 ± 10.4	1.01 (0.98–1.04)	0.554		
Gender						
Male	45 (45.0%)	55 (55.0%)	0.62 (0.31–1.24)	0.176[a]	0.78 (0.33–1.84)	0.566
Female	35 (33.7%)	69 (66.3%)				
Primary residence, m	157.3 ± 105.1	148.9 ± 105.4	1.00 (1.00–1.00)	0.652		
Pulse rate at 3,100 m	95.8 ± 11.7	101.9 ± 15.4	1.03 (1.00–1.05)	0.005[b]		
Body weight, kg	63.2 ± 11.5	63.5 ± 11.7	1.00 (0.97–1.03)	0.896		
BMI, kg/m^2	22.9 ± 2.7	23.1 ± 3.1	1.03 (0.93–1.14)	0.564		
SpO_2 , at 3,100 m, %	90.1 ± 2.5	87.6 ± 4.6	0.86 (0.79–0.93)	< 0.001[a]	0.87 (0.79–0.96)	0.006
History of mountaineering above 3,000 m						
Yes	38 (44.2%)	48 (55.8%)	0.70 (0.35–1.40)	0.313		
Never	42 (35.6%)	76 (64.4%)				
History of AMS						
Yes	5 (20.8%)	19 (79.2%)	2.71 (0.70–10.48)	0.147[a]	3.97 (0.96–16.48)	0.057
No	75 (41.7%)	105 (58.3%)				
Smoking habit						
Yes	9 (56.3%)	7 (43.7%)	0.47 (0.14–1.50)	0.204		
No	71 (37.8%)	117 (62.2%)				
Alcohol habit						
Yes	6 (42.9%)	8 (57.1%)	0.85 (0.23–3.15)	0.809		
No	74 (39.0%)	116 (61.0%)				

AMS: acute mountain sickness; BMI: body mass index; CI: confidence interval; OR: odds ratio; SpO_2: saturation of peripheral oxygen; 3MST: 3-Minute Step Test.

[a]Possible factors which *p* value less than 0.2 in univariate analysis were enrolled into further multivariate analysis.

[b]Pulse rate was eliminated in the further model, because pulse rate was moderately correlated with three-minute step score, SpO_2 (Pearson correlation coefficient = -0.54, -0.43, respectively).

in the case of an uncontrolled increase in speed.[15,17] However, all subjects in this study used the bus and, therefore, ascended at the same speed. This is in contrast with previous studies, in which all climbers ascended at different speeds. Our results revealed that the pre-departure 3MST, as a physical fitness indicator, is not related to the occurrence of AMS.

3MST at 3,100 m

Table 2 shows that at 3,100 m, the 3MST score was significantly associated with AMS in the univariate analysis ($p = 0.008$) but was not significantly associated with AMS in the multivariate analysis ($p = 0.087$). Further analysis revealed that a 1-point increase in the 3MST score at 3,100 m decreased the AMS risk by 4% (AOR = 0.96, 95% CI = 0.92–1.01). One interpretation of these statistical results is that the 3MST score at 3,100 m was not strongly associated with the presence of AMS, but it was positively correlated with tendency. Therefore, the 3MST could serve as a reference for further safe ascents.

SpO_2

Of all the factors investigated in this study, SpO_2 at 3,100 m had the strongest association with the presence of AMS in both the univariate and multivariate analyses (Table 2), which is consistent with some previous studies.[26,27] However, some studies yielded the opposite conclusion.[14,28,29] The reason for the different findings is unclear. In this study, a 1% increase in SpO_2 measured at 3,100 m was associated with a 13% decrease in AMS risk (AOR = 0.87, 95% CI = 0.79–0.96). A very slight change in the mean oxygen concentration was enough to affect the statistical results, suggesting that the utility of pulse oximetry was limited, made diagnosis difficult, and may be the reason for the controversial results.

Limitation

Due to the post hoc nature of this analysis, there were some possible confounding factors in the study. The first factor was the use of *R. crenulata* extract and placebo, as the study revealed no significant differences in the incidence of AMS between the *R. crenulata* extract and placebo groups (same incidence = 0.68; odds ratio = 1.0, 95% CI = 0.67–1.48, $p = 1.00$).

The second factor is the period effect. Because all participants ascended twice with a 3-month interval between ascents, the univariate analysis revealed that ascent II yielded a lower incidence of AMS (incidence ascent I:ascent II = 65.7%:55.9%; odds ratio = 0.66, 95% CI = 0.44–0.99, $p = 0.039$). Further multivariate analysis revealed no difference in incidence between the two ascents (odds ratio = 1.01, 95% CI = 0.56–1.82, $p = 0.966$).

Conclusion

This study of 204 observations showed no correlation between the pre-departure 3MST (250 m) score and AMS incidence. When the 3MST is used as an indicator of physical fitness, physical condition near sea level cannot predict whether high altitude sickness will occur.

Although the score of the 3MST at 3,100 m was not significantly related to the presence of AMS, increasing values showed a trend toward an increased occurrence of AMS. We recommend further study to determine the possible utility of the 3MST at high altitudes for predicting further safe ascents.

Conflicts of Interest

No authors have any competing interests.

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