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The effects of respiratory inhaled drugs on the prevention of acute mountain sickness

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Abstract

Background: Acute mountain sickness (AMS) is common in high-altitude travelers, and may lead to life-threatening high-altitude cerebral edema (HACE) or high-altitude pulmonary edema (HAPE). The inhaled drugs have a much lower peak serum concentrations and a shorter half-life period than oral drugs, which give them a special character, greater local effects in the lung. Meanwhile, short-term administration of inhaled drugs results in almost no adverse reactions.

Methods: We chose inhaled ipratropium bromide/salbutamol sulfate (combivent, COM), budesonide (pulmicortrespules, BUD), and salbutamol sulfate (ventolin, VEN) in our study to investigate their prophylactic efficacy against AMS. Since COM is a compound drug of ipratropium bromide and salbutamol sulfate, to verify which part of COM plays a role in the prevention of AMS, we also tested VEN in our experiment.

Results: In our study, Lake Louise scores (LLS) in the COM (1.14 ± 0.89 vs 1.91 ± 1.23, $P < .05$) and BUD (1.35 ± 0.94 vs 1.91 ± 1.23, $P < .05$) groups were both significantly lower than the placebo group at 72 hours. There were no significant differences in LLS scores among the 4 groups at 120 hours. The incidence of AMS in the COM group was significantly reduced at 72 hours (16.7% in COM group vs 43.4% in placebo group, $P < .05$) after exposure to high-altitude. There were no significant differences in AMS incidences at 120 hours among the 4 groups.

Conclusion: The prophylactic use of COM could prevent AMS in young Chinese male at 72 hours after high-altitude exposure. BUD also could reduce LLS but not prevent AMS at 72 hours. Ipratropium bromide maybe the effective drug in COM work on the prevention of AMS alone.

Abbreviations: AMS = acute mountain sickness, BMI = body mass index, BP = blood pressure, BUD = budesonide, COPD = chronic obstructive pulmonary disease, COM = ipratropium bromide/salbutamol sulfate, DBP = diastolic BP, HACE = high-altitude cerebral edema, HAPE = high-altitude pulmonary edema, HR = heart rate, LDL = low-density lipoprotein, LLSs = Lake Louise scores, SBP = systolic BP, SpO_2 = pulse oxygen saturation, TSH = thyroid-stimulating hormone, TC = total cholesterol, TG = triglycerides, VEN = salbutamol sulfate.

Keywords: acute mountain sickness, inhaled drugs, ipratropium bromide, pulmonary function, young Chinese male

1. Introduction

People traveling to high altitude over 2500 m often experience acute mountain sickness (AMS). Many factors have adverse effects on the traveler's body in the plateau environment, including thin air, low temperature, strong ultraviolet rays, and wind. Among these factors, hypoxia is the most dangerous factor. Hypoxia can lead to headache, dizziness, dyspnea, insomnia, and loss of appetite.[1,2] Hypoxia, namely inadequate oxygenation of the blood circulation, often occurs in people who ascend rapidly to highland, which could lead to AMS and sometimes even high-altitude cerebral edema (HACE).[3–6]

The AMS is a well-recognized phenomenon, which develops at high altitude when the adaptive capacities of the human body to acute hypoxia failed.[7–9] The risk of AMS is significant above 2500 m, and its prevalence is correlated with altitude, estimated about 9% to 25% at 2500 m, and about 47% to 75% above 4500 m.[4,10–13] Most of the time, AMS is begin, although which can potentially progress to life threatening complications, high-altitude pulmonary edema (HAPE) and HACE.[4,14] The diagnosis of AMS is not straightforward because it is based on nonspecific symptoms. However, the association of headache, nausea, vomiting, insomnia, and anorexia is suggestive, which arise within 4 to 8 hours following arrival at altitudes (>2500 m). The Lake Louise score (LLS) questionnaire is a validated tool that is commonly used to assess AMS.[15,16] A diagnosis of AMS is made when a person who has recently ascended to high-altitude reports a headache and has total LLS of 3 or greater.

China is a vast country, which has a lot of high-altitude regions, and natural disasters also often occur. For example, the Wenchuan earthquake (Sichuan Province, China, 2008) and Yushu earthquake (Qinghai Province, China, 2010) both

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XW and HC have contributed equally to this work.

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happened above 4000 m.[17] Gradual staged ascent can prevent AMS but is impractical in emergency situations.[17,18] Certain people need to ascend rapidly to high altitude, including those involved in military action, disaster relief, and helicopter operation. Moreover, emergent occasions at altitude, such as rescue work and military tasks, often call for immediate and excessively rapid ascents as well as great physical exertion. These actions may greatly increase the occurrence and severity of AMS. AMS occurs in 50% to 85% of unacclimatized individuals at 4500 to 5500 m.[7] In the relief work of Yushu earthquake (4000 m on average, Qinghai Province, China), incidence of AMS reached 80% among unacclimatized rescuers.[7] The emergency rescue teams, including people who come from the nearby high-altitude areas, also got a high incidence of acute altitude sickness.[19] Therefore, prevention and treatment strategies are necessary to reduce the incidence of AMS in people who rapidly ascend to plateau areas.

The relationship between lung function and AMS has been established in many studies. Generally, poorer pulmonary function leads to a higher incidence of AMS.[20,21] In Wu's study of more than 10,000 young workers who constructed the Qinghai Tibet railway, the young workers with mild to moderate asthma or chronic obstructive pulmonary disease (COPD) who given inhaled drugs had a similar incidence of AMS as the healthy workers.[22] We thus concluded that the respiratory inhaled drugs play an important role in improving lung function and reducing the incidence of AMS. Until now, the effectiveness of respiratory inhaled drugs for AMS prevention has not been fully investigated. In Chen's study, prophylactic BUD has been demonstrated to reduce the incidence and severity of AMS.[7,17] There had no relevant research reports on the role of other commonly used inhaled drugs in clinical respiratory, ipratropium bromide, and salbutamol sulfate in AMS. Therefore, we designed an open randomized controlled trial in which inhaled drugs were used for AMS prevention. The following are 3 kinds of inhaled drugs commonly used in clinical to improve pulmonary function, including ipratropium bromide/salbutamol sulfate (COM), budesonide (BUD), and salbutamol sulfate (VEN). BUD, an inhaled glucocorticoid with few systemic side effects, can improve pulmonary function of asthmatic patients. VEN, a short-acting β_2-agonist, was shown to relax airway smooth muscles and improve airflow through increasing transport of cross-epidermal sodium ions in alveolar epithelial cells.[23] COM is a compound inhaled drug including ipratropium bromide (β_2-agonist, the same composition as VEN) and salbutamol sulfate (atropine-like bronchodilator drug, whose mechanism of action is via an anticholinergic pathway and may decrease cyclic guanosine monophosphate).[24]

2. Materials and methods

2.1. Subjects

This study was approved by the Ethics Committee of Southwest Hospital, the Third Military Medical University, Chongqing, China and registered in the Chinese Clinical Trail Register (Clinical study on the prevention of acute altitude sickness by respiratory inhaled drugs, CHiCTR-PRC-16008441). Each group was given a verbal briefing about the study and told that the study was designed to examine the prophylactic efficacy of the inhaled drugs to AMS. Subjects who agreed to participate in this study signed written informed consent forms before the trial.

Eligible participants were healthy young male who lived a long term in 2000 m (18–28 years old). Participants with any one of the following conditions were excluded: high-altitude (>2500 m) exposure history in the past year; severe organic diseases, such as congenital heart disease, dysrhythmia, liver or kidney dysfunction, or psychological and neurological disorders; contraindications of BUD, VEN, or COM; other unsuitable conditions. The 125 healthy young males were recruited in this trial in Malong County, Yunnan Province, China, between July 19 and July 22, 2015, and followed-up from July 25 to August 2 in the period of traveling from Malong to Litang, Sichuan Province.

2.2. Clinical data collection

Clinical data collected included age, height, weight, and body mass index (BMI). Structured case report form questionnaires were used to record smoking and drinking history, medical history (overall health and HA exposure history in the past year). Baseline examinations were performed at 2000 m about 3 days before ascent to HA; these included measurement of blood pressure (BP), heart rate (HR), pulse oxygen saturation (SpO_2), blood glucose, and pulmonary function outcomes. Venous blood of each participant were obtained before ascent and at the 72 hours after ascent for measurement of serum lipid (total cholesterol [TC], triglycerides [TG], and low-density lipoprotein [LDL]) and thyroid-stimulating hormone (TSH).

2.3. Study protocol

The study protocol is illustrated schematically in Fig. 1. Group A received COM (compound ipratropium bromide solution for inhalation, 0.5 mg ipratropium bromide/3.0 mg salbutamol sulfate per inhalation, bid, BoehringerIngelheim, Reims, France), Group B received BUD (2.0 mg per inhalation, bid, AstraZeneca AB, Stockholm, Sweden), Group C was given VEN (salbutamol sulfate inhalation solution, 5.0 mg per inhalation, bid, GlaxoSmithKline, Boronia Victoria, Australia), Group D was given placebo (0.9% physiological salt solution, 5.0 mL per inhalation, bid, Chongqing, China). The subjects were fully informed and knew that they would be assigned to any of 4 groups and given inhalation for 3 days. During medication, the inhalation was given by the medical team.

2.4. High-altitude exposure and medical support

Subjects were taken to 4000 m (Litang County, Sichuan Province, China) from 2000 m (Malong County, Yunnan Province, China) in a 3 days trip by car on July 25 and began to take inhalation therapy. On July 28, they acutely ascended to 3450 m, which was defined as the earliest time of high-altitude exposure (Fig. 2). A medical team was responsible for monitoring subjects for adverse reactions related to the inhaled drugs. The subjects were also encouraged to report to the medical team if they had any adverse symptoms.

2.5. Pulmonary function evaluation

End-tidal of CO_2 ($EtCO_2$) and alveolar partial pressure of CO_2 ($PACO_2$) were measured with a desktop spirometer (Pony FX; COSMED, Roman, Italy) to evaluate the pulmonary function of the subjects. $EtCO_2$ and $PACO_2$ were measured by the researchers at baseline.

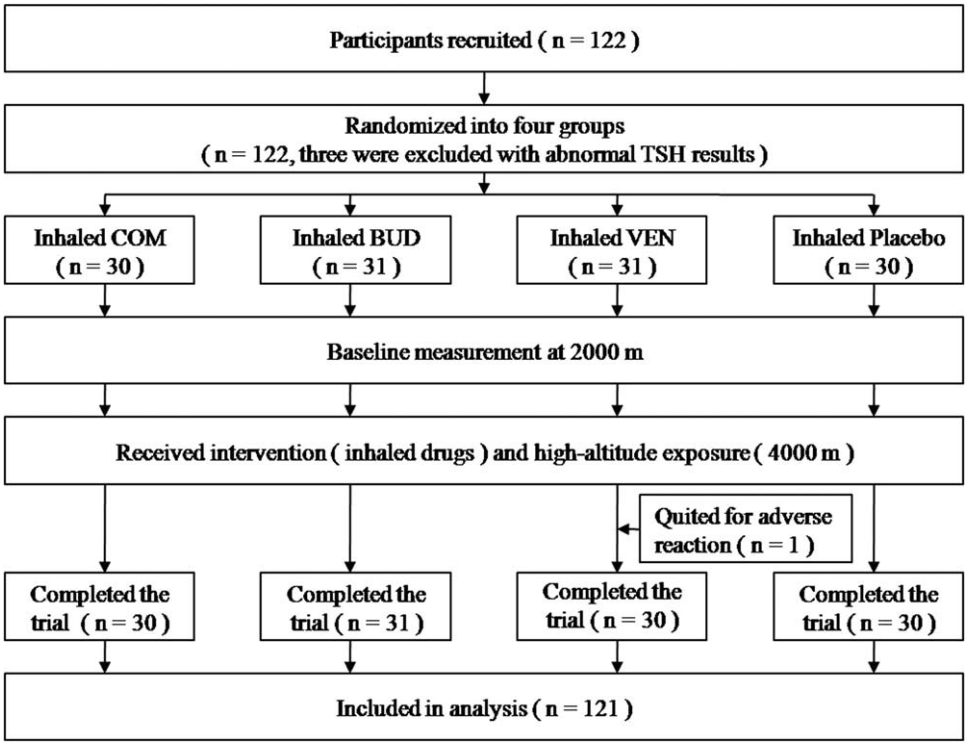

Figure 1. Consort flow chart of the study. BUD = budesonide, COM = ipratropium bromide/salbutamol sulfate, TSH = thyroid-stimulating hormone, VEN = salbutamol sulfate.

2.6. Blood pressure, HR, and SpO_2

Blood pressure was obtained using electronic sphygmomanometers (OMRON HEM-6200; OMRON Healthcare Ltd, Kyoto, Japan). HR and SpO_2 were measured using pulse oximeters (Nonin Onyx 9550; Nonin Medical, Inc, Plymouth, MA). Blood pressure, HR, and SpO_2 were measured 3 times after the subjects had rested in a quiet environment for 15 minutes or more. BP, HR, and SpO_2 were measured by the researchers at baseline, 24 hours, 72 hours, and 120 hours after high-altitude exposure.

2.7. Lake Louise score questionnaire and AMS

The LLS questionnaire includes 5 self-reporting symptoms: headache, gastrointestinal symptoms, fatigue/weakness, dizziness/lightheadedness, and difficulty in sleeping. Each symptom is scored 0-3, with 0 indicating none and 1-3 indicating mild, moderate, and severe, respectively. The LLSs were calculated for each individual. AMS is defined by a total score of 3 or more in the presence of headache. Its mild form has a score of 3-4, while its severe form has a score of 5 or more. LLSs were

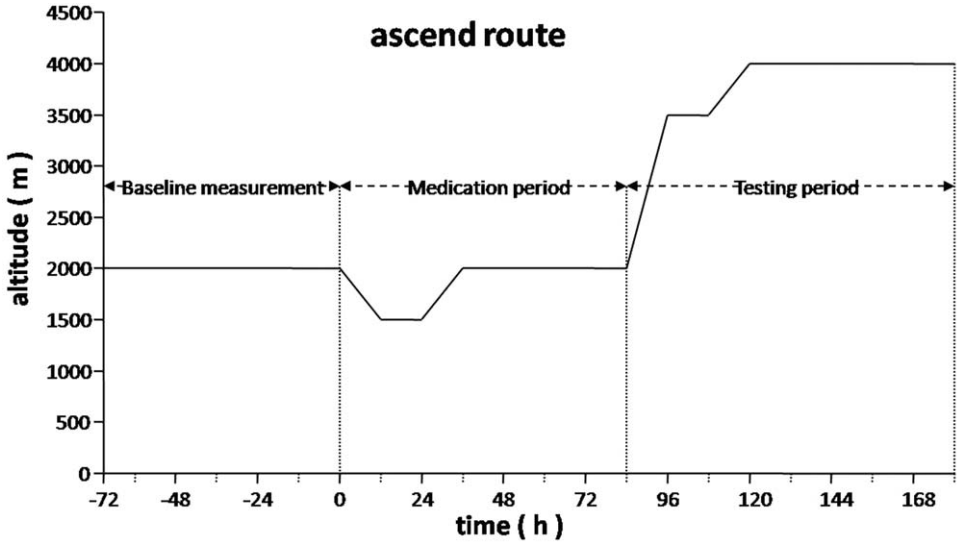

Figure 2. Ascent profile, medication, and examinations at altitude.

examined by the researchers at 72 and 120 hours after high-altitude exposure.

2.8. Statistical analysis

Ordinal variables were reported as mean ± standard deviation or as median (interquartile range). Nominal variables were reported as percentages. One-way analyses of variance were used for the comparisons of quantitative data among the 4 groups, assuming normal distribution of data and homogeneity of variances. If significant differences were observed, Student–Newman–Keuls tests were used for comparisons between each 2 groups. Chi-squared tests were applied for the comparisons of qualitative data among the 4 groups. Paired sample *t* tests were used to compare HR, SpO_2, and BP between lowland and altitude in each group. Kruskal–Wallis tests followed by Nemenyi tests were applied to compare age, BMI, and LLS score among the 4 groups. The incidences of AMS and its severe form were compared among the 4 groups using Chi-squared tests. A *P*-value of $<.05$ was considered statistically significant. Statistical analysis was performed with the SPSS software version 17.0 for Windows (Statistical Package for Social Science, Chicago, IL).

3. Results

3.1. Clinical and medical examination data

There were no significant differences in demographic data among the 4 groups, including age, weight, height, BMI, and body fat rate ($P > .05$). The medical examination results of HR, SpO_2, systolic BP (SBP), and diastolic BP (DBP), $EtCO_2$, $PACO_2$, TSH, and serum lipid (TC, TG, and LDL) did not differ among the 4 groups ($P > .05$) (Table 1).

3.2. Participant flow

Both thyroid function and hypoxia can lead to changes of body's metabolism.[25] To eliminate the effects of metabolic function on the experiment, we detected the serum TSH and serum lipid in all the participants. All the participants have a normal level of serum lipid. Based on the detection results of TSH, 3 participants were excluded (with TSH value of 6.01, 0.016, and 26.04 μIU/mL, respectively). Finally, there were 122 eligible participants recruited at Malong County. During intervention, 1 participant in the VEN group encountered adverse reactions, who stopped medication and withdrew. No subjects in the COM, BUD, and placebo groups reported adverse reactions related to the investigational drugs. Thus, 121 subjects completed the trial, whose data were included in analysis (30, 31, 30, and 30 in the COM, BUD, VEN, and placebo groups, respectively) (Fig. 1).

3.3. Lake Louise scores

In this study, the mean LLS were 1.49 ± 1.04, 0.86 ± 0.54 at 72 and 120 hours after exposure to high altitude. LLS in all the 4 groups declined at 120 compared to 72 hours. The mean LLS varied from 1.14 to 1.91 in the 4 groups at 72 hours (1.14 ± 0.89, 1.35 ± 0.94, 1.54 ± 1.08, 1.91 ± 1.23 for COM, BUD, VEN, and placebo group, respectively), COM and BUD groups were both significantly lower than the placebo group ($P = .015$ and $P = .016$, respectively), while VEN group did not reach significance. The mean LLS varied from 0.73 to 1.27 in the 4 groups at 120 hours (0.73 ± 0.50, 0.79 ± 0.52, 0.90 ± 0.71, 1.02 ± 0.74 for COM, BUD, VEN, and placebo group, respectively). There were no statistically significant differences in LLS at 120 hours among the 4 groups.

3.4. AMS incidence and severity

About 27.87% and 4.96% of participants had AMS compatible with LLS at 72 and 120 hours after exposure to high altitude. AMS incidence in all the 4 groups significantly declined at 120 hours compared to 72 hours (COM, 0% vs 16.7%, $P < .05$; BUD, 3.2% vs 25.8%, $P < .05$; VEN, 6.7% vs 29.0%, $P < .05$; placebo, 10% vs 43.4%, $P < .05$). COM group had lower incidence of AMS than placebo group at 72 hours (16.7% vs 43.4%, $P < .05$), while BUD (25.8% vs 43.4%, $P > .05$) and VEN (29.0% vs 43.4%, $P > 0.05$) group did not reach significance (Fig. 3A). There were no statistically significant differences in AMS incidence at 120 hours among the 4 groups.

The COM group and BUD group had the same severe AMS incidence compared to placebo group at 72 hours (6.5% vs 6.7%, $P > .05$; 6.5% vs 6.7%, $P > .05$, respectively), while VEN group had a higher severe AMS incidence than placebo groups (12.9% vs 6.7%, $P < .05$). There were no statistically significant differences in AMS incidences at 120 hours among the 4 groups (0%, 0%, 0%, and 3.33%, Fig. 3B).

Table 1

Clinical data and medical examination data of the subjects in the 4 groups.

Variable mean ± SD	COM (n = 30)	BUD (n = 31)	VEN (n = 30)	Placebo (n = 30)	*P*
Age, y	21.89 ± 2.78	21.35 ± 3.05	21.25 ± 2.35	22.83 ± 2.74	.183
Weight, kg	63.96 ± 4.90	64.50 ± 7.06	62.92 ± 5.99	63.17 ± 7.08	.777
Height, m	1.72 ± 0.05	1.71 ± 0.05	1.71 ± 0.04	1.70 ± 0.04	.590
BMI, kg/m^2	21.55 ± 1.31	21.94 ± 2.11	21.40 ± 1.68	21.73 ± 2.25	.725
Body fat, %	18.53 ± 2.65	19.73 ± 4.23	16.95 ± 4.48	18.01 ± 4.18	.069
HR, bpm	67.00 ± 12.31	69.53 ± 10.89	70.57 ± 12.38	65.65 ± 13.43	.475
SpO_2, %	96.64 ± 1.28	96.44 ± 1.72	96.63 ± 1.10	96.91 ± 1.16	.658
SBP, mm Hg	122.56 ± 8.85	121.16 ± 6.78	120.74 ± 10.13	120.17 ± 10.85	.811
DBP, mm Hg	89.22 ± 11.31	91.63 ± 10.59	90.22 ± 11.16	89.83 ± 5.23	.819
TSH, μIU/mL	1.30 ± 0.60	1.38 ± 0.42	1.46 ± 0.84	1.38 ± 0.54	.852
TC, mmol/L	3.33 ± 0.83	4.1 ± 0.76	3.57 ± 0.95	3.40 ± 0.93	.693
TG, mmol/L	0.72 ± 0.31	0.82 ± 0.43	0.78 ± 0.37	0.78 ± 0.36	.553
LDL, mmol/L	2.13 ± 0.60	2.57 ± 0.58	2.32 ± 0.61	2.27 ± 0.60	.167

SD = standard deviation, BMI = body mass index, HR = heart rate, bpm = beats/min, SPO_2 = pulse oxygen saturation, SBP = systolic blood pressure, DBP = diastolic blood pressure, TSH = thyroid stimulating hormone, TC = total cholesterol, TG = triglycerides, LDL = low-density lipoprotein.

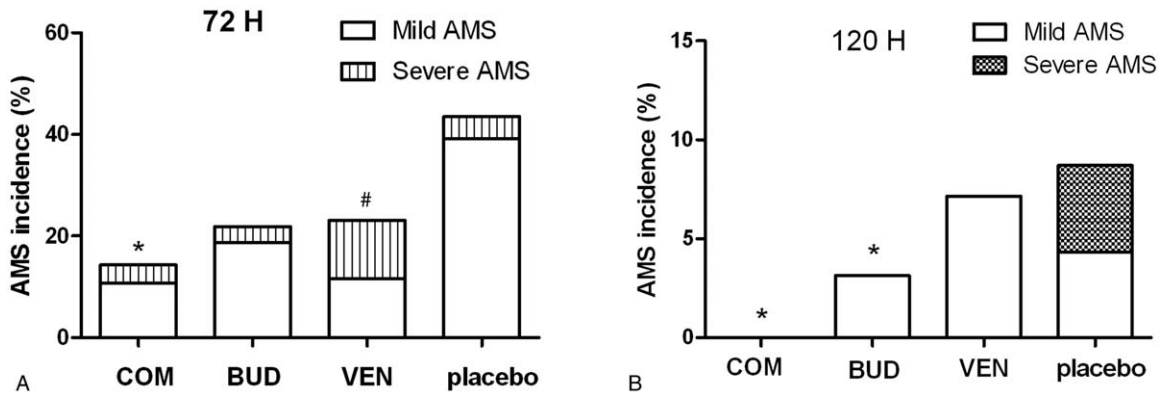

Figure 3. Incidence of acute mountain sickness (AMS) (mild, severe, and total) after high-altitude exposure in the 4 groups. (A) Incidence of AMS (mild, severe, and total) among the 4 groups at 72 hours after ascent to high altitude. *Total AMS incidence compared to the placebo group ($P < .05$), # Severe AMS incidence compared to the placebo group ($P < .05$). (B) Incidence of AMS (mild, severe, and total) after high-altitude exposure among the 4 groups at 120 hours. BUD = budesonide, COM = ipratropium bromide/salbutamol sulfate, VEN = salbutamol sulfate.

3.5. BP, HR, and SpO_2

Baseline measurements of BP, HR, and SpO_2 did not differ among the 4 groups.

The mean SpO_2 of all 121 subjects dropped from 96.6% to 91.0% with acute exposure to high altitude (level at 2500 m vs 24 hours after ascent; $P < .01$) and then went up gradually to 92.88% as the exposure to high-altitude continued (Fig. 4A). The mean SpO_2 did not return to the level before ascent at 120 hours (92.9% vs 96.6%, $P < .01$). Also, there was no statistically significant difference in SpO_2 among the 4 groups at 72 hours (89.38%, 92.48%, 90.90% for COM, BUD, and VEN, respectively, vs 91.29% for placebo; $P > .05$). The same phenomenon was observed at 120 hours ($P > .05$). SpO_2 went down at altitude compared with 2000 m in every group (all $P < .01$).

HR increased from 68.25 to 88.36 bpm at 24 hours after ascent ($P < .01$), and then dropped gradually to 79.85 bpm as the exposure to high-altitude continued in all subjects (Fig. 4A). HR at 72 hours after exposure were 76.35 ± 11.37, 81.23 ± 15.65, 79.35 ± 10.28, and 83.13 ± 9.49 bpm in COM, BUD, VEN, and placebo groups, respectively. There were no significant differences in HR among the 4 groups at 72 and 120 hours ($P > .05$). HR was elevated at altitude compared with 2000 m in all the groups ($P < .01$).

The BP also increased in all subjects at altitude compared with 2000 m (SBP, 126.6 mm Hg vs 121.2 mm Hg, $P < .05$; DBP, 100.8 mm Hg vs 90.3 mm Hg, $P < .01$) (Fig. 4B). There were no significant differences in SBP and DBP among the 4 groups at 72 and 120 hours after exposure at high altitude. However, the SBP and DBP did not change significantly in all the groups, whether at 24 or 72 hours (all $P > .05$).

The SpO_2 was negatively correlated with AMS scores in the COM group ($R = -0.45$, $P = .0489$); no other vital signs were found relevant to AMS scores. AMS-positive subjects demonstrated a greater reduction in SpO_2 as compared with AMS-negative subjects at 24 hours ($\Delta SpO_2 = SpO_2$ at HA-SpO_2 at 2000 m: $-11.00\% \pm 2.83\%$ vs $-8.47\% \pm 1.81\%$; $P < .05$). No correlations between SpO_2 and AMS scores were observed in the BUD or VEN groups. The increase in HR or reduction in SpO_2 showed no difference between the AMS-positive and AMS-negative subjects. Of note, no differences were observed in ΔSBP or ΔDBP between AMS-positive and AMS-negative subjects.

4. Discussion

The pathogenesis of AMS is not completely understood, but the lung function appears to be involved as evidenced by the fact that when compared with healthy subjects at altitude.[20,21]

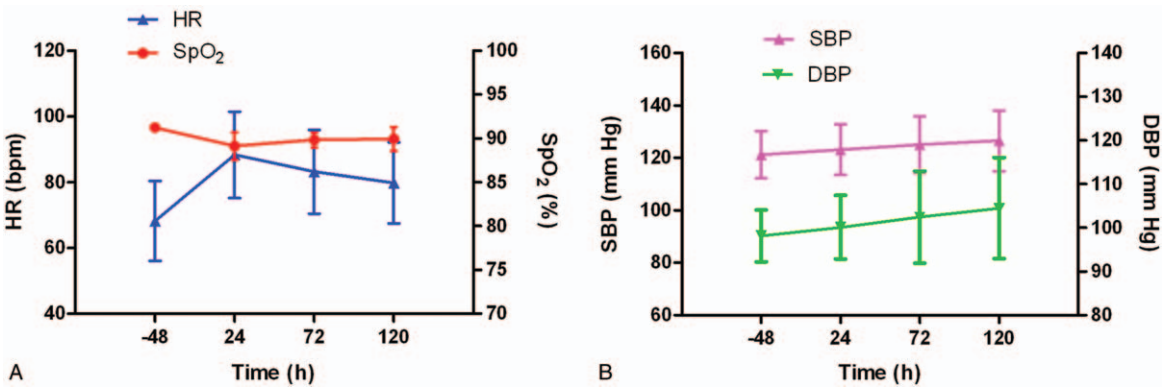

Figure 4. (A) Hear rate (HR) and SpO_2 averaged for all subjects from preascent through 120 hours after exposure to high altitude. (B) Systolic blood pressure (SBP) and diastolic blood pressure (DBP) averaged for each groups before and after high-altitude exposure.

Administration of inhaled drugs rather than oral drugs is the primary clinical method for improving pulmonary function. The inhaled drugs have a much lower peak serum concentrations and a shorter half-life period than oral drugs, which give them a special character, greater local effects in the lung.[26–28] Meanwhile, short-term administration of inhaled drugs results in almost no adverse reactions. Thus, we chose inhaled COM, BUD, and VEN in our study to investigate their prophylactic efficacy against AMS.

In our study, the prophylactic use of COM (0.5 mg ipratropium bromide/3.0 mg salbutamol sulfateper inhalation, bid) for 3 days in advance of high-altitude exposure significantly reduced the incidence of AMS. COM was superior to placebo, resulting in about a 30% reduction in the incidence of AMS. BUD and VEN also had a similar but nonsignificant trend. The subjects in COM group were well acclimated at 72 hours, with only 10% of subjects experiencing mild AMS at that time point. The beneficial effects of COM lasted at least 72 hours after high-altitude exposure and had no influence on the acclimatization of the body to high altitude. In COM group, subjects with AMS had a greater reduction in SpO_2 than those who were not diagnosed with AMS. This indicates that the reduction in AMS incidence is likely to be achieved by the maintenance of SpO_2 by inhaled COM. According to these findings, we speculate that inhaled COM may generate similar effects on the lung just like DXM, to improve the pulmonary function, thus increasing SpO_2, and preventing AMS.

A previous study demonstrated that inhaled BUD maintains the integrity of airway epithelia.[29] Inhalation of BUD may activate the glucocorticoid α-receptors and produce anti-inflammatory effects within the alveolar epithelium. These effects may antagonize negative effects of hypobaric hypoxic environments and decrease anoxia within the body. As reported by Zheng's and Chen's studies, prophylactic BUD could reduce the incidence and severity of AMS.[7,17] In our study, we found that BUD group had lower LLS than placebo group but the incidence of AMS were not different to placebo group. However, our sample number is small, minor differences in improve of pulmonary function and prevention of AMS by BUD may not have been found. The other reason may be the placebo group in Zheng's and Chen's studies was just given tablets, but in our study, the placebo group was given inhalation medication of physiological salt solution. The humidification treatment of airway may be helpful to protect airway.

All the drugs used in this trial may dilate bronchi and improve pulmonary ventilation, so we expected that there would be a useful one for the prevention of AMS. COM is a compound drug of ipratropium bromide and salbutamol sulfate, which used for the treatment of COPD by the mechanism via an anticholinergic pathway and may decrease cyclic guanosine monophosphate. To verify which part of COM plays a role in the prevention of AMS, we also tested VEN (salbutamol sulfate) in our experiment, the doses of salbutamol sulfate both in COM and VEN were in an efficacious dose for expansion of the airway. However, we found significant difference between COM and VEN groups. For prevention of AMS, treatment with COM has a lower incidence of AMS than VEN in this trial, even the dose of salbutamol sulfate in the VEN was higher than the dose in COM (5.0 mg vs 3.0 mg). This suggests that ipratropium bromide work on the prevention of AMS alone, and salbutamol sulfate has no effect on the prevention of AMS. Surprisingly, severe AMS incidences in the VEN group appeared to be even higher than placebo group at 72 hours, with significant differences. So one possible explanation is that salbutamol sulfate, a β_2-receptor agonist may increase HR, which increases oxygen consumption and aggravates hypoxia, causing adverse effects on acclimatization to high altitude.

It has been reported that higher DBP is correlated to higher AMS severity and lower SpO_2.[30,31] But we did not find differences in DBP among all the 4 groups at 72 and 120 hours. Serum lipid and TSH were not associated with both AMS prevalence ($P < .05$) and severity ($P < .05$) in our study, although these parameters are classical factors for metabolism function.

Our study had several limitations. We traveled to high altitude by car, which is not as "acute" compared with traveling by plane. However, an incidence up to 43% in the placebo group suggests that the protection from this slow ascent is insignificant. The limitations to this study also include its relatively small sample size. Our subjects were healthy young men, so our results cannot be extended to other ages or to females. In addition, the dose of salbutamol sulfate contained in the COM group (3.0 mg) was not the same as in the VEN group (5.0 mg). Furthermore, the detection of pulmonary diffusing capacity, and alveolar-arterial oxygen pressure difference was not involved, because of the poor experimental conditions at that field.

5. Conclusion

The prophylactic use of COM could prevent AMS in young Chinese male at 72 hours after high-altitude exposure. BUD also could reduced LLS at 72 hours but not prevent AMS. We speculate that ipratropium bromide in COM work on the prevention of AMS alone and salbutamol sulfate has no effect on the prevention of AMS.

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