CLINICAL RESEARCH STUDY

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Inhaled Budesonide and Oral Dexamethasone Prevent Acute Mountain Sickness☆

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ABSTRACT

BACKGROUND: This double-blind, randomized controlled trial aimed to investigate inhaled budesonide and oral dexamethasone compared with placebo for their prophylactic efficacy against acute mountain sickness after acute high-altitude exposure.

METHODS: There were 138 healthy young male lowland residents recruited and randomly assigned to receive inhaled budesonide (200 μg, twice a day [bid]), oral dexamethasone (4 mg, bid), or placebo (46 in each group). They traveled to 3900 m altitude from 400 m by car. Medication started 1 day before high-altitude exposure and continued until the third day of exposure. Primary outcome measure was the incidence of acute mountain sickness after exposure.

RESULTS: One hundred twenty-four subjects completed the study (42, 39, and 43 in the budesonide, dexamethasone, and placebo groups, respectively). Demographic characteristics were comparable among the 3 groups. After high-altitude exposure, significantly fewer participants in the budesonide (23.81%) and dexamethasone (30.77%) groups developed acute mountain sickness compared with participants receiving placebo (60.46%) ($P = .0006$ and $P = .0071$, respectively). Both the budesonide and dexamethasone groups had lower heart rate and higher pulse oxygen saturation (SpO_2) than the placebo group at altitude. Only the budesonide group demonstrated less deterioration in forced vital capacity and sleep quality than the placebo group. Four subjects in the dexamethasone group reported adverse reactions.

CONCLUSIONS: Both inhaled budesonide (200 μg, bid) and oral dexamethasone (4 mg, bid) were effective for the prevention of acute mountain sickness, especially its severe form, compared with placebo. Budesonide caused fewer adverse reactions than dexamethasone.

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KEYWORDS: Acute mountain sickness; Budesonide; Dexamethasone; Prevention; Randomized controlled trial

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Unacclimatized individuals rapidly ascending to high altitudes often suffer acute mountain sickness, a syndrome caused by hypobaric hypoxia. It usually results in headache, gastrointestinal symptoms, fatigue/weakness, dizziness/lightheadedness, and difficulty in sleeping. These unpleasant symptoms often cause impairment to health, life quality, and work ability. Acute mountain sickness can even progress to life-threatening high-altitude cerebral edema or high-altitude pulmonary edema if not treated adequately.[1]

The risk of acute mountain sickness may be low with a mild ascent profile. However, emergent occasions at altitude, such as rescue work and military tasks, often call for

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immediate and excessively rapid ascents as well as great physical exertion. These characteristics may greatly increase the occurrence and severity of acute mountain sickness, posing a serious threat to health and life. After the Yushu earthquake (4000 m on average, Qinghai Province, China) in 2010, AMS incidence reached 80% among unacclimatized rescuers for earthquake relief work. Death was even reported due to severe altitude diseases. To "rescue the rescuers" became a main task for the medical teams there.[2] Painful lessons were learned that high attention should be paid to the prevention of acute mountain sickness under emergent conditions.

CLINICAL SIGNIFICANCE

- Inhaled budesonide, a drug mainly used for the treatment of asthma and chronic obstructive pulmonary disease, was proven effective for the prevention of acute mountain sickness after acute high-altitude exposure but caused fewer adverse reactions than dexamethasone.
- Budesonide alleviated the impairment of high altitude on forced vital capacity, pulse oxygen saturation, and sleep quality.

Gradual staged ascent can prevent acute mountain sickness but is impractical in emergency situations. Acetazolamide and dexamethasone can prevent acute mountain sickness effectively.[3-5] They are both recommended by the Wilderness Medical Society with a recommendation grade of 1A.[6] Acetazolamide has mild side effects.[3,5] It is recommended to be started the day before ascent.[6] Its prophylactic efficacy is not sufficient during excessively rapid ascents.[7] Although oral dexamethasone may cause systemic side effects,[8-10] it should be considered with priority when a very rapid effect is required, as, for example, when rescue workers are called to ascend very fast.[11] The prevention of acute mountain sickness is more important but more difficult under emergent conditions.

Pulmonary function is often impaired in subjects who develop acute mountain sickness, compared with healthy ones at altitude.[12,13] It is controversial whether acute mountain sickness is related to interstitial pulmonary edema.[12-16] The mechanisms underlying the prophylactic efficacy of dexamethasone are not fully understood, but some may be related to the lung, such as upregulating alveolar apical membrane Na^+ channel and basolateral Na^+-K^+-ATPase,[17,18] stimulating surfactant secretion,[19] preventing pulmonary transvascular protein escape,[20] and enhancing the integrity of airway epithelia barrier.[21] Budesonide, an inhaled glucocorticoid with few systemic side effects, can improve pulmonary function of asthmatic patients. After being inhaled, budesonide may generate similar effects on the lung as dexamethasone, thus preventing acute mountain sickness.

The objective of this study was to investigate inhaled budesonide and oral dexamethasone compared with placebo for their prophylactic efficacy against acute mountain sickness after acute high-altitude exposure.

METHODS

Trial Design

This was a prospective, multi-arm, single-center, double-blind, randomized controlled trial.

Participants

Eligible participants had to be non-Tibetan healthy young male lowland residents (18-35 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; contraindications of budesonide or dexamethasone; other unsuitable conditions (**Appendix**, sections How were the participants recruited? and Details about exclusion criteria, available online).

Ethics Statement

This study was approved by the Ethics Committee of Xinqiao Hospital, the Second Clinic Medical College of the Third Military Medical University. Written informed consent was obtained from all subjects before study initiation. All clinical investigation obeyed the Declaration of Helsinki. Trial registration: Chinese Clinical Trial Registry, ChiCTR-PRC-13003296.

Randomization

An independent physician randomly assigned the subjects to 3 groups: the budesonide, dexamethasone, and placebo groups, using a computer-generated random number list with an allocation ratio of 1:1:1 (**Appendix**, Section Why is dexamethasone rather than acetazolamide used as a positive control? available online).

Interventions

Medication. The budesonide group received oral starch tablets plus inhalation of budesonide (200 μg, twice a day [bid]; in a dry powder inhaler; AstraZeneca AB, Södertälje, Sweden). The dexamethasone group received empty inhalers plus dexamethasone tablets (4 mg, bid; Guangdong Zhongsheng Pharmaceutical Co., Ltd., China). The placebo group received both inhaled and oral placebos (**Appendices 4-7**, available online).

Medication started 1 day before high-altitude (>2500 m) exposure and continued until the third day of exposure. Other personal medications were not allowed (**Appendix 8**, available online).

The subjects were aware of the main side effects of budesonide and dexamethasone. It was suggested that they discontinue medication and inform the researchers if there were any adverse reactions. During medication, the subjects were instructed in the correct way of inhalation.

High-Altitude Exposure and Examinations. Demographic data were collected during recruitment. Baseline examinations were performed at sea level (Chongqing,

China, 400 m). Then the subjects traveled to Litang County, Sichuan Province, China (3900 m) from Chongqing by car on July 3, 2013. On July 4, they acutely ascended to 2600 m from 650 m, which was defined as the earliest time of high-altitude exposure. They reached the destination at 3900 m on July 8. Symptoms related to acute mountain sickness, heart rate, and pulse oxygen saturation (SpO_2) were recorded at 96 hours after high-altitude exposure. Spirometry and sleep questionnaire were completed at 144 and 168 hours, respectively (**Figure 1**).

Outcome Measures

Primary outcome measure was the incidence of acute mountain sickness at altitude. Secondary outcome measures were as follows: the incidence of its severe form, its severity reflected by Lake Louise Scoring System (LLS) score,[22,23] heart rate, SpO_2, spirometric parameters, sleep quality assessed by questionnaires, and adverse reactions related to the investigational drugs.

Diagnostic Criterion. Acute mountain sickness was diagnosed by LLS,[22,23] which 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. Acute mountain sickness 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.

Heart Rate and SpO_2. Heart rate and SpO_2 were examined by pulse oximeters (Nonin Onyx® 9550; Nonin Medical, Inc., Plymouth, Minn).

Spirometry. Forced vital capacity (FVC), FVC %Pred. (percentage of the predicted value), forced expiratory volume in one second (FEV1), and FEV1 %Pred. were achieved with a portable spirometer (Minato AS-507; Minato Medical Science Co., Ltd., Osaka, Japan). Their difference values between sea level and altitude were computed. Spirometry was performed according to the guidelines of the American Thoracic Society.[24]

Sleep Questionnaire. The Pittsburgh Sleep Quality Index (PSQI)[25] and Epworth sleepiness scale (ESS)[26] were included in the sleep questionnaire.

The PSQI has 19 self-rating questions that evaluate sleep in 7 areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Each area is scored 0-3, with 3 reflecting the negative extreme. The sum of their scores yields the global PSQI score. The Chinese version of PSQI is a sensitive, reliable, and valid tool to assess sleep quality.[27] We adopted its 1-week version considering our follow-up plan. Because other medications were prohibited, we did not include "use of sleeping medication" in the total score.

ESS measures the chance of dozing off or falling asleep in 8 situations to reflect daytime somnolence status. Each situation is scored 0-3, with 3 representing the highest chance of dozing. The ESS score is the sum of them.

Sample Size

The placebo group was assumed to have the highest incidence of 60%. According to published studies concerning dexamethasone and our previous pilot trial concerning budesonide, the lowest incidence was assumed to be 25%. Assuming $s = 0.05$, $1\text{-}\beta = 0.8$, and considering a dropout rate of 20%, we calculated the sample size to be 138 cases (46 in each group) (**Appendix 9**, available online).

Blinding

Empty inhalers could not be distinguished from budesonide inhalers by vision or feel. Starch tablets were similar to

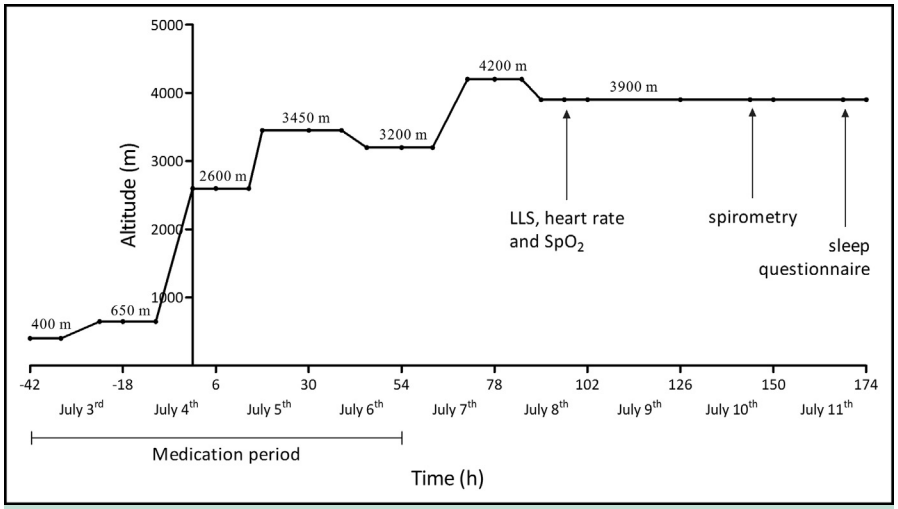

Figure 1 Ascent profile, medication and examinations at altitude. LLS = Lake Louise Scoring System; SpO_2 = pulse oxygen saturation.

dexamethasone tablets in shape, size, and color. The independent physician mentioned above repackaged these drugs in medicine boxes for each subject and reserved the blinding code. The subjects, researchers, and other physicians were blinded (**Appendix 10**, available online).

Statistical Methods

One-way analyses of variance followed by Student-Newman-Keuls tests were used to compare weight, height, heart rate, SpO_2, and the difference value of FVC and FEV1 among the 3 groups. Paired sample *t* tests were used to compare heart rate, SpO_2, FVC, and FEV1 between lowland and altitude in each group. Kruskal-Wallis tests followed by Nemenyi tests were applied to compare age, body mass index, smoking and drinking history, LLS score, and items of sleep questionnaire among the 3 groups. Paired sample Wilcoxon signed-rank tests were applied to compare items of sleep questionnaire between lowland and altitude in each group. The incidences of acute mountain sickness and its severe form were compared among the 3 groups using chi-squared tests. All tests were 2-tailed. Differences were considered statistically significant if $P < .05$, except when Bonferroni method was used. The statistical analyses were performed using SPSS 13.0 for Windows (SPSS Inc., Chicago, Ill).

RESULTS

Participant Flow

There were 138 eligible participants recruited at Chongqing, China (46 in each group after randomization). Before intervention, 10 subjects were lost to follow-up due to personal reasons (4, 3, and 3 in the budesonide, dexamethasone, and placebo groups, respectively). During intervention, 4 participants in the dexamethasone group encountered adverse reactions and discontinued medication before receiving any examination at altitude. Finally, 124 subjects completed the trial, whose data were included in analyses (42, 39, and 43 in the budesonide, dexamethasone, and placebo groups, respectively). Intension-to-treat analysis could not be used (**Figure 2**).

Demographic Data

There were no significant differences in demographic data among the 3 groups, including age, weight, height, and body

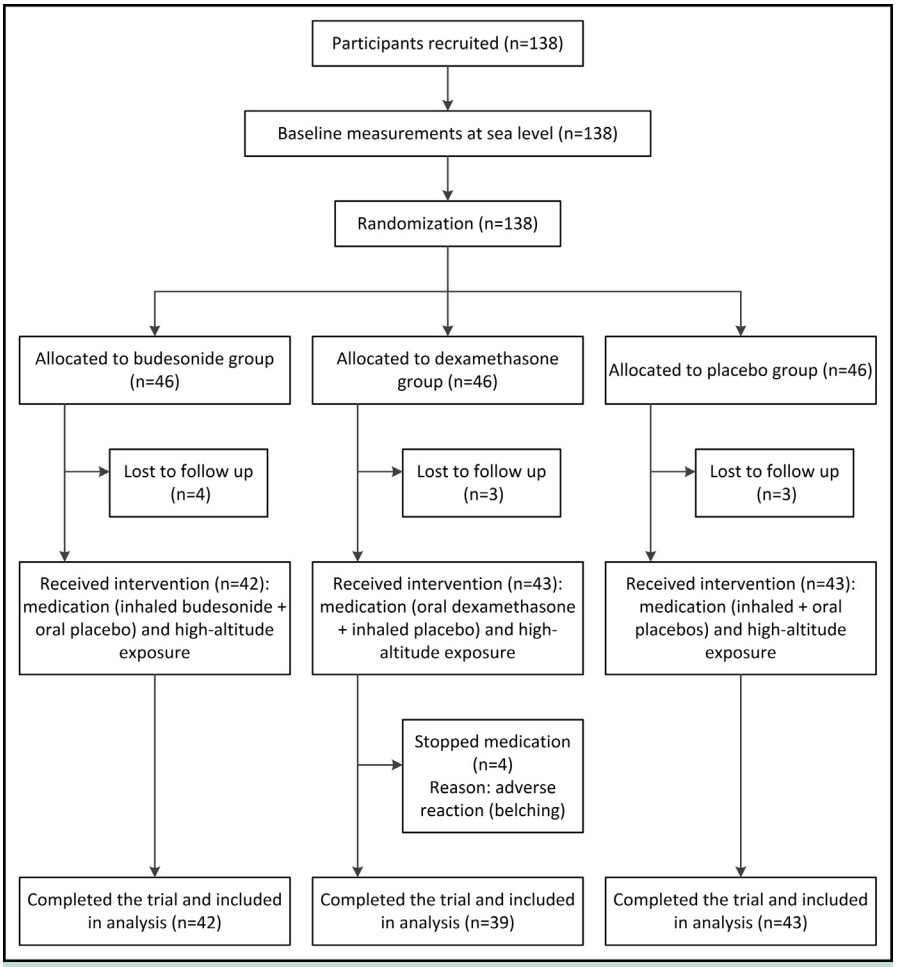

Figure 2 Flow diagram of the study.

Table 1 Demographic Data of the Subjects in the 3 Groups

Variable	Budesonide n = 46	Dexamethasone n = 46	Placebo n = 46	*P* Value
Age, mean ± SD, years	20.39 ± 2.40	20.78 ± 2.30	20.52 ± 2.35	.562
Weight, mean ± SD, kg	63.91 ± 7.68	61.83 ± 7.18	62.07 ± 6.86	.322
Height, mean ± SD, cm	173.09 ± 5.17	170.89 ± 4.23	172.03 ± 4.95	.094
BMI, mean ± SD	21.32 ± 2.28	21.13 ± 1.86	20.95 ± 1.95	.739
Smoking history				.669
Never, n (%)	11 (23.91)	8 (17.39)	12 (26.09)	
Occasionally, n (%)	6 (13.04)	12 (26.09)	8 (17.39)	
Mild, n (%)	26 (56.52)	19 (41.30)	24 (52.17)	
Moderate, n (%)	2 (4.35)	5 (10.87)	1 (2.17)	
Severe, n (%)	1 (2.17)	2 (4.35)	1 (2.17)	
Drinking history				.400
Never, n (%)	42 (91.30)	45 (97.83)	43 (93.48)	
Mild, n (%)	4 (8.70)	1 (2.17)	2 (4.35)	
Moderate, n (%)	0 (0.00)	0 (0.00)	1 (2.17)	
Severe, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	

BMI = body mass index.

mass index, as well as smoking and drinking history (Table 1).

The Incidence and Severity of Acute Mountain Sickness

After high-altitude exposure, significantly fewer participants in the budesonide (23.81%) and dexamethasone (30.77%) groups developed acute mountain sickness, compared with participants receiving placebo (60.46%) ($P = .0006$ and $P = .0071$, respectively). Relative risks for budesonide and dexamethasone compared with placebo were 0.394 (95% confidence interval [CI], 0.218-0.712) and 0.509 (95% CI, 0.300-0.864), respectively. Difference between the budesonide and dexamethasone groups was not significant (Figure 3).

At altitude, the incidences of severe acute mountain sickness in the budesonide (4.76%) and dexamethasone (7.69%) groups were both significantly lower than the placebo group (39.53%) ($P = .0001$ and $P = .0008$, respectively). Relative risks for budesonide and dexamethasone compared with placebo were 0.120 (95% CI, 0.030-0.489) and 0.195 (95% CI, 0.062-0.613), respectively (Figure 3).

LLS scores in the budesonide (1.64 ± 1.65) and dexamethasone (1.92 ± 1.72) groups were both significantly lower than the placebo group (3.42 ± 2.30) ($P = .0011$ and $P = .0144$, respectively).

Heart Rate and SpO_2

Baseline measurements of heart rate and SpO_2 did not differ among the 3 groups. Heart rate was elevated at altitude compared with sea level in every group (all $P < .001$). Both the budesonide and dexamethasone groups had lower heart rate than the placebo group at altitude (both $P < .05$) (Figure 4A).

SpO_2 went down at altitude compared with sea level in every group (all $P < .001$). Both the budesonide and dexamethasone groups had higher SpO_2 than the placebo group at altitude (both $P < .05$) (Figure 4B) (Appendix 11, available online).

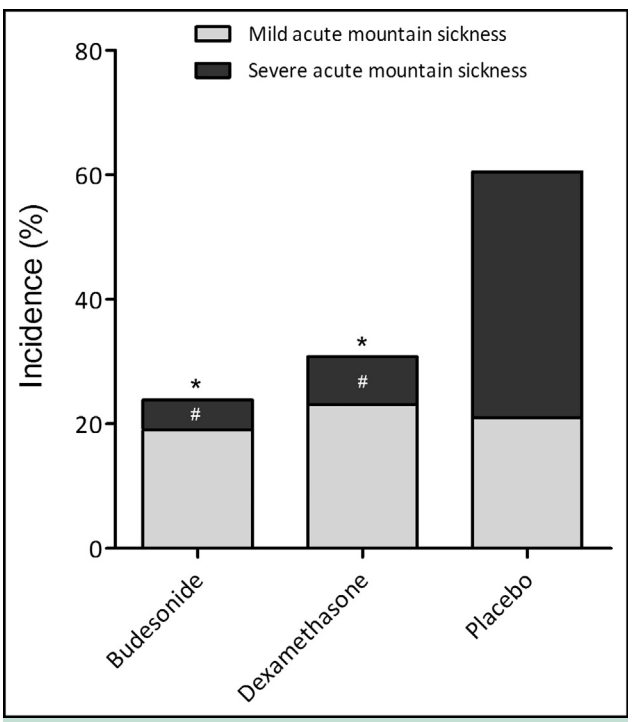

Figure 3 Incidences of acute mountain sickness (mild, severe and total) after high-altitude exposure in the 3 groups. *Significant difference of the total incidence of acute mountain sickness compared with the placebo group. #Significant difference of the incidence of severe acute mountain sickness compared with the placebo group.

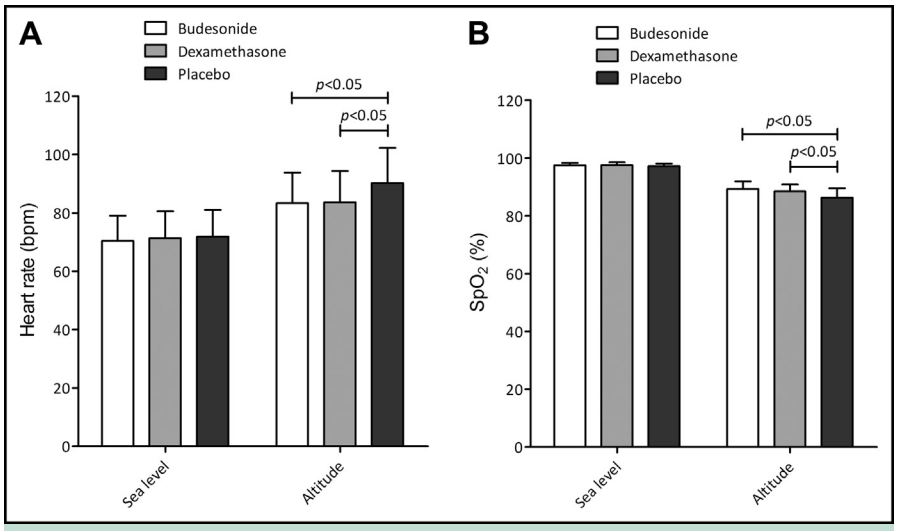

Figure 4 (**A**) Heart rate and (**B**) pulse oxygen saturation (SpO_2) at sea level and altitude in the 3 groups.

Spirometric Parameters

Spirometric parameters were similar among the 3 groups at sea level. In every group, FVC and FVC %Pred. dropped after high-altitude exposure, while FEV1 and FEV1 %Pred. did not change significantly. The budesonide group had significantly smaller ΔFVC and ΔFVC %Pred. (degree of decrement) than the placebo group (both $P < .05$), while dexamethasone versus placebo or dexamethasone versus budesonide showed no significant difference (Table 2).

Sleep Quality

ESS score, global PSQI score, and sub-scales of PSQI did not differ among the 3 groups at sea level. Comparisons of the difference value of each item among the 3 groups showed that the budesonide group was better than the placebo group in subjective sleep quality, sleep latency, sleep duration, and global PSQI score. Dexamethasone versus placebo and budesonide versus dexamethasone had no significant difference (Table 3).

Table 2 Spirometric Parameters at Sea Level and Altitude, and their Difference Values in the 3 Groups

Variable Mean ± SD	Budesonide n = 41*	Dexamethasone n = 39	Placebo n = 42*	*P* value†	*P* Value of Post Hoc Tests		
					P12‡	*P13*§	*P23*‖
Sea level							
FVC, L	4.35 ± 0.45	4.31 ± 0.37	4.34 ± 0.51	.888	—	—	—
FVC %Pred., %	99.85 ± 8.68	99.54 ± 7.26	100.00 ± 10.05	.971	—	—	—
FEV1, L	3.65 ± 0.35	3.68 ± 0.30	3.67 ± 0.40	.913	—	—	—
FEV1 %Pred., %	83.24 ± 6.45	83.90 ± 6.38	83.50 ± 8.03	.916	—	—	—
Altitude							
FVC, L	4.23 ± 0.47	4.11 ± 0.44	4.04 ± 0.48	.170	—	—	—
FVC %Pred., %	97.05 ± 9.15	94.97 ± 9.51	93.17 ± 8.76	.158	—	—	—
FEV1, L	3.63 ± 0.39	3.65 ± 0.39	3.61 ± 0.39	.906	—	—	—
FEV1 %Pred., %	82.71 ± 6.82	83.23 ± 8.66	82.24 ± 7.24	.841	—	—	—
Altitude - Sea level							
FVC, L	-0.13 ± 0.34¶	-0.19 ± 0.27¶	-0.30 ± 0.30¶	.041	>.05	<.05	>.05
FVC %Pred., %	-2.80 ± 7.60¶	-4.56 ± 6.45¶	-6.83 ± 7.04¶	.037	>.05	<.05	>.05
FEV1, L	-0.02 ± 0.26	-0.03 ± 0.20	-0.06 ± 0.25	.785	—	—	—
FEV1 %Pred., %	-0.54 ± 5.84	-0.67 ± 4.64	-1.26 ± 5.82	.814	—	—	—

FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; %Pred. = percentage of the predicted value.
*One case was excluded for poor quality of test.
†*P* value of the difference among the 3 groups.
‡*P* value of the difference between budesonide and dexamethasone.
§*P* value of the difference between budesonide and placebo.
‖P value of the difference between dexamethasone and placebo.
¶$P < .05$ for paired sample tests between sea level and altitude in one group.

Table 3 The Difference Values of Items of the PSQI and ESS in the 3 Groups

Items, mean ± SD	Budesonide n = 42	Dexamethasone n = 39	Placebo n = 43	*P* Value*	*P* Value of Post Hoc Tests		
					P12†	*P13*‡	*P23*§
Subjective sleep quality	−0.14 ± 0.81	−0.05 ± 0.69	0.40 ± 0.90‖	.011	.9392	.0208	.0598
Sleep latency	−0.60 ± 0.77‖	−0.41 ± 0.75‖	−0.05 ± 1.05	.028	.5244	.0280	.3342
Sleep duration	0.21 ± 0.92	0.28 ± 0.72‖	0.60 ± 0.85‖	.019	.9593	.0354	.0803
Habitual sleep efficiency	0.05 ± 0.94	0.13 ± 0.61	0.26 ± 1.05	.247	—	—	—
Sleep disturbances	−0.10 ± 0.66	0.00 ± 0.51	0.09 ± 0.81	.404	—	—	—
Daytime dysfunction	0.17 ± 0.93	0.36 ± 0.84‖	0.56 ± 1.05‖	.072	—	—	—
Global PSQI Score	−0.40 ± 3.08	0.31 ± 2.15	1.86 ± 3.93‖	.002	.6215	.0029	.0598
ESS score	0.43 ± 6.44	−0.31 ± 4.50	1.07 ± 5.70	.380	—	—	—

ESS = Epworth sleepiness scale; PSQI = Pittsburgh Sleep Quality Index.
**P* value of the difference among the 3 groups.
†*P* value of the difference between budesonide and dexamethasone.
‡*P* value of the difference between budesonide and placebo.
§*P* value of the difference between dexamethasone and placebo.
‖$P < .05$ for paired sample tests between sea level and altitude in one group.

Adverse Reactions

Four subjects in the dexamethasone group reported persistent belching after receiving medication for 2 days. They stopped medication and withdrew. No subjects in the budesonide and placebo groups reported adverse reactions related to the investigational drugs.

DISCUSSION

Key Findings

Dexamethasone is recommended for the prevention of acute mountain sickness by the Wilderness Medical Society with a recommendation grade of 1A,[6] but may cause systemic side effects.[8-10] In this study, we compared inhaled budesonide, oral dexamethasone, and placebo for the prevention of acute mountain sickness after acute high-altitude exposure. The results showed that both budesonide and dexamethasone were superior to placebo, resulting in about a 50% reduction in the incidence, mostly of the severe form. Budesonide had fewer side effects than dexamethasone and caused fewer dropouts. Both budesonide and dexamethasone alleviated the decrement of oxygenation and the increase of heart rates, but only budesonide demonstrated slightly less deterioration in FVC and sleep quality at high altitude.

Possible Mechanisms

The pathogenesis of acute mountain sickness is not completely understood, but the lung appears to be involved as evidenced by the fact that when compared with healthy subjects at altitude, those who develop acute mountain sickness tend to have lower SpO_2, lower pulmonary diffusing capacity, and higher alveolar-arterial oxygen pressure difference.[12,13] The alveolar space by analysis of bronchoalveolar lavage fluid appears not to be involved.[28] Yet it is controversial whether acute mountain sickness is related to interstitial pulmonary edema[12-16] or pulmonary artery pressure.[15,16]

Peak serum concentrations of inhaled budesonide are much lower than dexamethasone.[29-31] Budesonide also has a shorter half-life period than dexamethasone. This indicates that budesonide is not acting solely through systemic effects. Its local effects in the lung may be of greater importance.

The mechanisms underlying the prophylactic efficacy against acute mountain sickness of dexamethasone are not fully understood. Some may have relation to the lung, such as upregulating alveolar apical membrane Na^+ channel and basolateral Na^+-K^+-ATPase,[17,18] stimulating surfactant secretion,[19] preventing pulmonary transvascular protein escape,[20] and enhancing the integrity of airway epithelia barrier.[21] How any of these relate to the systemic symptoms of acute mountain sickness remains to be uncovered.

In our study, budesonide caused less decreased in FVC and its percent predicted value. Dexamethasone also had a similar but nonsignificant trend. Both budesonide and dexamethasone reduced the decrement of SpO_2. This may be a result of pulmonary function improvement, and may be related to the mechanisms described above.

According to these findings, we speculate that budesonide, an inhaled glucocorticoid, may generate similar but more potent local effects on the lung than dexamethasone, to improve the function of alveolar and airway epithelia, thus improving pulmonary function, increasing SpO_2, and preventing acute mountain sickness.

Sleep is often disturbed at altitude.[32] Nocturnal periodic breathing is common and disruptive to sleep.[33] A recent study on high-altitude pulmonary edema-susceptible subjects showed that prophylactic dexamethasone taken before ascent prevented severe hypoxemia and sleep disturbances.[34] According to our exploration based on subjective questionnaires, inhaled budesonide effectively alleviated the impairment of high altitude on sleep quality. However, we

did not utilize polysomnography. Whether budesonide affects nocturnal breathing and sleep architecture at altitude needs further exploration.

Limitations

We traveled to high altitude by car, which is not as "acute" compared with traveling by air. However, an incidence up to 60.46% in the placebo group suggests that the protection from this staged ascent is insignificant. We chose young male lowland residents as our target population because they comprise the majority of people to fulfill emergency tasks at altitude, during which immediate and excessively rapid ascent is often necessary. Therefore, our results cannot be extended to populations of other ages or females. We could not include an acetazolamide group, which may also be a limitation. However, we think it acceptable to include dexamethasone instead, because it also has a recommendation grade of 1A and should be considered with priority when a very rapid effect is required. Furthermore, studying 2 steroids, one largely limited to the lung and the other acting elsewhere in the body, may give some insight into the mechanisms underlying how corticosteroids are beneficial at high altitude.

CONCLUSION

In this randomized controlled trial, we innovatively demonstrated that both inhaled budesonide (200 μg, bid) and oral dexamethasone (4 mg, bid) were effective for the prevention of acute mountain sickness after acute high-altitude exposure compared with placebo. Inhaled budesonide causes fewer adverse reactions than oral dexamethasone. Budesonide had favorable effects on FVC and SpO_2 at altitude, which may be related to the mechanisms underlying its prophylactic efficacy. It also benefited sleep quality, which is often disturbed at altitude. All these advantages of inhaled budesonide make it a promising alternative for the prevention of acute mountain sickness.

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APPENDIX

1. Why is a placebo group included? How were the safety and rights of them guaranteed?

Budesonide had not been evaluated for prophylaxis against acute mountain sickness before. The study compared the investigational drug (budesonide), a positive control (dexamethasone), and a placebo control to obtain more information. We think it necessary to include a placebo group for the study.

Acute mountain sickness is a mild form of altitude illness. High-altitude cerebral edema and high-altitude pulmonary edema are more dangerous. The ascent profile was not that "acute" compared with traveling to a very high altitude by air. Passive ascending by car had less physical exhaustion compared with ascending on foot. The probability for severe altitude illnesses could be very low. During the study, health care was monitored by a medical team to prevent serious altitude illnesses. We also had an emergency plan to cope with serious cases if there were any, including oxygenation, immediate descent, drug therapy, and transfer to local medical institutions. So the safety of the placebo group was guaranteed.

Before signing written informed consents, the participants were aware of the purpose and process of the study, and knew that they could be assigned to any of the 3 groups, including the placebo group. They were also educated about high altitude illnesses and the investigational drugs. The participants had the right to quit this trial at any time if they wished. So the rights of the placebo group were guaranteed.

2. Why is dexamethasone rather than acetazolamide used as a positive control?

1) Both dexamethasone and acetazolamide can prevent acute mountain sickness. Comparisons between them have different conclusions, because different dexamethasone dosing, ascent profiles, and evaluation criteria may confound results. Because most cases only have mild acute mountain sickness and acetazolamide helps with acclimatization, acetazolamide is considered with priority. But it may not be sufficient to prevent acute mountain sickness when excessively fast ascent profiles are used.[1] The side effects of dexamethasone limit its application, thus it is not considered with priority in ordinary cases. Exceptions are if acetazolamide is contraindicated or when a very rapid effect is required, as, for example, when rescue workers are called to ascend very fast.[2] The prophylactic efficacy of dexamethasone is established, and it also has a recommendation grade of 1A by the Wilderness Medical Society.[3] So we think it acceptable to include dexamethasone as a positive control.
2) The mechanisms underlying the prophylactic efficacy of dexamethasone are not fully understood. Studying 2 steroids, one largely limited to the lung and the other acting elsewhere in the body, may give some insight into the mechanisms underlying how corticosteroids are beneficial at high altitude.

Double dummy placebos were used to guarantee blinding:

Group	Inhalers	+	Tablets
Budesonide group:	Budesonide inhalers	+	Starch tablets
Dexamethasone group:	Empty inhalers	+	Dexamethasone tablets
Placebo group:	Empty inhalers	+	Starch tablets

3) Our target population is young male lowland residents, who comprise the majority of people to fulfill emergency tasks at altitude, such as rescue work and military tasks. Under these emergent conditions, immediate and excessively rapid ascent is often necessary, and dexamethasone has to be considered with priority even though it has more side effects.[2]

3. How were the participants recruited?

The participants went to high altitude not only for the study, but also to fulfill tasks at altitude. They were recruited at Chongqing city (400 m). The study was not advertised. We got in touch with them through introduction from their leaders.

4. Details about exclusion criteria.

"Severe organic diseases" include heart, liver, or kidney dysfunction; malignant tumor; and psychological or neurological disorder. "Other unsuitable conditions" mainly relate to management convenience, for example, whether the participant could follow our arrangements at altitude.

5. Why were empty inhalers used as inhaled placebos?

The empty inhalers had the same appearance as budesonide inhalers, but contained no drug powder. So only air was inhaled. Pulmicort Turbuhaler (AstraZeneca, London, UK) has rather fine drug powder, and the volume of each inhalation is rather small, so that one do not feel or taste any medication when inhaling. We were sure that the subjects could not distinguish the empty inhalers from budesonide inhalers by vision, feel or taste.

6. Details about the inhaled placebo.

Drug powder was removed from the Pulmicort Turbuhaler to make the empty inhalers. This process was performed in an operating room in Xinqiao Hospital. After that, the empty inhalers were irradiated by ^{60}Co to be sterilized in the irradiation center of the Third Military Medical University. Attention was paid to make sure that the empty inhalers looked the same as budesonide inhalers. For example, to remove the drug powder, the packing box had to be opened, and the plastic label circling the cylindrical inhaler had to be removed. So packing boxes, manuals, and plastic labels were removed for both budesonide and empty inhalers. For another example, the appearance of inhalers must not be hurt.

7. Details about the oral placebo.

Starch tablets were produced by Chongqing Pharmaceutical Research Institute Co., Ltd., China to be the same to dexamethasone tablets in shape, size and color. They were

Table S1 Heart Rate and SpO_2 at Sea Level and Altitude

Variables Mean ± SD	Budesonide n = 42	Dexamethasone n = 39	Placebo n = 43	*P* Value*	*P* Value of Post Hoc Tests		
					P12†	*P13*‡	*P23*§
Sea level							
Heart rate, beats per min	70.38 ± 8.64	71.33 ± 9.28	71.88 ± 9.14	.658	—	—	—
SpO_2, %	97.48 ± 0.92	97.56 ± 0.94	97.19 ± 0.93	.065	—	—	—
Altitude							
Heart rate, beats per min	83.38 ± 10.42	83.59 ± 10.76	90.23 ± 12.04	.007	>.05	<.05	<.05
SpO_2, %	89.31 ± 2.57	88.49 ± 2.42	86.3 ± 3.31	<.001	>.05	<.05	<.05

SpO_2 = pulse oxygen saturation.
**P* value of the difference among the 3 groups.
†*P* value of the difference between budesonide and dexamethasone.
‡*P* value of the difference between budesonide and placebo.
§*P* value of the difference between dexamethasone and placebo.

also irradiated by ^{60}Co to be sterilized in the irradiation center of Third Military Medical University.

8. Details about dosing regimen.

The medication period is clearly shown in Figure 1. The first time for medication in a day was after breakfast and the second after dinner. The usage and dosage of both placebos were the same as the investigational drugs, respectively. Besides, although one budesonide inhaler contains 200 inhalations (100 μg in each inhalation), which is far more than the amount actually needed for one participant (16 inhalations in total), we insisted one inhaler for one person, because the lip of a person touches the suction nozzle during inhalation.

9. Details about sample size estimation.

Formula for hypothesis testing of overall rates among multiple groups of completely random design was used for sample size estimation:

$$n = 2\lambda \Big/ \left(2\sin^{-1}\sqrt{p_{max}} - 2\sin^{-1}\sqrt{p_{min}}\right)^2$$

We took $\alpha = 0.05$, $\beta = 0.2$. Since there were 3 groups, the degree of freedom was 2. So $\lambda_{0.05,\ 0.2(2)} = 9.63$. We hypothesized that the placebo group would have an incidence of 60%, and took $p_{max} = 0.6$. According to published literature and our previous pilot trial, both the budesonide and dexamethasone groups were assumed to have an incidence of 25%. So we took $p_{min} = .25$. We calculated to have $n \approx 37$. Considering a dropout rate of 20%, we finally decided to include 138 subjects, with 46 in each group.

The incidences of acute mountain sickness pretreated with budesonide or dexamethasone may be similar. Sample size could be much larger than now for a noninferiority trial. Therefore, this study was not designed to pay too much attention to the comparison between budesonide and dexamethasone.

So far, different studies concerning high altitude may adopt different ascent profiles, dosing regimen of dexamethasone, and even evaluation criterion (many earlier studies used Environmental Symptoms Questionnaire). Therefore, sample size estimation can be quite inaccurate.

10. How was blinding guaranteed?

The independent physician did only 2 things in this study: randomization and repackaging of drugs. He was not involved in other parts of the study, such as study design, recruitment, data collection, and health care.

1) Randomization:

The physician used a computer-generated random number list to allocate the subjects into 3 groups independently. He reserved the blinding code, so the grouping information was not available to the researchers, the subjects and other physicians for health care.

2) Repackaging of drugs:

The researchers gave the 4 kinds of investigational drugs (budesonide inhalers, empty inhalers, dexamethasone tablets, and starch tablets) to the independent physician mentioned above to be repackaged. The repackaging process was completed by the physician alone according to the grouping information that he created. He prepared one medicine box for each subject. The serial number and name of a subject were written on his box, and the drugs he should receive were put into it. After repackaging, the physician gave these medicine boxes to the researchers.

After these 2 processes, blinding was guaranteed.

11. Absolute values of heart rate and pulse oxygen saturation.

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