Postprint: A Study on the Efficacy and Safety of Intermittent Hypoxic Training for Preventing Acute Hypoxic Injury

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Abstract

Background Rapid ascent to high altitude can cause acute hypoxic injury, manifesting as varying degrees of clinical symptoms, some of which may progress to severe acute mountain sickness. However, current prevention and treatment methods are limited, and there is a lack of safe and effective approaches for preventing and mitigating its severity.

Objective To investigate the efficacy and safety of intermittent hypoxia training (IH) in preventing acute hypoxic injury by simulating a hypoxic environment at an altitude of 4,400 meters.

Methods From August 1, 2022, to October 31, 2022, 40 subjects were recruited through public solicitation at Beijing Xiaotangshan Hospital and randomly divided into two groups: an IH group (experimental group, n=20) and a sham training group (control group, n=20). The IH group received IH exposure intervention consisting of 10 min of hypoxia (oxygen concentration 13%, simulating an altitude of 3,800 m) and 5 min of normoxia at 21% oxygen concentration, with a total duration of 55 min, administered 2 times/day for 5 consecutive days. The control group received the same duration of normobaric normoxia intervention. On the first day after completion of the IH intervention training, subjects entered a simulated high-altitude hypoxic environment for 6 h, with the oxygen concentration set at 12% (equivalent to an altitude of 4,400 m). The Lake Louise Score (LLS) was used to assess the severity of acute mountain sickness (AMS) in subjects. Tissue oxygen saturation [peripheral oxygen saturation (SpO2), cerebral tissue oxygen saturation (ScO2)] and intracranial pressure (ICP) were collected at baseline, before acute high-altitude hypoxic environment simulation, and after 6 h of acute high-altitude hypoxic environment simulation.

Results After 6 h of acute high-altitude hypoxic environment simulation, the incidence of AMS and LLS in the experimental group were significantly lower than those in the control group (P<0.05). After 6 h of acute high-altitude hypoxic environment simulation, SpO2 in the experimental group was significantly higher than that in the control group (P<0.05). Within-group comparison results showed that SpO2 and ScO2 in both groups after 6 h of acute high-altitude hypoxic environment simulation were significantly decreased compared with baseline and before acute high-altitude hypoxic environment simulation (P<0.05). The decrease in SpO2 after 6 h of acute high-altitude hypoxic environment simulation compared with baseline in the experimental group was significantly smaller than that in the control group (9.30$±4.31*vs*.13.10±$6.66, P=0.039). ICP in the control group after 6 h of acute high-altitude hypoxic environment simulation was significantly increased compared with before acute high-altitude hypoxic environment simulation (P<0.05).

Conclusion IH training can improve the body's hypoxia tolerance, effectively reduce the incidence and severity of acute mountain sickness, and decrease ICP elevation caused by acute hypoxic exposure.

Full Text

Efficacy and Safety of Intermittent Hypoxic Training in the Prevention of Acute Hypoxic Injury

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Abstract

Background: Rapid ascent to high altitude causes acute hypoxic injury with varying clinical symptoms, some of which may progress to severe acute mountain sickness (AMS). However, current prevention and treatment methods are limited, and safe, effective approaches to prevent or reduce severity are lacking.

Objective: To investigate the efficacy and safety of intermittent hypoxic (IH) training in preventing acute hypoxic injury by simulating a high-altitude hypoxic environment equivalent to 4,400 meters. **Methods:** From August 1, 2022, to October 31, 2022, 40 subjects were recruited through public advertisement at Beijing Xiaotangshan Hospital and randomly divided into two groups: an IH group (experimental group, n=20) and a sham training group (control group, n=20). The IH group received IH exposure intervention twice daily for 5 consecutive days, consisting of 10 minutes of hypoxia (13% oxygen concentration, simulating 3,800 m altitude) alternating with 5 minutes of normoxia (21% oxygen concentration), for a total duration of 55 minutes per session. The control group received simultaneous normobaric normoxia intervention. On the first day after completing the IH intervention, subjects entered a simulated high-altitude hypoxic environment for 6 hours with oxygen concentration set at 12% (equivalent to 4,400 m altitude). The Lake Louise Scale (LLS) was used to assess AMS severity. Tissue oxygen saturation [peripheral oxygen saturation (SpO_2) and cerebral oxygen saturation (ScO_2)] and intracranial pressure (ICP) were measured at baseline, before acute hypoxia simulation, and after 6 hours of exposure. **Results:** After 6 hours of simulated acute high-altitude hypoxia, the experimental group showed significantly lower AMS incidence and LLS scores compared to the control group ($P<0.05$). SpO_2 in the experimental group was significantly higher than in the control group ($P<0.05$). Within-group comparisons revealed that SpO_2 and ScO_2 in both groups decreased significantly after 6 hours of hypoxia exposure compared to baseline and pre-exposure values ($P<0.05$). The magnitude of SpO_2 reduction from baseline was significantly smaller in the experimental group than in the control group ($9.30\$\pm4.31 vs. 13.10\pm\$6.66$, $P=0.039$). ICP in the control group increased significantly after hypoxia exposure compared to pre-exposure values ($P<0.05$). **Conclusion:** IH training can enhance hypoxia tolerance, effectively reduce AMS incidence and severity, and prevent ICP elevation caused by acute hypoxic exposure.

Keywords: Altitude sickness; Acute mountain sickness; Hypoxemia; Intermittent hypoxic training; Effectiveness and safety

Introduction

With increasing numbers of lowland residents traveling to high-altitude regions for tourism or work, the markedly lower atmospheric pressure and oxygen content in these areas trigger a series of physiological responses [1]. Acute hypoxic stress reactions resulting from insufficient adaptation to high-altitude environments are termed acute mountain sickness (AMS) [2]. AMS typically occurs in non-acclimatized individuals who rapidly ascend above 2,500 m, manifesting as headache, nausea, somnolence, dizziness, vertigo, fatigue, weakness, and insomnia of varying severity. In severe cases, it may progress to high-altitude pulmonary edema (HAPE) or high-altitude cerebral edema (HACE). The risk depends on individual susceptibility, altitude, and rate of ascent [3]. The inci-

dence of AMS is 10–20% at 2,500–3,000 m and can reach 50–85% at 4,500–5,000 m [4]. AMS has acute onset and rapid progression, endangering the health of individuals entering high-altitude areas and directly impacting work productivity and quality of life [5].

Current pharmacological prevention and treatment options for AMS primarily include oral acetazolamide and dexamethasone [2,6-7]. However, research indicates that acetazolamide has limited preventive effects on AMS during rapid ascent [8], while dexamethasone's use is restricted due to significant adverse effects. Intermittent hypoxic (IH) training involves periodic exposure to alternating normoxic and hypoxic conditions. Depending on the degree of hypoxic stimulus, cycle duration, and frequency, IH can produce either beneficial or detrimental effects on the human body [11]. Long-term chronic IH may cause hypertension, cerebrovascular and/or coronary artery disease, leading to developmental delay, cognitive impairment, and neurological degeneration due to cumulative effects of persistent hypoxic episodes [15]. Conversely, short-term IH (5–10 minutes per session), low-frequency (3–15 sessions per day), and mild-to-moderate hypoxia (9–16% oxygen concentration) can activate hypoxic signaling pathways, exert antioxidant effects, reduce inflammatory damage, and enhance resistance to hypoxic injury, thereby exerting protective effects [16]. As a promising training method, IH can improve adaptive potential and enhance athletic endurance [17-18]. Growing evidence suggests that short-term IH can improve motor function in spinal cord injury patients and increase exercise capacity in athletes [11-12]. With deeper understanding of IH's protective effects, a series of studies on IH for AMS prevention have been conducted [19-20]. However, despite various preventive protocols, standardized IH adaptation models and parameters remain lacking, along with theoretical support.

Therefore, this study employed a randomized, controlled, double-blind design to investigate the protective effects of IH against acute hypoxic injury by simulating high-altitude hypoxic environments.

Methods

Study Subjects

From August 1, 2022, to October 31, 2022, 40 subjects were recruited through public advertisement at Beijing Xiaotangshan Hospital and randomly divided into two groups: an IH group (experimental group, n=20) and a sham training group (control group, n=20). **Inclusion criteria:** (1) Age 18–45 years; (2) Baseline peripheral oxygen saturation (SpO_2) $\geq$ 90%, cerebral oxygen saturation (ScO_2) 58–82%, heart rate 60–100 beats/min, blood pressure 90–139/60–89 mmHg (1 mmHg = 0.133 kPa), respiratory rate 16–20 breaths/min; (3) Lifelong lowland residents who had not visited areas above 1,500 m in the previous 6 months. **Exclusion criteria:** (1) Women during menstruation, pregnancy, or lactation; (2) History of neurological, cardiovascular, or respiratory diseases

such as cerebrovascular disease, hypertension, coronary artery disease, or sleep apnea syndrome; (3) History of chest tightness or chest pain; (4) Abnormal coagulation mechanism and/or liver/kidney function; (5) History of drug or alcohol abuse; (6) Participation in other drug or medical device clinical trials within the previous 4 weeks; (7) Any condition deemed unsuitable by investigators. This study was approved by the Beijing Xiaotangshan Hospital Ethics Committee ([2022] Ethics Review No. 77), and all subjects voluntarily participated and provided informed consent.

IH Intervention

This study utilized a mask-based hypoxic device to achieve IH exposure. Under normobaric conditions, the device mixed ambient air with nitrogen to achieve the desired fraction of inspired oxygen (FiO_2). Subjects breathed oxygen-reduced gas through a mask respirator to simulate hypoxic environments. During recovery periods, subjects removed the mask to breathe ambient air (normoxia). Throughout IH intervention, subjects rested supine in a quiet environment while remaining awake. If significant hypoxia-related symptoms such as dizziness, headache, or palpitations occurred, subjects could remove the mask. The IH protocol consisted of 10 minutes of hypoxia (13% oxygen concentration, simulating 3,800 m altitude) alternating with 5 minutes of normoxia (21% oxygen concentration), for a total duration of 55 minutes per session. The experimental group received IH intervention twice daily, while the control group received simultaneous normobaric normoxia intervention for 5 consecutive days. Oxygen concentration settings for IH/sham training were managed by trained professionals. Both subjects and outcome assessors were blinded to group allocation.

Acute High-Altitude Hypoxia Simulation and Clinical Assessment

Beijing Xiaotangshan Hospital is equipped with a normobaric hypoxic chamber that can simulate altitude by setting oxygen concentration. On the first day after completing IH intervention, subjects entered the simulated high-altitude hypoxic environment for 6 hours with oxygen concentration set at 12% (equivalent to 4,400 m altitude). The Lake Louise Scale (LLS) was used to assess AMS severity. LLS evaluates four items: headache, dizziness, fatigue, and gastrointestinal symptoms, each scored 0–3 (none, mild, moderate, severe) for a total of 12 points. A total score ≥ 3 with headache is considered AMS [13-14].

Data Collection

Baseline demographic data (age, height, weight, blood pressure, heart rate, respiratory rate) were collected, and BMI was calculated. Tissue oxygen saturation (SpO_2, ScO_2) and intracranial pressure (ICP) were measured at baseline, before acute hypoxia simulation, and after 6 hours of exposure.

Study Termination Criteria

The study was terminated if subjects experienced: (1) SpO_2 < 70% of baseline value for 10 seconds; (2) Heart rate > 140 beats/min for 10 seconds; (3) Blood pressure ≥ 180/100 mmHg; (4) Respiratory rate > 30 breaths/min; (5) Electrocardiographic evidence of myocardial ischemia with chest pain or tightness; (6) Malignant arrhythmia; or (7) Other intolerable symptoms such as shortness of breath, dizziness, or headache.

Statistical Analysis

SPSS 26.0 software was used for statistical analysis. Normally distributed continuous data are presented as mean ± standard deviation ($\bar{x}\pm s$). Independent samples t-test was used for between-group comparisons, and paired t-test for within-group pre-post comparisons. Categorical data are presented as frequencies and percentages, with between-group comparisons using ^{2} test. Statistical significance was set at $P<0.05$.

Results

Baseline Characteristics

All 40 subjects completed the study. There were no significant differences between groups in age, BMI, systolic blood pressure, diastolic blood pressure, or heart rate ($P>0.05$) .

AMS Incidence and Severity

After 6 hours of simulated acute high-altitude hypoxia, the experimental group showed significantly lower AMS incidence and LLS scores compared to the control group ($P<0.05$) .

Tissue Oxygen Saturation and Intracranial Pressure

There were no significant between-group differences in SpO_2, ScO_2, or ICP at baseline or before acute hypoxia simulation ($P>0.05$). After 6 hours of hypoxia exposure, ScO_2 and ICP did not differ significantly between groups ($P>0.05$), but SpO_2 was significantly higher in the experimental group ($P<0.05$).

Within-group comparisons showed that SpO_2 and ScO_2 in both groups decreased significantly after 6 hours of hypoxia exposure compared to baseline and pre-exposure values ($P<0.05$). The magnitude of SpO_2 reduction from baseline was significantly smaller in the experimental group than in the control group ($9.30\$\pm4.31 vs. 13.10\pm\$6.66$, $P=0.039$). ICP in the control group increased significantly after hypoxia exposure compared to pre-exposure values ($P<0.05$) .

Discussion

AMS is a common high-altitude disease resulting from acute hypoxic injury when acclimatization mechanisms are not yet established [3,21]. Symptoms can appear as early as 1–2 hours after altitude exposure, sometimes delayed until 6–12 hours, with prolonged hypoxia increasing the risk of severe high-altitude illness [22]. Therefore, this study used 6 hours of simulated high-altitude hypoxia as the observation endpoint, with LLS assessing AMS incidence and symptom severity. The results demonstrated that the experimental group had significantly lower AMS incidence and severity compared to the control group.

SpO_2 is a sensitive indicator of hypoxia, reflecting the body's hypoxia tolerance [2,23]. In high-altitude hypoxic environments, reduced inspired oxygen partial pressure decreases the alveolar-capillary oxygen gradient, preventing complete oxygen diffusion into capillaries and causing gradual SpO_2 decline. When SpO_2 falls below a certain threshold, insufficient oxygen supply to tissues causes functional or organic changes and hypoxic symptoms. Research shows that after hypoxic pre-acclimatization, SpO_2 gradually increases as the body develops adaptive responses [20]. This study found that during 6 hours of simulated high-altitude hypoxia, the experimental group maintained higher SpO_2 levels than the control group, with a smaller magnitude of reduction from baseline, indicating that IH can improve hypoxia tolerance [24].

Acute hypoxia-induced reduction in SpO_2 decreases tissue oxygen delivery and utilization, leading to decreased ScO_2, which serves as a clinical indicator of cerebral autoregulation [25]. However, this study did not observe significant ScO_2 decline after 6 hours of hypoxia exposure, possibly because cerebral tissues can maintain better oxygen extraction from surrounding tissues within a certain timeframe, thus not triggering reactive cerebral vascular responses to hypoxia.

Acute hypoxia can cause intracranial pressure elevation, resulting in headache, nausea, vomiting, and in severe cases, cerebral edema and coma [26]. This study found that ICP increased by approximately 2.4 mmH_2O in the experimental group after acute hypoxia exposure, compared to about 24.6 mmH_2O in the control group. Moreover, compared to baseline, IH training did not increase ICP but instead decreased it by approximately 20.6 mmH_2O, demonstrating that this IH training protocol is safe and feasible and may exert beneficial physiological effects.

IH involves periodic exposure to alternating normoxic-hypoxic cycles. Depending on the degree of hypoxic stimulus, cycle duration, and frequency, IH can produce either beneficial or detrimental effects [11]. Long-term chronic IH may cause hypertension, cerebrovascular and/or coronary artery disease, leading to developmental delay, cognitive impairment, and neurological degeneration from cumulative hypoxic episodes [15]. However, short-term IH (5–10 minutes per session), low-frequency (3–15 sessions per day), and mild-to-moderate hypoxia

(9–16% oxygen concentration) can activate hypoxic signaling pathways, exert antioxidant effects, reduce inflammatory damage, and enhance resistance to hypoxic injury [16]. As a promising training method, IH can improve adaptive potential and athletic endurance [17-18]. With growing recognition of IH's protective effects, numerous studies on IH for AMS prevention have emerged [19-20]. Nevertheless, standardized IH adaptation models and parameters remain lacking, along with theoretical support.

This randomized, controlled, double-blind clinical trial employed a short-term, mild-to-moderate, low-frequency IH training protocol to simulate high-altitude hypoxia while monitoring tissue oxygen saturation and ICP, confirming that IH can enhance hypoxia tolerance and reduce AMS incidence and severity. All 40 subjects completed IH/sham intervention and 6 hours of simulated high-altitude exposure without termination or development of HAPE/HACE. No intolerable hypoxia-related symptoms were reported during IH intervention, and no significant decreases in tissue oxygen concentration or ICP elevation occurred pre- to post-IH training, demonstrating the safety of IH training.

This study has several limitations. First, the sample size was small and the trial was single-center. Second, the simulated altitude environment was normobaric hypoxia without reduced atmospheric pressure. Third, the simulated high-altitude exposure duration was relatively short. Fourth, the protective mechanisms of IH were not thoroughly investigated. Future research will expand sample sizes, simulate hypobaric hypoxic environments, conduct multidimensional assessments of high-altitude hypoxic injury, and explore the protective mechanisms of intermittent hypoxia in greater depth.

In summary, the IH training protocol consisting of 10 minutes of hypoxia (13% oxygen, simulating 3,800 m) alternating with 5 minutes of normoxia (21% oxygen) for a total duration of 55 minutes, administered twice daily for 5 consecutive days, effectively reduced AMS incidence and severity under simulated 4,400 m altitude conditions. Furthermore, IH training attenuated tissue oxygen saturation reduction and prevented intracranial pressure elevation caused by acute hypoxic exposure. Collectively, IH training demonstrates protective effects against acute high-altitude hypoxic injury.

Author Contributions

HUANG Dan: Conceived the study, designed the research, implemented the study, and drafted the manuscript. ZHANG Qihan, SONG Ge, WANG Qing, and LI Yu: Collected and organized data, performed statistical analysis, and prepared figures and tables. JI Xunming: Responsible for quality control, review, and supervision. WANG Yuan: Revised the manuscript and assumed overall responsibility for the article.

Conflict of Interest

The authors declare no conflict of interest.

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