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Therapeutic approaches for headache in acute mountain sickness: A review of best practices

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Resumen

Introduction: Acute Mountain Sickness (AMS) is a condition that results from the body failing to adapt to high-altitude environments, typically above 2,000 meters. The main symptom is headaches, which are primarily caused by sensitivity to hypoxia. The aim of this study was to identify the most effective alternatives for mitigating these symptoms.

Materials and methods: We performed a review using only Pubmed, following the PRISMA protocol (PROSPERO registration: CRD420251024258)..

Results: Herbal treatments do not provide significant pain relief for AMS and may interfere with the pharmacological efficacy of acetazolamide. When used alongside *Ginkgo biloba*, the odds ratio for acetazolamide relieving headache was lower compared to its use as a monotherapy, even in severe cases.

Discussion: The pathophysiology involves mitochondrial dysfunction and oxidative stress, which are compensated for by the production of prostaglandins and hyperventilation. Ultimately, this triggers headaches. Acetazolamide and dexamethasone are effective in preventing and reducing symptoms, while oxygen therapy and aspirin provide symptomatic relief. In contrast, herbal medicines such as *Ginkgo biloba* and *Rhodiola crenulata* have produced inconsistent results. Specific biomarkers (IL-1RA, HSP-70 and adrenomedullin) have been associated with AMS resistance. Finally, strategies such as four-week remote ischaemic preconditioning (RIPC) show promise in terms of altitude adaptation and the prevention of AMS.

Conclusions: A lack of standardized clinical trials and population heterogeneity remain major challenges in establishing a universal treatment standard for AMS. Future research should explore various drug combinations and reduced doses of acetazolamide to optimize analgesia across different populations.

Keywords: Acute mountain sickness, Altitude sickness, Altitude hypoxia, Secondary headache disorders, Headache, Cell hypoxia, Hypoxia-ischemia brain.

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Enfoques terapéuticos para la cefalea en el mal agudo de montaña: una revisión de las mejores prácticas

Abstract

Introducción: el síndrome del mal de montaña (SMM) es una condición que resulta de la incapacidad del organismo para adaptarse adecuadamente a ambientes de gran altitud,generalmente por encima de los 2.000 metros. La cefalea es el síntoma predominante y se asocia principalmente con mecanismos inducidos por hipoxia. El objetivo de este estudio fue identificar las alternativas más efectivas para mitigar estos síntomas.

Materiales y métodos: se realizó una revisión utilizando únicamente Pubmed, de acuerdo con las directrices PRISMA y registrada en PROSPERO (CRD420251024258).

Resultados: los tratamientos herbales no demostraron eficacia significativa en el alivio de la cefalea asociada al SMM y pueden interferir con la acción farmacológica de la acetazolamida. Cuando se utiliza en combinación con *Ginkgo biloba*, la razón de probabilidades de alivio del dolor con acetazolamida fue menor en comparación con su uso en monoterapia, incluso en casos graves.

Discusión: la fisiopatología del SMM involucra disfunción mitocondrial y estrés oxidativo, con mecanismos compensatorios como el aumento de la producción de prostaglandinas y la hiperventilación, lo que finalmente desencadena cefalea. La acetazolamida y la dexametasona son eficaces tanto en la prevención como en la reducción de los síntomas, mientras que la oxigenoterapia y la aspirina

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proporcionan alivio sintomático. En contraste, los tratamientos herbales como *Ginkgo biloba* y *Rhodiola crenulata* han mostrado resultados inconsistentes.

Biomarcadores específicos (IL-1RA, HSP-70 y adrenomedulina) se han asociado con resistencia al SMM. Finalmente, estrategias como el preacondicionamiento isquémico remoto (RIPC) durante cuatro semanas han mostrado resultados prometedores en la adaptación a la altitud y la prevención del SMM.

Conclusiones: la falta de estandarización en los ensayos clínicos y la heterogeneidad de las poblaciones estudiadas continúan siendo desafíos importantes para establecer un tratamiento universal para el SMM. Futuras investigaciones deben explorar combinaciones farmacológicas y dosis reducidas de acetazolamida para optimizar la analgesia en diferentes poblaciones.

Palabras clave: mal de altura, enfermedad de la altura, enfermedad de la montaña, cefaleas secundarias, cefaleas primarias, hipoxia de la célula, hipoxia-isquemia encefálica.

Introduction

Acute Mountain Sickness (AMS) is a clinical condition that results from the body failing to adapt to high-altitude environments, typically 2,000 meters above sea level, where hypobaric hypoxia and reduced atmospheric pressure prevail.

The diagnosis is primarily established using the Lake Louise Score (LLS). Clinical symptoms include headache, vertigo, asthenia, nausea, lipothymia, tinnitus, and insomnia, which are due to sensitivity to hypoxia (1-3). If left untreated, the condition may progress to life-threatening high-altitude cerebral or pulmonary edema (4). AMS can manifest in either acute or chronic forms, primarily due to inadequate physiological adaptation over short or extended periods, respectively (5).

The prevalence of AMS is notably high among mountaineers, skiers, and travellers who ascend rapidly without proper acclimatization. At altitudes between 3,000 and 5,000 meters, around half of all individuals experience AMS, with headache being the defining symptom (5-6). Although pharmacological prevention is effective; however, side effects such as paresthesia, dysgeusia, allergic reactions, and changes in urinary flow may reduce therapeutic adherence.

The literature search for this review revealed that identifying the most effective therapies for managing secondary headaches originating from AMS presented several challenges. One of the main difficulties encountered was the significant heterogeneity among the available clinical trials in terms of both methodology and outcome assessment criteria. The analyzed studies explored various therapeutic approaches, including the use of aspirin, acetazolamide, dexamethasone, G*inkgo biloba, Rhodiola crenulata*, oxygen therapy, Repeated Remote Ischemic Preconditioning (RIPC), and erythropoietin. However, they did not reach a clear consensus on the most effective prevention and treatment strategy.

Considering these limitations, this review aims to analyze the best available evidence on therapeutic and preventive approaches for hypoxia-induced headache in AMS, with the aim of identifying effective strategies to mitigate the impact of high-altitude exposure on individuals. Although there are some studies on risk factors, prevention and treatment, there is still disagreement about the effectiveness of certain prophylactic strategies. Therefore, synthesizing the best available evidence on clinical approaches and outlining directions for future research is essential to establish more robust guidelines for AMS management.

Objectives

General

To analyze the most effective therapeutic options for managing headaches induced by AMS.

Specifics

1. To compare the efficacy of acetazolamide monotherapy with its use in combination with herbal supplements (*Ginkgo biloba* and *Rhodiola crenulata*).
2. To evaluate the effectiveness of dexamethasone, oxygen therapy, RIPC, and erythropoietin for pain management in AMS-related headaches.

Methods

This study is a review conducted without meta-analysis, due to the methodological and clinical heterogeneity of the included studies. The review used the PubMed, SciELO, and Cochrane databases, covering publications from 1998 to 2025, with the final search performed on March 3, 2025. The research primarily used the PubMed database due to the scarcity of articles found and the specificity of the proposed theme, since it is more common in high-altitude regions. The search strategy employed the terms 'hypoxia headache', 'acute mountain sickness', high altitude headache', 'mountain syndrome' and 'headache', combined using the Boolean operators 'AND' and 'OR'. The research framework was guided by the PICO protocol: Population (P): individuals experiencing secondary headaches at high altitudes; Intervention (I): dexamethasone, aspirin, erythropoietin, oxygen therapy, acetazolamide, *Ginkgo Biloba* extract, RIPC, and *Rhodiola crenulata* root extract; Comparison (C): placebo; and Outcome (O): relief of headache symptoms. The study is registered with PROSPERO (ID: CRD420251024258).

Initially, 44 randomized clinical trials that were available in English and accessible in full were identified. The screening process was conducted via the Rayyan digital platform by two independent researchers working in a blinded manner to exclude duplicates and articles that did not align with the scope of the study. Following this analysis, 11 articles were selected for qualitative synthesis and organized in a spreadsheet for descriptive analysis based on their PICO components (Figure 1).

Results

To evaluate the efficacy of the interventions under study, each included article was analyzed in detail to summarise the primary pharmacological and clinical findings regarding the management of AMS and its associated headache. These findings are summarized in Table 1.

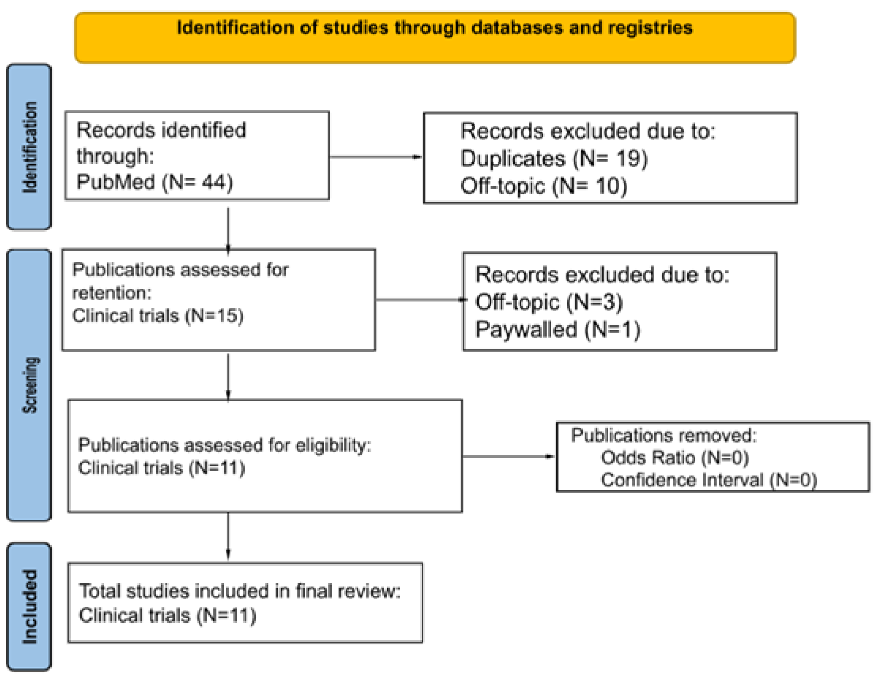

Figure 1. PRISMA flowchart

Source: Authors.

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Table 1. Summary of the key findings in each article

Author & Year	Country	Study Type	Objective	Key Findings
Chiu, T et al., (7)	China.	Clinical trial.	To evaluate the efficacy of *Rhodiola crenulata* in AMS prevention.	No significant differences were found between the treatment and placebo groups regarding AMS incidence.
Hall, D et al., (8)	Bolivia (La Paz).	Clinical trial.	To assess AMS symptomatology in lowlanders acutely exposed to high altitude.	Identified distinct symptom patterns; fatigue and sleep disturbances often occurred independently of headache.
Gertsch, J et al., (4)	Nepal (Mt. Everest).	Clinical trial.	To compare *Ginkgo biloba*, acetazolamide, and their combination for AMS prophylaxis.	*Ginkgo biloba* was ineffective and potentially reduced acetazolamide's efficacy. Acetazolamide (250 mg twice a day) remains the gold standard.
Benedetti, F et al., (1)	Italy (Matterhorn).	Clinical trial.	To analyze placebo responses and the efficacy of oxygen and aspirin for headache.	Hypoxia triggers headache via increased prostaglandin production (PGD_2, $PGF_2\alpha$, PGI_2, TXA_2, and PGE_2) and compensatory hyperventilation-induced alkalosis.
Vestergaard, M et al., (9)	-	Clinical trial.	To investigate the effects of hypoxia and aging on cerebral metabolism and lactate.	Hypoxia induces cerebral parenchymal modifications and increases lactate levels, which correlate with perfusion changes.
Feng, B et al., (2)	China.	Clinical trial.	To investigate which populations most benefit from oxygen therapy its optimal regimen.	Intermittent oxygen therapy significantly improved AMS symptoms and physiological biomarkers for up to 15 days post-treatment.
Wang, Z et al., (10)	China.	Clinical trial.	To assess varied RIPC protocols for preventing AMS after rapid ascent.	Repeated Remote Ischemic Preconditioning (RIPC) protocols demonstrated potential for AMS-induced headache analgesia.
Julian, C et al., (11)	United States of America.	Clinical trial.	To explore the link between AMS and biomarkers of blood-brain barrier (BBB) integrity.	AMS resistance is associated with elevated IL-1RA, HSP-70, and adrenomedullin levels.
Heo, K et al., (12)	South Korea.	Clinical trial.	To evaluate prophylactic erythropoietin (EPO) for AMS prevention.	EPO increased hemoglobin levels but failed to improve oxygen saturation (SpO_2) or prevent AMS symptoms.
Subudhi, A. et al., (3)	-	Clinical trial.	To identify cerebral hemodynamic mechanisms of acetazolamide and dexamethasone.	Both drugs effectively prevented AMS, though no common cerebral hemodynamic mechanism was identified.
Burtscher, M. et al., (6)	Austria.	Clinical trial.	To evaluate aspirin as a prophylactic measure against high-altitude headache.	Aspirin prevented moderate-to-severe headache in 93.4% of participants, even at lower SpO_2 levels.

Source: Authors.

Discussion

AMS is caused by cerebral hypoxia, which triggers the production of reactive oxygen species (ROS). This leads to mitochondrial dysfunction, neuronal apoptosis, and vascular injury. These mechanisms impair energy production and calcium homeostasis, as well as the integrity of the blood-brain barrier (BBB), thereby fostering a state similar to vasogenic edema and promoting ß-amyloid accumulation (9, 11).

Hypoxia further induces metabolic shifts, characterized by increased glycolysis and lactate accumulation, which is primarily cleared through the cerebrospinal fluid. Neuroimaging studies reveal hypoxic regions associated with elevated lactate levels in 50-80% of cases. As we age, oxidative stress intensifies, and levels of N-acetylaspartate (NAA), a marker of neuronal integrity, decline. This suggests that cerebral alterations related to AMS may lead to functional impairment and share common pathophysiological pathways with neurodegenerative conditions such as Alzheimer's disease (9).

According to Hall D, et al. (8), once these neurometabolic disturbances are understood, it becomes clear that the pathophysiology of AMS is multifactorial and is not usually regarded as a single clinical syndrome. It may be mistaken for other similar syndromes due to overlapping symptoms at high altitudes. In order to compensate for hypobaric hypoxia, the body initiates two primary pathways that contribute to secondary headaches. The first pathway involves increased production of eicosanoids due to their vasodilatory properties, particularly prostaglandins such as PGD2, PGF2, PGI2, and TXA2, especially PGE2. The second pathway involves compensatory hyperventilation, leading to respiratory alkalosis. Therefore, a primary goal of AMS treatment is to lower pH and blood pressure, which can be achieved by inducing metabolic acidosis with acetazolamide (1).

Regarding the treatments proposed by clinical trials, oxygen therapy has only proven effective for providing symptomatic relief, with no a significant impact on preventing the syndrome or accelerating biological acclimatization. However, Benedetti, F. (1) observed greater benefits from inhaling oxygen via a mask than from taking aspirin, although both provided effective analgesia for headaches. Oxygen use lowered pH and reduce minute ventilation but did not affect oxygen saturation (SpO2) as expected. Meanwhile, aspirin alleviated pain and decreased prostaglandin levels, particularly PGE2 and TXA2. Notably, the study revealed that respiratory alkalosis, resulting from compensatory hyperventilation, can directly stimulate PGE2 synthesis independent of COX activity.

Additionally, it was shown that regular oxygen inhalation for 30 minutes twice weekly at night improves sleep quality and reduces symptoms. Although the benefits may persist for up to 15 days after stopping the therapy, caution is advised as abrupt discontinuation might lead to withdrawal-like symptoms or dependency — a theory that has not been sufficiently investigated. There is also concerns that oxygen therapy could interfere with the body's natural adaptation to high-altitude environments. As responses vary significantly among individuals, a personalized management approach is necessary (2).

Regarding behavioral interventions, the review article by Luks and Hackett (13) suggests halting the ascent and resting at the current altitude. For pharmacological therapy, the review recommends the use of non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol to treat altitude-related headaches, antiemetics to treat nausea, and acetazolamide or dexamethasone depending on severity of the symptoms. For mild cases, the recommended dose of acetazolamide is 250 mg every 12 hours. For severe cases, dexamethasone is recommended at a dose of 4 mg every six hours, which can be used alongside acetazolamide. If symptoms persist or worsen, descent or supplemental oxygen is indicated. Thus, Descent and oxygen therapy remain the primary treatments for underlying hypoxia, while pharmacological agents accelerate acclimatization and reduce symptoms (14).

Burtscher et al. (6), revealed in their research that 24% of the placebo group developed moderate-to-severe headaches at lower SpO2 levels, compared to those who ingested only one aspirin tablet. However, no significant differences were found between the groups regarding heart rate following physical exercise.

In terms of pharmacological interventions, both acetazolamide and dexamethasone have been shown to be effective in preventing and reducing the severity of symptoms. Vestergaard et al. (9) found that acetazolamide decreases lactate clearance during sleep. Thus, it can be inferred that reducing lactate through blood acidification is an indirect therapeutic objective in AMS treatment, and it can be achieved using acetazolamide (1).

Furthermore, the American Family Physician in 2020 supports the use of acetazolamide for mild cases or as combination therapy. Dexamethasone is preferred for moderate or severe cases (13).

Studies comparing these drugs among patients in a hypobaric chamber observed a 70% reduction in symptoms compared to a placebo. Acetazolamide was also found to improve cerebral autoregulation and reduce middle cerebral artery velocity. Acetazolamide was associated with decreased middle cerebral artery (MCA) velocity and improved cerebral autoregulation. However, these vascular effects appeared to be independent of the occurrence of the syndrome and were not observed with dexamethasone use. While both drugs effectively reduce the prevalence and symptoms of AMS, these specific vascular findings were considered irrelevant to overall cerebral dynamics (3). These results are consistent with the robust effect demonstrated by acetazolamide at a dose of 250 mg twice daily, which cements its status as the gold standard for AMS treatment. Interestingly, lower doses, such as 125 mg twice daily, were also found to be effective, challenging the conclusions of previous meta-analyses that recommended higher dosing regimens (4).

In addition, a study investigated the specific biomarkers present in AMS-resistant (AMS-R) and AMS-susceptible (AMS-S) patients. The AMS-R group had significantly higher baseline levels of interleukin-1 receptor antagonist (IL-1RA), heat shock protein 70 (HSP-70) and adrenomedullin than the AMS-S group. Acetazolamide was found to increase IL-1RA levels, suggesting a potential preventive mechanism. Furthermore, both dexamethasone and acetazolamide were found to increase HSP-70 levels, indicating an induced protective response. HSP-70 is a protein crucial for cellular stress protection.

Regarding adrenomedullin, which is recognized for its anti-inflammatory properties and protection of the blood-brain barrier (BBB), its levels were more abundant in the resistant group and were increased by dexamethasone in susceptible patients, suggesting neurovascular protection and the promotion of diuresis. However, the overall pattern of inflammatory biomarkers was not significantly associated with AMS development, indicating that susceptibility to the condition is likely not driven by an exaggerated inflammatory response. Among the evaluated chemokines, only Macrophage Inflammatory Protein-1 (MIP-1) demonstrated a limited association with AMS, warranting further investigation (11).

Alternative strategies include erythropoietin (EPO) as a preventive measure for individuals who experience side effects from acetazolamide. EPO increased hemoglobin levels and may offer protective properties for the brain and other organs; though its effects on AMS are not fully understood, these additional benefits may play a role in preventing more severe symptoms. Nevertheless, the study had limitations such as short acclimatization time and a small pool of subjects. Still, the importance of gradual acclimatization remains paramount to reducing the risk of AMS (12).

A review by Nieto Estrada et al., (15) evaluated common pharmacological interventions for preventing AMS. Based on 64 randomized studies, the efficacy of acetazolamide was supported, showing that daily doses of 250 to 750 mg consistently reduce the risk compared to a placebo. However, it is accompanied by a higher incidence of paresthesia, and it has little to no effect on serious outcomes such as pulmonary or cerebral edema. Evidence for other drugs, such as budesonide and dexamethasone, remains inconclusive or is based on low-quality evidence, which points to the need for a larger and more robust study before these alternatives can be widely recommended (15).

Natural alternatives, such as *Ginkgo biloba* and *Rhodiola crenulata*, have produced inconsistent results, with some studies suggesting modest benefits and others finding no significant effect. According to Gertsch et al. (4) the use of *Ginkgo biloba* was ineffective and may even reduce the efficacy of acetazolamide in alleviating headaches when used in combination. These inconsistencies may be related to differences in preparation quality and dosage (4, 7).

Finally, Wang et al., (10) tested a non-pharmacological practice involving RIPC. This consists of exposing individuals to short intervals of ischemia. Administered over four weeks, RIPC reduced the incidence and severity of the condition, as well as improving gastrointestinal symptoms and vertigo. However, it had no significant impact on headache analgesia. Nevertheless, repeated RIPC attenuated the decrease in SpO2, suggesting that it may be an effective long-term strategy for adapting to altitude and preventing AMS.

Conclusion

The lack of standardized, controlled clinical trials, combined with significant heterogeneity in study populations and research protocols, makes it difficult to establish a definitive standard treatment for AMS. Consequently, future research should prioritize investigating diverse therapeutic combinations and progressively lower dosages, particularly of acetazolamide. Such efforts are essential to optimizing prophylaxis across varied populations while minimizing treatment-related adverse effects. Furthermore, continued research is necessary to identify and validate specific biomarkers for the effective monitoring and management of AMS.

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Ethical implications. This study did not involve experimentation with humans or animals, and therefore no approval from an ethics committee was required.

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Conflicts of interest. The authors declare no conflicts of interest.

AI disclosure statement. The authors declare that artificial intelligence tools were used exclusively for linguistic support and textual organization, without replacing critical analysis, scientific interpretation, or intellectual authorship of the content.

Data availability statement. The data used in this study are available upon request to the corresponding authors.

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