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Significance of the proper acclimatization, use of the acetazolamide and dexamethasone in prevention of acute mountain sickness (AMS) – literature review

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Summary:

Acute mountain sickness (AMS) is an ilness, that occurs in non-acclimatized individuals after rapid ascent to high altitude, typically above 2,500 metres (8,000 ft). The main causes of the AMS are: reduced air pressure and lower oxygen levels at high altitudes. The early symptoms of AMS are non-specific such as: headache, anorexia, nausea, vomiting, fatigue, dizziness, and sleep disturbance, but not all need to be present at one time. It is very important to recognise the early symptoms of AMS and to start the treatment, because untreated AMS can progress to the life-threatening: high altitude cerebral edema (HACE) and high altitude pulmonary edema (HAPE). Treatment of AMS consists of stabilization of the patient conditon, descent to lower altitude, oxygen therapy and administering acetazolamide and dexamethasone. The aim of this study was to evaluate the significance of the proper acclimatization, use of the acetazolamide and dexamethasone in prevention of acute mountain sickness (AMS).

Proper acclimatization, use of the acetazolamide and dexamethasone are highly effective in prevention of occurrence and reducing the symptoms of acute mountain sickness (AMS). Pharmacological prophylaxis is not necessary in low-risk situations but should be considered in addition to gradual ascent for use in moderate- to high-risk situations Acetazolamide should be strongly considered in climbers and travelers at moderate or high risk of AMS with ascent to high

altitude. Dexamethasone can be used as an alternative in individuals with a history of intolerance of or allergic reaction to acetazolamide. In rare circumstances (eg, military or rescue teams that must ascend rapidly to and perform physical work at >3500 m), consideration can be given to concurrent use of acetazolamide and dexamethasone.

Key words: acute mountain sickness; AMS; acclimatization; acetazolamide; dexamethasone;

INTRODUCTION AND PURPOSE

Traveling or climbing in mountainous regions requires adaptation and acclimatization to diminished partial pressure of oxygen at high altitude. If the acclimatization process fails, it may results with acute mountain sickness [1]. Acute mountain sickness (AMS) is an ilness, that occurs in non-acclimatized individuals after rapid ascent to high altitude, typically above 2,500 metres (8,000 ft). The main causes of the AMS are: reduced air pressure and lower oxygen levels at high altitudes. Potential risk factors of AMS include: home elevation, maximum sleeping altitude, rate of ascent, latitude, age, gender, physical condition, intensity of exercise, hemoglobin saturation, pre-acclimatization, prior experience at altitude, genetic make-up, and pre-existing diseases [1,2,3].

The early symptoms of AMS are non-specific such as: headache, anorexia, nausea, vomiting, fatigue, dizziness, and sleep disturbance, but not all need to be present at one time. Treatment of AMS consists of stabilization of the patient conditon, descent to lower altitude, oxygen therapy and administering acetazolamide and dexamethasone. It is very important to recognise the early symptoms of AMS and to start the treatment, because untreated AMS can progress to the life-threatening: high altitude cerebral edema (HACE) and high altitude pulmonary edema (HAPE) [4]. High altitude cerebral edema is a vasogenic cerebral edema, that occurs due to a disruption of the blood–brain barier. HACE is characterised by progressive decline in mental functions, declining level of consciousness, impaired coordination, slurred speech, and lassitude [5]. High altitude pulmonary edema is a noncardiogenic pulmonary edema, that occurs due to exaggerated hypoxic pulmonary vasoconstriction and elevated pulmonary artery pressure. Clinical features of HAPE are: cyanosis, tachycardia, tachypnoea and elevated body temperature generally not exceeding 38.5°C [6]. This two emergencies require immediate treatment, with a descent to lower altitude [5,6].

The aim of this study was to evaluate the significance of the proper acclimatization, use of the acetazolamide and dexamethasone in prevention of acute mountain sickness (AMS). Our study material consisted of publications, which were found in PubMed, ResearchGate and Google Scholar databases. In order to find the proper publications, the search has been

conducted with the use of a combination of key words like: "acute mountain sickness", "AMS", "acclimatization", "acetazolamide", "dexamethasone". The first step was to find proper publications from the last 40 years .The second step was to carry out an overview of the found publications. Based on this criteria, nine publications have been qualifed for the study.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Authors, tittle and year of pubblication	Material and methods	Results
Bloch K.E. et al., *Effect of Ascent Protocol on Acute Mountain Sickness and Success at Muztagh Ata, 7546 m*, 2008	34 healthy mountaineers were randomized to follow one of two protocols, ascending within 15 or 19 days to the summit of Muztagh Ata at 7546 m. Symptoms of the acute mountain sickness (AMS) were assessed with the Lake Louise Score (LLS).	In climbers ascending to very high altitudes, differences of a few days in acclimatization have a significant impact on symptom severity, the prevalence of AMS, and mountaineering success.
Beidleman B.A. et al., *Effect of Six Days of Staging on Physiologic Adjustments and Acute Mountain Sickness during Ascent to 4300 Meters*, 2009	11 low-altitude residents were measured PetCO2, SaO2, HR, MAP at sea-level (SL) and within 1 h of exposure to 4300 m in a hypobaric chamber prior to 6 d of staging at 2200 m (preSTG) and on the summit of Pikes Peak following 6 d of staging at 2200 m (postSTG). Symptoms of the acute mountain sickness (AMS) were assessed with the Environmental Symptoms Questionnaire.	Modest physiologic adjustments induced by staging for 6 days at 2200 m reduced the incidence and severity of AMS during rapid, high-risk ascent to 4300 m.
Gertsch J.H. et all., *Randomised, double blind, placebo controlled comparison of ginkgo biloba and acetazolamide for prevention of acute mountain sickness among Himalayan trekkers: the prevention of high altitude illness trial (PHAIT),* 2004	614 healthy western trekkers were assigned to receive ginkgo, acetazolamide, combined acetazolamide and ginkgo, or placebo). Symptoms of the acute mountain sickness (AMS) were assessed with the Lake Louise Score (LLS).	When compared with placebo, ginkgo is not effective at preventing acute mountain sickness. Acetazolamide 250 mg twice daily afforded robust protection against symptoms of acute mountain sickness.
Grissom C.K. et al., *Acetazolamide in the treatment of acute mountain sickness: clinical efficacy and effect on gas exchange*, 1992	12 climbers were randomly assigned to receive acetazolamide, 250 mg orally, or placebo. Symptoms of the acute mountain sickness (AMS) were assessed with the Lake Louise Score (LLS).	In established cases of acute mountain sickness, treatment with acetazolamide relieves symptoms, improves arterial oxygenation, and prevents further impairment of pulmonary gas exchange.

Basnyat B. et al., *Spironolactone does not prevent acute mountain sickness: a prospective, double-blind, randomized, placebo-controlled trial by SPACE Trial Group (spironolactone and acetazolamide trial in the prevention of acute mountain sickness group)*, 2011	311 healthy western trekkers were randomly assigned to receive at least 3 doses of spironolactone 50 mg bid, acetazolamide 250 mg bid, or visually matched placebo. Symptoms of the acute mountain sickness (AMS) were assessed with the Lake Louise Score (LLS).	Spironolactone (50 mg bid) was ineffective in comparison to acetazolamide (250 mg bid) in the prevention of AMS in partially acclimatized western trekkers ascending to 5000 m in the Nepali Himalaya.
Johnson T.S. et al., *Prevention of acute mountain sickness by dexamethasone*, 1984	8 young men received dexamethasone (4 mg every 6 hours) or placebo and they were exposed to a simulated altitude of 4570 m. Symptoms of the acute mountain sickness (AMS) were assessed with a questionnaire and an interview by a physician.	Dexamethasone may be effective in preventing the symptoms of acute mountain sickness.
Ellsworth A.J. et al., *A randomized trial of dexamethasone and acetazolamide for acute mountain sickness prophylaxis*, 1987	47 climbers were randomly assigned to receive acetazolamide 250 mg, dexamethasone 4 mg, and placebo every eight hours. Symptoms of the acute mountain sickness (AMS) were assessed with the clinical interview.	Prophylaxis with dexamethasone can reduce the symptoms associated with acute mountain sickness during active ascent .
Ellsworth A.J. et al., *Acetazolamide or dexamethasone use versus placebo to prevent acute mountain sickness on Mount Rainier*, 1991	18 climbers were randomly assigned to receive acetazolamide 250 mg, dexamethasone 4 mg, and placebo. Symptoms of the acute mountain sickness (AMS) were assessed with the Environmental Symptoms Questionnaire and a clinical interview.	Compared with placebo, dexamethasone appears to be effective for prophylaxis of symptoms associated with acute mountain sickness accompanying rapid ascent.
Maggiorini M. et al., *Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial*, 2006	29 adults with previous HAPE were randomly assigned to receive tadalafil (10 mg), dexamethasone (8 mg), or placebo. Symptoms of the acute mountain sickness (AMS) were assessed with the Lake Louise Score (LLS).	Dexamethasone prophylaxis may reduce the incidence of acute mountain sickness (AMS).

The studies of Bloch et al. and Beidleman et al. proved that acclimatization is time consuming but highly effective method of preventing of acute mountain sickness (AMS) [7,8]. Acclimatization is a series of adaptive changes to the high altitude in the respiratory, cardiovascular, hematologic systems and cellular adaptations that enhance oxygen delivery to the tissues and augment oxygen uptake. Exposure to hypoxia at high altitude results in the increase of the blood pressure, heart rate, cardiac output, respiratory rate, breathing depth, cerebral blood flow and the release of the hormone erythropoetin from the kidney, that stimulate red blood cell production in the bone marrow. The degree of altitude acclimatization developed is proportional to the altitude attained and the duration of exposure. The amount of time required for a person to become acclimatized depends also on the individual's physiology [9]. The study of Bloch et al. evaluated and confimed the hypothesis that in climbers

ascending to very high altitudes, differences of a few days in acclimatization have a significant impact on symptom severity, the prevalence of AMS, and mountaineering success. In this reserach more climbers randomized to slow ascent were able to reach the highest camp at 6865 m and ascend the summit of Muztagh Ata at 7546 m without AMS than climbers randomized to fast ascent [7]. The results of the Beidleman et al. study suggested that modest physiologic adjustments induced by staging for 6 d at 2200 m reduced the incidence and severity of AMS during rapid, high-risk ascent to 4300 m. In this reserach resting PetCO2 was unchanged from SL to preSTG , but decreased from preSTG to postSTG. Resting SaO2 decreased from SL to preSTG and increased from preSTG to postSTG. Resting HR and MAP did not change in any of the test conditions. The incidence and severity of AMS-C decreased from preSTG to postSTG [8].

The studies of Gersch et al., Grissom et al. and Basnyat et al. established a role for acetazolamide in prevention of acute mountain sickness (AMS) [10,11,12]. Acetazolamide is a carbonic anhydrase inhibitor with diuretic and anticonvulsant properties, used in the treatment of edema, glaucoma and in the prevention of AMS. The recommended adult dose for prophylaxis is 125 mg every 12 h. Although doses up to 750 mg daily are effective at preventing AMS compared to placebo, they are associated with more frequent and/or pronounced side effects, do not convey greater efficacy, and are not recommended for prevention. The pediatric dose of acetazolamide is 2.5 mg/kg every 12h (maximum - 125 mg/dose) [9]. The main object of the Gersch et al. reserach was to evaluate the efficacy of ginkgo biloba, acetazolamide, and their combination as prophylaxis against acute mountain sickness. This study revealed that ginko, when compared with placebo, is not effective at preventing acute mountain sickness and that acetazolamide 250 mg bid afford robust protection against symptoms of acute mountain sickness (AMS). The incidence of acute mountain sickness was 34% for placebo, 12% for acetazolamide , 35% for ginkgo 14% for combined ginkgo and acetazolamide. The proportion of patients with increased severity of acute mountain sickness was 18% for placebo, 3% for acetazoalmide 18% for ginkgo, and 7% for combined ginkgo and acetazolamide. Because of that ginkgo biloba should not be used for AMS prevention and acetazolamide is considered far superior for AMS prevention [10]. The reserach conducted by Grissom et al. showed that nn established cases of acute mountain sickness (AMS), treatment with acetazolamide relieves symptoms, improves arterial oxygenation, and prevents further impairment of pulmonary gas exchange. In this study five of six climbers treated with acetazolamide were healthy, whereas all climbers who received placebo still had acute mountain sickness. The alveolar to arterial oxygen pressure difference

decreased slightly in the acetazolamide but increased in the placebo group. Acetazolamide improved PaO2 when compared with placebo [11]. Basnyat et al. reserach confirmed that acetazolamide was more effective than spironolactone in preventing AMS. Spironolactone was not significantly different from placebo in the prevention of AMS. AMS incidence for placebo was 20.3%, acetazolamide 10.5%, and spironolactone 29.4%. Oxygen saturation was also significantly increased in the acetazolamide group vs spironolactone group [12]. The studies of Gersch et al., Grissom et al. and Basnyat et al. validate acetazolamide therapy as the standard of care for pharmacological prevention of acute mountain sickness (AMS) [10,11,12].

The studies of Johnson et al., Ellsworth et al. (1987), Ellsworth et al (1991) and Maggiorini et al. proved that dexamethasone is higly effective in prevention of acute mountain sickness [13,14,15,16]. Dexamethasone is a synthetic adrenal glucocorticoid with potent anti-inflammatory properties, used in the treatment of insufficient adrenocortical function, a variety of inflammatory disorders and in prevention of AMS. The recommended adult doses are 2 mg every 6 h or 4 mg every 12 h. Very high doses (4 mg every 6 h) may be considered in very high-risk situations, such as military or search and rescue personnel being airlifted to altitudes >3500 m with immediate performance of physical activity. Dexamethasone should not be used for prophylaxis in pediatric patients [9]. The study of Johnson et al. confirmed that dexamethasone may be effective in preventing the symptoms of acute mountain sickness (AMS). In this research dexamethasone (4 mg every 6h), begun 48 hours before ascent and continued throughout 42-hour exposure, significantly decreased the symptoms of AMS as assessed both by questionnaire and clinical intervie [13]. The study of Ellsworth et al. (1987) proved that dexamethasone may be effective in preventing from the symptoms of acute mountain sickness (AMS). In this research the group taking dexamethasone reported less headache, tiredness, dizziness, nausea, clumsiness, and a greater sense of feeling refreshed at the summit of Mount Rainier or high point attained above base camp. In addition, climbers reported fewer problems of runny nose and feeling cold, symptoms unrelated to acute mountain sickness [14]. The study of Ellsworth et al. (1991) showed that compared with placebo, dexamethasone appears to be effective for prophylaxis of symptoms associated with acute mountain sickness accompanying rapid ascent. In this reserach the use of dexamethasone significantly reduced the incidence of acute mountain sickness and the severity of symptoms at the summit of Mount Rainier or high point attained above base camp [15]. The study of Maggiorini et al. confirmed that dexamethasone prophylaxis may reduce the incidence of acute mountain sickness (AMS). In this reserach 8 of

9 participants receiving placebo, 7 of 10 receiving tadalafil, and 3 of 10 receiving dexamethasone developed AMS [16].

Proper acclimatization, use of the acetazolamide and dexamethasone are highly effective methods of prevention of occurrence and reducing the symptoms of acute mountain sickness (AMS). The first priority should be ensuring the proper acclimatization. With travel above 3000 m, individuals should not increase their sleeping elevation by more than 500 m/day and should include a rest day every 3 to 4 days. Pharmacological prophylaxis is not necessary in low-risk situations but should be considered in addition to gradual ascent for use in moderate- to high-risk situations Acetazolamide should be strongly considered in climbers and travelers at moderate or high risk of AMS with ascent to high altitude. Dexamethasone can be used as an alternative in individuals with a history of intolerance of or allergic reaction to acetazolamide. In rare circumstances (eg, military or rescue teams that must ascend rapidly to and perform physical work at >3500 m), consideration can be given to concurrent use of acetazolamide and dexamethasone. This strategy should be avoided except in these particular or other emergency circumstances that mandate very rapid ascent [9].

CONCLUSIONS

1. Acute mountain sickness (AMS) is caused mainly by the diminished partial pressure of oxygen at high altitude.
2. It is very important to recognise the early non-specific symptoms of AMS and to start the treatment, because untreated AMS can progress to the life-threatening: high altitude cerebral edema (HACE) and high altitude pulmonary edema (HAPE).
3. Proper acclimatization, use of the acetazolamide and dexamethasone are highly effective methods of prevention of occurrence and reducing the symptoms of acute mountain sickness (AMS).
4. The first priority should be ensuring the proper acclimatization - with travel above 3000 m, individuals should not increase their sleeping elevation by more than 500 m/day and should include a rest day every 3 to 4 d.
5. Pharmacological prophylaxis is not necessary in low-risk situations but should be considered in addition to gradual ascent for use in moderate- to high-risk situations.
6. Acetazolamide should be strongly considered in climbers and travelers at moderate or high risk of AMS with ascent to high altitude.

7. Dexamethasone can be used as an alternative in individuals with a history of intolerance of or allergic reaction to acetazolamide.
8. In rare circumstances (eg, military or rescue teams that must ascend rapidly to and perform physical work at >3500 m), consideration can be given to concurrent use of acetazolamide and dexamethasone.

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