International Journal of Cardiology 173 (2014) 133–138

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Dexamethasone for the prevention of acute mountain sickness: Systematic review and meta-analysis

Enjie Tang [a,b,c], Yu Chen [c], Yongjun Luo [b,c,*]

[a] Battalion 8 of Cadet Brigade, Third Military Medical University, Chongqing 400038, PR China
[b] Department of Military Medical Geography, Third Military Medical University, Chongqing 400038, PR China
[c] Key Laboratory of High Altitude Medicine (Ministry of Education), Third Military Medical University, Chongqing 400038, PR China

ARTICLE INFO

Article history:
Received 13 December 2013
Received in revised form 1 March 2014
Accepted 9 March 2014
Available online 15 March 2014

Keywords:
Acute mountain sickness (AMS)
Dexamethasone
Prophylaxis

ABSTRACT

Background: AMS is a disease that occurs when accessing high altitude (HA) or upon exposure to a higher altitude after acclimatising over 3000 m. Evidence shows that drugs can prevent AMS. The function of dexamethasone for preventing AMS is important. No systematic review has previously been published about the effect of dexamethasone. The effect of intervention is unclear, which has limited the use of dexamethasone in the prevention of AMS.

Methods: We searched PubMed and Embase for studies from inception to July 2013. We selected randomised controlled trials including dexamethasone versus placebo as prophylaxis for AMS. The studies included were required to provide a clear dose of dexamethasone, the final altitude and clear diagnostic criteria used to judge the AMS severity of symptoms and incidence. Finally, 8 studies were included in this review. There were 116 participants in the experimental groups and 110 in the control groups. Three different doses of dexamethasone were used in these studies (8, 12, and 16 mg/d).

Result: Eight of the 79 considered studies were eventually added to the meta-analysis. We used the fixed-effect model (RevMan 5.0) based on the heterogeneity ($I^2 = 0\%$, $p = 0.43$). Dexamethasone could reduce the incidence of AMS with an odds ratio of 6.03 (95% CI, 2.23 to 21.00) for dexamethasone compared with placebo; the p value for overall effect was less than 0.00001.

Conclusions: Our systematic review suggests that oral dexamethasone is effective in preventing AMS. Additionally, there is some evidence that the effect of dexamethasone is related to height and dosage.

© 2014 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Acute mountain sickness (AMS) is a disease that occurs when accessing high altitude (HA) or upon exposure to a higher altitude after acclimatising over 3000 m [1–5]. In this type of environment, in addition to exerting a wide influence on the functions of human organ systems, hypoxia can also cause AMS, which is likely to develop into high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE). HAPE and HACE are the most common life-threatening illnesses in HA [6–8]. AMS is easily encountered at HA and has a spectrum of symptoms, such as vomiting, nausea, headache, fatigue, dizziness and sleep disturbance [9,10]. Measures that actively prevent and treat hypoxia are effective in the prevention of AMS. By slowing down the oxygen consumption of the body, the rate of oxygen content in various tissues and organs under low oxygen conditions is increased, reducing the damage of hypoxia to the body and improving the content of superoxide dismutase in the body. Although gradually staged ascent is still the most useful way to prevent AMS [11]. Rest, symptom treatment, oxygen supplementation, dexamethasone, and acetazolamide were used to treat the AMS also [7,12].

Dexamethasone is a long-acting glucocorticoid that can reduce the permeability of cells and the capillary wall, reduce the leakage of pulmonary inflammatory liquid and inhibit the formation of histamine and other substances [13]. There is substantial evidence that dexamethasone can reduce the symptoms of AMS [14–16]. Although dexamethasone is widely used as acetazolamide in the clinic [17]. Sometimes, it is recommended only in case of intolerance to acetazolamide. The function of dexamethasone for the prevention of AMS should not be ignored [12].

No systematic reviews have previously been published on the effects of dexamethasone treatment in AMS. Because of the lack of trials designed to test the role of dexamethasone in AMS, the effective dose

* Corresponding author at: College of High Altitude Military Medicine, Third Military Medical University, Chongqing 400038, PR China. Tel.: +86 23 6875 2396; fax: +86 23 6875 2384.
E-mail address: luoyongjun2011@gmail.com (Y. Luo).

http://dx.doi.org/10.1016/j.ijcard.2014.03.019
0167-5273/© 2014 Elsevier Ireland Ltd. All rights reserved.

and intervention method of dexamethasone are unclear. There is limited clinical use of dexamethasone in the prevention of AMS. In this systematic review, we aimed to analyse the effects of dexamethasone on AMS. As a result, we offer clinicians more information about dexamethasone use for AMS, which could help them advise people who go to HA.

2. Materials and methods

2.1. Literature search

We searched PubMed and Embase for studies from inception to July 2013. A sensitive search strategy was formulated to find eligible trials. The keywords were "dexamethasone", "altitude" or "mountain sickness", "randomised controlled trial" and "placebo". We examined full reports on dexamethasone versus placebo for prophylaxis against AMS. We included randomised controlled trials that had a clear statement of intervention and a randomised plan for either dexamethasone or placebo. There were no limits to the sample size. Some experiments included other drugs, but we only analysed the relevant information.

2.2. Outcome measures

Our primary objective was to assess the use of dexamethasone in preventing altitude sickness. The Lake Louise scoring system is a common standard for diagnosing AMS and scoring the level of symptoms [18]. This scoring system was established at the 1991 International Hypoxia Symposium. However, only 2 of the articles that met our inclusion criteria for recent years used the Lake Louise scoring protocol to assess AMS. If the score was more than 3, AMS was diagnosed. The studies we selected that did not use the Lake Louise scoring protocol used some other standard, such as the Environmental Symptoms Questionnaire, AMS Symptom Questionnaire, General High-Altitude Questionnaire, or clinical examination, to assess AMS. We compared the scoring systems and excluded trials that lacked obvious incidence or diagnosis of AMS or for which the results were not comprehensible [19].

2.3. Study selection criteria

We introduced randomised controlled trials to evaluate the function of dexamethasone in preventing AMS. We were concerned only with adult human patients and studies that reported on the sample conditions before the trial. Studies that were not in English and unpublished reports were not included. We excluded trials that lacked a placebo and studies that did not give clear data on the intervention and control groups. The final altitudes were not restricted. Some articles included other drugs, but we only analysed the relevant data. The remaining articles were reviewed and analysed in full.

2.4. Statistical analysis

We assessed the effect of dexamethasone in the prevention of AMS in this meta-analysis. We used a chi-square-based Q-test and I-squared test to assess the heterogeneity. If the heterogeneity was considered insignificant ($p > 0.05$), the pooled OR estimate of the studies were calculated according to the fixed-effects model ($p < 0.05$) [10,20,21]. If heterogeneity was present, we use a random effects model to explain the heterogeneity instead of using the fixed-effects model. An unadjusted OR consistent with a 95% CI was used to evaluate the effect of dexamethasone between the intervention and control groups. The aforementioned statistical analysis was performed with RevMan 5.0 (The Cochrane Collaboration). We investigated the publication bias by a funnel plot; the standard error in the funnel plot of log (OR) of every study was assessed against its OR. The asymmetric plot implied a possibility of publication bias.

3. Results

3.1. Description of studies

We retrieved 79 studies from PubMed and Embase. After assessing all studies according to the prespecified exclusion criterion, 8 studies were eventually added to the meta-analysis (Fig. 1). The articles included were published between 1984 and 2011 [22–29]. There were 116 participants in the experimental groups (sample size ranged 6 to 38) and 110 in the control groups (sample size ranged 6 to 35). The mean final altitude was 4057 m (range 2050 to 4875). In 7 of the 8 trials, the final altitude was more than 4300 m. The report at a relatively low altitude of 2700 m included two subgroups, which were at 2050 m and 2700 m, and there was a relationship between the height and drug prevention effect [26]. All studies compared the effect of dexamethasone with placebo in preventing AMS.

Two of the eight studies were carried out in a hypobaric chamber. The remaining studies were processed in the field. Six of the eight trials used the environmental symptom's questionnaire, General High-Altitude Questionnaire or AMS Symptom Questionnaire for diagnosing AMS. The remaining two studies used the Lake Louise scoring system and Lake Louise questionnaire. (Table 1 shows the characteristics of the assessed studies.)

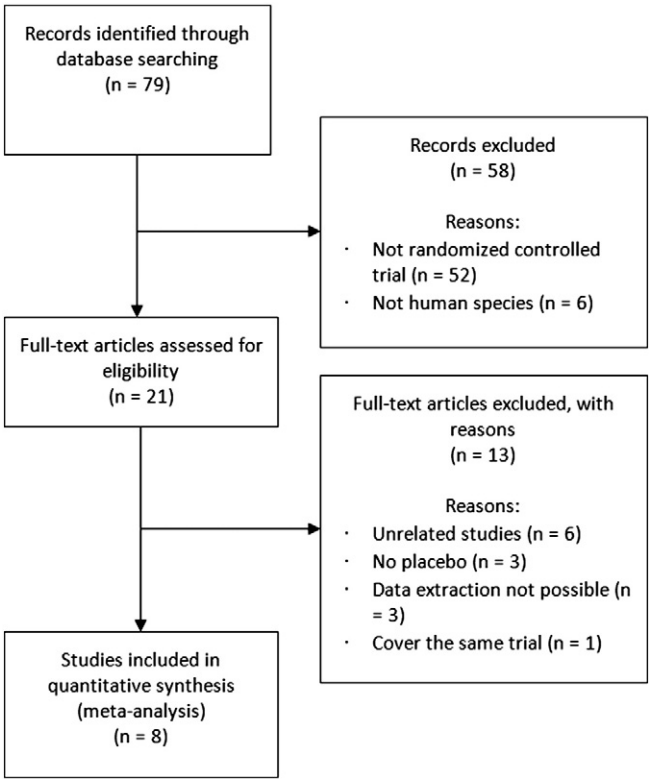

Fig. 1. Study selection for inclusion.

3.2. Risk of bias

The method of randomisation was not adequately presented in the 8 studies, and the sample selection bias was relatively high in these trials. Different methods were used to diagnose AMS; two studies applied the Lake Louise scoring system [22,23], three studies used the Environmental Symptoms Questionnaire [24,25,29], one study was assessed by the AMS Symptom Questionnaire [26], one trial used both the Environmental Symptoms Questionnaire and the General High-Altitude Questionnaire [28], and the last used a combination of the AMS Symptom Questionnaire and the Environmental Symptom Questionnaire [27], which are likely to bias the outcome. Details of the ascent plan and the delivery of dexamethasone were not included.

3.3. Sensitivity analysis

We assessed 8 articles and found that dexamethasone could reduce the incidence of AMS (Fig. 2). The funnel plot showed evidence of symmetry (Fig. 3), which allowed us to use the fixed-effects model (RevMan 5.0) to get the OR for each study based on the heterogeneity ($I^2 = 0\%$, $p = 0.43$). Dexamethasone could reduce the incidence of AMS, with an odds ratio of 6.03 (95% CI, range from 2.23 to 21.00) for dexamethasone compared to placebo; the p value for the overall effect was less than 0.00001. (Table 2 shows the morbidity of AMS.)

3.4. Intervention of AMS

Three different doses of dexamethasone were used in these studies (8, 12, and 16 mg/d). All trials were in divided doses with oral

Table 1
Characteristics of the included randomised controlled clinical trials.

First author	Year	Max altitude (m)	Participant quantity (male/female) [quality]	Intervention	Dose (mg)	Diagnosis of AMS with cut-off value	Mode of ascent	Note
Johnson	1984	4570	1. Dex 8 (8/0); 2. Plac 8 (8/0). [Residing at sea level. No potential]	Day 1, begun on dexamethasone or placebo. Day 2, entered the altitude chamber, which was maintained at sea-level pressure. Day 3, the chamber was evacuated to a barometric pressure equivalent to an altitude of 4570 m. Stayed at the altitude for the next 42 h. Three weeks after the first exposure, did a cross over to the other treatment.	4 mg/6 h	AMS-C > 0.7 and AMS-R > 0.6	Hypobaric chamber	Dexamethasone has a greater effect on sick samples (AMS-C > 0.7). Do not increase symptoms of no AMS samples.
Allan J	1987	4392	1. Dex 17 (15/2); 2. Plac 14 (14/0). [Residing at sea level. No potential]	Dexamethasone 4 mg or lactose placebo every 8 h beginning 24 h before ascent. Active ascent to a base camp at approximately 3000 m averaged 6.8 h. The ascent to the summit (4392 m) began in the early morning (between 1 A.M. and 2 A.M.) on the second day and was followed by return to road's end the same day.	4 mg/8 h	ESQ + GHAQ > 2	Transport and climbing	The greatest effect dexamethasone had is on the symptom of dizziness, but significant differences also occurred in other symptoms related to the syndrome (headache, refreshed, nausea, irritable and tired).
Hackett	1988	4400	1. Dex 7 (7/0); 2. Plac 8 (8/0). [No AMS before enrolment in this study]	Subjects received either placebo or 2 mg dexamethasone every 6 h starting 1 h before flying by helicopter to high altitude, then performed heavy work until they were too ill to continue.	2 mg/6 h	AMS-C > 0.7 and AMS-R > 0.6	Transport	2 mg of dexamethasone every 6 h did not prevent AMS in active soldiers rapidly transported to high altitude.
Montgomery	1989	2700	1. Dex 38 (28/10); 2. Plac 35 (21/14). [Low altitude residents of less than 450 m. No potential]	Randomised to take either 4 mg of dexamethasone acetate or an identical-appearing placebo every 6 h for a total of six doses. Drug administration began within 3 h after arrival at the altitude.	4 mg/6 h	AMSSQ	Transport	Two final heights comparing that no beneficial effect was observed at 2050 m, while dexamethasone could reduce symptoms at 2700 m. The reasons for dexamethasone's lack of efficacy at 2050 m are unknown.
Ellsworth	1991	4392	1. Dex 10 (5/5); 2. Plac 10 (5/5). [Residing at sea level. No potential]	24 h before starting to receive the drug until descent from the peak. They took drugs during one of their ascents. During the other ascent, they received placebo.	4 mg/8 h	AMS-C > 0.7 and AMS-R > 0.6	Transport and climbing	No attack in the dexamethasone group.
Hussain	2001	4578	1. Dex 6 (6/0); 2. Plac 6 (6/0). [Low altitude residents of less than 500 m. No potential]	Medication started 24 h before ascent to the high altitude (4578 m) and continued for five days as follows: A. Placebo (multivitamin) tablet every 12 h. B. Dexamethasone 4 mg tablet every 12 h.	4 mg/12 h	AMS-C > 0.7 and AMS-R > 0.7	Transport and climbing	In the dexamethasone group, one person had an ESQ score of 29. The other five subjects in the group had lower mean ESQ scores (9.00 ± 1.06) than the placebo (11.83 ± 1.58). AMS-C and AMS-R scores of the different groups were almost similar.
Maggiorini	2006	4559	1. Dex 10 (9/1); 2. Plac 9 (7/2). [With a history of HAPE]	Participants started taking the medication twice daily on the morning of the day before ascent to high altitude and continued intake until the end of the study.	8 mg/12 h	LLS > 4	Transport and climbing	
Subudhi AW	2011	4875	1. Dex 20 (16/4); 2. Plac 20 (16/4). [No AMS before enrolment in this study]	Medications were begun 24 h prior to chamber decompression and continued during hypoxia. Dexamethasone (4 mg/8 h) and placebo on cerebral hemodynamics under baseline, normoxic conditions (Pb-625 mm Hg, 1650 m) and during 10 h of exposure to hypobaric hypoxia (Pb: 425 mm Hg, 4875 m) in an environmental chamber.	4 mg/8 h	LLS > 3	Hypobaric chamber	Dexamethasone would improve cerebral autoregulation in hypoxia, thereby reducing the threat of AMS.

Dex = dexamethasone; Plac = placebo; AMS-C = Acute Mountain Sickness Score-Cerebral; AMS-R = Acute Mountain Sickness Score-Respiratory; ESQ + GSAQ = combine, abbreviated version of the Environmental Symptoms Questionnaire and the General High-Altitude Questionnaire; LLS = Lake Louise Symptom score; AMSSQ = AMS Symptom Questionnaire. All were randomised, double blind, placebo controlled clinical trials.

administration. None of these trials stated that they used modified release dexamethasone. There is no clear relationship between the dose and effect; evidence shows that only the high dose of dexamethasone could prevent the symptoms of AMS, but this dose can be dangerous [30]. However, 12 or 16 mg daily was a suitable dose. One study with two different final heights found a relationship between the dexamethasone effect and height. Dexamethasone had a stronger effect of decreasing the incidence of AMS symptoms when AMS occurred at a higher altitude [26,31].

Two trials were performed in a hypobaric chamber, and the remaining 6 trials utilised climbing as the mode of ascent. Intervention had a better performance in the hypobaric chamber than in the field.

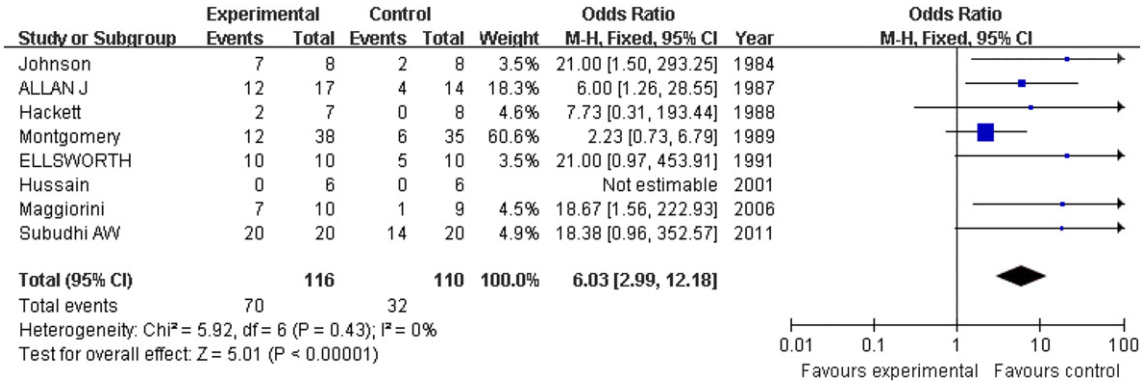

Fig. 2. Dexamethasone vs placebo forest plot. A summary of the treatment effect (odds ratio) is shown under the fixed-effects model. Trials were within a corresponding 95% confidence interval (95% CI). Events refer to no AMS incidence.

Volunteers in seven of the eight trials were healthy, low altitude residents, residing at elevations lower than 500 m. The final study was composed of participants with a history of HAPE [23].

4. Discussion

This is the first systematic meta-analysis evaluating the use of dexamethasone prophylaxis to prevent AMS. Aggregate data of the systematic review from randomised-controlled trials provided consistent evidence that intervention with dexamethasone is more effective than placebo for preventing AMS, which shows that there are significant benefits associated with dexamethasone prophylaxis. Our results suggest that dexamethasone is effective at preventing AMS when used alone.

Hypotonic hypoxia can decrease the function of the adrenal cortex, decreasing glucocorticoid secretion, which results in a decrease of the blood capillary toughness [32]. Cell membrane permeability increased, further increasing oedema and resulting in failure of tissues and organs [33]. Dexamethasone can mitigate the effects of adrenal cortex malfunction, enhancing the toughness of the capillaries and cell membranes and improving the body's ability to resist hypoxia [34]. At the same time, dexamethasone has anti-inflammatory effects and can effectively reduce and prevent tissue inflammation, stabilise the function of tissues and cells, and prevent dysfunctional tissue oedema that occurs from a lack of oxygen [33,35].

Due to its strong side effects on the hypothalamic–pituitary–adrenal axis [36,37], dexamethasone could only be a short-term preventive medicine for AMS and should not be used for longer than three days [38]. Moreover, there is some evidence that glucose metabolism is affected by dexamethasone [39]. Marquet's study shows that dexamethasone increases glucose levels [40]. Some studies have shown that increases in insulin and glucose levels would decrease the sensitivity to insulin after dexamethasone treatment [41,42]. Individuals with low insulin sensitivity and low erythropoietin levels are more susceptible to AMS [39]. The effect of dexamethasone on the autonomic nervous system is elevated; dexamethasone could increase the heart rate, and people who are HAPE susceptible have a higher excitability of the sympathetic nerve [43], which explains why dexamethasone contributes to AMS.

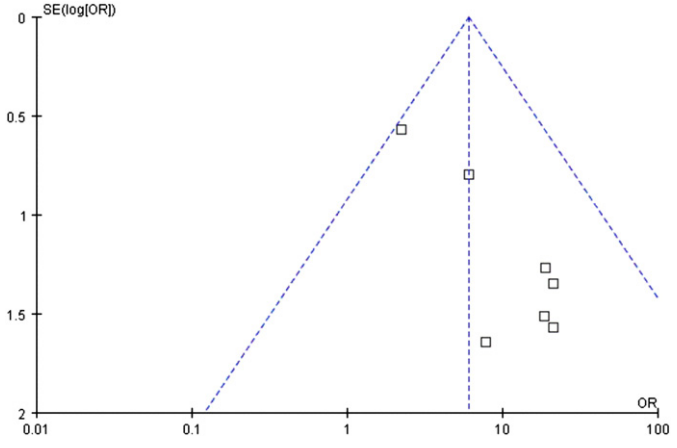

Fig. 3. Dexamethasone vs placebo funnel plot. There was no publication bias found. Each point represents a separate study for the indicated association.

One included trial which used Environmental Symptoms Questionnaire score to evaluate the effect of drug had 100% morbidity in both the intervention and control groups [24]. In the intervention group, one person had an ESQ score of 29 while the remaining five participants had a lower mean ESQ score (9.00 ± 1.06) than the placebo group (11.83 ± 1.58). Considering the intervening measure in this trial, drug intervention (4 mg/12 h) began in the 24 h before ascent and continued in the last five days. The daily dose and duration may contribute to the prevention effect, but we should not ignore the fact that dexamethasone can prevent AMS.

The risk of AMS reduction associated with dexamethasone prophylaxis was related to the maximum altitude reached [31]. One of the studies [26], which divided the participants into two subgroups who reached 2050 m and 2700 m, included in our analysis provides the evidence that dexamethasone has a better performance when used at a higher altitude compared to a lower altitude.

There are some limitations to our systematic review. First, there is a spectrum of symptoms in AMS, and the degree of each symptom contributes to the AMS attack. Studies included in this review did not use a standard definition of AMS; thus, the AMS incidence of every trial was biassed. One of the eight studies enrolled volunteers with a history of HAPE [23], which would increase the incidence of AMS. Due to the lack of data on dexamethasone trials, we cannot make a firm conclusion on the relationship between the effect and the intervention strategy. The start time, duration, dosage and maximum height are associated with the effect of prevention [31]. Additional studies should examine the relationship between these factors. Mature drug prevention methods should consider the influence of adverse reactions. Some of the studies we extracted were low quality, and the effect of dexamethasone could have been affected by the method of randomisation, speed of ascent and adverse reactions. The tendencies still need to be revealed in future data.

This systematic review provides evidence that dexamethasone is effective for AMS prophylaxis when used alone. Future research could thoroughly characterise this intervention strategy, including the relationship between the rate of ascent, total length of journey and efficacy of dexamethasone. A standard definition of AMS should be validated and universally applied, such as the Lake Louise scoring system, in diagnosing AMS. The research on dexamethasone in AMS is still insufficient. A standard will improve the future analysis of data.

Table 2
Severity and morbidity of AMS.

First author		Johnson	Allan J	Hackett	Montgomery		Ellsworth	Hussain	Maggiorini	Subudhi AW
AMS score	Dexamethasone	AMS-C: 0.26 ± 0.08; AMS-R: 0.31 ± 0.06; CI: 0.28 ± 0.07	C-pos: 2.68 ± 1.2; C-neg: 1.94 ± 1.2; AMS-R: 1.93 ± 0.9	2.6 ± 0.6 (ranged from 0 to 4)	0.94 ± 1.11	1.52 ± 1.50	AMS-C 0.26 ± 0.16; AMS-R 0.20 ± 0.19	24 h: ESQ score: 14.5 ± 3.04; AMS-C: 0.72 ± 0.24; AMS-R: 0.65 ± 0.20 72 h: ESQ score: 10.67 ± 3.56; AMS-C: 0.63 ± 0.20; AMS-R: 0.45 ± 0.18	2.5 (ranged from 1.0 to 5.0)	AMS-susceptible subjects: 1.3 ± 0.8; AMS-resistant subjects: 0.7 ± 0.7
	Placebo	AMS-C: 1.09 ± 0.18; AMS-R: 0.64 ± 0.09; CI: 1.10 ± 0.11	C-pos: 1.74 ± 1.2; C-neg: 3.0 ± 1.1; AMS-R: 2.93 ± 1.1	4.6 ± 1.0 (ranged from 2 to 11)	0.84 ± 1.44; t = 2.95	1.24 ± 1.33	AMS-C 1.11 ± 1.02; AMS-R 1.45 ± 1.27	24 h: ESQ score: 11.83 ± 1.58; AMS-C: 0.853 ± 0.23; AMS-R: 0.75 ± 0.27 72 h: ESQ score: 9.33 ± 2.42; AMS-C: 0.78 ± 0.15; AMS-R: 0.55 ± 0.18	7.0 (ranged from 6.0 to 10.2)	AMS-susceptible subjects: 4.0 ± 0.6; AMS-resistant subjects: 1.1 ± 0.7
Morbidity		P: 75%; D: 12.5%	P: 73%; D: 30%	P: 100%; D: 71.4%	P: 82.9%; D: 68.6%	P: 16%; D: 20%	P: 50%; D: 0%	P: 100%; D: 100%	P: 88.9%; D: 30%	P: 30%; D: 0%

AMS-C = Acute Mountain Sickness Score-Cerebral; AMS-R = Acute Mountain Sickness Score-Respiratory; CI = physician's clinical interview; ESQ score = Environmental Symptoms Questionnaire; AMS-R = AMS-resistant subjects; AMS-S = AMS-susceptible.
AMS-Cerebral symptoms were divided into positive and negative clusters in Allan J's study. The positive cerebral average (C-pos) contained the "symptoms" satisfied, refreshed, happy, active, and energetic. The negative cerebral average (C-neg) represented the symptoms dizzy, tired, drowsy, lazy, sleepy, and trouble sleeping at altitude.

5. Conclusion

Our systematic review suggests that oral dexamethasone is effective in preventing AMS, and there is some evidence that the effect is related to the height and dosage, but these relationships still need further discussion.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (no. 81372125).

References

[1] Eide III RP, Asplund CA. Altitude illness: update on prevention and treatment. Curr Sports Med Rep 2012;11:124–30.
[2] Luo Y, Zhou Q, Huang J, Luo R, Yang X, Gao Y. Medical continuing education: reform of teaching methods about high altitude disease in China. High Alt Med Biol 2013;14:181–2.
[3] Luo Y, Yang X, Gao Y. Mitochondrial DNA response to high altitude: a new perspective on high-altitude adaptation. Mitochondrial DNA 2013;24:313–9.
[4] Luo Y, Zhou Q, Luo R, et al. Building a three-dimensional high altitude medical education system to match the needs of high altitude populations. Wilderness Environ Med 2012;23:376–7.
[5] Imray C, Booth A, Wright A, Bradwell A. Acute altitude illnesses. BMJ 2011;343:d4943.
[6] Kedzierewicz R, Cabane D. Acute mountain sickness and high altitude cerebral and pulmonary edema. Rev Prat 2013;63:18–26.
[7] Luo Y, Yang X, Gao Y. Strategies for the prevention of acute mountain sickness and treatment for large groups making a rapid ascent in China. Int J Cardiol 2013;169:97–100.
[8] Guo P, Luo H, Fan Y, Luo Y, Zhou Q. Establishment and evaluation of an experimental animal model of high altitude cerebral edema. Neurosci Lett 2013;547:82–6.
[9] Moraga FA, Flores A, Serra J, Esnaola C, Barriento C. *Ginkgo biloba* decreases acute mountain sickness in people ascending to high altitude at Ollague (3696 m) in northern Chile. Wilderness Environ Med 2007;18:251–7.
[10] Luo Y, Chen Y, Zhang Y, Gao Y. The association of angiotensin-converting enzyme gene insertion/deletion polymorphisms with acute mountain sickness susceptibility: a meta-analysis. High Alt Med Biol 2012;13:252–7.
[11] Hackett PH, Rennie D, Levine HD. The incidence, importance, and prophylaxis of acute mountain sickness. Lancet 1976;2:1149–55.
[12] Schoene RB. Dexamethasone: by safe means, by fair means. High Alt Med Biol 2005;6:273–5.
[13] Urner M, Herrmann IK, Booy C, Roth-Z' Graggen B, Maggiorini M, Beck-Schimmer B. Effect of hypoxia and dexamethasone on inflammation and ion transporter function in pulmonary cells. Clin Exp Immunol 2012;169:119–28.
[14] Keller HR, Maggiorini M, Bartsch P, Oelz O. Simulated descent v dexamethasone in treatment of acute mountain sickness: a randomised trial. BMJ 1995;310:1232–5.
[15] Wilson MD, Hart LL. Prophylaxis and treatment of altitude sickness with dexamethasone. Ann Pharmacother 1993;27:733–5.
[16] Rock PB, Johnson TS, Larsen RF, Fulco CS, Trad LA, Cymerman A. Dexamethasone as prophylaxis for acute mountain sickness. Effect of dose level. Chest 1989;95:568–73.
[17] Murdoch D. Altitude sickness. Clin Evid (Online) 2007;2007.
[18] Luks AM, McIntosh SE, Grissom CK, et al. Wilderness Medical Society consensus guidelines for the prevention and treatment of acute altitude illness. Wilderness Environ Med 2010;21:146–55.
[19] Wagner DR, Teramoto M, Knott JR, Fry JP. Comparison of scoring systems for assessment of acute mountain sickness. High Alt Med Biol 2012;13:245–51.
[20] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–48.
[21] Luo Y, Chen Y, Zhang Y, Zhou Q, Gao Y. Association of endothelial nitric oxide synthase (eNOS) G894T polymorphism with high altitude pulmonary edema susceptibility: a meta-analysis. Wilderness Environ Med 2012;23:270–4.
[22] Subudhi AW, Dimmen AC, Julian CG, Wilson MJ, Panerai RB, Roach RC. Effects of acetazolamide and dexamethasone on cerebral hemodynamics in hypoxia. J Appl Physiol 2011;110:1219–25.
[23] Maggiorini M, Brunner-La Rocca HP, Peth S, et al. Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial. Ann Intern Med 2006;145:497–506.
[24] Hussain MM, Aslam M, Khan Z. Acute mountain sickness score and hypoxemia. J Pak Med Assoc 2001;51:173–9.
[25] Ellsworth AJ, Meyer EF, Larson EB. Acetazolamide or dexamethasone use versus placebo to prevent acute mountain sickness on Mount Rainier. West J Med 1991;154:289–93.
[26] Montgomery AB, Luce JM, Michael P, Mills J. Effects of dexamethasone on the incidence of acute mountain sickness at two intermediate altitudes. JAMA 1989;261:734–6.
[27] Hackett PH, Roach RC, Wood RA, et al. Dexamethasone for prevention and treatment of acute mountain sickness. Aviat Space Environ Med 1988;59:950–4.
[28] Ellsworth AJ, Larson EB, Strickland D. A randomized trial of dexamethasone and acetazolamide for acute mountain sickness prophylaxis. Am J Med 1987;83:1024–30.
[29] Johnson TS, Rock PB, Fulco CS, Trad LA, Spark RF, Maher JT. Prevention of acute mountain sickness by dexamethasone. N Engl J Med 1984;310:683–6.
[30] Cushing TA, McIntosh SE, Keyes LE, et al. Performance-enhancing drugs-commentaries. Wilderness Environ Med 2012;23:207–11.

[31] Maggiorini M. Prevention and treatment of high-altitude pulmonary edema. Prog Cardiovasc Dis 2010;52:500–6.
[32] Julian CG, Subudhi AW, Wilson MJ, Dimmen AC, Pecha T, Roach RC. Acute mountain sickness, inflammation, and permeability: new insights from a blood biomarker study. J Appl Physiol 2011;111:392–9.
[33] Patir H, Sarada SK, Singh S, Mathew T, Singh B, Bansal A. Quercetin as a prophylactic measure against high altitude cerebral edema. Free Radic Biol Med 2012;53:659–68.
[34] Lac G, Marquet P, Chassain AP, Galen FX. Dexamethasone in resting and exercising men. II. Effects on adrenocortical hormones. J Appl Physiol (1985) 1999;87:183–8.
[35] Fischer S, Renz D, Schaper W, Karliczek GF. In vitro effects of dexamethasone on hypoxia-induced hyperpermeability and expression of vascular endothelial growth factor. Eur J Pharmacol 2001;411:231–43.
[36] Subedi BH, Pokharel J, Goodman TL, et al. Complications of steroid use on Mt. Everest. Wilderness Environ Med 2010;21:345–8.
[37] Basu M, Sawhney RC, Kumar S, Pal K, Prasad R, Selvamurthy W. Glucocorticoids as prophylaxis against acute mountain sickness. Clin Endocrinol (Oxf) 2002;57:761–7.
[38] Coote JH. Medicine and mechanisms in altitude sickness. Recommendations. Sports Med 1995;20:148–59.
[39] Spliethoff K, Meier D, Aeberli I, et al. Reduced insulin sensitivity as a marker for acute mountain sickness? High Alt Med Biol 2013;14:240–50.
[40] Marquet P, Lac G, Chassain AP, Habrioux G, Galen FX. Dexamethasone in resting and exercising men. I. Effects on bioenergetics, minerals, and related hormones. J Appl Physiol (1985) 1999;87:175–82.
[41] Abdelmannan D, Tahboub R, Genuth S, Ismail-Beigi F. Effect of dexamethasone on oral glucose tolerance in healthy adults. Endocr Pract 2010;16:770–7.
[42] Ludvik B, Clodi M, Kautzky-Willer A, et al. Effect of dexamethasone on insulin sensitivity, islet amyloid polypeptide and insulin secretion in humans. Diabetologia 1993;36:84–7.
[43] Duplain H, Vollenweider L, Delabays A, Nicod P, Bartsch P, Scherrer U. Augmented sympathetic activation during short-term hypoxia and high-altitude exposure in subjects susceptible to high-altitude pulmonary edema. Circulation 1999;99:1713–8.