Original Article

Efficacy of acetazolamide for the prophylaxis of acute mountain sickness: A systematic review, meta-analysis, and trial sequential analysis of randomized clinical trials

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Abstract:

BACKGROUND: Acute mountain sickness (AMS) is a benign and self-limiting syndrome, but can progress to life-threatening conditions if leave untreated. This study aimed to assess the efficacy of acetazolamide for the prophylaxis of AMS, and disclose factors that affect the treatment effect of acetazolamide.

METHODS: Randomized controlled trials comparing the use of acetazolamide versus placebo for the prevention of AMS were included. The incidence of AMS was our primary endpoint. Meta-regression analysis was conducted to explore factors that associated with acetazolamide efficacy. Trial sequential analyses were conducted to estimate the statistical power of the available data.

RESULTS: A total of 22 trials were included. Acetazolamide at 125, 250, and 375 mg/bid significantly reduced incidence of AMS compared to placebo. TAS indicated that the current evidence was adequate confirming the efficacy of acetazolamide at 125, 250, and 375 mg/bid in lowering incidence of AMS. There was no evidence of an association between efficacy and dose of acetazolamide, timing at start of acetazolamide treatment, mode of ascent, AMS assessment score, timing of AMS assessment, baseline altitude, and endpoint altitude.

CONCLUSION: Acetazolamide is effective prophylaxis for the prevention of AMS at 125, 250, and 375 mg/bid. Future investigation should focus on personal characteristics, disclosing the correlation between acetazolamide efficacy and body mass, height, degree of prior acclimatization, individual inborn susceptibility, and history of AMS.

Keywords:

Acetazolamide, acute mountain sickness, high altitude, prophylaxis, randomized controlled trials

Acute mountain sickness (AMS) is a syndrome of headache, nausea, light-headedness, fatigue, and dyspnea that affects approximately 10%–25% of unacclimatized individuals ascending above 2,500 m to up to more than 80% above 4500 m.[1-4] Although AMS is usually a benign and self-limiting condition, if leave untreated, it can progress to life-threatening high altitude cerebral edema (HACE) or high altitude pulmonary edema (HAPE). A gradual ascent to permit acclimatization remains to be the most effective strategy to prevent AMS.[5] However, it is often logistically infeasible in AMS-susceptible population, recreational and tactical situations. Therefore, the search for effective, reliable, and readily available prophylactic agents with a low adverse effect profile become important.

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For the chemoprophylactic prevention of AMS, acetazolamide is the drug of choice. Acetazolamide is proposed to prevent AMS through the inhibition of renal carbonic anhydrase that induces urinary bicarbonate wasting diuresis, resultant metabolic acidosis, cerebrospinal fluid bicarbonate decrease and ensuing fall in fluid pH that stimulates the central chemoreceptors to respond more fully to hypoxic stimuli.[6,7] Acetazolamide has been proven to be effective in preventing AMS with dosage range from 125 mg twice daily (bid) to 375 mg bid.[8,9] However, the debate on the optimal dosage is still ongoing. There have been successive recommendations to decrease acetazolamide dosage for AMS prevention in the past several decades, usually to minimize side effects including headache, nausea, polyuria, and dysgeusia.[9,10] These adverse effects are similar to AMS symptoms, which can result in misdiagnoses and underestimation of the treatment effect. Yet, others suggested that a low dosage (125 mg bid) could not fully prevent AMS.[11]

Several attempts have been made to disclose the prophylactic effect of acetazolamide for AMS. However, previous meta-analyses mainly and only focused on identifying the effective dosage of acetazolamide in preventing AMS.[8,9] The influence of other confounding factors that considered to affect treatment effect of acetazolamide, including altitude at start of prophylaxis, altitude reached, mode of ascent, acetazolamide pretreatment and ascent rate,[12-14] are still vacant. With new publications, the present meta-analysis aimed to provide updated information about the efficacy of acetazolamide in the prophylaxis of AMS, and try to disclose when and for whom it should be recommended and the optimum dose for clinicians to prescribe.

Methods

Protocol

This systematic review and meta-analysis is reported according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guideline.[15]

Search strategies

Electronic databases, including PubMed, EMBASE, Scopus, CINAHL and the Cochrane Central Register of Controlled Trials, were searched in June 2020 without language and date restriction. Searches were conducted using search terms "acetazolamide" OR "Diamox" in combination with "AMS" OR "altitude illness" OR "high altitude headache" OR "high altitude." All initially identified studies were screened on the basis of titles and abstracts by two independent reviewers. The potentially eligible studies were examined in full-text. Bibliographies of the included trials and relevant reviews were manually searched for additional eligible trials. Disagreement between reviewers was resolved by discussion or the opinion of a third reviewer.

Eligibility criteria

The inclusion criteria were set as follows: (1) Randomized clinical trials (RCTs) published in full-text with sufficient data for extraction. Both parallel and crossover studies were included.; (2) Participants were healthy individuals without a history of previous AMS, underlying medical conditions (such as diabetes mellitus), and altitude related illness (such as high altitude cerebral edema or high altitude pulmonary edema); (3) Comparison of treatment effect must be made between acetazolamide treatment and placebo; (4) The primary outcome was the incidence of AMS; (5) The trials must include a detailed definition for identifying AMS.

The exclusion criteria were set as follows: (1) Conference abstracts, animal experiments, non-randomized or quasi-RCTs, and case report/series; (2) Trials that were unrelated to the current research topic or did not primarily assess prevention of AMS; (3) Studies without a placebo group or only compare treatment effect of acetazolamide with other medications; and (4) Researches that were conducted with simulated altitude in a hypobaric chamber.

Data extraction

Extraction of data was performed by two reviewers independently using pilot-tested standardized data charts, and disagreement was resolved by negotiation or a third reviewer. The study details (author and publication year), populations (demographic details), treatments (dosage, timing and duration), conditions (baseline altitude, endpoint altitude, mode of ascent, rate of ascent), and outcome characteristics (definition of AMS, timing of AMS assessment) were recorded. The incidence of AMS was considered as primary outcome variable while incidence of severe AMS, headache, severe headache, paresthesia, adverse events, and oxygen saturation were the secondary outcomes.

Quality assessment

Two reviewer independently assessed the quality of the included RCTs using the seven-point Jadad scale.[16] Each study was assessed for randomization, allocation concealment, double blinding, and withdrawals and dropouts. Each study was scored from 0 to 7. Studies with scores of 4–7 were considered as high quality, while scores of 0–3 represented poor or low quality.

Data synthesis

Data on primary and secondary outcomes from comparable groups of trials were pooled using the Stata software version 15.0 (Stata Corporation, College Station, TX, USA). Meta-analysis of dichotomous variables was expressed as risk ratio (RR) with 95% confidence

intervals (CI), whereas continuous variables were determined as weighted mean differences with 95% CI. A $P < 0.05$ was considered statistically significant. Between-trials heterogeneity and consistency were evaluated with Q statistic, I^2 statistics and P value.[17] An I^2 statistics of >50% with a P <0.05 on the Q test was defined as a significant degree of heterogeneity. Then, a random effects model was used for data pooling.

Random effects univariate and multivariate meta-regression analyses were conducted to explore the source of heterogeneity if possible. The analysis was accomplished by fitting covariables to study details (publication year and risk of bias), participant demographics (age, sex, and sample size), intervention details (dosage, timing and duration), ascent conditions (baseline altitude, endpoint altitude, mode of ascent, rate of ascent), and outcome characteristics (definition of AMS, timing of AMS assessment). Then, all covariates were entered into a multivariate meta-regression model using a backward elimination approach with a removal criterion of $P > 0.05$. Between subgroup interaction was also tested using meta-regression models; a $P < 0.05$ indicated a significant difference.

Subgroup analyses were performed using the abovementioned covariates or according to the source of heterogeneity if possible. Sensitivity analysis was accomplished by omitting each study one by one to identify trials that disproportionately contributed to the summary estimate and the observed heterogeneity.

Trial sequential analysis was performed to assess the risk of random errors by combining an estimation of required information size with an adjusted threshold for statistical significance in the cumulative meta-analysis.[18,19] O'Brien-Fleming method of alpha-spending function was used with 5% alpha error, 80% power, and a clinically relative risk reduction of 15% for assessing the statistical significance of the estimate.

The number needed to treat (NNT) was determined using the inverse of the absolute risk reduction, which is equivalent to the control event rate minus the experimental event rate. Publication bias was explored using Deeks funnel plot and Egger's asymmetry testing. $P < 0.05$ confirmed the existence of publication bias.

Results

Search results

Initial database searches yielded 978 articles after removal of duplicates, of which 107 were potentially appropriate for inclusion in the meta-analysis. Of these, 85 studies were excluded for not meeting our predefined inclusion criteria, yielding 22 trials for inclusion in the meta-analysis. The PRISMA flow diagram of literature search is shown in Figure 1.

Study characteristics

The 22 selected trials comprised of 2019 participants with 1094 subjects receiving acetazolamide and 925 taking placebo.[11,12,20-39] The proportions of males ranged from 49% to 100%, and the mean age ranged from 20.3 to 43.6 years. Three different doses of acetazolamide (125 mg, 250 mg, and 375 mg/bid) were applied. One study used 85 mg thrice daily and was included in the 125 mg/bid group for purposes of analysis.[29] In two trials, two intervention groups with different doses of acetazolamide were compared with a shared placebo group.[11,21] For all analyses except the subgroup analysis based on acetazolamide dosage, the two active treatment groups in the two trials were pooled into one group. Ten of the studies recruited subjects as they ascended to high altitude and the other 12 trials recruited participants prior to ascent. The baseline altitude at which study participants were enrolled ranged from see level to 4358 m. The endpoint altitude ranged from 3561 to 5896 m. Four types of assessment tools were used to identify AMS in the included studies. The Lake Louise Symptom score (LLS) the most commonly used assessment scale, which was used in 16 studies.[40] Three trials applied the Environmental Symptoms Questionnaire.[41] Of the remaining three studies, one used the General High Altitude Questionnaire,[42] two used a questionnaire developed by the authors.[24,30] More detailed information

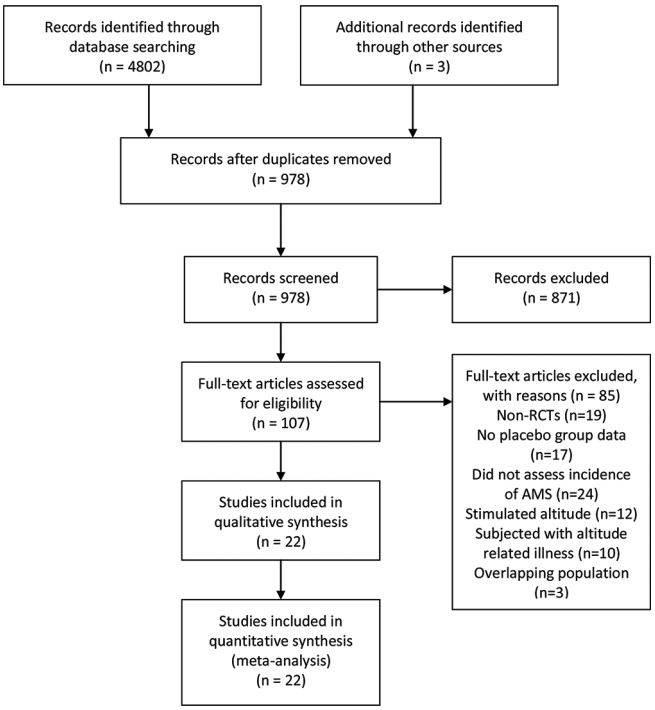

Figure 1: Preferred reporting items for systematic reviews and meta-analysis flow diagram of literature search and study selection

about patients characteristics and intervention regimens are presented in Tables 1 and 2.

According to the Jadad scale assessment, 16 trials with a score ≥4 were considered as high quality. The remaining 6 trials were ranked as low quality since they did not describe specific method of randomization, allocation concealment or double blinding method. Distributions of quality assessment in each study are presented in Supplemental Table 1.

Primary outcome

The incidence of AMS after ascending to high altitude was evaluated in 22 trials. Independent of the baseline and other risks, the overall effect of all trials combined showed that acetazolamide treatment significantly reduced the incidence of AMS compared with placebo, with a RR of 0.51 (95% CI, 0.44–0.58; $P < 0.0001$; $I^2 = 0\%$) [Figure 2]. Among the incidence of AMS, the proportion of severe AMS, which was defined as participants with LLS ≥5, was reported in 7 trials. Acetazolamide treatment showed to have significantly lower incidence of severe AMS compared with placebo (RR = 0.70, 95% CI, 0.52–0.95; $P = 0.02$; $I^2 = 3.6\%$).

Subgroup and meta-regression analyses

Subgroup analysis stratifying studies based on acetazolamide dose suggested that acetazolamide at doses of 125 (RR = 0.57, 95% CI, 0.45–0.72; $P < 0.0001$; $I^2 = 0\%$), 250 (RR = 0.54, 95% CI, 0.45–0.64; $P < 0.0001$; $I^2 = 0\%$), 375 (RR = 0.44, 95% CI, 0.26–0.74; $P = 0.002$; $I^2 = 53.9\%$) mg/bid were all effective in preventing the incidence of AMS compared with placebo [Figure 3]. However, treatment effect did not differ significantly with increasing doses of acetazolamide according to the result of meta-regression analysis [Table 3].

Subgroup analysis based on publication year, sample size, mean age, proportion of male subjects, study quality, timing at start of acetazolamide treatment, mode of ascent, AMS assessment score, timing of AMS assessment, baseline altitude, and endpoint altitude were also performed. In all subgroups, acetazolamide expressed significant treatment effect in reducing the risk of AMS compared with placebo [Table 3]. However, none of the variables was significantly related to the treatment effect of acetazolamide in the meta-regression analysis [Table 3].

Number needed to treat

The NNT was 6 (95% CI, 4–11) in the acetazolamide 125 mg/bid subgroup, 5 (95% CI, 4–8) in the 250 mg/bid subgroup, and 3 (95% CI, 2–4) in the 375 mg/bid subgroup.

Secondary outcomes

The incidence of headache and severe headache was reported in 7 and 4 trials respectively, and pooled result revealed a significant reduction in the incidence with acetazolamide compared to placebo [Table 4]. Most trials did not systematically report adverse events. Assessable data revealed that the use of acetazolamide was associated with significantly more incidence of paresthesias, frequency of micturition, dysgeusia, and dizziness, but less incidence of drowsiness [Table 4]. Significant higher oxygen

Table 1: Basic characteristics of the included randomized controlled trials

Author	Year	Location	Type of subject	Acetazolamide (*n*)	Age (years)	Placebo (*n*)	Age (years)	Male (%)
Basnyat	2003	Mount Everest	Trekkers	74	35.8±12.1	81	33.9±11.4	67.1
Basnyat	2006	Mount Everest	Trekkers	126	37.9±11.1	41	38±11.4	64.7
Basnyat	2008	Mount Everest	Trekkers	187	37.9±12.5	177	39.4±12.1	62.64
Basnyat	2011	Mount Everest	Trekkers	95	37.2±12	64	39.4±13.1	66.04
Burki	1992	Karakorum	Volunteers	6	20.2±1.5	6	20.7±1.4	100
Caravita	2015	Capanna Regina Margherita	Volunteers	20	-	21	-	51.22
Carlsten	2004	La Paz, Bolivia	Tourists	22	35.2±8.2	11	35.2±9.5	-
Chow	2005	White Mountain	Volunteers	20	32 (25-42)	20	33.5 (24-65)	57.5
Ellsworth	1987	Mount Rainier	Climbers	15	29.3±9.1	15	30.1±9.0	93.33
Gertsch	2004	Mount Everest	Trekkers	118	36.4±11.0	119	36.4±10.8	70.46
Gertsch	2010	Mount Everest	Trekkers	97	39.1±12.0	65	39.2±12.1	68.52
Hackett	1976	Mount Everest	Hikers	71	-	49	-	71
Hillenbrand	2006	Mount Everest	Nepali trekking porters	55	-	54	-	-
Kayser	2008	Mount Everest	Volunteers	44	-	16	-	91
Larson	1982	Mount Rainier	Climbers	29	28.7±0.9	30	29.2±1.0	84.38
Lipman	2017	White Mountain	Volunteers	35	-	35	-	52.86
Moraga	2007	Ollague Andes	Volunteers	12	23.3±1.2	12	22.2±1.1	100
Parati	2012	Capanna Regina Margherita	Lowlanders	19	-	20	-	48.72
Salvi	2013	Capanna Regina Margherita	Lowlanders	19	35.6±7.1	20	37.0±9.5	48.72
Vanpatot	2008	Pikes Peak	Volunteers	22	22.9±5.37	22	23.7±6.29	50
Wang	2013	Lhasa	Volunteers	11	24.6±1.6	10	24.7±1.7	100
Zell	1988	Sierra Nevada Mountains	Backpackers	6	-	8	-	62.5

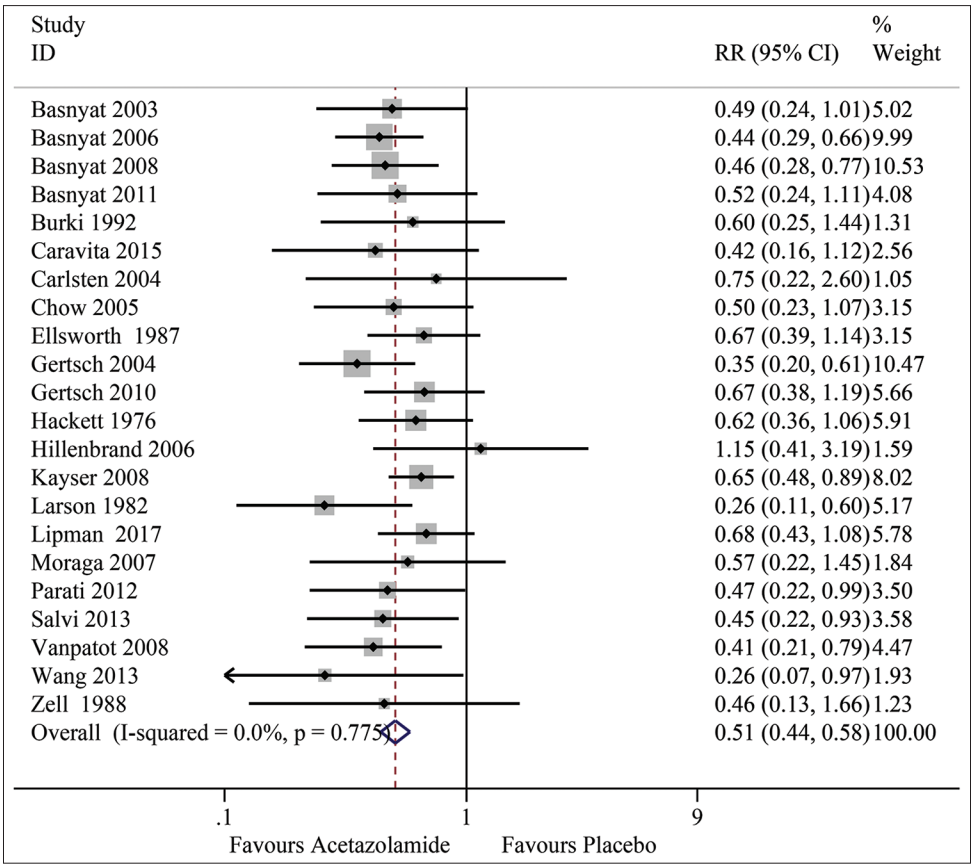

Figure 2: Incidence of acute mountain sickness compared between acetazolamide and placebo groups

saturation was observed in the acetazolamide group compared with placebo (MD = 3.21, 95% CI, 2.31–4.12; $P < 0.0001$; $I^2 = 76.8\%$). The incidences of HACE and HAPE were reported in four trials, and only one case of HACE was found in the placebo group in the study of Chow *et al*. 2005.[26]

Trial sequential analysis

For TAS of the incidence of AMS, the adjusted optimal information size were 2340, 2283, and 353 for acetazolamide at 125, 250, and 375 mg/bid, respectively. Results of all three subgroups showed that Z-curve (the blue line) crossed the upper trial sequential monitoring boundary for benefit. Hence, available evidence was sufficient confirming the prophylactic effect of acetazolamide at 125, 250, 375 mg/bid against AMS [Supplemental Figures 1-3].

Sensitivity analysis

Sensitivity analysis was conducted in all of the assessed outcomes. The estimate of treatment effects was similar between the original analysis and the sensitivity analyses in all subgroups.

Publication bias

Begg's funnel plot and Egger's test showed no evidence of publication bias in the incidence of AMS for acetazolamide at 125 mg/bid (P value of Begg's test = 0.54; P value of Egger's test = 0.86), and 250 mg/bid (P value of Begg's test = 0.58; P value of Egger's test = 0.43).

Discussion

This meta-analysis was conducted to further verify or update the previous understandings of acetazolamide for the prophylaxis of AMS. In consistent with previous findings,[8,9,43,44] results of the present meta-analysis also showed that acetazolamide at doses of 125, 250, 375 mg/bid was significantly efficacious in decreasing the incidence of AMS. There is concern that sample size of the subgroup analysis based on doses of acetazolamide is small. Especially for the findings of acetazolamide 375 mg/bid subgroup analysis which were based on data from only three studies. This brings into question the reliability and reproducibility of the results. Results of TAS indicated that the current evidence was adequate confirming the preventive effect of acetazolamide at 125, 250, 375 mg/bid against AMS, and it would be extremely unlikely that addition of new trials would deny their effects.

The optimal dose of acetazolamide for the prevention of AMS has been contentious for many years. The previous

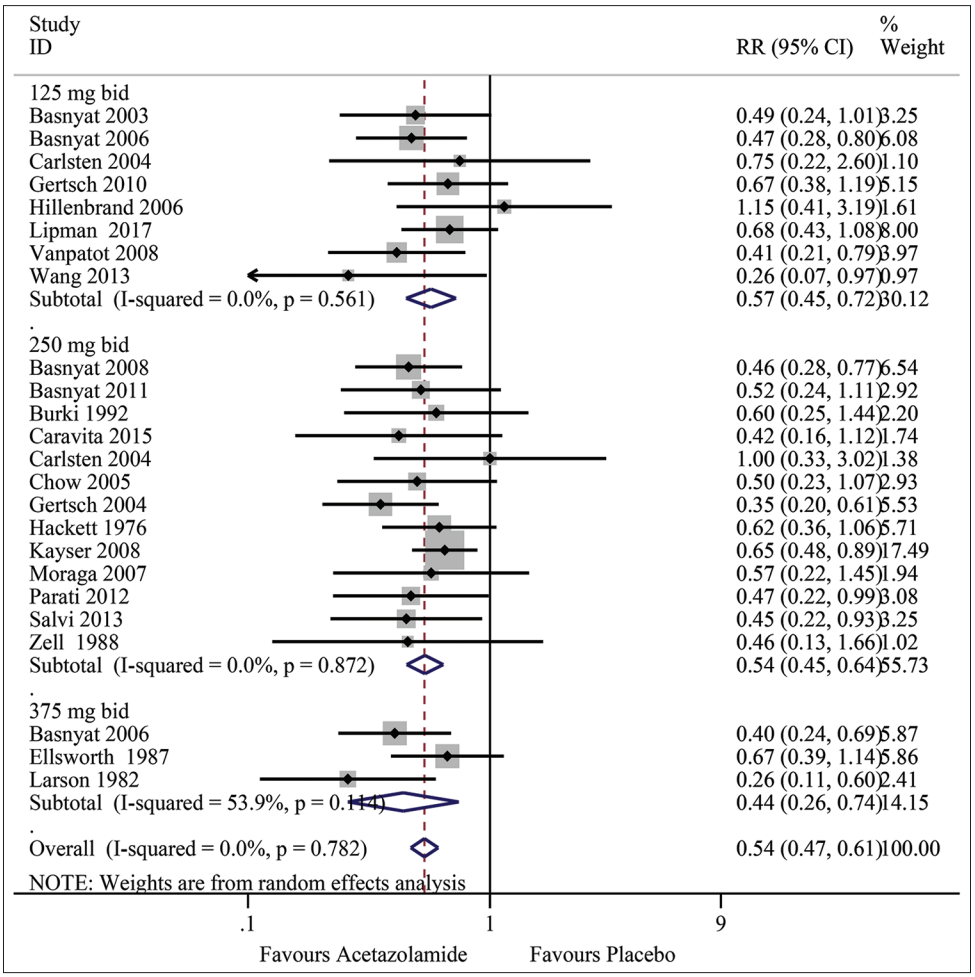

Figure 3: Efficacy of acetazolamide by dose

study reported weak evidence of dose-responsive for acetazolamide in the prevention of AMS.[8] Our results also demonstrated decreased RR with increased doses. Nevertheless, meta-regression analysis did not prove any significant difference in treatment effect with increasing doses of acetazolamide. Therefore, the present study could only conclude that acetazolamide at 125 mg/bid was the lowest effective dose for the prevention of AMS. The determination of the most optimal dose for AMS prevention needs further evidence and direct comparison. In the recent year, an even lowest dose of acetazolamide (62.5 mg/bid) has been discussed. Two studies have compared the treatment effect of acetazolamide 62.5 mg/bid with 125 mg/bid in the prevention of AMS.[45,46] The two trials were not included in our meta-analysis because they did not contain a placebo group. Yet, additional analysis was also conducted based on the two studies. Pooled results showed that acetazolamide 62.5 mg/bid was noninferior to the acetazolamide 125 mg/bid for prevention of AMS ($P = 0.624$). However, increased AMS incidence and symptom severity corresponded to lower weight-based and body mass index dosing, with similar side effects between groups. The current evidence did not support the use of acetazolamide at 62.5 mg/bid for the prevention of AMS.

According to previous arguments,[8,21,47] we expected to see different treatment effects of acetazolamide with different timing at start of acetazolamide treatment, mode of ascent, timing of AMS assessment, baseline altitude, and endpoint altitude, but these were not demonstrated by our data. Results of meta-regression analysis suggested that the above factors might not have significant influence on the treatment effect of acetazolamide for prevention of AMS. To decide which patients are likely to benefit most from acetazolamide, other factors, such as degree of prior acclimatization, individual inborn susceptibility, and history of AMS, should be the next focus.

In line with the previous reports, our study also detected that the use of acetazolamide was accompanied by increased occurrence of paresthesias, frequency of micturition, and dysgeusia. However, sparse and limited data from the included studies precluded any analysis on the differences in adverse events profile.

Table 2: Acetazolamide intervention and ascent profiles

Author	Year	Dosage (mg/bid)	Start time	Evaluation time	AMS scale	Definition of AMS	Mode of ascent	Start altitude	End altitude
Basnyat	2003	125	Day 1 of ascent	At rest in the evening	LLQ	LLQ ≥3; headache + 1 symptoms	Climb	4243	4937
Basnyat	2006	125/375		The morning after arrival	LLQ	LLQ ≥3; headache + 1 symptoms	Climb	3440	4928
Basnyat	2008	250	Day 1 of ascent	36-96 h after beginning of drug	LLQ	LLQ ≥3; headache + 1 symptoms	Climb	4250	5000
Basnyat	2011	250	Day 1 of ascent	36-96 h after beginning of drug	LLQ	LLQ ≥3; headache + 1 symptoms	Climb	4300	5000
Burki	1992	250	Day 1 of ascent	32-56 h after arrival	Clinical observation	Dizziness, nausea/vomiting, headache	Transport	518	4450
Caravita	2015	250	1 day before ascent	Every morning at HA	LLQ	LLQ >4	Transport and climb	122	4559
Carlsten	2004	125/250	Within 2 h of airport arrival	At 0, 6, 12, and 24 h from initiation of medication	LLQ	LLQ ≥3 must including headache	Transport	3630	3630
Chow	2005	250	1 day before ascent	24 h after HA	LLQ	LLQ ≥3; headache + 1 symptoms	Transport	1230	3800
Ellsworth	1987	375	1 day before ascent	Within 15 min of reaching HA	ESQ-III	AMS-C >0.7; AMS-R >0.6	Transport and climb	1300-1600	4392
Gertsch	2004	250	3 or 4 doses before ascent	The morning after arrival	LLQ	LLQ ≥3; headache + 1 symptoms	Climb	4358	4928
Gertsch	2010	85 thrice	Minimum of 3 doses before ascent	The morning after arrival	LLQ	LLQ ≥3; headache + 1 symptoms	Climb	4358	4928
Hackett	1976	250	Day 1 of ascent	-	-	AMS ≥2 (0 to 5 point scale)	Transport and climb	3440	4243
Hillenbrand	2006	125	-	-	LLQ	LLQ ≥3; headache + 1 symptoms	Climb	3440	4930
Kayser	2008	250	-	Daily around 6 pm after at least 2 h of rest after arrival	LLQ	LLQ ≥3 including headache	Transport and climb	Sea level	5896
Larson	1982	375	1 day before ascent	-	GHAQ	Headache of moderate or greater severity, nausea of slight or greater severity, or both	Transport and climb	1300-1600	4394
Lipman	2017	125	Day 1 of ascent	The evening and next morning at HA	LLQ	LLQ ≥3; headache + 1 symptoms	Transport and climb	1240	3810
Moraga	2007	250	1 day before ascent	The morning after arrival	LLQ	LLQ ≥3	Transport	Sea level	3969
Parati	2012	250	3 days before ascent	At least 4 h after reaching HA	LLQ	LLQ ≥3	Transport and climb	122	4559
Salvi	2013	250	3 days before ascent	-	LLQ	LLQ ≥3	Transport and climb	122	4559
Vanpatot	2008	125	3 days before ascent	After 24 h at HA	ESQ-III; LLQ	Combination of AMS-C score ≥0.7 and an LLS ≥3	Transport	1600	4394
Wang	2013	125	3 days before ascent	Daily for around 6:00 pm	LLQ	LLQ ≥3	Transport	402	3561
Zell	1988	250	2 days before ascent	Every 12 h at altitudes above 3650	ESQ-III	ESQ >0.7	Transport and climb	3650	4050

AMS=Acute mountain sickness, LLQ=Lake louise questionnaire, ESQ=Environmental symptoms questionnaire, GHAQ=General high altitude questionnaire, HA=High altitude, LLS=Lake louise symptom score, AMS-C=AMS-cerebral, AMS-R=AMS-respiratory

Table 3: Results of subgroup and meta-regression analyses

Subgroups	Number of study	Subgroup analysis				Meta-regression analysis		
		RR	95% CI	*P*	I^2 (%)	Change in logRR	95% CI	*P*
Dose (mg/bid)								
125	8	0.57	0.45-0.72	<0.001	0	Reference		
250	13	0.54	0.45-0.64	<0.001	0	−0.04	−0.36-0.27	0.776
375	3	0.44	0.26-0.74	0.002	53.9	−0.11	−0.55-0.34	0.621
Publication year								
<2010	15	0.50	0.42-0.58	<0.001	0	Reference		
>2010	7	0.54	0.42-0.71	<0.001	0	0.02	−0.3-0.35	0.877
Sample size								
<100	14	0.51	0.43-0.62	<0.001	0	Reference		
>100	8	0.50	0.41-0.62	<0.001	0	−0.05	−0.34-0.24	0.72
Mean age								
<35	9	0.52	0.41-0.67	<0.001	11.1	Reference		
>35	10	0.49	0.41-0.59	<0.001	0	−0.06	−0.38-0.26	0.691
Proportion of male subjects (%)								
<70	12	0.50	0.42-0.60	<0.001	0	Reference		
>70	8	0.49	0.39-0.60	<0.001	31.2	0.06	−0.23-0.35	0.681
Study quality								
Low	15	0.51	0.44-0.60	<0.001	0	Reference		
High	7	0.49	0.36-0.67	<0.001	0	−0.05	−0.41-0.32	0.797
Timing at start of acetazolamide treatment								
Day 1 of ascent	7	0.55	0.43-0.71	<0.001	0	Reference		
1-3 days before ascent	12	0.45	0.36-0.55	<0.001	0	−0.09	−0.43-0.25	0.58
Mode of ascent								
Climb	8	0.51	0.42-0.62	<0.001	12.3	Reference		
Transport and climb	13	0.51	0.42-0.62	<0.001	0	−0.002	−0.29-0.29	0.989
AMS assessment score								
LLQ	17	0.51	0.44-0.59	<0.001	0	Reference		
Others	8	0.54	0.44-0.66	<0.001	0	−0.05	−0.2-0.3	0.662
Timing of AMS assessment								
At rest	7	0.58	0.47-0.72	<0.001	0	Reference		
Next morning	8	0.48	0.35-0.56	<0.001	0	0.15	−0.19-0.49	0.357
Baseline altitude								
Sea level	12	0.51	0.42-0.62	<0.001	0	Reference		
High altitude	10	0.51	0.41-0.62	<0.001	0	−0.04	−0.33-0.24	0.749
Endpoint altitude								
<4000	5	0.57	0.41-0.80	0.001	0	Reference		
4000-4500	6	0.48	0.36-0.65	<0.001	0	0.03	−0.41-0.47	0.903
>4500	11	0.50	0.42-0.60	<0.001	0	0.12	−1.29-1.53	0.88

AMS=Acute mountain sickness, LLQ=Lake Louise questionnaire, CI=Confidence interval, RR=Risk ratio

Table 4: Results of secondary outcomes

Outcomes	Number of study	RR	95% CI	*P*	I^2 (%)
Headache	7	0.49	0.36-0.66	<0.001	57.9
Severe headache	4	0.46	0.26-0.82	0.08	0
Paresthesias	4	4.30	2.11-8.77	<0.001	86.7
Frequency of micturition	5	1.45	1.10-1.90	0.009	72.2
Dysgeusia	3	3.32	1.36-8.08	0.008	0
Dizziness	4	0.37	0.17-0.81	0.013	0
Drowsiness	3	0.66	0.45-0.96	0.030	0

CI=Confidence interval, RR=Risk ratio

Due to commonly observed adverse effect with acetazolamide, researchers have evaluated various other agents. Based on the included data, head-to-head comparison of treatment effect of acetazolamide with dexamethasone,[27,39] and acetazolamide with ginkgo biloba,[26,28,34] was conducted additionally. Compared with acetazolamide, dexamethasone (P = 0.40) seemed to have better while ginkgo biloba (P = 0.15) have lower treatment effect, although the result did not reach statistical significance. The previous investigation showed a better adverse effect profile toward the dexamethasone and ginkgo biloba when compared with acetazolamide.[26-28] Therefore, combined treatment of acetazolamide with other agents might be a new direction to improve treatment effect and safety profile of acetazolamide for prevention of AMS.

Several limitations need to be noticed. Although meta-regression analysis has controlled most of arguable factors, the effect of rate of ascent could not be assessed due to uneven data. We thought that subgroup analysis based on mode of ascent can somewhat reflect rate of ascent, as subjects ascended by climbing would be more gradually while ascend involved transportation would be more rapid. However, firm conclusion about the influence of rate of ascent could not be reached without more robust study data. Some of the demographic characteristics, such as body mass, height, gender, and age, have been purposed to affect the efficacy of acetazolamide.[20] These factors need to be addressed in the future. Most of the included trials only contained a small sample size, which might have the tendency to overestimate the efficacy of a treatment.[48] Thus, further well-designed, large, randomized dose-finding studies in nonacclimatized subjects with various rate of ascent are needed to confirm or refute the results of our meta-analysis.

Conclusion

Based on the current findings, there is adequate evidence confirming the significant efficacy of acetazolamide at doses of 125, 250, 375 mg/bid in reducing incidence of AMS. Thus, future investigation should focus on finding the optimal dose and suitable subjects to maximize the therapeutic effect of acetazolamide. In addition, factors including timing at start of acetazolamide treatment, mode of ascent, timing of AMS assessment, baseline altitude, and endpoint altitude show to have little influence on the treatment effect of acetazolamide. Future prescription of acetazolamide should tailor to personal need taken degree of prior acclimatization, individual inborn susceptibility, and history of AMS into consideration. Alternatively, combined treatment of acetazolamide with other agents can be another approach to improve treatment effect for the prevention of AMS.

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Conflicts of interest
There are no conflicts of interest.

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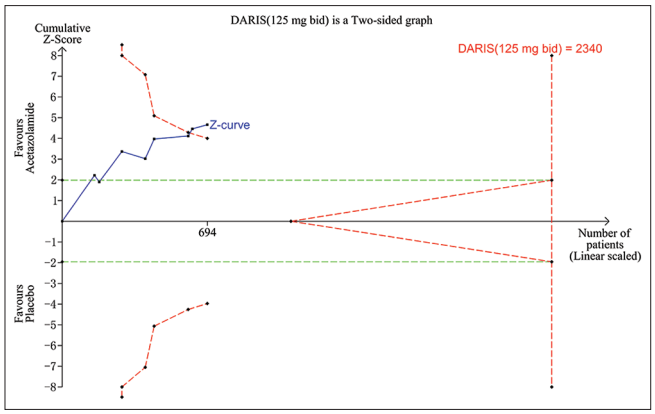
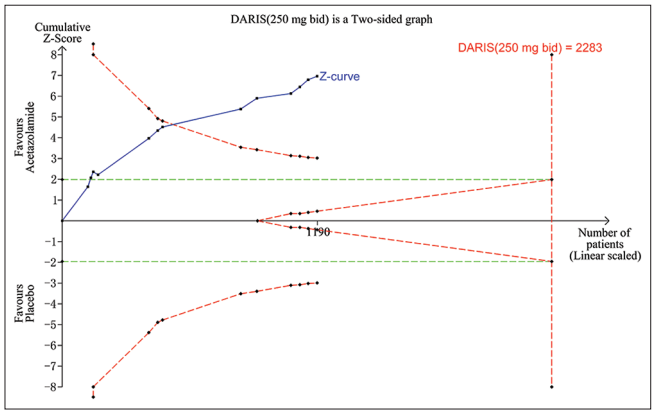
Supplementary Table 1: Quality assessment results Jadad Scale for reporting randomized controlled trials

Author	Year	Randomization	Concealment of allocation	Double blinding	Withdrawals and dropouts	Total	Quality
Basnyat	2003	2	2	2	1	7	
Basnyat	2006	2	2	2	1	7	
Basnyat	2008	2	1	2	1	6	
Basnyat	2011	2	1	2	1	6	
Burki	1992	1	0	1	1	3	
Caravita	2015	1	0	1	1	3	
Carlsten	2004	1	1	1	1	4	
Chow	2005	2	2	2	1	7	
Ellsworth	1987	2	1	1	1	5	
Gertsch	2004	1	1	1	1	4	
Gertsch	2010	1	1	1	1	4	
Hackett	1976	1	0	1	1	3	
Hillenbrand	2006	2	1	2	1	6	
Kayser	2008	1	1	1	1	4	
Larson	1982	1	1	1	1	4	
Lipman	2017	2	1	1	1	5	
Moraga	2007	2	0	1	0	3	
Parati	2012	1	1	1	1	4	
Salvi	2013	1	1	1	1	4	
Vanpatot	2008	1	1	1	0	3	
Wang	2013	1	0	1	1	3	
Zell	1988	1	1	1	0	3	

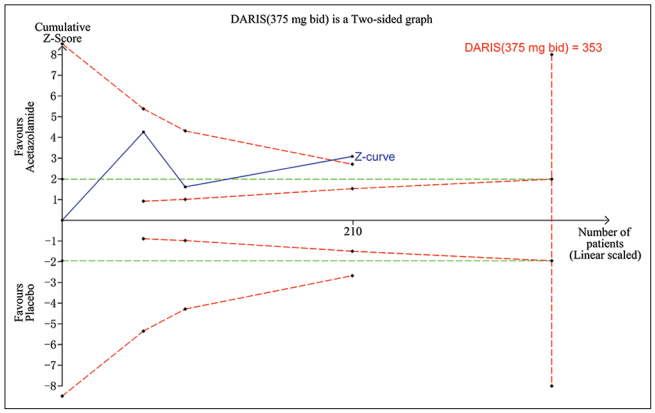
Ranking criteria: 0-3 stars for “low;” 4-7 stars for “high”



Supplemental Figure 1: Trial sequential analysis of acetazolamide at 125 mg/bid versus placebo on the incidence of acute mountain sickness



Supplemental Figure 2: Trial sequential analysis of acetazolamide at 250 mg/bid versus placebo on the incidence of acute mountain sickness



Supplemental Figure 3: Trial sequential analysis of acetazolamide at 375 mg/bid versus placebo on the incidence of acute mountain sickness