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REVIEW ARTICLE

Efficacy of NSAIDs for the prevention of acute mountain sickness: a systematic review and meta-analysis

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Background: Acute mountain sickness (AMS) can occur in anyone going to a high altitude. Non-steroidal anti-inflammatory drugs (NSAIDs) have been studied for the prevention of AMS with mixed results. In this systematic review, we analyze all existing data on the use of NSAIDs to prevent AMS using the Lake Louise Scoring System (LLSS) in different randomized clinical trials (RCTs).

Methods: Electronic literature searches for relevant studies were identified through MEDLINE, EMBASE, SCOPUS, and Cochrane library up to June 2013. RCTs involving NSAIDs compared to placebo in patients undergoing ascent to a height of at least 3,800 m were included. Odds ratios (OR) were calculated and combined using fixed-effect model meta-analysis if $I^2 = 0\%$. Differences between groups were calculated using the inverse variance of the standard mean differences. Between-study heterogeneity was assessed using the I^2 statistics.

Results: In three clinical trials involving 349 patients, AMS using LLSS occurred in 26.92% of patients on NSAIDs and 43.71% on placebo (OR 0.43; CI [confidence interval] 0.27–0.69, $I^2 = 0\%$, $p = 0.0005$), NNT = 6. Minor outcome of end point Spo2 was not significant in the two groups (IV = 0.74; 95% CI −0.20–1.69, $I^2 = 81\%$, $p = 0.12$). Similarly, a change in Spo2 from baseline was also not significant in the two groups (IV = 0.05; 95% CI −0.28–0.37, $I^2 = 44\%$, $p = 0.78$).

Conclusion: NSAIDs might be a safe and effective alternative for the prevention of AMS. However, further larger population studies and studies comparing NSAIDs to acetazolamide and dexamethasone in the future may provide further data to its relative efficacy.

Keywords: *altitude sickness*; *acute mountain sickness*; *anti-inflammatory agents*; *non-steroidal*; *ibuprofen*; *headache*

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Every year, thousands of people travel to high-altitude destinations worldwide for recreational purposes, work-related activities, or pilgrimage. Anyone traveling to a high altitude is at risk of developing acute mountain sickness (AMS). However, it is seen more commonly above 2,500 m (8,250 feet) (1). The risk also depends on the rate of ascent, prior acclimatization, young age, history of prior altitude illness, and inborn susceptibility (2, 3). As defined by the 1991 Lake Louise Consensus (4), AMS is a group of symptoms associated with hypobaric hypoxemia above 2,500 m. It usually manifests with headache, which is often associated with fatigue, lightheadedness, anorexia, nausea and vomiting, and disturbed sleep with frequent awakening (1, 3). Typically, symptoms occur after 6–12 hours of ascent. It is usually self-limited. However, if untreated it can progress to the life-threatening high altitude cerebral edema (HACE) (1, 5).

Although the mechanism of AMS/HACE is not well understood, therapies commonly used for prophylaxis such as acetazolamide and glucocorticoids in general target the known physiological effects of AMS such as fluid retention, hypoventilation, impaired gas exchange, and heightened sympathetic response (2). Non-steroidal anti-inflammatory drugs (NSAIDs) however have been thought to work at the pathogenesis level, inhibiting the

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inflammatory cyclooxygenase pathway, and are thought to have some utility in the prevention of AMS. There are a few studies showing effectiveness of NSAIDs in the prevention of AMS but they have been limited by their small sample size. However, a systematic review of literature with regard to NSAIDs and prevention of AMS is lacking. The aim of this study is to synthesize and analyze the available evidence, including the aforementioned clinical trials. As the assessment of AMS is subjective and potentially prone to bias, we chose to include only randomized, placebo-controlled, double-blind studies that clearly defined the diagnosis of AMS.

Methods

Studies assessing the use of NSAIDs versus placebo as an intervention for the prophylaxis of AMS were considered for inclusion in our study. Studies were required to randomize the participants to either NSAIDs or placebo group before ascent. A protocol for this meta-analysis was prospectively devised that details the background, objectives and eligibility criteria of studies, outcomes, and statistical methods. This is available for review upon request to investigators.

Literature search and data extraction

The PRISMA statement for reporting systematic reviews recommended by the Cochrane Collaboration was followed for conducting this meta-analysis (Fig. 1). Systematized search of MEDLINE, EMBASE, SCOPUS, Cochrane library, and clinical trials.gov (inception to August 2013) were carried out to identify eligible randomized clinical trials (RCTs). PubMed, Cochrane Library, EMBASE, and SCOPUS databases were searched using the search terms under two search themes and combined using the Boolean operator 'AND'. For the theme 'NSAID', we used a combination of MeSH, entry terms, and text words: NSAID, NSAIDs, non-steroidal anti-inflammatory drugs, ibuprofen, carbasalate, naproxen, aspirin, salicylate, salicylic acid, and ketorolac. For the theme 'Acute Mountain Sickness', AMS, acute mountain sickness, mountain sickness, high altitude cerebral edema, HACE, and high altitude cerebral oedema were all used. No language restrictions were used. Bibliographies belonging to included papers, known reviews, and relevant articles were looked into for additional trials. To minimize data duplication as a result of multiple reporting, we compared papers from the same author. Two authors (SG and MRA) screened and retrieved reports and excluded irrelevant studies. Relevant data were extracted by two authors (SG and MRA) and checked by another (PK and RP). An additional investigator (AP) participated in the review process when uncertainty about eligibility criteria arose. From each study, we extracted and tabulated mean age, gender, altitude, type, and dose of NSAIDs used as well as primary and secondary indicators of efficacy and adverse events (Table 1).

Study selection and evaluation for the review

We selected studies that were randomized and compared the use of NSAIDs versus placebo in the prevention of AMS. The steps of the literature search process are summarized in Fig. 1.

The eligibility criteria for this meta-analysis were 1) randomized controlled trials (RCTs) of healthy human subjects between age 18 and 65, 2) population residing in an altitude less than 1,240 m with ascent of at least 3,800 m above the sea level, 3) prophylaxis with either NSAIDs or placebo for AMS, and 4) AMS clearly defined using the Lake Louise Scoring System (LLSS). The RCTs were excluded if they were unrelated to the current research topic and if they did not primarily assess prevention of AMS (e.g. studies looking at aspirin for the prevention of high altitude headache, or HAH). The studies were also excluded if the participants were pregnant or thought to be pregnant, lived or slept at an altitude greater than 1,240 m in the past week, were indigenous or local population (due to physiological adaptation to the altitude), had symptoms consistent with AMS at baseline, signs or symptoms of a substantial acute infection, taken any NSAIDS, steroids or acetazolamide within 1–3 days before enrolment or had a history of HACE or pulmonary edema. Conference abstracts were not included in our meta-analysis.

Three studies were included in our review and were slightly different. The first study by Gertsch et al. was an RCT looking at the preventive effect of 600 mg of ibuprofen or placebo three times daily before and during the ascent on 232 Western trekkers from 4,240 or 4,358 m to 4,928 m in Mt. Everest in Nepal. The second study by Lipman et al. recruited 75 healthy adult volunteers living at low altitude who were randomized to receive ibuprofen or placebo three times daily starting 6 hours before the ascent from 1,240 to 3,810 m in White mountains in California. Similarly, a third study by Kayser et al. looked at the preventive effect of calcium carbasalate 380 mg/day or placebo on altitude-naive subjects from sea level to 5,896 m. All of these RCTs looked at the incidence and severity of AMS as measured by LLSS as their primary outcome.

Assessment of risk of bias

The quality of included studies were independently evaluated by two reviewers (SG and MRA) using the guidelines provided by Cochrane Collaboration tool for assessing risk of bias (6). All of the studies were assessed for random sequence generation, allocation concealment, blinding of participants, incomplete outcome data, and selective outcome reporting and free from other biases. Each domain of risk was assigned as 'adequate' for low risk, 'inadequate' for low risk, and unclear in cases not mentioned (Supplementary Table 2).

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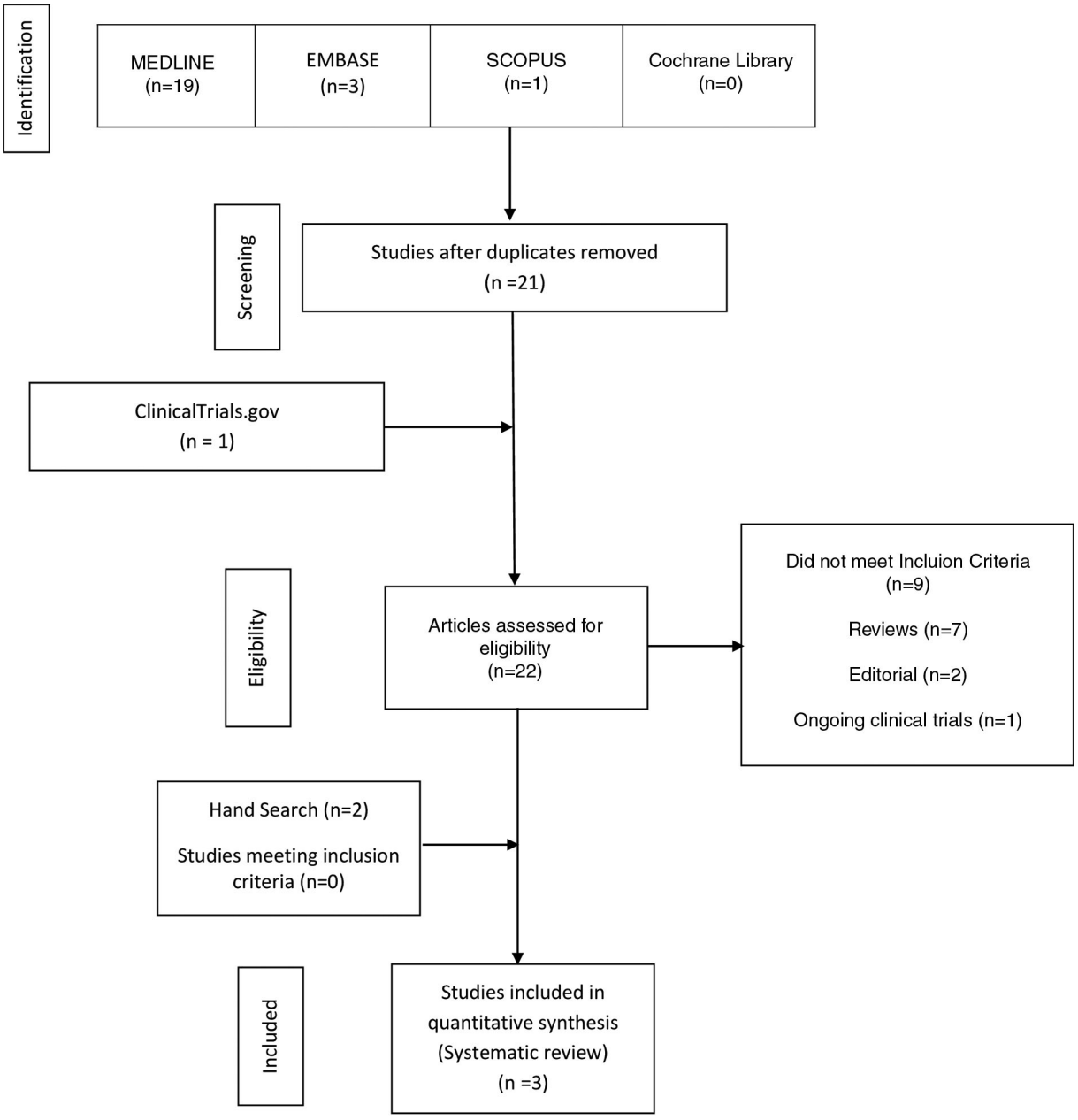

Fig. 1. PRISMA flow diagram showing the screening and inclusion of the studies.

Outcome measures

The primary outcome measure for this study was prevention of AMS using LLSS (score used to diagnose AMS and its severity developed by panel of experts in 1991). All the included studies used Lake Louise Criteria for diagnosing AMS. According to the Lake Louise consensus criteria, AMS is defined as the presence of headache with at least one other symptom after recent ascent to altitude: gastrointestinal (GI) disturbance (anorexia, nausea, vomiting), dizziness/light headedness, insomnia, or fatigue. These five symptoms are scored as per the degree of their severity and a composite score of 3 or more is consistent with a diagnosis of AMS (7). The studies without a clear definition of AMS or proper randomization were excluded. In the study by Meehan et al., Environmental Symptom Questionnaire (ESQ) was used to identify AMS. However, the data was reported in terms of severity of AMS and the incidence of AMS was unclear among the study population (8). Hence, Meehan's study had to be excluded from our meta-analysis. Secondary outcomes included difference in arterial oxygen saturation (SpO2) and the severity of headache defined by the Visual Analog Scale (VAS).

Statistical analysis

All outcome comparisons and treatment effects were calculated with RevMan version 5.2 (Cochrane Collaboration,

Table 1. Baseline characteristics of the studies

Study setting	Final altitude (meter)	Participants	Intervention	Outcomes	Notes
Gertsch 2012, Mt Everest Nepal	4,928	$N=232$ mean 37 years, 65% male, intervention 123 (mean age 38), control 109 (mean age 36)	600 mg of ibuprofen three times daily, visually matched placebo, treatment for 1–2 days depending on ascent	Diagnosis of AMS as defined by LLSS	Participants were recruited at Pheriche (4,280 m) or Dingboche (4,358 m) which may have introduced selection bias or reduced the incidence of AMS among participants
Kayser 2008, Mt Kilimanjaro	5,896	$N=75$, mean age 37 years, 91% male, intervention 15, placebo 16	Carbasalate 380 mg/day, visually matched placebo, treatment for 6 days	Diagnosis of AMS as defined by LLSS	Mixed study design; two controlled arms comparing placebo to calcium carbasalate, third uncontrolled arm for subjects who opted out for prophylactic acetazolamide
Lipman 2012, White mountains, California	3,810	$N=86$, mean age 36.6, 67% male, intervention 44 (mean age 38.4), placebo 42 (mean age 34.8)	Four doses of ibuprofen 600 mg, visually matched placebo, treatment for 1 day	Diagnosis of AMS as defined by LLSS	Participants recruited at 1,240 m, possible mild degree of acclimatization

Oxford, United Kingdom). The summary odds ratio (OR) and 95% confidence intervals (CI) were estimated using a fixed effects method if I^2 was 0. To control for heterogeneity if present, random effect models were used for this meta-analysis as their assumption account for presence of variability among the studies. We also performed a sensitivity analysis using the inverse variance method to pool ORs that were adjusted for baseline differences between the two treatment arms. We calculated the I^2 statistics to evaluate the percentage of heterogeneity among the trials. When interpreting heterogeneity, I^2 values less than 30% were considered as low heterogeneity, less than 60% as moderate, and greater than 60% as high (9). A P-value of <0.05 was used as the level of significance. The results are reported in a forest plot with 95% CI. ORs were calculated for each outcome. Cochrane calculator was used to determine the number needed to treat (NNT) to prevent one event of AMS.

Results

Included studies

Three studies satisfied inclusion criteria for this meta-analysis. The studies were carried out in Mount Everest, Nepal; Mount Kilimanjaro, Tanzania; White Mountains, California, USA (2, 4, 9). Both males and females were included in these studies with a total of 349 participants (74% males). The height of the altitude ranged from 3,810 to 5,896 m with a mean of 4,801 m. Of the included studies, two studies evaluated the effect of ibuprofen with placebo (1, 10) and one study compared calcium carbasalate with placebo (11). All of the studies used LLS for the diagnosis of AMS (1, 10, 11). For a detailed description of the study characteristics, please refer to Table 1.

Prevention of AMS in all included trials

In three clinical trials involving 349 patients, AMS as defined by LLSS occurred in 49 of 182 (26.92%) treated with NSAIDs and in 73 of 167 (43.71%) treated with placebo. The combined effect size was OR $=0.43$ (95% CI 0.27–0.69, $Z=3.47$, $P=0.0005$, $I^2=0\%$). The absolute risk reduction was 16.8%. The NNT to prevent AMS was six (Fig. 2).

Sensitivity analysis

A sensitivity analysis was performed including studies that used only ibuprofen for a total of 318 participants. Again, this was assessed using LLSS. The combined effect size OR $=0.43$ (95% CI 0.27–0.69, $Z=3.47$, $P=0.0005$, $I^2=0\%$). AMS occurred in 49 of 167 (29.34%) treated with ibuprofen and 73 of 151 (48.34%) treated with placebo. The absolute risk reduction was 19.00%. The NNT to prevent AMS was five (Supplementary Fig. 3).

Subgroup analyses

Subgroup analysis of headache severity using VAS was also found to be significant in two groups (inverse variance of standard mean difference (IV) $=-0.29$; 95% CI -0.51– -0.07, $I^2=0\%$, $p=0.01$). Minor outcome of end point Spo2 was not significant in the two groups (IV $=0.74$; 95% CI -0.20–1.69, $I^2=81$, $p=0.12$).

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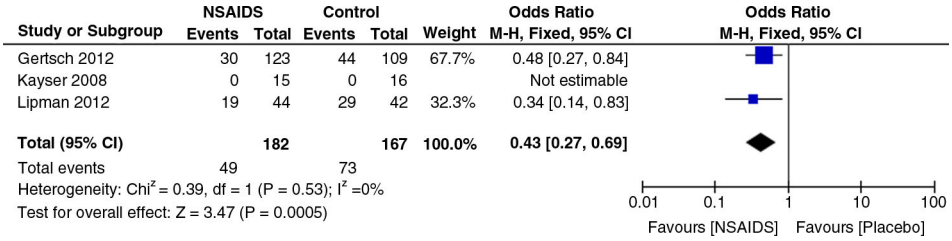

Fig. 2. Meta-analysis of AMS incidence using the LLSS. Comparator: NSAIDs versus placebo.

Similarly, a change in Spo2 from baseline was also not significant in the two groups (IV = 0.05; 95% CI −0.28–0.37, I^2 = 44%, p = 0.78) (Supplementary files 2 and 3).

Discussion

The incidence and severity of AMS can be lowered by the use of acetazolamide or dexamethasone (3, 12). However, the use of NSAIDs continues to be an area of debate. This is, to the best of our knowledge, the first systematic review and meta-analysis of NSAIDs in the prevention of AMS. It summarizes all the available evidence on the efficacy of NSAIDs in the prevention of AMS. An extensive database search identified 22 studies of interest, out of which only three met our inclusion criteria. A study by Ho B et al. using ibuprofen 400 mg three times daily was not included in our study since this study looked at a different outcome (hypoxic ventilatory response rather than AMS) (13). Our analysis incorporated 349 patients from these three studies, which try to overcome the limitation that the previous trials faced due to low sample size. Analysis of data from these trials suggests that NSAIDs might be an effective alternative for the prevention of AMS, which is consistent with the findings of two of the RCTs included in the study (1, 10).

It is well known that the baseline risk of AMS depends on the rate and mode of ascent, altitude reached, level of prior acclimatization, age and individual susceptibility (11). The trials relating to acetazolamide in the prevention of AMS show that it may be less effective in steep climbing profile settings. Also the dose of acetazolamide remains a subject of debate, and further studies will be needed in this regard (3). In our review, a separate analysis for rate and mode of ascent could not be performed as not all of the included studies clearly mentioned this.

In two of the included studies (Lipman and Gertsch), ibuprofen 600 mg three times daily was used. The total doses of ibuprofen used before the ascent varied among the trials. While Lipman et al. used a single dose of ibuprofen, Gertsch et al. used three different doses of ibuprofen before the ascent. Similarly, in another study by Kayser et al., participants were given calcium carbasalate (380 mg/day equivalent to approximately 300 mg acetylsalicylic acid). This study did not find carbasalate to be effective for the prevention of AMS. However, these results should be viewed with caution as the study lacked sufficient power (n = 31). Our review suggests the possible efficacy of NSAIDs for the prevention of AMS. However, larger studies are needed to establish the validity of these findings. Moreover, optimum dosage and timing of these requires further study. One study has been done with a head-to-head comparison between NSAIDs and acetazolamide, which found similar efficacy of NSAIDs in the prevention of AMS (10). The previous studies relating to the prevention of AMS with acetazolamide and dexamethasone demonstrated that the NNT to prevent one case of AMS with acetazolamide ranges from 3 to 8 (14) and 2 to 4 with dexamethasone (15). In our review, the NNT to prevent AMS was found to be six, which is comparable with that of acetazolamide. Also in our subgroup analysis, ibuprofen was found to have a NNT of five. Hence, we suggest that ibuprofen might be a reasonable alternative for the prevention of AMS. We took into account the standard LLSS for AMS for uniformity. Previous studies with aspirin in the past demonstrated a significant protective effect of aspirin for HAH (16, 17). However, these studies were not included in our analysis since they only looked at headache incidence and not AMS in its entirety. Our review also shows that NSAIDs help in the prevention of headache (using VAS) (1, 10). Since headache is an important feature of AMS, there are concerns that the masking of headache by NSAIDs could potentially make the diagnosis difficult. Future studies are needed to address this potential risk.

There was no significant difference in the endpoint SpO2 or change from baseline between the participants. This is in sharp contrast to the increased resting SpO2 noted with acetazolamide which is attributed to an increase in ventilation and improved oxygenation (11). Therefore, this further supports the hypothesis that NSAIDs act through a different pathway, likely at the cellular level by modulating inflammation rather than increasing the ventilation.

NSAIDs are generally well tolerated. Significant side effects include GI upset and kidney injury, especially in dehydrated patients. A possible serious complication associated with NSAIDs is a risk of GI bleed, which may be significantly increased at high altitudes where the incidence of gastric erosions has been shown to increase. However, all of the studies looking at this potential

complication lacked sufficient power (18, 19). The widely used acetazolamide is not without side-effects such as paresthesia, dizziness, confusion, fatigue, taste disturbance, nausea, vomiting and polyuria. Similarly, dexamethasone is associated with significant side effects such as adrenal suppression. It should be taken until descent if started due to concerns for loss of protective effect and rebound symptoms when withheld abruptly (2, 20).

Our findings need to be interpreted with caution. Small sample size, subjective scoring system and only one study comparing NSAIDs to the proven therapies for prevention of AMS are the most concerning limitations. We also suggest that pharmacological agents should not replace the proven preventive measures such as slow ascent for acclimatization. Finally, one should bear in mind that AMS can still occur in rapidly ascending non-acclimatized climbers with any of the prophylactic agents.

Limitations

Our study has several limitations. Although we included only those studies that clearly defined the diagnosis of AMS by using LLSS, the LLSS scoring system itself is prone to subjective bias. Since headache is one of the five components of LLSS, any drug that may decrease headache can potentially lower the scores thus falsely giving an impression of improved outcomes on VAS. A similar possibility exists with dexamethasone, which may lower LLSS due to its anti-emetic action. Since the endpoints used to measure the efficacy of NSAID like headache have this inherent flaw, better objective measures of outcome would have been helpful.

Similarly, there were differences in the study design of the included trials. Gertsch et al. studied the ascent from around 4,000 to 5,000 m while Lipman et al. studied the ascent from 1,240 to 3,810 m. The other study by Kayser et al. was done in climbers starting at sea level and reaching a final altitude of 3,810 m. Two of these studies (Gerstch and Lipman et al.), that showed the benefits of ibuprofen, constituted approximately 91% of the subjects. The smaller trial by Kayser et al. using carbasalate did not show any benefit. With this systematic review, we attempt to synthesize the role of NSAIDs in the prevention of AMS with the currently available data. Due to the various issues with the studies as outlined above, it is hard to reach a final conclusion at this point. Hence, further well-designed studies in non-acclimatized patients, with broader ranges of altitude needs to be conducted. Some of the smaller trials have shown a superior effect of a combination of acetazolamide and dexamethasone compared to acetazolamide alone (21, 22). However, there have been no trials looking at the effect of NSAIDs and the other proven therapies. Lastly, studies in the future would need to have uniform criteria for the diagnosis of AMS and to quantify its severity.

Conclusion

Our systematic review and meta-analysis suggests that NSAIDs might be a safe and effective alternative for the prevention of AMS. However, further larger population studies will have to be done before recommending it as an alternative to the commonly used acetazolamide or dexamethasone. Also trials comparing NSAIDs to acetazolamide and dexamethasone in the future may provide further data to its relative efficacy.

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Competing interest and funding

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