Sleep Medicine 51 (2018) 105–114

Contents lists available at ScienceDirect

Sleep Medicine

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

Review Article

Pharmacological agents for improving sleep quality at high altitude: a systematic review and meta-analysis of randomized controlled trials

Fanyi Kong [a, *], Guoyi Liu [b], Jingjing Xu [a]

[a] Department of Neurology, Kunming General Hospital of Chengdu Military Command, People's Liberation Army, School of Clinical Medicine, Kunming Medical University, No. 212, Yunnan Province, PR China
[b] Department of Neurology, First Affiliated Hospital of Kunming Medical University, Yunnan Province, PR China

ARTICLE INFO

Article history:
Received 16 November 2017
Received in revised form
13 March 2018
Accepted 2 June 2018

Keywords:
Sleep disorder
Sleep quality
High altitude
Pharmacological treatment
Meta-analysis

ABSTRACT

Several hypnotic agents commonly recommended for improving sleep at sea level are discouraged at high altitude. We aimed to evaluate the efficacy and safety of drugs prescribed for improving sleep quality in patients with acute exposure to high altitudes by conducting a systematic review and meta-analysis. An electronic search was executed for randomized controlled trials comparing drug treatments with placebo and no-treatment conditions, which used objective sleep parameters or subjective sleep quality evaluations. Eight studies (152 participants) were included in the meta-analysis and involved trials using acetazolamide, temazepam, zolpidem, zaleplon, and theophylline. Generally, the nonbenzodiazepines were reported to be superior and safe in improving sleep quality. Participants who were administered zaleplon or zolpidem reported a significant improvement in subjective sleep quality. As measured by polysomnography, both zaleplon and zolpidem improved the total sleep time, sleep efficiency index, and stage 4 sleep duration, whereas they decreased the wake-after-sleep onset without impairing ventilation. In contrast, temazepam was not superior to placebo in terms of quicker onset of sleep and better sleep quality. On the other hand, acetazolamide and theophylline both reduced the sleep efficiency index. The present results favored zaleplon and zolpidem in improving both the objective and subjective quality of sleep without impairing ventilation.

1. Introduction

Every year, thousands of people come from the lowlands to the Qinghai-Tibetan plateau, the highest and largest plateau in the world, for job hunting and sightseeing. Currently, there are hundreds of thousands of non-native people working and living in these areas at altitudes ranging from 4000 to 5072 m. Altitude-related health problems present a major medical risk for non-native workers and tourists. Poor-quality sleep, characterized by poor subjective quality, increased awakenings, frequent arousals, marked nocturnal hypoxemia, and periodic breathing, is a common experience for new arrivals at high altitudes. This condition may progressively worsen due to decreased arterial oxygen desaturation [1], as hypoxemia at high altitudes is most severe during sleep [2]. It has been previously demonstrated that poor sleep adversely affects cognitive abilities [3], whereas increased sleep fragmentation may account for some of the deteriorated daytime performances at high altitude [2]. We previously reported that impaired subjective sleep quality was an independent predictor of decreased intelligence quotient (IQ) and verbal short-term memory at high altitudes [4].

Hypoxemia is one of the primary independent contributors to poor sleep quality at high altitudes [5]. However, clinicians often encounter pharmacological limitations for improving sleep at high altitudes, as current sleeping medications are prescribed for sleep disturbances at sea level. For example, it has been reported that benzodiazepines (BZDs) may cause hypoventilation at high altitudes [6], triggering respiratory abnormalities during sleep [7–9]. However, zolpidem, a non-BZD hypnotic agent, did not affect sleep architecture in healthy participants or in patients with insomnia. Additionally, zolpidem did not deteriorate ventilation or oxygen saturation (SaO_2) in patients with chronic obstructive pulmonary disease [10,11]. Other hypnotic agents, such as eszopiclone and diphenhydramine, have not been studied in patients at high

* Corresponding author. Department of Neurology, Kunming General Hospital of Chengdu Military Command, People's Liberation Army, School of Clinical Medicine, Kunming Medical University, No. 212, Daguan Road, Kunming, 650032, Yunnan Province, PR China. Fax: +86 871 64774607.
E-mail address: kfy9989@hotmail.com (F. Kong).

https://doi.org/10.1016/j.sleep.2018.06.017
1389-9457/

altitudes. In theory, medications for improving sleep quality at high altitudes should not affect sleep architecture or deteriorate ventilation and SaO_2.

Previous findings suggested that only a few medications may be helpful at high altitudes, including theophylline and carbonic anhydrase inhibitors (acetazolamide), which are determined to increase ventilation and oxygenation, effectively reducing periodic breathing. Additional drugs that may be useful include γ-aminobutyric acid (GABA) receptor agents such as zolpidem and zaleplon, temazepam, and the integripetal rhodiola herb, which is a traditional Chinese herb. However, strong clinical evidence supporting the effectiveness and safety of these agents has not been demonstrated. Therefore, we conducted a systematic review and meta-analysis of medications for sleep disorders at high altitudes, to provide evidence-based choices for clinicians to treat new arrivals in high-altitude regions.

2. Methods

2.1. Inclusion criteria for considering studies for this meta-analysis

We adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. The following inclusion criteria were considered: (1) randomized controlled trials (RCTs) studying the efficacy and safety of any agent at high altitude or simulated altitudes above 2500 m; (2) trials including non-native residents or new arrivals of any age and sex to high altitude; (3) trials of drug treatment, including herbs and traditional Chinese medicines, regardless of the dosage, treatment duration, and route of administration; (4) trials including control interventions, namely placebo or no treatment; and (5) trials assessing the study drug (ie, if trials included a combined treatment of the study drug and another agent), and comparisons were made with the other treatment alone.

The exclusion criteria included trials comparing drugs with Chinese herbs or those comparing different herbs, because these studies failed to reach any conclusions regarding the efficacy of Chinese herbs for treatment of sleep disorders.

2.2. Types of outcome measures

The primary outcome measures were: (1) objective sleep parameters, such as the total sleep time (TST), sleep onset latency (SOL), sleep duration, wake after sleep onset (WASO), and sleep efficiency (SE); and (2) ventilation during sleep, as measured by arterial oxygen saturation.

The secondary outcome measures were the subjective sleep quality, including self-reported sleep quality improvement, and the improvement in standardized sleep scales (eg, responses to sleep log questions).

2.3. Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed (1966 to March 2017), EMBASE (1980 to March 2017), Allied and Complementary Medicine Database (AMED, 1985 to March 2017), and sleep bibliography (www.websciences.org/bibliosleep/, 1991–2017) for articles published in English. We also searched Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS), and the China Biological Medicine Database (CBM-disc, 1979 to March 2017) for articles published in Chinese. The following medical subject headings were used for searching relevant papers: 'sleep disorder' OR 'sleep disturbance' OR 'sleep quality' OR 'insomnia' OR 'treatment' OR 'acetazolamide' OR 'temazepam' OR 'zolpidem' OR 'zaleplon' OR 'eszopiclone' OR 'diphenhydramine' OR 'diazepam' OR 'rhodiola' AND 'altitude'. The search strategies are provided in the Appendix. We also searched the reference lists of all relevant papers for further studies and contacted pharmaceutical companies to identify further published and unpublished studies.

2.4. Data collection

Two reviewers independently scanned titles and abstracts retrieved from the initial searches and selected potentially relevant studies for further consideration. The full texts were obtained when the information given in the title or abstract met the pre-stated eligibility criteria. The same two reviewers extracted data from the included trials on the details of patient characteristics, study altitude, sample size, randomization, allocation concealment, blinding, interventions, and outcomes using a data extraction form. The sleep parameters collected as outcomes included TST, SOL, sleep duration, WASO, SE, and arterial oxygen saturation. Subjective sleep quality measures, including self-report of sleep quality improvement, improvement in standardized sleep scales, daytime dysfunction, periodic breathing, and sleep apnea were also collected. Missing data were obtained from the study authors when possible. Disagreements between the reviewers were resolved through discussion or a third party if necessary.

2.5. Assessment of the risk of bias

We assessed the methodological quality of each included trial in terms of selection bias, performance bias, attrition bias, and detection bias. This was accomplished by recording the method of randomization, the generation of allocation sequence, allocation concealment and blinding (both that of participants and investigators), and the number of participants lost to follow-up, according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement (checklist of information, item 3a–11b) [13]. The modified Cochrane Collaboration's tool [14] for quality assessment of RCTs was used to assess the risk of bias.

2.6. Statistical analysis

Data on the continuous outcomes were expressed as weighted mean difference (WMD) when measured on the same scale, and as standardized mean difference (SMD) when different measures of the same outcome were used in different trials. Dichotomous data on outcomes were expressed as risk ratios (RR) with 95% confidence intervals (CI).

Sensitivity analyses were performed by deleting trials with low quality, such as inadequate allocation concealment or unclear randomization method, to evaluate the impact of the study quality on the final results, provided that sufficient data were available. However, no enrolled studies had adequate allocation concealment, and the only two trials that reported the randomization method used the same intervention. Therefore, sensitivity analyses were not performed.

Clinical heterogeneity was assessed by noting differences between trials in regard to sex, duration of the sleep disorder, and altitude. Methodological heterogeneity was evaluated by noting the study design factors, including randomization concealment, blinding, and loss to follow-up. Statistical heterogeneity was assessed by the standard χ^2 test and calculation of the I^2 value. An I^2 value greater than 50% or a χ^2 test at the 0.1 level indicated significant heterogeneity. In case of no significant heterogeneity, we synthesized data in the meta-analysis when the interventions and outcome measures were the same by a fixed-effects model; otherwise, a random-effects approach was used. If data permitted,