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Original Article

Melatonin improves sleep in children with epilepsy: a randomized, double-blind, crossover study

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ABSTRACT

Objective: Insomnia, especially maintenance insomnia, is widely prevalent in epilepsy. Although melatonin is commonly used, limited data address its efficacy. We performed a randomized, double-blind, placebo-controlled, crossover study to identify the effects of melatonin on sleep and seizure control in children with epilepsy.

Methods: Eleven prepubertal, developmentally normal children aged 6–11 years with epilepsy were randomized by a software algorithm to receive placebo or a 9-mg sustained release (SR) melatonin formulation for four weeks, followed by a one-week washout and a four-week crossover condition. The pharmacy performed blinding; patients, parents, and study staff other than a statistician were blinded. The primary outcomes were sleep onset latency and wakefulness after sleep onset (WASO) measured on polysomnography. The secondary outcomes included seizure frequency, epileptiform spike density per hour of sleep on electroencephalogram (EEG), and reaction time (RT) measures on psychomotor vigilance task (PVT). Statistical tests appropriate for crossover designs were used for the analysis.

Results: Data were analyzed from 10 subjects who completed the study. Melatonin decreased sleep latency (mean difference, MD, of 11.4 min and $p = 0.02$) and WASO (MD of 22 min and $p = 0.04$) as compared to placebo. No worsening of spike density or seizure frequency was seen. Additionally, slow-wave sleep duration and rapid eye movement (REM) latency were increased with melatonin and REM sleep duration was decreased. These changes were statistically significant. Worsening of headache was noted in one subject with migraine on melatonin.

Conclusion: SR melatonin resulted in statistically significant decreases in sleep latency and WASO. No clear effects on seizures were observed, but the study was too small to allow any conclusions to be drawn in this regard.

1. Introduction

Epilepsy affects 1% of the population in the United States [1]. Sleep-related comorbidities are considerably higher in children with epilepsy than in unrelated healthy controls [2] and in patients with nocturnal seizures and refractory epilepsy [3]. In adults with epilepsy, 55% have insomnia [4] and 34% have sleep-onset insomnia, whereas 52% have maintenance insomnia [5].

Melatonin is considered in the treatment of circadian rhythm disorders, jet-lag disorders, and shift-work sleep disorders. However, it has been widely used as a hypnotic agent in children with neurological disorders, including patients with epilepsy [6]. There is evidence that patients with epilepsy, especially refractory epilepsy, have reduced melatonin levels [7–9]. However, it is not clear whether exogenous melatonin improves sleep in children with epilepsy or affects seizure control or daytime functioning.

We performed this study to fill this literature gap, using a sustained release (SR) melatonin formulation because of concerns not only about sleep onset but also sleep maintenance insomnia in this population.

Abbreviations: WASO, Wakefulness after sleep onset; MD, Mean difference; SR, Sustained release; AEDs, Antiepileptic drugs; SBQ, Sleep behavior questionnaire; PLM, Periodic limb movement; EEG, Electroencephalogram; SL, Sleep onset latency; AASM, American Academy of Sleep Medicine; SE, Sleep efficiency; PVT, Psychomotor vigilance task; RTs, Reaction times; BASC-PRS, Behavior Assessment System for Children – Parent Rating Scales; QOLCE, Quality of Life in Childhood Epilepsy; SD, Standard deviation; AHI, Apnea–hypopnea index; OI, Obstructive index; PLMI, Periodic limb movement index.

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2. Methods

Our primary research question was "Does melatonin shorten sleep onset latency (SL) and reduce wakefulness after sleep onset (WASO) in children with epilepsy as compared to placebo?"

This study was approved by the institutional review board (IRB) at the Cincinnati Children's Hospital Medical Center (CCHMC). Written informed consent was obtained for all subjects from parents or legal guardians and assent from subjects who were 11 years old. The study was registered with ClinicalTrials.gov (NCT00965575).

2.1. Trial design

This was a randomized, double-blind, placebo-controlled, cross-over study using SR melatonin at a 9-mg dose. There are limited data for the use of melatonin in children with epilepsy. In pediatric clinical practice, doses as high as 18 mg have been used [10]. We selected a 9-mg dose, as doses of 9–10 mg have been used safely and effectively, and are well tolerated in children with epilepsy in other studies [11–13]. As this study assessed the hypnotic effects of melatonin, the dose was given 30 min prior to bedtime. Antiepileptic drugs (AEDs) were maintained at stable doses throughout the study. Adverse events were determined at each in-person/phone-call visit and were recorded in the subject's chart. Our study was originally designed to allow enrollment of subjects with refractory epilepsy, but this proved difficult due to inability to maintain their AEDs at stable dosages, as well as the common presence of cognitive, psychiatric, or developmental comorbidities, which were considered as enrollment exclusions. Hence, it was difficult to find and recruit subjects for this reason. Furthermore, due to three overnight sleep studies, most parents preferred the study being completed during summer vacations, which also caused a delay in recruitment.

Study participant disposition is summarized in Fig. 1. The study design is shown in Fig. 2. After baseline testing and eligibility determination, subjects were randomized to receive placebo or melatonin for four weeks. After one week of washout, the subjects who were initially placed on placebo received melatonin for

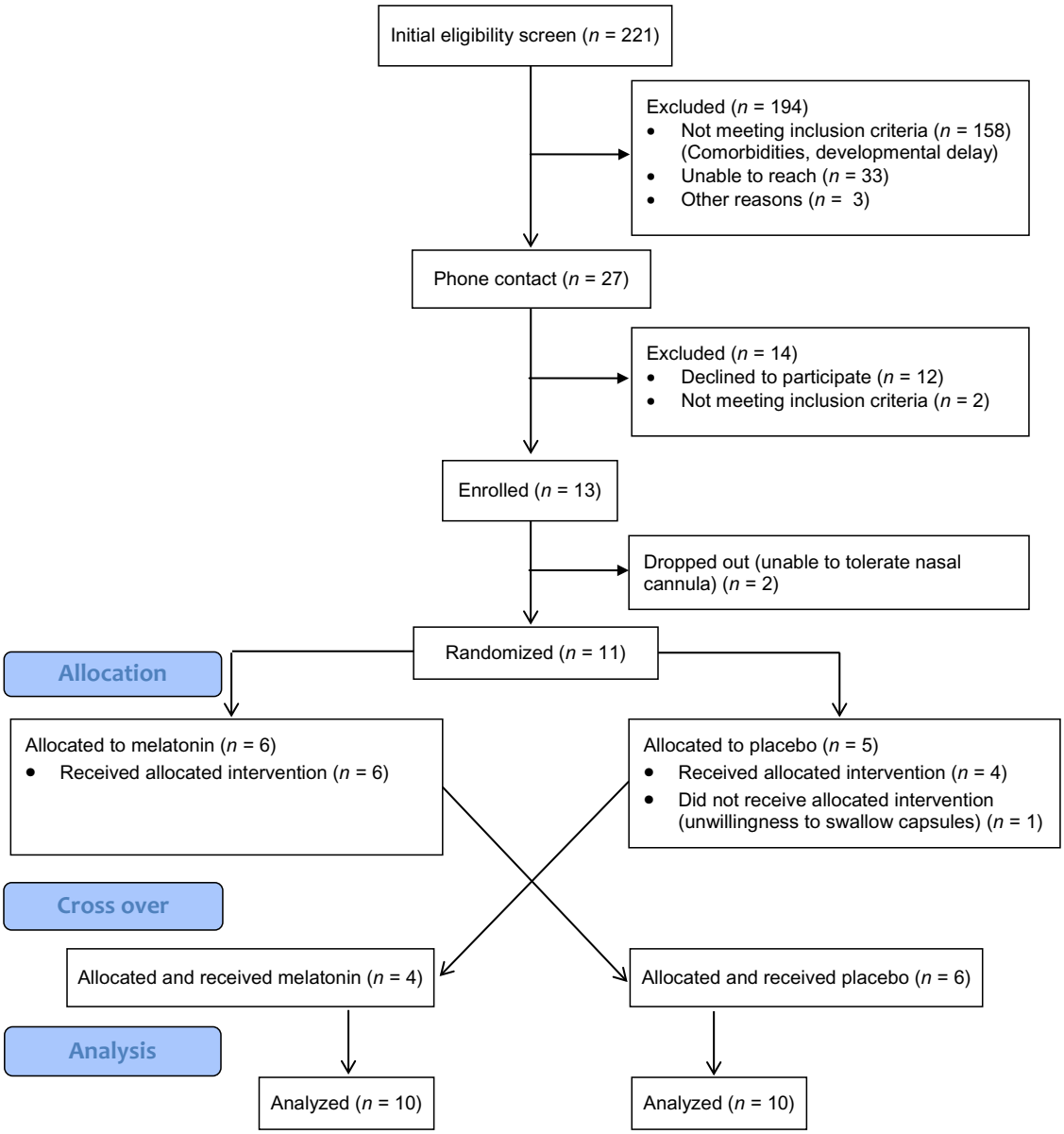

Fig. 1. CONSORT diagram.