Letters

RESEARCH LETTER

Home-Based Trials in Adolescent Migraine: A Randomized Clinical Trial

Randomized trials are needed to identify safe and effective migraine preventive treatments for children. Conventional trials typically require frequent in-person study visits.[1] Many families decline study participation, citing time and distance.[2] Home-based trials are a novel, participant-centered design innovation wherein most or all study procedures are completed remotely using technology.

Melatonin is safe and effective for migraine prevention in adults.[3] In this pilot study, we assessed the feasibility of a home-based trial of melatonin for adolescent migraine prevention.

Methods | We conducted a randomized, double-blind, placebo-controlled pilot study of melatonin, 3 mg (Rugby Laboratories), vs placebo for migraine prevention in children aged 12 to 17 years. Participants were recruited via our clinic, flyers, social media, print advertisements, and parent letters (**Table 1**). Screening occurred on our study website; eligible participants were invited for a 1-time study center enrollment visit. Diagnosis of migraine by International Classification of Headache Disorders, 3rd edition (beta version) criteria[4] was confirmed by a pediatric headache neurologist. Remaining study procedures were conducted from home. The institutional review board of the University of California, San Francisco approved this study (clinicaltrials.gov identifier: NCT02344316). Parents provided written informed consent and adolescents provided assent.

Participants received a nightly text message on their smartphone that linked to a secure web-based electronic headache diary. Study staff monitored diary compliance and provided reminders. After a 28-day baseline, those with 80% or greater diary compliance and the requisite number of headaches were randomized to melatonin or placebo for 12 weeks. Study medication was shipped to homes. Participants recorded sleep using Fitbits (Fitbit Inc). Sleep data synced to participants' smartphones or computers and automatically transferred to the study database via application program interface calls. Adverse events were assessed via telephone twice monthly. The enrollment goal was 30 participants.

The aims of this study were to (1) determine the success vs cost of various recruitment strategies, (2) demonstrate enrollment feasibility, (3) estimate study completion rate, (4) estimate variance in headache outcomes using home-trial methodology, and (5) assess adverse events. Mann-Whitney, χ^2, and Fisher exact tests as well as multivariable linear regression were used.

Results | *Feasibility*. Initially, adolescents with 6 to 14 migraine/migrainous days per month not taking prevention therapy were eligible. However, after 4 months, only 17 of 128 participants (13.3%) passed screening and only 10 enrolled. The main reasons for screen failure were (1) too many (n = 51) or too few (n = 38) headaches and/or (2) taking prevention therapy (n = 48). We broadened inclusion criteria to allow participants with stable prevention and 2 to 24 migraine days per month. We also increased social media advertisements. Thereafter, 20 additional participants enrolled in 7 weeks. A 31st enrolled entirely remotely using telemedicine as a proof of principle. Twenty-six fulfilled randomization criteria; 5 had too few migraine/migrainous days to randomize.

Table 1. Participant Recruitment and Costs

Characteristic	Participants Recruited, No. (%) (n = 31)	Estimated Cost per Enrolled Participant, US$
Clinic recruitment	6 (19)	NA
Newspaper advertising	3 (10)	250
Social media advertising (eg, Facebook and Google+)	11 (35)	155
Electronic medical record letter invitation	10 (32)	155
Other	1 (3)	NA

Abbreviation: NA, not applicable.

Melatonin. Baseline characteristics were similar between groups, except the Pediatric Migraine Disability Assessment score (headache-related disability) was higher in the melatonin group. Outcome data were available for 23 of 26 participants (89%). Mean migraine days was lower in the melatonin group vs the placebo group in the final 4 weeks of treatment (the primary outcome measure) but was not statistically significant (mean [SE] days, 3.6 [0.9] vs 4.9 [1.7]; difference, −1.3; 95% CI for difference, −5.1 to 2.6). Adjusted mean (SE) days with migraine was 3.1 (1.3) in the melatonin group and 5.4 (1.4) in the placebo group (difference, −2.3; 95% CI for difference, −6.3 to 1.8). Sleep outcomes did not differ. There were no serious adverse events (**Table 2**). Three participants withdrew (2 from placebo group and 1 from melatonin group).

Discussion | This pilot study demonstrates the feasibility of home-based trials for adolescent migraine. With optimized inclusion criteria and social media recruiting, we exceeded our enrollment goal. Web-based electronic headache diaries and physiologic data from a wearable device proved feasible for collecting data and allowed for timely data collection and compliance monitoring. The study completion rate was excellent (89%).

There were no serious adverse events. Migraine days in the final 4 weeks were lower in the melatonin group compared with the placebo group, which could be due to chance. A fully powered study is merited. Based on the observed variance, we

Table 2. Adverse Events in Melatonin Group vs Placebo Group

Adverse Event	No. (%)	
	Melatonin, 3 mg (n = 13)	Placebo (n = 13)
Episode of fever	0	1 (8)
Accident	0	3 (23)[a]
Daytime tiredness	2 (15)[b]	0
Unscheduled medical visit for migraine	2 (15)	0
Low iron on blood work	1 (8)	0
Episode of vomiting	1 (8)	0

[a] One participant was kicked in the ribs, 1 kicked in the testicle, and 1 was a passenger in a motor vehicle collision.

[b] One participant chose to discontinue the study drug but continued to provide headache data and was included in the intent-to-treat analysis; the other had tiredness just for 1 day and continued taking the study drug.

would need 75 participants per arm to detect a difference of 2.3 migraine days per month.

Conclusions | Home-based trials can accelerate neurological therapeutic development and may be preferable for certain patient populations.

Amy A. Gelfand, MD, MAS
William Qubty, MD
Irene Patniyot, MD
Barbara Grimes, PhD
Mark J. Pletcher, MD, MPH
Peter J. Goadsby, MD, PhD
Steven R. Cummings, MD

Author Affiliations: Pediatric Headache Program, Department of Neurology, University of California, San Francisco (Gelfand, Qubty, Patniyot, Goadsby); Department of Epidemiology and Biostatistics, University of California, San Francisco (Grimes, Pletcher, Cummings); Department of Medicine, University of California, San Francisco (Pletcher, Cummings); National Institute of Health Research-Wellcome Trust Clinical Research Facility, King's College London, United Kingdom (Goadsby); San Francisco Coordinating Center, California Pacific Medical Center Research Institute, University of California, San Francisco (Cummings).

Corresponding Author: Amy A. Gelfand, MD, MAS, Pediatric Headache Program, Department of Neurology, University of California, San Francisco, Mission Hall Box 0137, 550 16th St, 4th Floor, San Francisco, CA 94158 (amy.gelfand@ucsf.edu).

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Study concept and design: Gelfand, Pletcher, Goadsby, Cummings.
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Drafting of the manuscript: Gelfand, Grimes, Goadsby.
Critical revision of the manuscript for important intellectual content: Gelfand, Qubty, Patniyot, Pletcher, Cummings.
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Supervision: Gelfand, Pletcher, Goadsby.

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