



Brief Report

Postdischarge secobarbital after ED migraine treatment decreases pain and improves resolution^{☆,☆☆}

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Abstract

Objective: The objective of the study was to determine whether the addition of postdischarge oral secobarbital to standard emergency department (ED) migraine headache therapy improves pain relief and headache resolution compared with placebo.

Setting: The setting is an urban ED with 70 000 yearly visits.

Methods: This is an Institutional Review Board–approved, randomized, nonconsecutive, double-blinded, concealed, and placebo-controlled clinical trial. Patients with a clinical diagnosis of migraine underwent standard ED treatment and were discharged with 2 tablets of either secobarbital 100 mg or placebo. At home arrival, subjects recorded headache pain on a visual analog scale (VAS), took 1 tablet, and went to bed, taking the second tablet after 1 hour if not asleep. Upon awakening, subjects completed a second VAS and survey.

Statistical analysis: The VAS data were analyzed using 2-tailed *t* test with unequal variance. Headache resolution data were analyzed using Fisher exact test.

Results: Fifty subjects were enrolled. Complete data and follow-up were available for 30 subjects (60%). Fourteen subjects received placebo; 16 received secobarbital. Secobarbital subjects reported an average headache pain decrease of 25 mm (−13 to −38) compared with an average increase of 3 mm (−13 to 19) in the placebo group (*P* = .01). Ninety-four percent of the secobarbital group vs 50% of the placebo group had complete or partial headache resolution (*P* < .02). All subjects in the secobarbital group reported some relief.

Conclusions: Addition of postdischarge oral secobarbital to a standard ED migraine treatment regimen decreased headache pain at 24 hours after discharge and improved the rate of headache resolution compared with placebo.

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1. Introduction

Migraine and related primary headache syndromes are a common cause of emergency department (ED) presentation, accounting for more than 3% of visits annually [1]. Although etiology is still debated, migraine onset has been linked to stress, fatigue, and decreased sleep quality in the night

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preceding the attack [2]. A recent investigation reported sleep disturbances as migraine triggers in 50% of subjects [3]. In this study, sleep also proved to be an important palliative factor, as 85% of the subjects chose to sleep or rest because of headache and 75% were forced to sleep or rest because of headache. Although currently approved therapeutic agents for migraine include 5HT-1 agonists (eg, sumatriptan, zolmitriptan) and the ergot alkaloids, a 2003 study of primary headache in the ED (95% of which met International Headache Society [IHS] diagnostic criteria for migraine) noted that only 7% of patients were treated with such migraine-specific medications [4]. Most of the subjects were treated with a "migraine cocktail" consisting of antiemetics with or without nonsteroidal anti-inflammatory drugs or opiate analgesics. All of the subjects reported requiring sleep or rest and were unable to return to normal function. In addition, the investigators reported that 60% of the subjects continued to have headache 24 hours after ED discharge.

Although sleep induction is recognized clinically as a treatment of migraine headaches, supporting evidence has been scant [5]. Barbiturate agents, although prescribed less often than in the past, possess sedative and sleep-inducing properties and are generally safe at low doses and for short durations. We conducted a study to determine whether subjects receiving ED treatment of presumptive migraine headache experienced greater pain relief and perceived headache resolution when treated with postdischarge oral secobarbital vs placebo.

2. Methods

The study used a prospective, double-blinded, randomized, placebo-controlled, and concealed design. Because of resource constraints, the study was conducted using a nonconsecutive convenience sample of patients presenting for treatment of presumptive migraine. We compared the effect of postdischarge secobarbital vs placebo to decrease pain associated with migraine. The trial was conducted from January 2002 to April 2003 at the ED of an urban level-I trauma center with an annual census in excess of 40 000 patients. Our institutional review board reviewed and approved the study.

2.1. Patients

Eligible subjects were male and nonpregnant female patients aged 18 to 65 years who presented with headache that treating physicians considered consistent with an established prior history of migraine, or whose ED evaluation excluded other etiologies, and who met IHS classification for migraine with or without aura [6]. Commonly, these signs and symptoms included history of recurrent attacks, duration of 4 to 72 hours, possessing at least 2 of the following

characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, aggravated by routine physical activity (eg, walking or climbing stairs); and accompanied by 2 or more of the following: nausea, vomiting, photophobia, phonophobia, or osmophobia.

Exclusion criteria were secondary headache syndromes; initial systolic blood pressure greater than or 160 mm Hg or diastolic blood pressure greater than 100 mm Hg; allergy or hypersensitivity to secobarbital; history of hepatitis, cirrhosis, or other liver diseases; use of alcohol within 12 hours of ED presentation; use of anticoagulants; requirement for hospitalization; or retrospectively, any subject who withdrew or for whom a completed data set was unavailable. Written informed consent was obtained, and an individual data sheet was prepared during ED treatment and completed after the final disposition. Missing data points were sought retrospectively in medical records. After further headache history and physical examination, subjects underwent standard treatment at physician discretion, which generally included intravenous fluids, antiemetics, ketorolac, and opiate rescue therapy as required, with the goal of reducing headache by 50% during the ED course. As a matter of local preference, 5HT-1 agonist medications were not routinely used in the ED where the study was conducted. After completion of treatment, the investigator completed a data sheet; and the ED phase of the study was terminated. At that time, each subject received a follow-up data sheet with self-addressed stamped envelope for return within 72 hours of discharge. Upon home arrival, each subject was instructed to open the packet and mark the "arrival at home" visual analog scale (VAS) on data sheet 2, take 1 tablet from the study vial (containing either 2 secobarbital 100-mg tablets or placebo), and attempt to sleep. They were instructed to take the second tablet if they were still awake 1 hour after the initial dose and attempt to sleep again. Regardless of effect, they were instructed to complete the "pain level at 18-24 hours after home medication" VAS on data sheet 2 and to complete the remainder of the questions on the survey sheet. Lastly, they were instructed to return the VASs and questionnaires to the investigators in the addressed stamped envelope that was provided. At a time interval between 36 and 48 hours after discharge, the investigators attempted to contact each subject by telephone to confirm their condition, answer questions, and remind them to return the questionnaire and VAS documents. If necessary, the investigators placed a second call at 5 days if the questionnaire and scales were not received by that time. The study was then terminated for the respective subject.

2.2. Randomization

At ED discharge, the patients were randomly assigned to receive either two 100-mg secobarbital tablets or 2 placebo tablets. Secobarbital and placebo tablets were formulated to appear identical. Randomization was performed using a standard random number generation table.

Table 1 Demographics of study subjects

	Secobarbital	Placebo
n	16	14
Age (95% CI)	45 (40-50)	44 (37-50)
Sex (female)	94%	100%
Took 1 tablet	54%	18%
Took 2 tablets	46%	82%
Age at migraine onset (95% CI)	21 (16-27)	26 (20-32)
Age diagnosed by physician	25 (20-31)	27 (23-32)
Migraines per month	6 (0-11)	4 (2-7)
Medications used in ED		
Triptans	0	0
Phenothiazines	16	14
Ketorolac	7	8
Opiates	7	8

2.3. Outcome measures

The primary outcome measure was change in perceived headache pain, compared between secobarbital and placebo groups, as measured via 100-mm nonhatched and zero-anchored VAS. A *significant decrease in pain* was defined as greater than 12 mm between the postdischarge pre- and posttreatment VAS. Both the VAS metric and the magnitude of posttreatment analgesic effect have been validated previously [7]. The secondary outcome measure was the difference in self-reported headache resolution rate (complete, partial, or none) between the secobarbital and placebo groups.

2.4. Statistical analysis

Comparative continuous data between treatment and control groups was analyzed by 2-tailed *t* test assuming unequal variance. An initial goal of 140 subjects with completed data was set to detect a mean difference in pain perception of 12 mm on the VAS between the

treatment and control groups, with an anticipated standard deviation of 25 mm per group, an α error of .05, and a power of 80%.

3. Results

No adverse events were reported by any subjects, with the exception of sedation. During the study period, 50 eligible patients were identified and enrolled. All but one had a prior history of migraine headache. Six were excluded because of misplaced consent documentation; 14 others failed to return their surveys despite callback. Thirty patients completed the treatment protocol and returned their data sheets, yielding a 60% return rate. The study was interrupted prematurely because of nonavailability of secobarbital through our facility's pharmacy. An interim analysis was conducted; and after discovery of statistically significant results, the investigators terminated the study to report results.

Among the subjects, 14 received placebo and 16 received secobarbital. Demographic comparison of the control and experimental groups yielded no significant differences (Table 1). The average change in reported headache pain for the placebo group was an increase of 3 mm (95% confidence interval [CI], -13 to 19 mm) at 24 hours after ED discharge. In the secobarbital group, the average change in reported headache pain was a decrease of 25 mm (95% CI, -13 to -38 mm), with all of these subjects reporting some improvement at 24 hours after ED discharge. These results are depicted in Fig. 1.

Of the 16 secobarbital subjects, 15 self-reported partial or complete headache resolution (94%; 95% CI, 81%-100%), compared with 7 of the 14 placebo subjects (50%; 95% CI, 24%-76%), yielding an odds ratio for headache resolution of 15 (95% CI, 1.9-108; Fisher exact $P = .012$). This translated into a number needed to treat of 2.3 subjects treated with secobarbital to affect one additional partial or complete headache resolution. These results are depicted in Fig. 2.

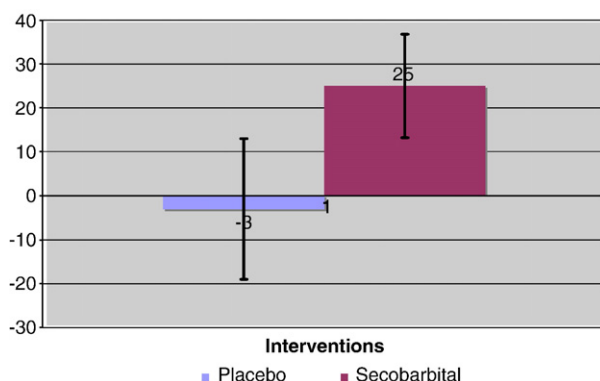


Fig. 1 Average change in headache severity with treatment measured from pre-/postintervention 100-mm VASs.

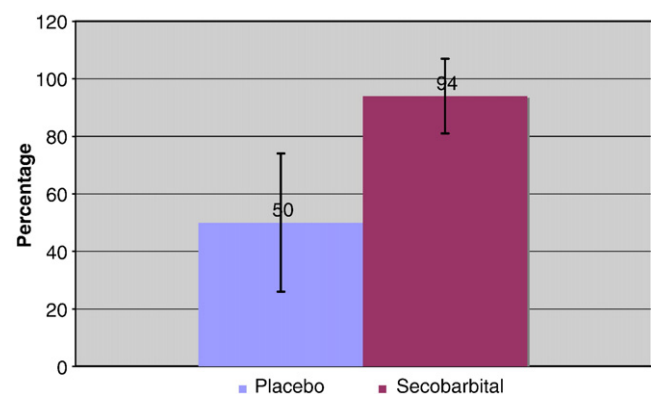


Fig. 2 Proportion of complete or partial resolution.

4. Discussion

Both quality and quantity of sleep may impact headache in the migraineur. In our study, the addition of post-discharge secobarbital decreased headache pain reported at 24 hours after ED discharge and improved self-reported rates of headache resolution. We surmise that improvement in outcome for our experimental group was likely attributable to the pharmacologic effect of secobarbital, most notably an improvement in the depth and possibly duration of sleep.

Secobarbital is a barbiturate hypnotic agent. It lost favor due largely to its narrow therapeutic index, addiction potential, and deleterious interaction with ethanol [8]. Counterbalancing these disadvantages, secobarbital remains as one of the more efficacious agents for the induction of deep sleep states for relatively long durations, particularly when compared with other more common hypnotic agents such as zolpidem or temazepam. It is noteworthy that we encountered no adverse events in our study sample, suggesting that secobarbital is likely to be both efficacious as well as safe when used in similar dosages to those used in this study and if only prescribed for occasional use.

The management of headache requires a multifactorial approach. End points for adequate pain relief on ED discharge, along with anticipated headache resolution, are often moving targets. Therapeutic agents used commonly in the ED setting are often inadequate to provide sustained relief after discharge [4]. Reported rebound or recurrence rates include 34% to 53% for sumatriptan [9-11], 10% for dexamethasone [12], and rates ranging from 11% to greater than 60% for antiemetics, nonsteroidal anti-inflammatory drugs, and opiates [13]. The results of this study compare favorably: after initial ED treatment and discharge, less than 7% of subjects treated with secobarbital reported rebound vs 50% of those receiving placebo.

5. Limitations

Because of human resources constraints, we were forced to enroll subjects as a convenience sample, exposing the study to the risk of selection bias. Not standardizing the definition of migraine headache beyond the patient's report and International Classification of Headache Disorders Version 2 (ICHD-2) criteria allowed for the entry into the study of patients with perhaps varied etiologies for their headache.

Although we encouraged clinicians to use a common pathway for pharmacologic management of enrolled subjects, we chose not to use a single ED treatment algorithm for migraine because of concern that such rigidity may preclude physician or patient.

Although neither weight-based nor approaching the maximum safe adult dosage, we chose 100 to 200 mg as

our study dosage both to avoid potential intoxication and for ease of packaging because our institution's available secobarbital strength was 100 mg.

Our study did not enroll a sample size sufficient for valid subgroup analysis. It is possible that a particular ED intervention or group characteristic accounted for the different results in the 2 groups, and we were unable to elucidate that variable because of lack of power. We were also unable to determine if particular patient populations (ie, those with "true" migraine headaches by strict ICHD-2 criteria or those who ultimately possessed tension, cluster, or mixed headaches) might have had more or less benefit from our intervention.

Despite thorough attempts at obtaining complete follow-up, our postdischarge survey loss of 40% possesses a significant risk for recall bias. We believe that the similar respective sample sizes for secobarbital and placebo groups (16 in the secobarbital group, 14 in the placebo group), along with comparable demographic and epidemiologic rates (Table 1), may offer some mitigation.

6. Conclusion

We report the results of a randomized, double-blinded, placebo-controlled clinical trial comparing secobarbital to placebo for postdischarge treatment of migraine headache in subjects receiving initial treatment in the ED. We detected significant decreases in self-reported headache pain, as well as a nearly 2-fold improvement in the rate of headache resolution in the secobarbital group. We conclude that postdischarge hypnotic therapy for migraine patients treated in the ED is warranted and should be considered as a viable treatment adjunct in these patients. Future investigation of the relative efficacy of other commonly available hypnotic agents in this setting is warranted.

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