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Gelstat Migraine® (sublingually administered feverfew and ginger compound) for acute treatment of migraine when administered during the mild pain phase

PI

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Treatment of migraine headaches is often delayed due to assessing the potential severity of an evolving headache or anticipating unwanted consequences from prescription medication. Studies have demonstrated improved pain-free response when prescription treatments are taken during the mild headache phase of a migraine. This study was designed to evaluate the efficacy of an OTC product, GelStat Migraine®, when taken in the early, mild pain phase of migraine.

Material/Methods: An open-label study enrolling 30 subjects, male and female, with a one-year history of migraine meeting IHS diagnostic criteria with or without aura, 2-8 migraines per month and ≤15 headache days per month. Inclusion required having migraines that consistently started at mild and worsened to moderate or severe, if untreated, in at least 75% of attacks. Subjects also had to be able to distinguish migraine from non-migraine headaches and reliably identify migraine early in the course of an attack. One headache was treated in the mild pain phase with GelStat Migraine®, a combination of feverfew and ginger.

Results: 29 evaluable subjects completed the study, all treating at mild pain. Two hours after treatment, 48% were pain-free with 34% reporting a headache of only mild severity. 29% reported a recurrence within 24 hours. Side effects were minimal and not serious. 59% of subjects were satisfied with Gelstat Migraine® therapy and 41% preferred GelStat Migraine® or felt it was equal to their pre-study medication.

Conclusion: GelStat Migraine® is effective as a first line abortive treatment for migraine when initiated early during the mild headache phase.

key words: **Migraine • herbal migraine treatment • GelStat Migraine® • OTC**

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BACKGROUND

Migraine is a recurrent episodic disorder characterized by headache associated with other symptoms such as nausea, sensory sensitivity, muscle pain, and cognitive disruption. The functional impact of attacks can range from requiring bed rest to creating minimal interference with daily function. This variability in functional impairment can be observed in the attack patterns of different migraine sufferers as well as from attack to attack within the same sufferer. As a consequence, migraine sufferers frequently delay therapy in an effort to more adequately assess their therapeutic need [1]. Two-thirds of migraine sufferers (in a large survey of 1160 subjects) reported delaying or avoiding taking prescription medication because of concerns about adverse effects [2]. This "wait and see" approach can prolong the duration of symptoms associated with an individual attack, increase attack-related disability and diminish the efficacy of abortive pharmaceutical interventions. Recent advances in drug therapy and interventional strategies have significantly improved the treatment outcomes for acute episodes of high impact migraine. However, despite the availability of prescription medications designed specifically to treat migraine, there is a consistent preference among migraine sufferers to treat with OTC (over-the-counter) medications: 57% of migraine headache sufferers report using only OTC medications for treatment, virtually unchanged from 10 years earlier (59%) [3]. In addition, the quantities of abortive therapies available to patients with migraine are often restricted resulting in many migraine sufferers being selective in the use of prescribed migraine abortive medications. In pragmatic terms, many migraine sufferers utilize multiple medications, both OTC and prescription, selecting one form or another depending on the severity of the attack or even in combination during the same attack. Frequently, if a migraine attack builds slowly, patients may begin therapy with a more available OTC product and use their prescribed medication if their initial intervention is unsuccessful. However, relatively little research has been conducted to ascertain the success or value of utilizing an OTC product in conjunction with a prescription product used as rescue.

Several clinical investigations have been undertaken to determine the efficacy of OTC products as a first line intervention for attacks of migraine [4,5]. However, these studies have generally pre-selected subjects with histories of less severe migraine and have not necessarily addressed the efficacy of OTC products in populations of migraine sufferers most likely to be seeking medical care. In addition, these studies treated migraine attacks when the headache was moderate to severe and may not provide data indicative of newer treatment strategies. Studies of several triptan drugs have demonstrated improved pain-free efficacy when these drugs are taken during the mild headache phase in attacks that are likely to evolve into moderate to severe headaches [6–8]. This treatment paradigm has been called "early intervention" though it is more technically correct to consider early intervention as treating when the migraine pain is still mild. Multiple studies with triptan medications have demonstrated improved pain-free efficacy [6–8]. In addition, some studies suggest lower recurrence rates when triptans are utilized during the mild pain phase of a migraine attack rather than during the moderate to severe headache phase [6,9].

Recent surveys suggest that the early intervention treatment strategy, while demonstrating significantly improved efficacy with triptan medications, is not widely utilized by migraine sufferers [1]. Rationale given by patients for delaying pharmacological intervention is that they wanted to see if the headache was "really a migraine" and if an individual attack was severe enough to warrant treatment with prescription medication. This desire to avoid, whenever possible, the use of the prescription medication may relate to both the occurrence of undesired side effects and the limited number of prescription treatments available in any given time period. Paradoxically, if effective treatment is delayed, this therapeutic response to migraine treatment medication is often diminished.

Patients, however, may realize that not all attacks of migraine necessarily require high end abortive therapy and often communicate that non-prescription treatments, taken early in the evolution of a migraine attack, can be effective in terminating the attack. To date few studies have been undertaken to ascertain the efficacy of non-triptans used in the early intervention paradigm. This report is of an open-label study using GelStat Migraine®, a combination of feverfew and ginger, as initial intervention during the mild pain phase in a population of migraine sufferers with histories of moderate to severe migraine attacks. Any previous uses of the ingredients of the product under study have been conducted with much higher doses than those employed here: therefore, no correlation has been addressed.

MATERIAL AND METHODS

This open-label study, approved by a central institutional review board, was conducted at a single headache specialty clinic. Thirty subjects, male and female, at least 18 years of age with at least a one year headache history meeting International Headache Society (IHS) diagnostic criteria for migraine without or with aura (IHS 1.1 or 1.2) were eligible for enrollment. Inclusion required 2–8 migraines per month with no more than 15 headache days per month. Subjects with a history of basilar, ophthalmoplegic or hemiplegic migraines were excluded as well as history of headaches secondary to head trauma. Subjects were required to have migraines that consistently started at mild and worsened to moderate or severe (if untreated) in at least 75% of attacks. They also had to be able to distinguish migraine from non-migraine headaches and reliably identify migraine early in the course of an attack.

All concomitant medications could be continued if the dosage of the medication was stable and did not change during the study period. Exclusion criteria in the study included current use of feverfew as migraine prophylaxis, hypersensitivity or allergy to any of the ingredients in the study medication or a recent history of alcohol or drug abuse. Any subjects with a history or evidence of intrinsic coagulation defects, bleeding diseases or current use of anticoagulant therapy were also excluded. Women who were pregnant, breastfeeding or at risk of pregnancy were not allowed to participate and females of childbearing potential were required to use a reliable method of birth control during the study period.

Informed consent was signed by all subjects before screening that included a complete history and physical exami-

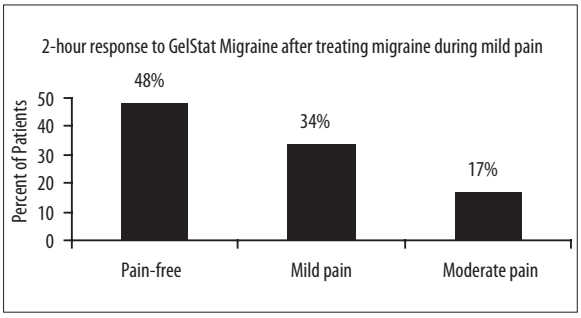

Figure 1. Pain response at 2 hours following treatment with GelStat Migraine®.

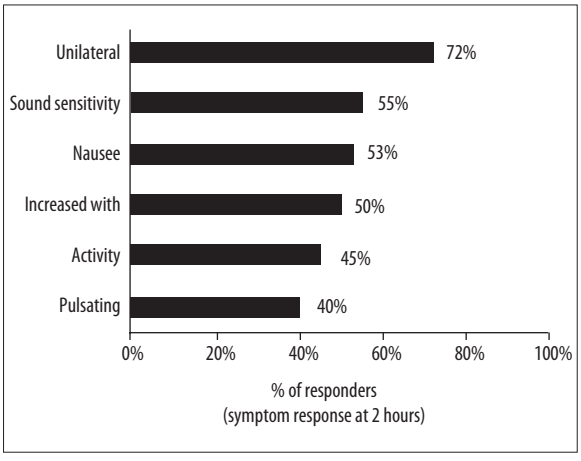

Figure 2. Symptom eesponse at 2 hours.

nation. Completion of a Satisfaction with Medication questionnaire documented subjects' opinion of their current headache therapies. Subjects were instructed to treat one headache at onset, when the pain severity was mild, with GelStat Migraine®, a combination of feverfew and ginger, prepared in a single-use, disposable plastic applicator. The initial treatment consisted of two 2 ml doses of medication, each dose administered sublingually 5 minutes apart, each held for 60 seconds before swallowing. A second treatment (2 additional doses administered in the same manner) could be used between 60 minutes and 24 hours for persistent or recurrent migraine pain. Subjects were allowed to take their usual migraine therapy 2 hours after the initial dose of study medication if additional rescue medication was needed. Time of onset of headache, characteristics, associated symptoms, time of treatment, time of meaningful relief and response to treatment at 30, 60, 90, 120 minutes and 24 hours was recorded in a paper diary. Recurrence of migraine pain, severity and use of a second treatment of study medication or other rescue treatment was also recorded.

Subjects returned to the clinic following treatment of one headache for discussion of their response to treatment, diary review and evaluation of any reported adverse events. The Satisfaction with Medication questionnaire (completed at screening and exit visits) was "how effective was the medication in relieving your migraine pain and other migraine symptoms?" The choice of answers consisted of "very satisfied, satisfied, neutral, dissatisfied and very dissatisfied." The Treatment Preference questionnaire completed at the end of the study allowed the subjects to select either a preference of "medication used to treat migraine before study, medication used during the study (GelStat Migraine®) or no preference."

The data collected: Pain severity and associated symptoms pre-treatment and at 30, 60, 90, 120 minutes and 24 hours after study drug, doses of study drug, rescue medications, adverse effects, pre-study medication, and response to Satisfaction and Preference questionnaires. Results were calculated from data entered on an Excel spreadsheet. Responses were tallied and percentages determined.

RESULTS

Thirty subjects, 24 females and 6 males, were enrolled in the study. Thirty completed the study; however, one male was excluded from the data analysis due to treatment of a severe headache that resulted in a protocol violation. The age range of the 29 subjects was 21 to 65 with an average age of 42. At baseline, twenty-two subjects fulfilled IHS diagnostic criteria for migraine without aura (IHS 1.1) and 7 met criteria for migraine with aura (IHS 1.2).

All 29 subjects treated a migraine in the mild headache phase with GelStat Migraine® 17/29 (59%) reported additional associated symptoms (nausea, light or sound sensitivity) at the time of initiating treatment. The length of time between onset of pain and dosing with study medication varied from treatment at onset to11 hours following onset with a median dosing time of 20 minutes after onset of pain. Reasons for delaying treatment included "wanted to make sure it was a migraine" or "hoped it would go away" and a lengthy aura-like symptom without significant pain.

21/29 (72%) subjects took a second treatment of medication (two 2ml doses) after one hour, 2/21 were pain-free but still took the additional dose because they were experiencing associated symptoms. 13/29 (45%) subjects took additional rescue medication within the 24 hour period.

Two hours after initial treatment, 14/29 (48%) subjects were pain-free and 10/29 (34%) reported mild headache severity. 5/29 (17%) reported the headache had progressed to moderate severity (Figure 1). 8/29 (28%) subjects experienced associated symptoms (nausea, light and sound sensitivity) at 2 hours following initial treatment. At 2 hours, 13/18 (72%) subjects experiencing unilateral pain at Baseline were symptom-free, 6/11 (55%) subjects experiencing sound sensitivity at Baseline were symptom-free, 8/15 (53%) subjects experiencing light sensitivity at Baseline were symptom-free, 4/8 (50%) subjects experiencing nausea at Baseline were symptom-free, 5/11 (45%) subjects experiencing headache worsened by activity were symptom-free, and 4/10 (40%) subjects experiencing a pulsating quality at Baseline were symptom-free (Figure 2).

Of 14 subjects pain-free at 2 hours, 4/14 (29%) had return of headache during the 24 hours following initial treatment (2/4 reported recurrence to moderate headache severity and 2/4 returned to mild pain.) 4 subjects experienced an increase in pain between 2 and 24 hours, 2/4 worsened to severe intensity and 2/4 worsened to moderate intensity.

Side effects were reported by 4/29 (14%) subjects and none were serious. Of the 4 patients, 3 reported unpleasant taste and one experienced a transient burning sensation under the tongue.

At screening, 20/29 (69%) of subjects were satisfied with their pre-study migraine medications, 8/29 (28%) were dissatisfied and 1/29 (3%) was neutral. Prior to entry into the study, 9/29 (31%) subjects treated only with triptans, 8/29 (28%) used triptans and OTCs, 6/29 (21%) treated only with OTCs and 6/29 (21%) treated with other prescription medications.

Following treatment of migraine with GelStat Migraine®, 17/29 (59%) subjects were satisfied with the study medication, 11/29 (38%) were dissatisfied, and 1/29 (3%) was neutral. 7 of the 8 subjects dissatisfied with their pre-study migraine treatment at screening were satisfied with treatment with GelStat Migraine®. Of 17 who were satisfied with GelStat Migraine®, 11 had previously treated migraines with triptans or a combination of triptans and OTCs. 12/29 (41%) subjects preferred GelStat Migraine® or felt it was equal to their pre-study medication. Of those who used triptans or triptans in combination with OTCs, 7/17 (41%) preferred GelStat Migraine® to their pre-study medication or had no preference.

Discussion

Management of individual patients with migraine can be a challenging clinical problem. For many migraine sufferers, attack patterns vary in terms of clinical symptoms and the impact of individual migraine attacks. Numerous studies have been conducted to assess the efficacy of pharmacological intervention during moderate to severe headache particularly with the triptan class of migraine medications. More recently, large studies have been conducted treating migraine attacks early in their evolution while pain is mild and have demonstrated improved 2-hour pain-free efficacy when compared to treatment initiated during moderate to severe headache. However, studies have not been conducted on non-triptan medications as initial treatment in an early intervention treatment paradigm.

Treatment needs can vary considerably for individual migraine attacks. Some attacks may resolve without treatment while others require high end abortive treatment. When migraine attacks are associated with an identifiable mild headache phase many patients wait to see if the attack will progress and become more severe. In part, this may reflect reluctance to utilize prescription therapy without being certain it is necessary and the fact that non-prescription treatments have not been integrated into a treatment plan as an effective treatment tool. Unfortunately, for whatever reason, delayed treatment of acute attacks may result in poor patient outcome.

Subjects in this study were selected for inclusion because they reported identifiable mild headache phase associated with at least 75% of their migraine attacks. They generally treated with study medication both early and while the headache was mild. 14/29 (48%) were pain-free at 2 hours and an additional 10/29 (34%) did not progress past mild headache. Only 5/29 (17%) progressed to a moderate headache and no subjects progressed to severe headache. 4/29 (14%) experienced recurrence of headache with only 2 reporting moderate severity. For a selected group of patients with migraine attacks that begin with a mild pain phase and typically progress to moderate or severe pain, GelStat Migraine® was an effective first line early intervention. Further, it is important to note that the initiation of GelStat Migraine® does not delay the use of any rescue medication should they become necessary. This is critical since recent studies have demonstrated that at least for the triptan medications, treatment efficacy for early intervention is determined more by pain intensity (mild pain) than by time [1,4].

In this study only 6/29 (21%) were using OTC product to treat their migraines and 23/29 (79%) were using prescription medications with or without OTCs. Most (21/29 or 72%) were satisfied at baseline with their treatment medications. After treatment 17/29 (59%) were satisfied with using GelStat Migraine® as an initial intervention.

There are several limitations to the present study. It is an open-label study of only thirty subjects. The subjects' histories of headaches that typically progressed to moderate or severe were self-reported and not documented by baseline diaries. Without a placebo arm, the number of attacks that may have resolved spontaneously, or never progressed beyond mild headache, can only be surmised from other studies of early intervention with triptans. However, it is unlikely that it would approach the 83% successful (pain-free or mild at 2 hours) results of the study, especially since the recurrence rate of headache of moderate to severe intensity was only 7%. In addition, subjects in this study treated only one migraine attack so there is no data on treating multiple attacks. However, despite these limitations it would appear that GelStat Migraine® was efficacious, well tolerated, and well accepted by a majority of the subjects in this study.

Conclusions

This open label study suggests that GelStat Migraine® appears to be effective as a first line abortive treatment for migraine when initiated early during the mild headache phase of the attack in subjects with migraine who experience and can identify, with regularity, the mild headache phase of their attack. Satisfaction with GelStat Migraine® was reported by 59% of subjects and was well tolerated. Further, more stringent studies of GelStat Migraine® are warranted in migraine treatment.

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