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A unique medium chain triglyceride-containing micronutrient complex: Effects on migraine symptoms compared to quality of life

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Abstract

Purpose: Migraine headaches and associated symptoms are prevalent medical issues. Medium-chain triglyceride (MCT)/nootropic-based compounds have demonstrated benefits in multiple domains. This study assessed the potential relief provided from a unique, high-concentration MCT/nootropic component blend on migraine frequency, duration, secondary symptoms, and quality of life (QOL) during a 60-day clinical investigation.

Methods: Forty (n=40) chronic migraine sufferers [migraineurs] were prospectively randomized to participate in the double-blinded study. Both intervention (n=30) and control (n=10) participants were required to maintain lifestyle patterns for the trial duration. Migraine surveys used electronic response forms to allow subjects increased ease and safety during the COVID-19 pandemic.

Results. The intervention subjects experienced reduction in migraine episodes by 53%, from 11.6 to 5.4 per month, after 60 days of supplement use. The average episode duration decreased from 260 minutes to 158 minutes, a 39% improvement. Time lost due to severe migraine effect was reduced from an average of more than five days per month to just over two per month, a decrease of 55%. A combined measure of secondary symptoms, which aggregate to illustrate migraine intensity, also decreased according to subject rating by an average of 37%. Self-assessed QOL scales improved by 43% in the intervention cohort. The control subjects showed no significant changes in any measures.

Conclusion: Consumption of a unique, nootropic brain complex significantly improved migraine symptoms, including episode frequency, duration, severity, and lost days due to dysfunction. The formulation also beneficially impacted secondary effects and self-reported QOL.

Keywords: Migraine; Quality of Life (QOL); Headache; Ketones; Nootropics; Pain

1. Introduction

The third most prevalent global illness is migraine headaches and their associated symptoms, evidenced by 12% of the total population suffering from this condition, including about 40 million people in the U.S. Migraine is a top-20 cause of emergency room visits requiring substantial urgent intervention [1-3]. A high percentage of migraine episodes result in both temporary and long-term disability due to time lost from employment, education, housework, recreation, or other activities [4-7].

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Migraine is typically classified as a neurological disease with multiple causes and factors. Current drug treatments and other modalities for migraineurs may have limited effectiveness when considering the wide range of symptoms [8-13]. Initially, many migraineurs may try to self-medicate as they feel pressure from the social stigma. Various professional treatments are sometimes higher in cost than they can comfortably afford. Many migraineurs wait until they experience severe symptoms that are not amenable to self-directed approaches before seeking intervention [14-18]. At that point there is also accompanying loss of attendance in work, social, educational, or other endeavors.

Possibly more important to an overall improvement in function is how migraine affects QOL. Depression, anxiety, and stress result from migraine and are migraine triggers. Stress is modulated by lifestyle, and stress affects lifestyle and function. Depression, anxiety, and sleep patterns have the same relationship and serve as measurable effects of migraine and related improvement metrics. As migraine is complex and has an extensive array of effects that are not evenly distributed, QOL and secondary symptom ratings are subject to wide individual variances and areas of impact [19]. However, migraineurs are very aware of these personal factors and the resulting influence on their life.

Previous research demonstrated that migraines and resultant specific symptom levels could further amplify psychiatric disorders and lead to increased suicide risk [20, 21]. Because of this established connection, migraines, their associated symptoms and QOL, may be predictive of overall mental health. This is relevant in day-to-day functioning and more extreme reactions to personal perceptions of life, such as tendencies for self-harm. The severity of migraine symptoms and specific frequency and duration similarly may affect this risk in vulnerable groups such as the chronically ill, military veterans, and older individuals [22, 23].

Severity related to QOL, and the development of other actions can be a singular metric or a combination. Some research has reported that migraine with aura is a more accurate predictor of increased risk of self-harm or suicide, while other studies have determined that the presence of aura is not required [24, 25]. One explanation for this dichotomy may be that migraine symptoms are multi-factorial and diverse, so one metric alone is unlikely to be a significant predictor. As there is a time/symptom progression for each migraineur, it is reasonable that the episode severity and how it matches personal improvement goals, expectations, and experience is a more relevant issue in QOL. Consequently, this is a powerful mental and physical state metric due to the combination of individual factors [16, 26, 27].

While drug treatment for migraine has progressed, it may not provide the same relief for every migraineur. Several drug classifications are available. Additionally, onabotulinum toxin A and nerve modulation for pain signaling have been employed. More pharmaceuticals have been developed for treatment and prevention in recent years. These treatments may require interventions such as various modes of parenteral administration. Oral and nasal compounds are available that affect the 5-HT receptor agonists of the dopamine pathway. Calcitonin gene-related peptide receptor antagonists are also used for prevention and treatment. They may be administered by subcutaneous and intravenous injections, although some newer drugs are available as oral agents [28-31].

As with other drugs, reported side effects reported include nausea, fatigue, and somnolence. In addition, there can be application site reactions and sedation [32, 33]. Cost can amount to hundreds of dollars per month, although insurance may cover a part of the costs if certain treatment conditions are met. Most currently used drugs have been assessed primarily based upon decreases in episode frequency [34-37]. Published reports indicate that extended treatment times are required for the most effective reduction in episode frequency.

There is less comparable research on nutritional and other therapies applied to migraine treatment and QOL. This is likely due to a lack of comparative study and definitions. For example, "nutritional therapy" can include caloric restriction, carbohydrate restriction, ketone-production diets, and avoiding "trigger" foods such as alcohol, caffeine, or sugar. In addition, exercise strategies include a spectrum from yoga to interval training, each of which is quite different in cognitive integration and actual physiological effects. Thus, evaluating these varying routines is complicated.

Despite the lack of working definitions and cohesive research in these areas, migraineurs have a strong interest in alternative therapies, specifically natural supplements. For many, the potential side effects of medications result in a substantial interest in non-pharmaceutical treatments.

One such area of interest has become ketones, which are manufactured in the liver from MCTs and delivered to the brain as fuel. Attention to the benefits of both ketogenic diets and related compounds [38] such as MCTs are propelling the exploration of these for cognitive realms and reduction in migraine severity [39-41]. With aging, individuals may also increasingly use ketones as a fuel source for the brain.

One of the most effective strategies is exogenous MCT products because they are strongly ketogenic with a growing body of evidence demonstrating improvement in mood, cognitive function, and symptom progressions [42,43]. The most reasonable postulate for these beneficial results is that ketones provide consistent fuel for the brain under many adverse conditions.

While having some positive impact, ketogenic diets do not provide discrimination between the benefits of the ketogenic component rather than merely a decrease in dietary carbohydrates. It is thought that much of the migraine effect from a ketonomic approach had a basis in carbohydrate reduction. Exogenous ketogenic products, like MCTs, lower glycemic index and stabilize blood sugar [44, 45]. Since ketogenic diets are difficult to follow, using an exogenous MCT product can allow benefits without significant dietary regimentation.

In a setting of so many possible methods of therapeutic intervention for migraine headaches, this pivotal clinical trial examined the effect of a unique, natural proprietary nutritional complex on a spectrum of impact and related QOL. The prospective, randomized, double-blind, placebo-controlled study design adds credibility to these findings and may inform for possible future assessments of natural products for this severe disabling condition.

Given those considerations, this investigation examined the effects of an exogenous, specialized MCT-containing complex on primary migraine symptoms such as episode frequency, duration, and loss of productive days. In addition, the study assessed reductions in secondary symptoms and improvements in QOL ratings.

2. Material and Methods

The study was a double-blind intervention vs. placebo trial which used a 3: 1 randomization ratio of intervention to control subjects.

Migraine sufferers were selected based upon initial criteria that included an average of six or more migraine occurrences per month and a stable lifestyle and medication regimen. Potential subjects were also required to have a capable smartphone, tablet, or computer for forms and rating scales. Those meeting all requirements were then directed to fill out complete medical history forms, agree to a detailed informed consent, and a study-related migraine description evaluation which would be completed again at the end of the project.

This novel hybrid questionnaire instrument, in two parts, was developed to avoid issues noted with other investigative scales. Many traditional measurements are perceived as too lengthy, requiring frequent re-ratings, prolonged survey time, which generally adds a measurement bias and lower compliance, and may use scoring criteria which may be difficult for the subject to understand [46-49]. The Colorado Center for Health and Sports Science Institutional Review Board (CCHSS IRB) reviewed the applicants, with forty (N=40) subjects being accepted into and completing the study. The random assignment resulted in 30 subjects participating in the intervention group, with ten subjects using a placebo compound.

For the 30 days before initiating supplement consumption, participants rated migraine frequency per month, duration in minutes, and missed life episodes (employment, education, housework, and social situations). The survey also included severity areas specific to migraines, including throbbing pain, light and sound sensitivity, nausea, pain on one side, vision changes, mood, vomiting, feeling drained, and vertigo. The participants also rated overall QOL and general ratings for cognitive function, sleep satisfaction, and stress levels.

These secondary factors were rated on a scale from 0-100, with significant rating points of 0 being no issues, 50 having moderate problems, and 100 showing severe issues. It appeared reasonable that this approach would allow the subject more precision in assigning values to symptom severity. The symptom details to be monitored are listed in Table 1. Based upon an optimistic view, the scale was reversed for the QOL ratings. The 100-point rating indicated perfect function in that area, while a 0-rating identified constant issues and could not be worse. Each scale had definitions, yet the scale also allowed the subject to enter another number rating if the pre-defined points did not precisely determine their feeling and experience in that area.

A literature review and subject interviews before study implementation indicated that a combination of migraine scales and individual factors was the appropriate strategy to best determine the most meaningful effects of the study supplement [50-53]. This strategy appeared to provide a complete view concerning how a unique MCT/nootropic compound might or might not benefit migraineurs. The same survey components were used with participants for the final 30 days of the 60-day trial.

Table 1 Survey Areas

Primary Survey Areas
Number of Migraine Incidents, 30-day total
Average Minutes per Incident
Number of Days/Events Lost Due to Migraines
Secondary Survey Areas
Light Sensitivity
Sound Sensitivity
Nausea
Pain on One Side
Vision Changes/Blurred Vision
Vomiting
Mood Changes
Feeling Drained
Vertigo/Dizziness
Throbbing/Pulsating Pain
Quality of Life
Quality of Life, Overall
Cognitive Function
Sleep Satisfaction
Stress Levels

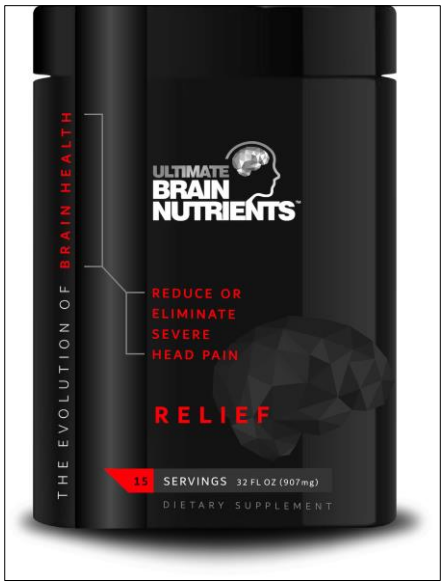

Figure 1 Intervention Product

As this was a contact-less study, the supplement or placebo was individually shipped to each participant. Detailed instructions for the supplement or placebo were provided online and in paper form with the shipments. Instructions

included consuming the supplement or placebo (generally with some food) every day at their scheduled time preference. The intervention product consisted of the proprietary nootropic ingredient combination (*Relief*, Healthy Extracts, Inc.) and employed a mild vanilla flavor (Figure 1). The placebo compound had essentially the same flavor profile yet contained no potentially efficacious compounds. Subjects were directed to maintain consistent lifestyle patterns, work, medical treatments, and daily routines.

3. Results

The self-report scale and questionnaire data compared migraine parameters and symptoms for the 30-day baseline period before supplementation to after consuming the supplement for 60 days. Values are reported as simple, summary numbers with significance levels (p<.05) from T-tests for each area comparing the intervention versus the control group and change as positive or negative (Table 2). Statistically significant changes are shown in red and positive trends in blue. Except for one (stress) of the 17 parameters measured, the control group never matched any of the beneficial trends or significant effects achieved in the intervention cohort. There were no adverse side effects noted from supplementation in any study participant.

Table 2 Control vs. Intervention Group Summary

Metric	Pre-value	Post-value	Change	% Change	Significance
Episodes per 30 days					
Control	8.8	8.3	-0.5	6	
Intervention	11.6	5.4	-6.1	53	0.0004
Minutes Per Episode					
Control	265	247	-18	7	
Intervention	260	158	-102	39	0.0105
Lost Days/Events					
Control	4.9	4.5	0.4	9	
Intervention	5.33	2.4	2.93	55	0.0087
Secondary Symptoms					
Throbbing Pain					
Control	62.4	62.4	0	0	
Intervention	65.43	48.27	17.6	27	0.0560
Light Sensitivity					
Control	48.3	49.4	1.1	2	
Intervention	58.1	42.8	15.3	26	0.0264
Sound Sensitivity					
Control	45.9	40.5	4.4	9	
Intervention	68.6	41.7	26.9	39	0.0267
Nausea					
Control	50.9	40.3	10.5	21	
Intervention	38	24.7	13.3	35	0.1584
Pain on One Side					
Control	61.3	63.3	2	3	
Intervention	64.33	39	25.3	39	0.0048
Vision Changes					
Control	94	94	0	0	
Intervention	38.9	23.07	15.83	41	0.0896
Vomiting					
Control	21	23	2	-9	

Intervention	21.87	8.83	13.04	60	0.0043
Mood Changes					
Control	8.1	7.9	0.2	2	
Intervention	6.03	3.77	2.26	37	0.0196
Feeling Drained					
Control	73.5	66.2	7.3	10	
Intervention	67.26	41.53	25.73	38	0.0449
Vertigo					
Control	39.5	31.4	8.1	20	
Intervention	40.8	29.5	11.3	28	0.3901
Quality of Life Ratings					
Overall Quality of Life					
Control	58.7	60	1.3	2	
Intervention	46.73	67.03	20.3	43	0.00003
Cognitive Function					
Control	62.4	65.7	3.3	5	
Intervention	59.33	69.22	9.89	17	0.0370
Sleep Quality					
Control	60.55	66.05	6.6	11	
Intervention	55.77	66.68	10.91	20	0.1897
Stress Rating					
Control	47	54.5	7.5	16	
Intervention	53.8	59.32	5.52	10	0.4115

Full 60-day reported migraine frequency decreased from an average of 11.6 episodes to 5.4, a reduction of 53% for the intervention group (Figure 2).

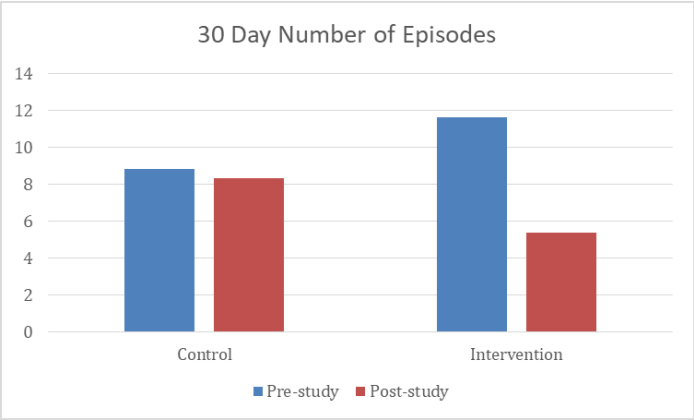

Figure 2 Migraine Episodes, Control versus Intervention

The average duration per migraine episode in the intervention group also decreased from 260 minutes to 152 minutes. (Figure 3).

For the intervention group, the number of days lost to migraine episodes in such areas as employment, education, housework, or social situations fell from an average of just over five per month to just above two per month (Figure 4).

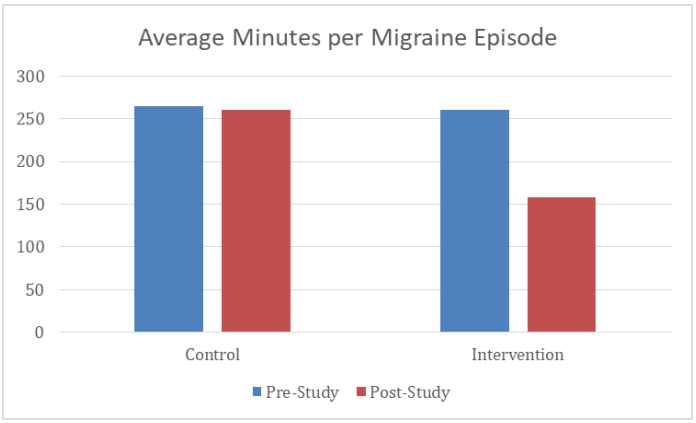

Figure 3 Average Minutes per Migraine Episode, Control vs. Intervention

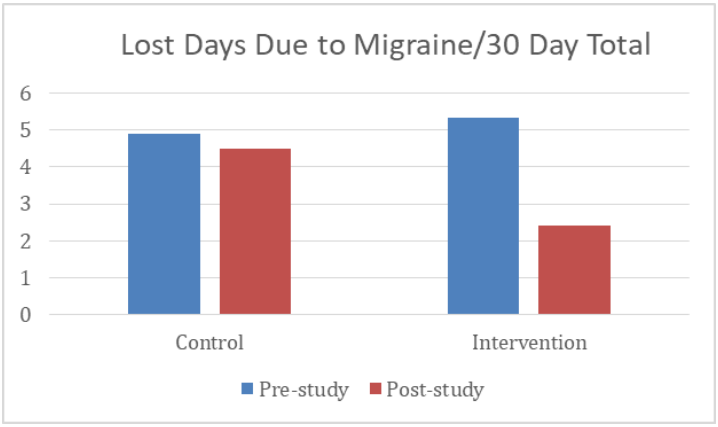

Figure 4 Days Lost to Migraine Episodes, Control versus Intervention

The secondary migraine symptoms also showed decreases across the numerical rating scale after consuming the supplement (Figure 5). In this self-reported section, subjects were directed to rate the amount of disability or effect during each migraine incident. The scale allowed flexibility since subjects could use the sliding scale to add fine effect points for each parameter. The percentage decreases for the intervention group were as follows: throbbing pain 27%, light sensitivity 26%, sound sensitivity 27%, nausea 13%, single-sided pain 25%, vision changes 41%, vomiting 60%, mood changes 37%, feeling drained 38%, and vertigo/dizziness 28%. The average decrease for the combination of all measures was 37%.

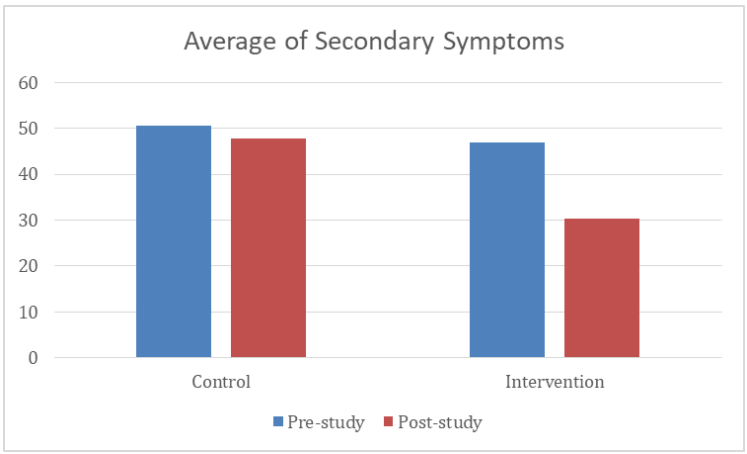

Figure 5 Changes in Secondary Symptom Areas

QOL ratings in the intervention group improved from 47.73 to 67.03, a statistically significant change. While cognitive function, sleep satisfaction, and overall stress ratings in the intervention group trended beneficially upward, the individual magnitude of differences from the control group were slightly less compared to the overall average QOL metric (Figure 6).

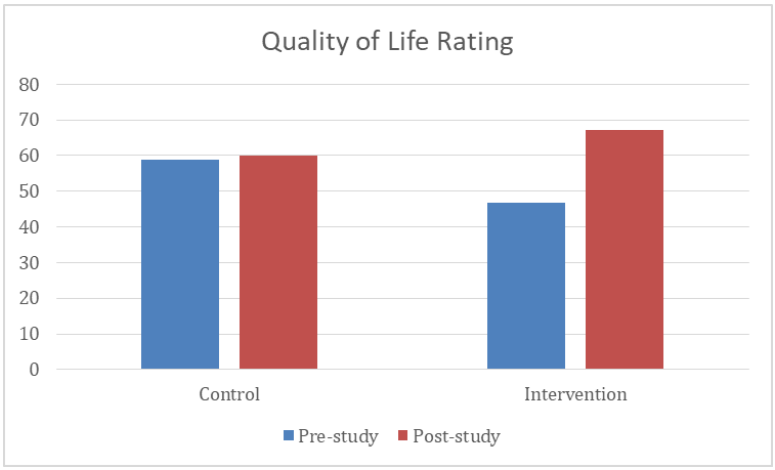

Figure 6 Quality of Life Ratings

4. Discussion

While this investigation encompassed a limited period, the beneficial outcomes seem quite substantial considering that the study compound was a natural supplement. While not intended to be directly compared, the results appear favorable in terms of positive effects when considering migraine medications that recently became commercially available [30-32, 37].

In addition, migraineurs have a wide range of symptoms and interactions between symptoms as this is a multi-dimensional disease. This is also the likely reason why studies demonstrate varying results as not all interventions produce the same effects in all domains for all subjects. An examination of subjects in the intervention group revealed a strong trend of specific symptom reduction. If the initial adverse symptom was more pronounced, the improvement from the intervention was more significant than for subjects with a minimal baseline rating for the symptom.

It can be theorized that another 30 days of using the intervention may have demonstrated further improvement in the variables. While not specifically analyzed, treatment subjects noted in final exit interviews that they felt continued improvement as time progressed in the study. This appears to conform to what is observed for other interventions that routinely demonstrate increasing benefit the longer the therapy is applied [34-36].

It appears that specific exogenous MCT/nootropic combination products, if they are proven to be highly ketogenic, can improve brain function by increasing ketone levels and energy mechanisms [54-56]. Another factor to consider is that the microbiome may aid function in various applications from cognitive health to performance improvement [57]. In further physiological terms, effective MCT/nootropic complexes aid in energy regulation, both with regular activity and during intense exertion [58, 59].

Several mechanisms of action may be implicated in the effects of ketogenesis in migraineurs. Mounting scientific data has recently shown that migraines are a significant response to cerebral energy deficiencies or oxidative stress levels exceeding those that can be managed by natural physiologic antioxidant activity [60,61]. Ketones are an alternative fuel source for the brain and may address certain deficiencies to adequately manage glucose metabolism imbalance. As signaling molecules and energy substrates, ketones may address other migraine physiology components, such as underlying mitochondrial function, inflammation, and oxidative stress.

Oxidative stress damages cells, tissues, organs and body proteins, lipids, and DNA. If the damage happens to neurons, various neurological conditions, including migraine headaches, may occur. In addition to excess free radicals, acute and chronic inflammatory reactions also contribute to the spectrum of injury. Neurogenic inflammation, cellular extravasation, vasodilatation, mast cell activation, and the release of pro-inflammatory mediators may stimulate trigeminal nerve afferents leading to symptom sensitization in the migraineur [62, 63]. Exogenous ketogenic

MCT/nootropics, if they are in a scientifically proven combination, can impact these factors and improve migraine pathophysiology. In addition, 3-hydroxybutyrate, the principal ketone body produced by the metabolism of MCT and the active ketone agent for brain energy, can reduce inflammation and address aspects of metabolic-related disorders [64]. Ketones also appear to have a strong anti-inflammatory response. Thus, various causative mechanisms in migraines may account for the positive MCT/nootropic effect, including metabolites as signaling molecules, efficient mitochondrial energy generation, and reduction of oxidative damage, inflammation, brain stimulation, and hyper-excitability as well as signaling feedback with the overall human microbiome [61, 65, 66].

Finally, it is postulated that the investigated MCT/nootropic combination resulted in the subjects having more energy with subsequently improved attention to lifestyle, thereby mitigating migraine frequency and severity. This may be one of the reasons overall QOL improved in the intervention group. Healthy intestinal flora and function are also related to serotonin and dopamine, thereby improving mood, and modulating migraine headaches [66-70]. QOL factors are a particularly critical component of the migraine experience, and migraineurs view the improvement of this parameter as a meaningful health metric.

5. Conclusion

This controlled clinical experience demonstrated the efficacy of a natural, safe, proprietary, cost-effective supplement intended for migraine prevention and relief benefits. The formulation complex provided improvements in episode frequency, duration, symptoms, limitation of daily activities, and QOL. The product does not require a prescription and has not been associated with adverse side effects. There is now an efficacious alternative or adjunct to other interventions in the challenge to improve the life experience of migraineurs. It appears that this supplement can also be used alone or in combination with other therapeutic approaches to address this disabling chronic medical condition.

Compliance with ethical standards

Acknowledgments

The product's manufacturer, Healthy Extracts, Inc. [HE], provided the product for the study. Otherwise, HE did not have input into study design, data gathering, or final format. GMH and RWK provided content relative to MCT background and mechanistic interactions from their extensive knowledge and experience with MCT products and migraine etiology. NEW was responsible for study design, research mechanics and protocol, and subject monitoring. In addition, NEW was the initial author of the paper and orchestrated the final form.

Disclosure of conflict of interest

RWK and GMH are shareholders in HE but did not contribute to study design, data collection, or result analysis. All parties did review the final document for accuracy. NEW reports no conflicts of interest with the project.

Statement of informed consent

All subjects were provided with informed consent as to the purposes of the study and possible side effects and alternatives. Each subject's consent was affirmed verbally before signature and then given to the CCHSS IRB for review and approval. Subjects were informed the results would be pooled into overall data outcome sets, but no self-identifying information would be released during or after the study.

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