

An innovative approach to treatment of chronic migraine, and craniofacial neuralgia

Abstract

Importance: Migraine is a worldwide distributed problem. New approach to chronic migraine and craniofacial neuralgia may simplify long term and curative treatment in contest to current multi drug, and short term abortive measures.

Objective: To measure the efficacy and safety of simultaneous administration of Dexamethasone, Lidocaine, and Thiamine to the trigeminal nerve branches as well as greater and lesser occipital nerve in chronic migraine, craniofacial neuralgia.

Design, setting, and participants: A single center, randomized, patient centered pilot study by diagnosing chronic craniofacial and migraine patients. Patients with previous diagnostic medical interventions and treatment modalities age 12-87 selected. Patients recruited by their approach to our clinic.

Main outcome and measures: Efficacy and safety in relief of migraine and craniofacial neuralgia by De Novo algorithm in short term and long term workforce individuals.

Results: Our data showed that nearly 96%-98% Patients responded with complete relief after being treated with combined Dexamethasone, Lidocaine, and Thiamine mixture (DE NOVO). 2%-4% experienced major relief in frequency and intensity of their migraine attacks. From 550 patients treated 36 revealed loss of work hours or went through disability for their chronic migraine headaches.

Conclusion and relevance: Among the patients with chronic craniofacial neuralgia and migraine headaches simultaneous bilateral administration of Dexamethasone, lidocaine and thiamine (pat.), showed more effective and superior results than to the most current abortive and surgical modalities. In our trial children age 10 and adult all ages tolerated the treatment well without incident of major adverse event. De Novo treatment is cost effective, safe and does reduce need for multi pharmacy treatment for complicated episodic, chronic migraine headache and craniofacial pain.

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Introduction

Migraine headache seems to demonstrate a dis-balance between sympathetic and parasympathetic innervation of the cerebrovascular system rather than direct central cortical cause. Migraine seems to be a chronic periodic vasoconstriction triggered by sympathetic peripheral nerves embedded in the vasa nervorum, which are predilection to anoxia/hypoxia and consequent acute neuro-inflammatory reaction, possible neuritis and perineuritis. It is well known that acute neuro-inflammatory reaction releases neuropeptides which may potentiate additional vasoconstriction in the neuro vascular supply. In consequence, congestion of post capillary venous system in the perineurium/epineurium may distribute to anoxia and hypoxia in the peripheral nerves. Consequently, anoxic/hypoxic environment in the cell membrane causes changes in ion channels by blockage of oxygen dependent Na^+/K^+ -ATPase Ion transport system alongside of the nerve membrane in general.¹ It understands that P-type ion transport (ATPase dependent) in the nerve cell membrane is a mitochondrial and oxygen dependent mechanism. We understand that ion exchange in the nerve cells is a proactive energy dependent influx and efflux of ions not a passive Symport of ion and glucose bio-transportation mechanism as actively seen in the same membrane.¹ As nerve cell anoxia is dangerous and an irreversible process, the hypoxia is a reversible process and the nerve membrane could recover by vasodilative oxygenation

immediately in few sounds, minutes or hours. Neural membrane is a unique biological organ. Understanding of its molecular biochemistry would help to provide exclusive knowledge of neurogenic pain and other nerve diseases.

Study design

Methods

A simultaneous bilateral approach in the treatment of trigeminal neuralgia (TGN), chronic migraine headaches (CMH), and cluster headaches (CH) has never been studied nor attempted. Almost in all tree type of craniofacial pain, the trigeminal nerve and greater occipital nerves are involved. Literature of headache communities around the world witnessing trial of injections of B6-vitamin, steroids or lidocaine/Bupivacaine in single use or even mixture. Majority of current treatment options, however, are ineffective or just partial abortive. We reviewed our clinical experience and designed an algorithmic approach to the treatment of medically intractable migraines pain that can be treated by a simple non-surgical and non-aggressive intervention. We reviewed data from several view of point from broad spectrum of pharmaceutical and interventional approaches. We searched the bibliographic databases MEDLINE, EMBASE and PASCAL Biomed tile June 2012. We also reviewed the reference lists from identified articles including reviews and meta-

analyses of treatment studies. Furthermore, we studied booklets of scientific congresses in the field of neurology for potentially relevant studies. Additional reports were identified from the reference lists of the retrieved papers, and by contacting experts in the field. A comprehensive study of the knowledge of cell biochemistry and molecular cell biology provided a broad spectrum of understanding in the active cell life on a daily basis in the event of hypoxia, cell messaging system, and its understanding. An in depth study of current cell biochemistry and molecular biological signaling mechanism was essential in understanding of event in the migraine attack and craniofacial pain.

Recent data in the field of anatomy of trigeminal nerve, sympathetic and parasympathetic behavior in neurovascular system, as well as physiology and role of the autonomous ganglia in this matter studied. It is hypothesized that silencing-de-silencing bio switches,² of the parasympathetic/sympathetic nervous system locally would affect, and balance the sympathetic/parasympathetic stimulatory effect of the peri-vascular autonomic nervous system in the peripheral nerve vascular supply, and it may happen by induction of genetic expressive inhibition of COX-2, and nearly all pro-inflammatory cytokines-genes.³ We further hypothesized that a combination of defined concentration of Dexamethasone phosphate, a synthetic adrenocortical steroid, 1% Lidocaine hydrochloride, and Thiamine (Vitamin B1) a water soluble vitamin may concomitantly potentiate induction of mRNA that promote provocation of gene expression and its inhibitory effect of nearly all proinflammatory cytokines genes.³ The patient centered outcomes of this prospective Pilot study was to evaluate the effectiveness and safety of simultaneous administration of Dexamethasone, Lidocaine, and Thiamine into the branches of trigeminal nerve, the greater and lesser Occipital nerve bilaterally for the treatment of acute and chronic trigeminal neuralgia and chronic migraine headaches. Based on vasoconstriction and Neuro-inflammation notion we developed De Novo algorithm and medication.

Eligibility criteria

The study was conducted by Corona Doctors Medical Clinics a multispecialty clinic an educational and treatment center in Corona, southern California. Patients were recruited by announcement and immediate approach for treatment at the clinic. Patients age 12-87 years who were able to distinguish migraine attacks as distinct from other headaches, able to read, comprehend, and legibly and reliably record information, able to provide written, informed consent, and respond to pre and post treatment questionnaires (in minors legal guardian) included. All Patients but one had already comprehensive diagnostic procedures as well as distinct abortive medications and treatments history.

Exclusion criteria

Exclusion criteria: patient with malignant hypertension, history of stroke, TIA or diagnosis of brain aneurysm, Neuro-stimulator implant, trigeminal tractotomy, TGN/Occipital nerve Neurectomy, Microvascular decompression procedure(MVD), Allergies, chronic sinusitis, Glaucoma or gross ophthalmologic disorders, and hypersensitivity to Dexamethasone, Lidocaine, or Thiamine were excluded from study.

Randomization and study drug administration

Patient was randomly recruited at the time of acute attack by accepting proposed treatment vs current available alternatives.

Consent obtained. All selected ages received the same dosage and mixture of medications. Fresh, aseptic and sterile solution prepared for each patient in the dosage of: Dexamethasone phosphate, (pH adjustment 7.0-8.5) 20mg, Lidocaine HCl 1%-each ml contains Lidocaine HCl 10 mg, Sodium Chloride 7mg, Methylparaben 1mg, Water for Injection q.s.(pH range 5.0-7.0) 40mg, and compounded Thiamine, Vitamin B 1 a water soluble vitamin 100mg per ml. Medication prepared in sterile fashion in 1ml syringes using 30G and 27G needle for injection. At each site total of five of 1ml syringes used. According to protocol at each injection site a 0.1ml of combined medication administered. A volume of 0.3ml-0.4ml considered for the ascending and descending branches of greater Occipital nerve at each side. Intra-trochlear space and SPG approached upon severity and resistance of symptoms. By return of patient with new trigger point(s) we treated certain branches involved in neuralgia, adding 1.6mg, 0.4ml dexamethasone and 5mg/0.5ml lidocaine, and 20mg/0.1ml thiamine.

Follow-up and outcomes

We followed up all patients with return to clinic or telephone consultation/mailed questionnaire form in one, and 4 weeks, 6 months and one year. In a limited number of patients we were able to follow up to over 8 years. No one excluded from study or withdrew. 12 patients lost to follow up. The primary study outcome was relief of neuralgia symptoms, and number of symptoms relieved following De Novo procedure. Included in follow up communications adverse reaction and side effects of medications. 40 patients followed up for over 2 year's period consequently. One patient returned with frequent unilateral non responding temporal tinnit sign and pain, associated with seizure type activities. An exploratory surgery revealed a temporal neural ganglion as cause of craniofacial neuralgia (verified by pathology). One patient with unilateral maxillary pain revealed presence of a dental filling "crack" as cause of continuous trigger. One patient with posttraumatic cervical arthritis and miss alignment showed trigger for nocturnal occipital nerve neuralgia but not typical migraine headaches. In one other patient we witnessed reduction of Seizure activity, which may related to her Migraine symptoms. Total number of patients with relief without Migraine relapse/recurrence: 95% (38/40 patients). One patient underwent cerebral vascular procedure with recurrence in his migraine. 2 patients or 5% reported major relief of their migraine symptoms, but with episodic relapsing and remission.

Average period of relief without remitting and relapsing was 15.24 months. Longest migraine relief period reported by a patient was 65 months (2013). Youngest patient was 12 years old and oldest was 87 year old. Shortest period suffering of migraine symptoms was one year and longest 60 years. 10 male and 30 female (33% to 77%). Data studied in August 2013 by ending the research, and recruitment. In addition, we collected data from 36 individuals who were in work relation for the period of 2008-2016 to evaluate their functionality following our treatment. This cohort partially included in our previous trial panel. 28 individuals responded to our inquiry. 8 individuals lost to address changes or did not respond. Of 28 patients almost 100% reported consequent steady work performance without interruption of their job performance or loss of work hours following their treatment.

Data management

Data collected at the end of study. Patients were contacted one for last time. Clinical symptom's parameter and relief length were analyzed by each individual patient. Taken to the account each

patient's comorbidities, type of previous medications, abortive interventions and psycho-social life style changes. Long term data collected in December 2016 through February 2017 only from workforce individuals. A modified MIDASQ (Migraine Disability Assessment Questionnaire) was put together measure the impact of headaches on the patients work environment and disability after De-Novo treatment. The information on this questionnaire was analyzed to evaluate the effect of De-Novo treatment on this group of patients.

Clinical Analysis

All primary analyses were based on the efficacy and safety of De-Novo algorithm. Previous studies showed that the pattern of trigeminal neuralgia, specifically migraine headaches in each individual may differ from other one. Migraine may affect an individual as early as age 7 and younger. It is prevalent in both genders with predilection in females. Chronic migraine in general accompanied by complications such as persistent aura, associated with nausea and vomiting, seizures, and recurrent abdominal tenderness/cramps often called abdominal migraine. Chronic migraine may cause benign paroxysmal (sporadic) vertigo, torticollis and feeling of numbness and tingling in the extremities. Actually, the feature of migraine in adult and children are almost the same. The only difference may be the level of pain tolerance and conscious handling of the events. Neuralgia of lingual nerve may often is mistaken by clinicians as Cerebrovascular attack. Our data analysis revealed that Diagnosis of Migraine is in first instance clinical, imaging steps provides only safety in diagnosing Cerebrovascular comorbidities. Previous studies have shown the nature of trigeminal neuralgia and migraine as neurovascular. However, our investigation in the nature of neurovascular cause demonstrated presence of sympathetic and parasympathetic role of vasoconstructive nature of migraine. De-Novo treatment is composed of two components: Combination medication and Treatment approach. Analysis of results in De-Novo participants group compared to patient underwent an abortive modality showed that De-Novo treatment:

- a. Reduced dosage of medication used in each treatment session.
- b. Less painful injection sites, more tolerability and adherence.
- c. Less reported remittance and relapses of migraine headaches.
- d. Reduced number of non migraines e.g. clusters headaches experiences.
- e. Very Minimal invasive approach.
- f. No otherwise major expected adverse reactions, no contraindications because of minimal dosage of medication except for hypersensitivity to components.
- g. Acceptance of all age patients with no limitation of their comorbid health conditions.
- h. Ambulatory procedure, same day clinical intervention without special medical or costly preparation.
- i. Cost effective for patients, insurances and for clinicians.
- j. High treatment tolerance by younger and oldest patients.
- k. No need for any maintenance medications or life style modifications after the treatment.
- l. It is available to medical providers by a short educational session.

Safety evaluation

Safety was assessed by either component given adverse reaction in clinical setting. Occurrence of physical and neurological symptoms assessed by follow up examinations and questionnaire in next day, one week, one month and 12 month schedule. No major pharmaceutical adverse events recorded.

Interpretation

How human and other mammals defend their life against the physical world? Human and animals, and lifeless violent physical world of our planet crush in each other with grime results for living creatures. Human make gear for defense, and get wiser. Upon journey of life, pain understands the straightforward escaping the distress of physical world. Primarily, pain caused by hypoxia. Sympathetic and parasympathetic nervous system genetically designed as initial primitive internal defense mechanism. It is universal to almost all species on the earth. Its mechanism and pattern may differ on the ground and in avian environment living species. Autonomous nervous system is an internal alert system communicating with our physical world. The plasticity and highly fragile human body system is defenseless against the law of physics such as gravity and weight, wavelength and light, velocity and acceleration, electricity, and more. Question arise how the warning system inside us works? There is a warning system with its signals embedded in our whole system as human being. Fundamental of defense mechanism in almost all species is the same. It's warning signal pronounced mostly by pain or other symptoms such as nausea, vomiting, diarrhea, spasm of the airways and throat, visual loss. Warning signals modified by molecular receptors of five somatosensory systems:

- a. Gustatory system (taste).
- b. Olfactory system (smell).
- c. Vestibulo-Auditory system (balance/hearing).
- d. Visual system.
- e. Somatosensory, tactile system (touch), are managed by a higher sophisticated regulatory system in the brain centers.

Navigation of animal life for survival in response to physical environment controlled by one and each of the somatosensory organs as a first line defense mechanism. Somatosensory system is the only efficient intelligent programming resource for brain. However, later in the process of evolution arise emotional sensory system from communication in the path of the civilization. Therefore, the power of emotional sense genetically imbedded in the civilized animal's brain and behavior. The Limbic system is responsible for awareness threshold and is our major emotional center. It receives input from all somatosensory organs and analyses the data to determine how safe the physical and emotional environment we are entering, is. Emotional sense modifies the concept of internal stressor as modifier of sympathetic signals in a self-defense approach. Factors such as bright lights and ultraviolet waves, flickering lights, as well as certain visual patterns, smells, noises, tastes may trigger migraine. Life style stressors may also trigger a migraine attack, and it has been hypothesized that visual cortical hyperexcitability can be responsible for migraine too. We witnessed that migraine is bilaterally induced; however the dominant reaction with major pain pattern reveals itself at one side. We did try first to treat the dominant side in several cases. Patients returned back with more severe unusual pain pattern

at the opposite side. We did experiment to treat patients with mainly occipital neuralgia complains, they returned with new expression of trigeminal neuralgia symptoms later. The conclusive pattern of our algorithm shaped from mentioned selective experiences. A profound study into the mechanism of medications utilized in the treatment of the trigeminal neuralgia and migraine, their adverse reaction, their role as rescue or abortive agent did not satisfied our ambition of migraine treatment. Major studies of 21st Century at the level of molecular biochemistry and molecular biology indicated the presence of signaling system at the cellular and cell -organelle level play significant role. Genetic modification of altered balanced signals in autonomous nerve system components were the key understanding in our approach.

The role of Dexamethasone

It is well postulated that ischemia induces tissue damage, and changes the cell biology. If it is not interrupted, it may cause cell death and permanent damage. Pain a major subjective protective system in mankind and animal manifests itself as rapid signaling system. Repetitive ischemic events of the nerve cells in craniofacial pain per se migraine defining dis-balance between ongoing ischemic event and oxygenation status of the nerve cell, locally. Suppressing Cytokine-Driven Inflammation is one of the Pluripotent effects of the glucocorticoids. Glucocorticoids are used widely on a chronic basis to treat most autoimmune diseases. Although there are several mechanisms by which glucocorticoids reduce inflammation, a major one may be to reduce expression of cytokine-induced genes. Glucocorticoids enter all cells and bind to the cytoplasmic steroid receptor and then this complex translocate to the nucleus where it is recognized by specific DNA sequences.⁴

Molecular biologic effect of glucocorticoids by penetrating the cell membrane and binding to DNA induce suppression of transcription by opposing transcription factors AP-1 and NF- κ B. AP-1 and TNF- α which potentiate genes encoding almost all proinflammatory cytokines.⁵⁻¹⁰ Glucocorticoids also suppress expression of inflammatory genes encoding T cell growth factors such as IL-2, IL-4, IL-15, and IL-17 as well as interferon- γ (IFN- γ). In addition, glucocorticoids reduce expression of genes encoding COX-2, inducible nitric oxide synthase and intracellular adhesion molecule-1 (ICAM-1), which are normally, induced by the cytokines IL-1 β and TNF- α . Glucocorticoids increase expression of genes encoding anti-inflammatory molecules, such as the cytokine IL-10 and the IL-1 type 2 decoy receptor.¹¹ The gene suppressive effect of glucocorticoids per se Dexamethasone switching the key signals by silencing the hyper-activated proinflammatory signals. The promotion of those signals may encode balance between sympathetic/parasympathetic mechanism at the level of vascular-neuronal capillaries. Induction of nitric oxide synthase changing the status of hypoxia consequently relieves pain by the inhibition of COX-2 and inhibition of nearly all proinflammatory cytokines-genes¹²⁻¹⁵ that plays an important role in the pain signaling.

Thematically, neurobiological signals affecting neurovascular regulation. Cell surface receptors are the gateway through which the cell senses respond to environment. Most physiologically important processes are initiated by interaction of cell-surface receptors with extracellular mediators resulting in intracellular signal transduction cascade. Step by step understanding of molecular biologic action of glucocorticoids by sophisticated worldwide research in molecular biochemistry and molecular biology providing significant insight into

cell membrane receptor, their activation and deactivation, genetic signaling, and genetic structural biology. These novel subjects may disclose the magic of the neural and neurovascular diseases, migraine and trigeminal neuralgia. So far author believes regulatory gene elements play a major role in silencing and de-silencing pattern of the neurovascular disorders such as craniofacial neuralgia (migraine) and high possibly also in Chronic Cerebrospinal Venous Insufficiency disorder (CCSVI), ALS and more. These diseases are acquired later in the path of life and they are not born defects as the etiology and pattern of disease demonstrates.

The role of Lidocaine

As local anesthetics is broadly studied. Utilization of lidocaine locally provides alleviation of painful Dexamethasone administration at the injection site. At the other hand it blocks sympathetic nerve fibers penetrating vas Vasorum and vasa nervorum at the site of nerve branches and sympathetic ganglia. Vasodilation at capillary level of adventia ends hypoxia inhibits the synthesis of prostaglandins at neuronal-junctional level. Lidocaine is a well-established multipurpose local anesthetic. Its effect characterized by rapid onset and immediate duration of 90-120 minutes. Lidocaine alters signal conduction in neurons by blocking the fast voltage gated sodium channels in the neuronal cell membrane that are responsible for signal propagation of pain to brain. Pain is the results of anoxia, by stimulation of cascade of inflammatory cytokines.¹²⁻¹⁵ Alteration of voltage gated signals creates the anesthetic effect by not merely preventing pain signals from propagating to the brain but by stopping them before they begin. Blockage of the signals at the post synaptic neuron level potentiate excellent vasodilatory effect of the lidocaine by blocking signals of sympathetic nerve at the level of adventia of vasa nervorum. This mechanism eases hyperemia, relief from hypoxic event, and pain relief.

The role of Thiamine

2-[3-[(4-Amino-2-methyl-pyrimidin-5-yl)methyl]-4-methyl-thiazol-5-yl]ethanol

Molecular Formula: C₁₂H₁₇CIN₄OS

We were originally interested and curious in the role of gene expression of the Cytotoxins such arachidonic acid, COX2, Interleukins, and TNF- α as provocateur of the pain at the nerve endings. Interestingly more molecular studies were provided by thiamine than any other vitamin. Localized pattern of pain in trigeminal neuralgia, and migraine headaches independent of their trigger cause lighted possible presence of a local inflammatory reaction and consequent central propagation of pain. The conclusion of studies transposed the idea of combination use of dexamethasone phosphate, lidocaine and thiamine in De Novo treatment of migraine and trigeminal neuralgia. Thiamine or Vitamin B1 is a water soluble vitamin, and is colorless organo-sulfur compound with a chemical formula C₁₂H₁₇CIN₄OS. Its phosphate derivate is involved in many cellular processes. The best characterized form is thiamine pyrophosphate (TPP), a coenzyme in the catabolism of sugars and amino acids. Thiamine play role in the biosynthesis of neurotransmitter acetylcholine and gamma-aminobutyric acid (GABA), and myelin synthesis which are essential for brain function. Thiamine deficiency associated with serious fatal outcome if untreated. Well-known thiamine deficiency in CNS associated with optic neuritis and polyneuritis in Beriberi. However, its deficiency in liver shown is not associated with irreversible

neurological lesions. Storage form is albumin bound differ in the body: approximately 90% of total thiamine in the blood is erythrocyte bound; brain tissue, kidneys, myocardocyte and liver contain major storage sources of it.^{16,17}

Thiamine regulates the expression of some genes that code for enzymes using thiamine diphosphate as cofactor. Thiamine deficiency diminishes the mRNA levels of transketolase and pyruvate dehydrogenase. Thiamine can function in a number of non-genomic biological mechanisms such as inflammation, protein expression, oxidative stress, and cellular metabolism.¹⁸ Its role in cell metabolism link it to cancer pathology and tumor cell proliferation.¹⁹ Prostaglandins (PGs) and Cyclooxygenase-2 (COX2) play primary role in inflammatory process. COX2 participates in conversion of arachidonic acid in prostaglandins, and consequently induction of pro-inflammatory cytokines. Animal model research revealed that the expression of COX2 mRNA and PGE2 were selectively increased in vulnerable regions in the symptomatic stages of thiamine deficient encephalopathy.²⁰ Yadav and associates in 2010,^{21,22} emphasized the inhibiting role of thiamine in IL-1 β induced COX2 and its product PGE2 cytotoxicity by genetic blockage. In addition, at the level endothelial layer of the small caliber arteries and capillaries nourishing nerves, benfotiamine showed significant prevention in lipopolysaccharide induced macrophage death and monocytes adhesion to endothelial cells. These anti-inflammatory effects of benfotiamine are clearly mediated through the regulation of arachidonic acid pathway in macrophages.²³

Conclusion

Migraine and trigeminal neuralgia in all its definitions are indefinite process on the earth experienced by all species, brought to knowledge by human. It is part of our genetic calculation for continuity of survival on the planet of earth. Overall seen there are over 50 different medical modalities in treatment of migraine worldwide available. Almost 75% of pharmaceuticals prescribed are off label used and empiric with magnificence side effects in long term use. New class of medication of CGRP-receptor monoclonal in horizon. Diet and supplemental, biofeedback, hypnotic and tribal shamanic regional modalities not included.²⁴⁻²⁸ Respecting the dignity of healthy life for human kind shows that De-Novo[™] treatment and formula provides longer relief of migraine with one treatment session in 95% to 98% of cases including chronic cluster headaches than any other current modalities. Due to its therapeutic action in some frequently observed clinical syndromes, thiamine has been advised and used over a long period. The minimal dose of utilization in De-Novo formula by infiltration pathway near trigeminal nerve branches may potentiate the genetic expression of mRNA by Dexamethasone and lidocaine. Nine years of experiences (2006-2015) with De-Novo formula demonstrated that its components are safe, and efficient if administered simultaneously and bilaterally. DE-NOVO algorithm in treatment of chronic migraine and trigeminal neuralgia is less aggressive, less costly, safer, and demonstrate longer pain relief.

In addition, De-Novo components are widely available, inexpensive, and administration is safe and practical by all medical specialties with minimal training.^{29,30} Our approach is different because it is allowing patients at any age return to their work environment without interruption, benefit major corporates in saving of work hour loss, and tremendous benefit to little patients in long term exposure to pharmacological substances and their devastating side effects.

With respect to all the efforts, understanding of the mechanism of migraine propulsion is the key to designing additional novel and more effective and universal treatment. Preventive strategies for craniofacial neuralgia, migraine headache, and chronic cluster headache exacerbations in adult and children need to be conducted at further cooperative level. We are aware that not every migraine is the same; each one presents its own characteristics. As the physical effect of environment is pluripotent. In our search for CURE we were not able to find a definition for cure of migraine headaches. An intention to stimulate the scientist for cure of migraine set the goal for us to provoke. We do not believe migraine headaches are life time disease of a migraineur. Human and mammalian never ever getting freedom of headaches but of migraine. At this point, any long-term relief (over 3-4 years) of migraine symptoms and craniofacial neuralgia may come near to cure.

Author contribution

Dr. Owiesy had full access to all data in the study and takes full responsibility for integrity of the data and accuracy of data analysis.

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Conflict of interest

Author declares that there is no conflict of interest.

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