An innovative treatment of chronic migraine and trigeminal neuralgia

BACKGROUND AND OBJECTIVES

A simultaneous treatment of trigeminal and occipital nerves never been studied. Migraine headaches or craniofacial neuralgia involving in 90% of cases both trigeminal and greater occipital nerves. Treatment of one nerve without simultaneous treatment of the other did not prove helpful in any of our cases. However, simultaneous treatment of all and both nerves resulted in longest discontinuation of migraine and craniofacial pain.
The interaction of genetic signaling with cell surface receptor is a new subject in molecular biochemistry and biology. It is hypothesized that the genetic signals silencing and de -silencing within the autonomic nerve system per se balances the stimulatory effect of the perivascular sympathetic and parasympathetic systems in the peripheral nerves. This effect may be caused by induction of genetic expressive inhibition of cyclooxygenase-2(COX-2) and nearly all pro inflammatory cytokine genes. However, laboratory research studies on animal models reveal that the neural vascular supply and its control by autonomic nerves paly an interesting role in the bio- mechanisms of the cell anoxia and hypoxia and in neuro inflammatory mechanism of the nerve cell. Various external signals in the physical environment may cause the original primary sympathetic gene hyper-expression that silences parasympathetic progression and regulatory genes in the peripheral vasa nervorum.

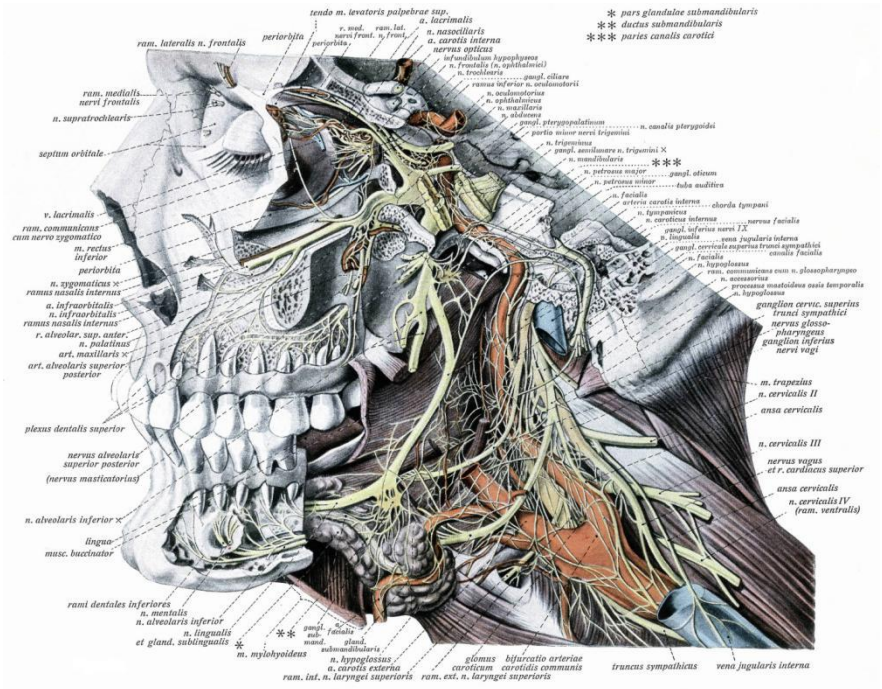
A combination of gene modulating medications: dexamethasone, lidocaine, and thiamine may act as extracellular mediator on cell surface receptors, resulting in an intracellular signal transduction cascade. This signal cascade may express the synthesis of proteins that control the primarily deranged sympathetic signal in the trigeminal nerve system. This de novo approach to the treatment of migraine and trigeminal neuralgia can serve patients of all ages during the research and post-research period and may provide a long-term, pain- free, and relapse-free life span.

The objective of this study was the efficacy and safety of simultaneous administration of dexamethasone, lidocaine, and thiamine into the trigeminal nerve branches and the greater and lesser occipital nerve for treatment of chronic migraine, and craniofacial neuralgia.

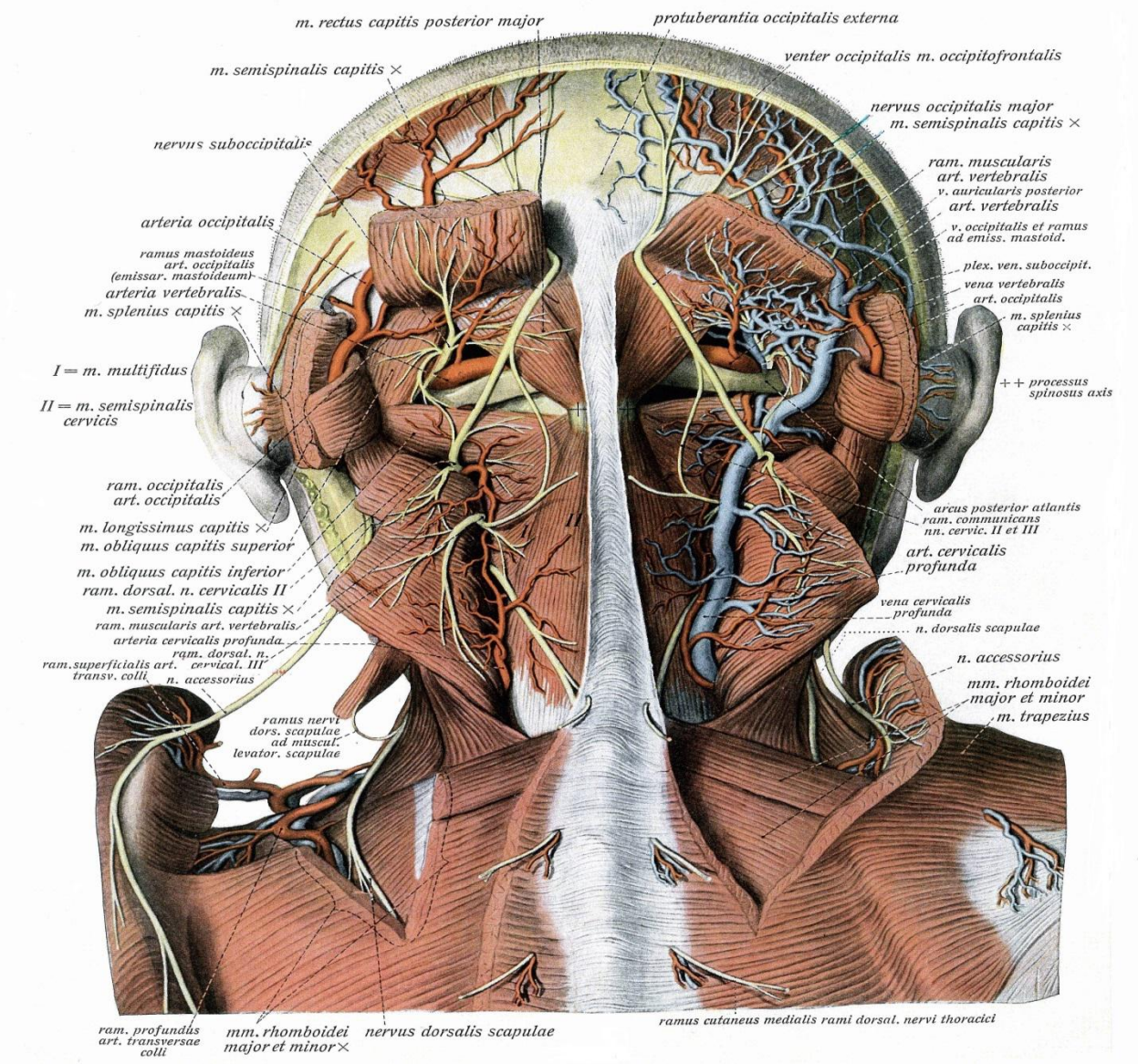
METHOD

- ✓ The study is a single- center, randomized, patient- centered pilot study of chronic migraine and craniofacial patients in status migrainous with and without aura.

- ✓ Study participants recruited by responding to a flyer announcement.
- ✓ Participants are 12-87 years old with previous diagnostic, medical abortive, prophylactic interventions and treatment modalities. Migraine patients are identified by medical history and prior diagnosis of chronic migraine by a neurology specialist or primary care physician.
- ✓ The patient's abortive and prophylactic medications are identified, tapered and discontinued (except for NSAIDS) prior to treatment initiation.
- ✓ Patients who are not currently prophylactic medications intake treated upon exacerbation of their symptoms and arrival at our clinic.
- ✓ Study forms indicating initial pain points and pain migration routes in the head and neck, including presence or absence of ophthalmoplegia , are obtained prior to treatment. If available, medical records are evaluated.
- ✓ Trigger modalities, pain quality and quantity (measured on a scale of 1-10), and disability level are included in the patient's profile.
- ✓ Preparation and simultaneous administration of a mixture of dexamethasone phosphate total dose of 16 mg, *4mg/ml*, Lidocaine HCL 1% 100mg, *10mg/ml,* and Thiamin**(B1), 100mg/ml** in conducted in a single session into the accessible branches of the trigeminal nerve in the first, second, and third divisions, as well as into the greater and lesser occipital nerve.
- ✓ The procedure and combination of medication is called the de-novo algorithm.



Trigeminal nerve branches and parasympathetic ganglia accessible to de-novo treatment



Greater and lesser occipital nerve with ascending and descending division. Rami communicants play a major role in propagating pain signals

Study Period

The index period (June, 1 2007 – September, 2013) for our study starts on the day that the first patient randomly approached our clinic with acute exacerbation of migraine and non-response to traditional prophylactic and abortive formulas.

Study follow-ups: one week, 4 weeks, 26 weeks, and 52 weeks

June 1, 2007 [redacted] September 30, 2013

Study Sample and Criteria

- ✓ Patient ages ranged from 12 years old (parental consent was obtained) to 87 years old.
- ✓ Forty patients (10 male and 30 female) participated in the study.
- ✓ Patients were randomly selected from those who approached our clinic seeking treatment for acute exacerbation with status migrainous.
- ✓ All but one patient had profound diagnosis and imaging studies of chronic migraine.
- ✓ All patients exhausted their treatment with abortive and prophylactic medications during the previous 12 months.
- ✓ All Patients had several emergency department visits in the last 3 months.
- ✓ All patients and their guardian of one minor, could distinguish migraine from other type of headache. Patients could read, comprehend, and reliably record daily migraine information in a diary.
- ✓ Patients provided written consent for treatment and agreed to one year follow-up visits and communication.
- ✓ No medical comorbidity discrimination was specified for this study.

Exclusion Criteria

- ✓ Uncontrolled hypertension, including contraceptive induced.
- ✓ History of stroke, transient ischemic attack, or non-migraine-related seizure.
- ✓ History of brain aneurysm, implantation of any type of neuro-stimulator, trigeminal tractotomy, trigeminal or occipital nerve neurectomy, or microvascular decompression.
- ✓ Hypersensitivity or allergy to any components of de novo formula.

RESULTS

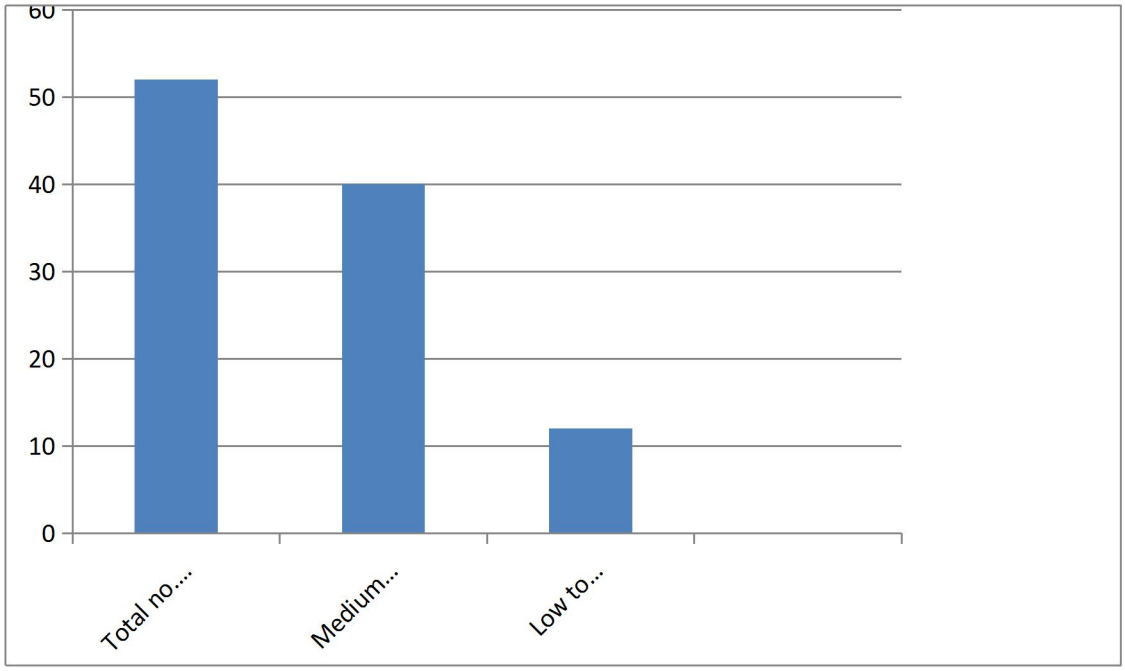
- ✓ We recruited 52 patients who qulified for the de-novo treatment. Of those, 12 patients showed low or no adherence to post-treatment follow ups and were excluded from statistical evaluation, and 40 completed planned follow-ups. All patients received the same clinical evaluation and treatment per protocol.

- ✓ Out of 40 patients, 38(95%) experienced long-term resolution of their migraine or craniofacial neuralgia and 2 (5%) experienced major relief of their complex and chronic migraine with episodic relapse and remisssion.
- ✓ The avergae length of migraine free period was 15.24 months.
- ✓ The single longest migraine free period was 65 months until the end of the trial in 2013.
- ✓ One patient did not demonstrate any respond to treatment. An exploratory revision of rt. Temporo-parietal muscle and fascia revealed presence of a neuroma of zygomatico-facial nerve. A Neuronectomy resulted in complete resolution of migraine and craniofacial neuralgia.
- ✓ One patien had a a chronic apical abscess of the right molar, which was extracted, resulting in migraine- free status.
- ✓ One patient had moderate to severe post-traumatic cervical arthrosis with neural space stenosis.Although the cervicalgia continued, migraine symptoms were alleviated after de-novo treatment.
- ✓ One patient underwent brain surgery for previously undetected berry aneurysm a year after resolution of his migraine. His mgraines recurred, but after receiving a second treatment, he again became migraine-free.

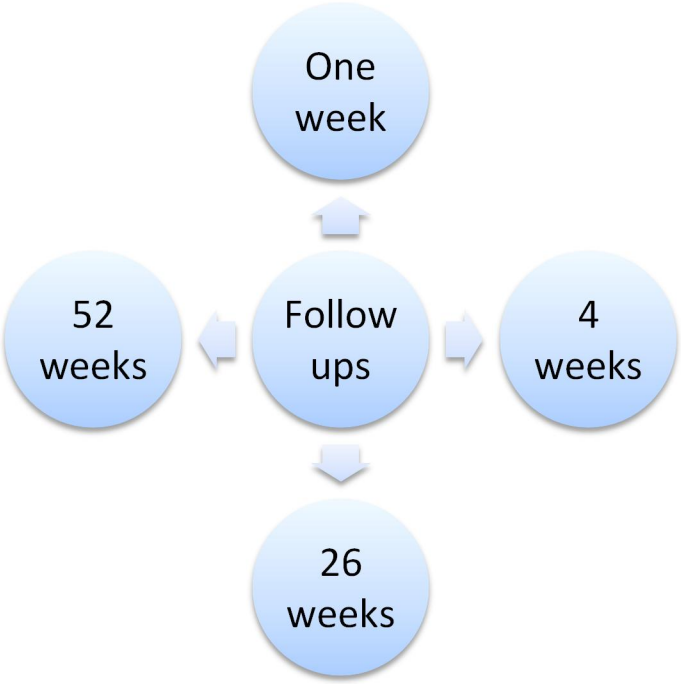
Demographic characteristics , level of adherence, post-de novo treatment visits

Age, mean (SD)	15.07 (9.94)	Non adherence	Med.-high Adherence	complication
Female	75%	21% # 12	75% # 40	1, ecchymosis of upper eyelid
Male	25%	2%	25%	0
Abortive treatment	97.5%	100%	97.5%	1, no prior treatment
Prophylactic treatment	97.5%	100%	97.5%	1, no prior treatment

Patient adherence, post - de-novo treatment



Periodic follow ups in person, written or by e-mail communications



DISCUSSION

The autonomic nervous system is an internal alert system that communicates with our physical world. The fragile human body is defenseless against the laws of physics, such as gravity, weight, light, velocity, acceleration, and electricity. The human body, like most species, has a warning system that includes signals. These signals include pain, nausea, vomiting, diarrhea, airway spasms, and vision loss. These warning signals are modified by molecular receptors of the somatosensory systems.

We were originally interested in the role of gene expression of the cytotoxins, such arachidonic acid, COX-2, interleukins, and TNF-α as causes of pain at the nerve endings. A localized pattern of pain in trigeminal neuralgia and migraines, independent of their triggers, demonstrated possible presence of a local inflammatory reaction and consequent central propagation of pain, as result. **Many Headaches centers of major neurology departments around the world have been utilizing lidocaine or a combination of corticosteroids-lidocaine, in the treatment of migraine and trigeminal neuralgia but only in selected single nerve branches suggesting trigger points as cause of migraine.**

Prostaglandins and COX-2 play primary roles in the inflammatory process. COX-2 participates in the conversion of arachidonic acid into prostaglandins and consequently the induction of pro-inflammatory cytokines. Animal model research reveals that the expression of COX-2 mRNA and prostaglandin E2 were selectively increased in vulnerable regions in the symptomatic stages of thiamine deficient encephalopathy. (20) The anti-inflammatory effects of thiamine are mediated through the regulation of the arachidonic acid pathway in macrophages. (23)

Gene suppressors called glucocorticoids (e.g., dexamethasone) down regulate key signals in genes by silencing hyper-activated, pro-inflammatory proteins. The promotion of those signals may help to balance the sympathetic and parasympathetic mechanisms at the level of vascular-neuronal capillaries. Induction of nitric oxide synthase changes the status of hypoxia and consequently relieves pain by the inhibiting COX-2 and nearly all pro-inflammatory cytokines genes (19,23,24,25).

Studies of acute cardiovascular protective effect of corticosteroids demonstrated that treatment of human endothelial cells with the corticosteroid, dexamethasone, stimulated eNOS activity in a concentration-dependent manner with a maximal 2.7-fold increase occurring at a concentration of 100 nM. The increase in eNOS activity by dexamethasone was significant after 10 min of stimulation and peaked at 30 to 60 minutes before gradually decreasing at 24 hours. Other corticosteroids utilized as well. Indeed, the activation of eNOS by dexamethasone correlated with dexamethasone -induced NO-dependent Vaso-relaxation.

Lidocaine alleviates the pain of dexamethasone administration at the injection site. It also blocks sympathetic nerve fibers from penetrating the vasa Vasorum and vasa nervorum at the site of the nerve branches and sympathetic ganglia. Vasodilation at the capillary level of adventia stops hypoxia and inhibits the synthesis of prostaglandins at the neuronal-junctional level. 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. Interestingly, studies that are more molecular have been conducted using thiamine than any other vitamin. Thiamine can function in several non-genomic biological mechanisms, such as inflammation, protein expression, oxidative stress, and cellular metabolism. (18) Its role in cell metabolism links it to cancer pathology and tumor cell proliferation. (19)

CONCLUSION AND RELEVANCE

Among the patients with chronic craniofacial neuralgia and migraines, simultaneous bilateral administration of dexamethasone, lidocaine, and thiamine showed more efficacy and superior results than most current abortive, prophylactic, and surgical modalities. In our trial, all participants tolerated the treatment well without incident or major adverse event. Most of working patients were returned to work with No Evidence of debilitating Disease Activity. The de novo treatment is cost effective, safe, and reduces the need for poly-pharmacy, and repeated treatment. Superiority of the de novo approach is embedded in modification of gene expression as a fundament of migraine and trigeminal neuralgia treatment.

Faro T. Owiesy, MD, Corona Doctors Medical Clinics, 802 Magnolia Ave., Suite 106. Corona, CA, 92879; owiesymd@gmail.com

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53- Dr. k. Christopher Garcia is also Professor of Molecular and Cellular Physiology and of Structural Biology at Stanford University School of Medicine.